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Risk and Protective Factors Associated With Substance Use Disorders in Adolescents With First-Episode Mania

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Abstract

Objective—Adolescents with bipolar disorder (BD) are more likely to develop substance use disorders (SUDs) than adolescents without psychiatric disorders, but to our knowledge specific risk factors underlying this relationship have not been prospectively examined. The purpose of this study was to identify predictors of developing SUDs following a first manic episode.

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Method—Participants aged 12 to 20 years and hospitalized with their first manic episode associated with bipolar I disorder (BP-I) were recruited as part of the University of Cincinnati First-Episode Mania Study and prospectively evaluated for patterns of substance use. Follow-up ranged between 17 and 283 weeks (mean=113, SD=71.9). Demographic and clinical variables were compared between adolescents with and without SUDs.

Results—Forty-nine of 103 adolescents (48%) with BD either had a SUD at baseline or developed one during follow-up. Seventeen of 71 (24%) participants who did not have a SUD at study entry developed one during follow-up (median=40 weeks). Later onset of BD, manic (vs. mixed) mood episode, and co-morbid disruptive behavior disorders were associated with an increased risk of developing a SUD in univariate analyses. Adolescents treated with psychostimulant treatment prior to their first manic episode were significantly less likely to develop a SUD independent of attention-deficit/hyperactivity disorder (ADHD) diagnosis. Co-morbid posttraumatic stress disorder (PTSD) and psychotic symptoms were the strongest predictors of SUD development.

Conclusion—Our results confirm high rates of SUD in adolescents with BD. Additionally, our findings identify potential risk factors associated with SUDs in adolescents with BD. These data are preliminary in nature and should be explored further in future studies.

Keywords

Adolescents; bipolar disorder; substance use disorders; mania; first-episode

Introduction

Epidemiologic data suggest several factors may be associated with the development of substance use disorders (SUD) in adolescents. Specifically, adolescent boys appear to be more likely than girls to develop a SUD.[1–3] Low socioeconomic status also has been associated with an increased risk for cannabis use disorders, while higher socioeconomic status is associated with increased alcohol use.[2,4–5] A positive family history of SUDs increases the risk of adolescents developing a SUD themselves.[6] White adolescents also have higher rates of SUDs than non-white adolescents, especially alcohol use disorders.[2–3,6–7] The risk of developing a SUD also increases over the course of adolescence. For example, Swendsen et al. reported that 15.1% of adolescents aged 17–18 years met *DSM-IV* criteria for alcohol abuse as opposed to only 1.3% of adolescents aged 13–14 years, with similar trends for drug abuse.[3]

In addition to demographic and family history risk factors, studies have found a high prevalence of psychiatric disorders including mood disorders, conduct disorder (CD), attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), and psychotic disorders in youth with SUD.[6,8–22] These disorders are also associated with a younger onset of SUDs.[11,15,17]

Individuals with bipolar disorder (BD) have particularly high risk of developing a SUD,[8,10–11,13–14,23–26] and this relationship persists even when controlling for other co-morbid psychiatric conditions including ADHD, disruptive behavior disorders, and anxiety

disorders.[9–10,23,27–28] Recent studies suggest that adolescent-onset, rather than child-onset, BD is associated with the highest risk for developing a comorbid SUD.[23–24,28] Patients with co-morbid substance use and BD have a worse course of illness, including increased suicide attempts,[26,29–33] poor medication adherence,[34] rapid cycling,[35] and poorer overall functioning.[36–37] Furthermore, co-morbid substance use and BDs have been associated with high rates of legal problems, unwanted pregnancies, HIV infection risk behaviors, and abortion in adolescents.[24,38] Identifying characteristics of adolescents with BD who are most susceptible to developing SUDs may help establish targeted early prevention/intervention strategies.

With these considerations in mind, the purpose of this study was to examine clinical and demographic characteristics associated with SUDs in adolescents with BD and to identify potential risk and resilience factors associated with the onset of a SUD following hospitalization for a first manic episode.[34,39] Based on the results of prior studies of characteristics of SUDs in adolescents with and without a psychiatric disorder, we hypothesized that adolescents with BD who were boys, older, white, and/or had a family history of SUDs would be more likely to have a SUD. We also hypothesized that adolescents with BD and co-morbid psychiatric disorders, including disruptive behavioral disorders, ADHD, and psychotic disorders would be more likely to have a SUD. Additionally, we hypothesized that adolescents with BD who displayed the characteristics listed above would be more likely to develop a SUD during follow-up.

Method

Participants

Study participants (N=103) were adolescents between 12 and 20 years of age, diagnosed with bipolar I disorder (BP-I) and hospitalized for the first time for a manic or mixed episode. These study participants were a subset of those who had previously participated in published studies examining alcohol and cannabis abuse following a first manic episode,[40–41] and they were recruited as part of the University of Cincinnati First-Episode Mania Study between July 1999 and November 2005. Participants were included if they (1) met *DSM-IV* criteria for a current manic or mixed episode, (2) had no previous psychiatric hospitalizations, and (3) did not receive prior treatment with antidepressants, antipsychotics, or mood stabilizers, including anticonvulsants and lithium. Patients previously treated with stimulants were not excluded from this study. Patients were excluded if their psychiatric symptoms were due to medical illness or substance use withdrawal, or if they had a documented IQ of less than 70. After study procedures were fully explained, written assent was obtained from the adolescents if younger than 18 years old, and written consent was obtained from their legal guardians or from any study participants who were 18 years of age or older. This study was approved by the University of Cincinnati and the Cincinnati Children’s Hospital Medical Center Institutional Review Boards.

Assessments

At baseline, diagnoses were established using the Washington University at St. Louis Kiddie-Schedule Affective Disorders and Schizophrenia (WASH-U-KSADS)[42] or, if the

participant was 18 years of age or older at index hospitalization, the Structured Clinical Interview for *DSM-IV* Axis I Disorders – Patient Edition (SCID-I/P).[43] The K-SADS or the SCID-I/P were administered by trained interviewers, who were study-related psychiatrists or psychologists, with high diagnostic agreement (unweighted kappa=0.94). For establishing reliability for each diagnostic interview (i.e. K-SADS or SCID-I/P), interviewers were initially trained to administer the interview by a psychologist or psychiatrist who was a trained interviewer. Once the new interviewers had watched many interviews and had the opportunity to administer interviews, they each rated 10 interviews. Scores were based on the overall diagnostic reliability of 10 interviews between two raters for diagnoses. Age of onset of BD was defined as the age at which the participant first met full *DSM-IV* criteria for an episode of depression, mania, or hypomania. A mixed episode was defined as meeting criteria for both a manic and a major depressive episode for at least a one-week period. Psychosis was defined by the presence of delusions or hallucinations. Adolescents and their primary caregivers were interviewed separately, and responses were combined in order to determine diagnoses. Demographic information was gathered through interviews with the adolescent and his or her legal guardian. Socioeconomic status was determined using the 4-factor Hollingshead Scale.[44]

Procedures

Participants completed a diagnostic assessment at the time of hospitalization. As part of this longitudinal study, participants returned for follow-up assessments one month following hospital discharge and at four-month intervals from baseline thereafter. During each visit, participants and investigators reviewed week-by-week symptoms of SUDs and mood disorders, with extra attention being given to times at which there was a change in symptoms. The Addiction Severity Index (ASI)[45] and SCID substance use module were administered at each follow-up assessment. Onset of SUDs was determined to the nearest week through best-estimate procedures[46] using data collected during each follow-up visit. SUD diagnoses were evaluated for false positives through urine drug screens. Completed weeks of follow-up assessment ranged from 17 weeks to 283 weeks (median=104, SD=71.9) and varied based on when patients enrolled relative to the study's completion and when patients were lost to follow-up.

Statistical Analysis

All participants were initially grouped by presence or absence of lifetime SUD diagnosis, where lifetime included any individual who had a SUD at baseline or developed one during follow-up. Group comparisons of demographic and clinical characteristics were compared between youth with bipolar disorder and lifetime SUD and those without using either two-sample t-tests or Wilcoxon rank sum tests for continuous variables. Binary variables were compared using chi-square or Fisher's exact tests. A proportional hazards (PH) model was used to estimate the hazard ratio of SUD onset for each variable. Based on these univariate comparisons, variables with p-values ≤ 0.20 were entered into a multivariate PH model. For comparison, a secondary forward stepwise selection procedure was also used to fit a multivariate PH model with p-value ≤ 0.20 as the entry criterion.

Individuals who did not have a SUD at baseline were then grouped according to whether or not they developed a SUD during the course of follow-up. Similar analyses were performed using two sample t-tests, Wilcoxon rank sum tests, chi-square tests, and Fisher's exact tests. Additionally, for the follow-up analyses, study variables were used individually in PH models to predict time to SUD onset during follow-up. Since only 17 participants had a SUD during follow-up and predictor cell sizes were reduced in follow-up (e.g., cases of PTSD), no multivariate analyses were done in this sub-sample.

All independent variables were examined to ensure that they met the proportional hazards assumption in the PH models, and none exhibited serious deviation from this assumption. All hypothesis testing was two-sided with a significance level of 0.05. Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina).

Results

Characteristics Associated with Lifetime SUDs in Adolescents with BD

Forty-eight percent of first-hospitalization manic adolescents (n=49) either had a co-morbid SUD prior to the onset of mania or developed one during the course of follow-up (Table 1). Cannabis abuse or dependence was the most common SUD (41/49, 84%). Of the 49 participants who developed a SUD, cannabis abuse or dependence developed in 27 of the individuals (55%) before any other SUD. Thirty-two of the 49 (65%) participants were diagnosed with a SUD prior to or at index hospitalization. Twenty of these individuals developed a SUD prior to their first mood episode and subsequent onset of BD, while 9 developed a SUD following onset of their first mood episode but prior to index hospitalization, and 3 developed a SUD concurrently with BD.

Clinical and demographic characteristics were compared between youth with BD with and without SUDs and are displayed in Table 2. Unlike previously cited studies,[1–22] participants with and without SUDs did not differ in sex, race, socioeconomic status, or in rates of co-occurring ADHD, anxiety disorders, or PTSD. Psychosocial treatment prior to index hospitalization was also not significantly different between groups. However, later age at index hospitalization, later age at onset of BD, baseline psychotic symptoms, physical or sexual abuse, and a manic (vs. mixed) mood episode at baseline were significantly associated with co-morbid SUDs ($p<0.01$ for all variables) while prior treatment with stimulants was significantly associated with not having a SUD ($p<0.01$).The association between co-morbid disruptive behavior disorders and having a lifetime SUD trended toward significance ($p=0.07$), as did pre-hospitalization psychosocial treatment ($p=0.11$).

The demographic characteristics were entered into a univariate proportional hazards (PH) model, also shown in Table 2. Baseline psychosis (hazard ratio [HR]=1.8, 95% CI=1.0 to 3.2, $p=0.05$), physical or sexual abuse (HR=2.5, 95% CI=1.3 to 4.8, $p=0.01$), and co-morbid PTSD (HR=2.8, 95% CI=1.2 to 6.7, $p=0.02$) all significantly increased the risk for having a lifetime SUD diagnosis. In contrast, prior exposure to psychostimulant medication significantly decreased the risk of having a lifetime SUD diagnosis (HR=0.3, 95% CI=0.1 to 0.8, $p=0.01$).

A multivariate PH model was constructed using all variables with p≤0.20 from the univariate PH model in Table 2: age of onset of BD, psychosis, disruptive behavior disorders, physical or sexual abuse, PTSD, and prior treatment with stimulants. Of these variables, only psychosis (HR=2.0, 95% CI=1.0 to 3.9, p=0.05) and physical or sexual abuse (HR=2.7, 95% CI=1.3 to 5.6, p=0.01) remained significant predictors of a lifetime SUD diagnosis (Table 3). Similar results were obtained using a forward stepwise selection procedure which yielded physical or sexual abuse as a significant predictor (p=0.02) and psychosis as a borderline predictor (p=0.07).

Characteristics Associated with SUD Development Following a First Manic Episode in Adolescents

Thirty-two of the original 103 study participants with first-episode mania (31%) were already diagnosed with a SUD at the time of index hospitalization and were excluded from subsequent analyses of risk factors associated with the development of SUDs following hospitalization for a first manic episode, bringing the sample size to N=71 for these analyses.

Seventeen of 71 participants (24%) developed a SUD during follow-up (Table 1). The median time to onset of any SUD was 40 weeks following index hospitalization. Cannabis abuse or dependence was the first SUD to develop in 9 of the 17 participants (53%) who developed a SUD. The most common SUD was alcohol abuse or dependence, which occurred in 13 of the 17 participants (76%) who developed a SUD, followed by cannabis abuse or dependence (12/17, 71%).

The results of the univariate analyses, including group comparisons using two sample t-tests or Wilcoxon rank sum tests and chi-squared or Fisher's exact tests, and a PH model, are shown in Table 4. Participants who developed and did not develop a SUD during follow-up did not significantly differ in age, sex, race, socioeconomic status. Physical or sexual abuse, prior psychosocial treatment, and rates of cooccurring anxiety disorders and ADHD also did not significantly differ between the two groups. Participants who developed a SUD had significantly later age of onset of BD (14.4 years [SD=2.8] vs. 12.1 years [SD=3.6]; p=0.02). Psychosis at baseline was also significantly associated with developing a SUD (p<0.01). In addition, co-morbid disruptive behavior disorders and PTSD were significantly associated with developing a SUD during follow-up (p=0.02 and p=0.03, respectively). Conversely, treatment with stimulants prior to the onset of BD was significantly associated with not developing a SUD during follow-up (p=0.03).

The univariate PH models produced similar findings, but suggested an additional risk factor. In the PH model, a baseline manic (vs. mixed) episode significantly predicted the development of a SUD (HR=2.7, 95% CI=1.0 to 7.0, p=0.04). Consistent with the results of the group comparisons, baseline psychosis was the strongest predictor of developing a SUD (hazard ratio [HR]=3.8, 95% CI=1.3 to 10.8, p=0.01) followed by PTSD (HR=3.3, 95% CI=1.1 to 10.2, p=0.04). Later age of onset of BD also remained a significant predictor of developing a SUD (HR=1.2, 95% CI=1.0 to 1.3, p=0.02). Additionally, patients with prior exposure to stimulants were significantly less likely to develop a SUD (HR=0.2, 95% CI=0.1 to 1.0, p=0.05). Co-morbid disruptive behavior disorders predicted the development

of a SUD at a trend level (HR=2.5, 95% CI=0.9 to 7.1, p=0.09). The hazard ratio for prior psychosocial treatment was not constant over time and thus a treatment × time interaction variable was included in this model. After examination of the survival curves (not shown), participants with prior psychosocial treatment had lower risk of SUDs for approximately the first 2 years of follow-up but then higher risk for the remainder of the follow-up period.

Discussion

The present study replicated the high rates of SUDs among adolescents with BD,[9–10,23,27–28] The rate of SUD in our sample (49/103, 47.6%) is slightly higher than the rates reported by Wilens et al.[10] and Kenneson et al.[27] (34% and 43%, respectively). Our slightly higher rate is most likely due to the fact that we examined an inpatient sample of BP-I adolescents, whereas the aforementioned studies included BPII and BP-NOS participants and/or included outpatients. Our rate is higher than the rate reported in Goldstein et al.[25] (47.6% vs. 16%). However, Goldstein's sample was also outpatient and included BP-II and BP-NOS. Furthermore, our sample included older participants, (12–20 years vs. 12–17 years).

Our analyses revealed several characteristics that were associated with a lifetime SUD diagnosis in adolescents with BD, as well as several risk factors that were associated with the development of a new SUD following a first manic episode in adolescence. Of these latter factors, psychosis and PTSD showed the strongest evidence of predicting a new-onset SUD. Our results are consistent with those of Kenneson and colleagues,[27] who found in a retrospective study that adolescent –rather than childhood – onset BD, oppositional defiant disorder, and anxiety disorders, including PTSD, were significant predictors of later developing a SUD. Our study was similar in design to Goldstein et al.[47] with the exception that our sample was an inpatient sample of BP-I patients and that our participants were not diagnosed with BD prior to hospitalization, thus allowing us to prospectively track the development of SUDs from the onset of BD. Nevertheless, our study replicates the result that disruptive behavior disorders may predict SUD development in adolescents with BD.

As noted, baseline psychosis was the greatest risk factor for developing a SUD in adolescents with BD, which supports and extends the findings of previous studies.[19–21,48] For example, in a prospective study Duffy et al.[48] found an association between psychotic features and the risk of developing a SUD in youth who were at familial risk for BD. Moreover, several other characteristics we identified as predictors of SUD have been associated with SUDs in adolescents with BD in prior studies, including later age of onset of BD[23,25,28] and disruptive behavior disorders.[11,15,17,28] Thus, taken together, our study and prior work by others converge to suggest that both the developmental timing of symptom onset as well as cooccurring psychopathology may influence the development of SUDs.

Our findings are also consistent with those of previous studies demonstrating high rates of substance misuse among patients diagnosed with PTSD.[6,49–51] Steinbuchel et al.[51] found that SUDs developed in 72% of the participants diagnosed with all three disorders, which taken along with our findings emphasizes the need for clinical vigilance in young people with these risk factors. It is important to note that this finding is limited by a small sample of

participants diagnosed with PTSD. However, we believe our result is valid given the extensive evidence supporting PTSD as a risk factor for the development of SUDs, though we cannot exactly determine the impact of PTSD on the development of SUDs in this sample.

Although this study did not investigate reasons for substance use, it is possible that SUDs developed as a result of using substances to self-medicate or to cope with symptoms of BD. Studies by Thornton et al.[52] and Hein et al.[53] support this hypothesis as an explanation for substance use in patients with psychosis and PTSD, respectively. Additionally, several studies report that adolescents with BD cite the mood-altering effects of substances as a major reason for their use,[54–55] further suggesting that self-medication may be a prominent reason for developing SUDs after the onset of BD. An alternative explanation is that the impulsivity associated with mania may contribute to developing SUDs.[56] Consequently, additional studies are needed to identify the mechanisms underlying vulnerability to SUDs in individuals with BD in general and especially in those with psychosis or co-morbid PTSD, specifically.

Our data suggested that treatment with psychostimulants prior to the index manic or mixed episode may protect adolescents with BD from developing a SUD. Participants who had been prescribed stimulants had roughly 1/4 the risk for developing SUD. One explanation for this finding is that the stimulants were effectively treating ADHD, which has been shown to protect against developing a SUD. Indeed, Biederman et al.[57] suggested that the treatment of ADHD, rather than stimulants themselves, is protective against developing a SUD. However, in our cohort, rates of prior stimulant exposure were similar in those with and without ADHD – 41% vs. 29% (p=0.29), respectively – and ADHD and non- ADHD groups with prior stimulant exposure were equally likely to develop a SUD (8.3% vs. 8.3%, p=1.00). Because this was a naturalistic study and study physicians were generally not directly involved in treatment, we cannot determine why some participants without ADHD were treated with stimulants. However, it is possible that the youth without ADHD receiving stimulants were misdiagnosed by primary care physicians and were actually displaying symptoms characteristic of mania. A possible explanation for the protective effect of stimulants is that the sustained levels of increased dopamine caused by prolonged exposure to stimulants may prevent the spike in dopamine associated with the “high” of drugs, thus reducing the likelihood of addiction.[58–59] Alternatively, participants with substance use and other risk factors for developing a SUD may have been less likely to receive a stimulant prescription from their treating clinician due to concern about abuse of the stimulant. Given the small sample and the preliminary nature of the data, further studies that prospectively examine the relationship between stimulant treatment and prevention of SUDs in adolescents with BD are needed to learn more about these processes, which might help clinicians develop treatment approaches to prevent SUDs in these patients.

The present study is limited by a relatively small sample group of adolescents with BD who developed new onset SUDs during follow-up, which minimized the number of predictors that were included in the multivariate analyses and the accuracy with which effect sizes could be estimated. A further limitation involves the finding that prior stimulant exposure was associated with a lower rate of lifetime SUD. Patients who had a SUD prior to

hospitalization were possibly less likely to be prescribed stimulants due to their abuse potential, which might have biased our results. However, this bias was eliminated in the analysis of predictors of SUD development following a first manic episode, as participants with a prior SUD diagnosis were excluded from the analysis, and a statistically significant association remained.

Despite these limitations, this study has several strengths, including its prospective design, naturalistic approach, length of follow-up, and its comprehensive assessment of psychiatric and substance-related symptoms. Consequently, the results of this study provide valuable information about risk and protective factors associated with SUD development in youth with BD and therefore may be useful to guide targeted preventative strategies. Future directions include examining specific relationships between substance use and clinical characteristics in our sample (e.g. cannabis use and psychosis) as well as a propensity model to further explore the relationship between stimulants and SUDs. Further empirical data to identify a broader range of clinical and biological risk and protective factors for developing substance use in adolescents with BD are needed.

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Clinical Guidance

- Adolescents with bipolar disorder have a particularly high risk of developing a substance use disorder
- Substance use disorders in individuals with bipolar disorder are associated with increased suicide, poor medication adherence, and poorer overall functioning
- Substance use should be closely monitored in adolescents with bipolar disorder
- Clinicians should advise adolescents with bipolar disorder and their parents about the risk of developing substance use disorders and the associated poor outcomes
- In particular, close attention should be given to adolescents with bipolar disorder who have experienced trauma (mental or physical) and/or who have psychotic symptoms

Table 1

Types of Substance Use Disorders (SUDs) in First-Episode Manic Adolescents

Type of SUD	FEM adolescents* (N=103)	FEM adolescents without SUD at baseline** (n=71)	Median time to SUD onset during follow-up (weeks) (n=17)
Any SUD	49 (48%)	17 (31%)	40
Cannabis	41 (40%)	12 (17%)	53.5
Alcohol	37 (36%)	13 (18%)	53
Opioids	7 (7%)	4 (6%)	55
Cocaine	6 (6%)	2 (3%)	82
Sedative/hypnotics	4 (4%)	2 (3%)	136.5
Amphetamines	2 (2%)	1 (1%)	39
Inhalants	1 (1%)	0 (0%)	N/A
Type of first SUD			
Cannabis	27 (26%)	9 (13%)	54
Alcohol	12 (12%)	5 (7%)	36
Poly-drug	9 (9%)	3 (4%)	53

Note: FEM=first-episode manic

* Includes all participants in the cohort including those who developed a SUD prior to or at baseline as well as those who developed one during follow-up

** Includes all participants who did not have a SUD prior to or at baseline

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Table 2

Associations between Clinical Characteristics and Lifetime Substance Use Disorders (SUDs) in Adolescents with Bipolar Disorder (BD)

						Proportional Hazards Model		
	No SUD during follow-up (n=54)		SUD during follow-up (n=49)		Group Comparison p-value	Hazard Ratio (95% CI)		p-value
Age at FEM hospitalization (years)	14.9	(2.1)	17.0	(2.4)	<0.01	1.1	(1.0, 1.2)	0.23
Sex, female	29	(54%)	24	(49%)	0.63	1.0	(0.6, 1.8)	0.88
Race, white	40	(74%)	36	(73%)	0.94	1.1	(0.6, 2.0)	0.87
Age onset BD (years)	12.1	(3.6)	15.2	(3.3)	<0.01	1.1	(1.0, 1.2)	0.16
Socioeconomic status	36.5	(13.2)	36.0	(13.1)	0.71	1.0	(1.0, 1.1)	0.62
Affective state, manic	12	(22%)	24	(49%)	<0.01	1.3	(0.8, 2.4)	0.33
Psychosis	17	(31%)	30	(61%)	<0.01	1.8	(1.0, 3.2)	0.05
ADHD	21	(39%)	18	(37%)	0.82	0.8	(0.4, 1.4)	0.39
Disruptive behavior disorder (CD or ODD)	20	(37%)	27	(55%)	0.07	1.5	(0.8, 2.6)	0.20
Physical or sexual abuse (n=101)	3	(6%)	12	(25%)	<0.01	2.5	(1.3, 4.8)	0.01
Psychosocial treatment	37	(69%)	26	(53%)	0.11	0.7	(0.4, 1.2)	0.23
Anxiety disorder (includes PTSD)	7	(13%)	10	(20%)	0.31	1.4	(0.7, 2.8)	0.36
PTSD	2	(4%)	6	(12%)	0.15	2.8	(1.2, 6.7)	0.02
Prior treatment with stimulants	22	(41%)	5	(10%)	<0.01	0.3	(0.1, 0.8)	0.01

Note: Mean (SD) or n (%) shown; ADHD=attention-deficit/hyperactivity disorder; CD = conduct disorder; FEM = first episode manic; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder.

Table 3

Multivariate Hazard Ratios for Time to Substance Use Disorder (SUD) Onset

	Hazard ratio (95% CI)	p-value
Age onset bipolar disorder (years)	1.04 (0.95, 1.14)	0.38
Psychosis	1.96 (1.00, 3.86)	0.05
Disruptive behavior disorder (CD or ODD)	1.42 (0.77, 2.63)	0.26
Physical or sexual abuse	2.67 (1.28, 5.60)	0.01
PTSD	2.06 (0.79, 5.41)	0.14
Prior treatment with stimulants	0.45 (0.17, 1.19)	0.11

Note: CD = conduct disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder.

Table 4

Associations between Clinical Characteristics and Substance Use Disorder (SUD) Development during Follow-Up

	No SUD during follow-up (n=54)		SUD during follow-up (n=17)		Group Comparison p-value	Proportional Hazards Model		
						Hazard Ratio (95% CI)		p-value
Age (years)	14.9	(2.1)	15.7	(2.3)	0.15	1.2	(1.0, 1.4)	0.13
Sex, female	29	(54%)	9	(53%)	0.96	1.0	(0.4, 2.6)	0.98
Race, white	40	(74%)	11	(65%)	0.54	1.6	(0.6, 4.5)	0.33
Age onset bipolar disorder (years)	12.1	(3.6)	14.4	(2.8)	0.02	1.2	(1.0, 1.3)	0.02
Socioeconomic status	36.5	(13.2)	35.0	(12.9)	0.70	1.0	(1.0, 1.1)	0.68
Affective state, manic	12	(22%)	8	(47%)	0.06	2.7	(1.0, 7.0)	0.04
Psychosis	17	(31%)	12	(71%)	<0.01	3.8	(1.3, 10.8)	0.01
ADHD	21	(39%)	8	(47%)	0.55	0.8	(0.3, 2.2)	0.70
Disruptive behavior disorder (CD or ODD)	20	(37%)	12	(71%)	0.02	2.5	(0.9, 7.1)	0.09
Physical or sexual abuse	3	(6%)	1	(6%)	1.00	0.6	(0.1, 4.6)	0.62
Prior psychosocial treatment	37	(69%)	10	(59%)	0.46	0.8	(0.3, 2.2)	0.67
Anxiety disorder (includes PTSD)	7	(13%)	5	(29%)	0.14	1.6	(0.6, 4.7)	0.37
PTSD	2	(4%)	4	(24%)	0.03	3.3	(1.1, 10.2)	0.04
Prior treatment with stimulants	22	(41%)	2	(12%)	0.03	0.2	(0.1, 1.0)	0.05

Note: Mean (SD) or n (%) shown; ADHD=attention deficit/hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder.