Predictors of First-Onset Substance Use Disorders During the Prospective Course of Bipolar Spectrum Disorders in Adolescents

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Objective: Substance use disorders (SUD) are common and problematic in bipolar disorder (BP). We prospectively examined predictors of first-onset SUD among adolescents with BP. **Method:** Adolescents (12–17 years old; N = 167) in the Course and Outcome of Bipolar Youth (COBY) study fulfilling criteria for BP-I, BP-II, or operationalized BP not otherwise specified, without SUD at intake, were included. Baseline demographic, clinical, and family history variables, and clinical variables assessed during follow-up, were examined in relation to first-onset SUD. Participants were prospectively interviewed every 38.5 ± 22.2 weeks for an average of 4.25 ± 2.11 years. **Results:** First-onset SUD developed among 32% of subjects, after a mean of 2.7 ± 2.0 years from intake. Lifetime alcohol experimentation at intake most robustly predicted first-onset SUD. Lifetime oppositional defiant disorder and panic disorder, family history of SUD, low family cohesiveness, and absence of antidepressant treatment at intake were also associated with increased risk of SUD, whereas BP subtype was not. Risk of SUD increased with increasing number of these 6 predictors: 54.7% of subjects with 3 or more predictors developed SUD vs. 14.1% of those with fewer than 3 predictors (hazard ratio = 5.41 95% confidence interval = 2.7–11.0 $p < .0001$). Greater hypo/manic symptom severity in the preceding 12 weeks predicted greater likelihood of SUD onset. Lithium exposure in the preceding 12 weeks predicted lower likelihood of SUD. **Conclusions:** This study identifies several predictors of first-onset SUD in the COBY sample that, if replicated, may suggest targets for preventive interventions for SUD among youth with BP. Treatment-related findings are inconclusive and must be interpreted tentatively, given the limitations of observational naturalistic treatment data. There is a substantial window of opportunity between BP and SUD onset during which preventive strategies may be used. J. Am. Acad. Child Adolesc. Psychiatry, 2013;52(10):1026–1037. **Key Words:** bipolar, predictors, prevention, prospective, substance use disorder

Bipolar disorder (BP) among adults is the axis I disorder most strongly associated with substance use disorders (SUD; i.e., abuse of or dependence on alcohol and/or drugs). At least 50% of adults with BP meet criteria for SUD at some point in their lives.[1] Comorbid SUD among adults with BP is associated with reduced medication adherence and quality of life, delayed recovery, hastened relapse, greater symptomatic burden, and increased functional impairment, suicide attempts, violence, and polarity switches into mania.[2] Similar to adults, the prevalence of SUD is significantly greater among adolescents with BP as compared to adolescents without BP.[3,4] SUD among adolescents with BP is associated with earlier recurrences, and more treatment nonadherence, suicide attempts, legal problems, pregnancy, and academic failure.[5-8]

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Previous retrospective and cross-sectional studies have described a number of correlates of comorbid SUD among adolescents with BP, including older age, panic disorder, oppositional defiant disorder/conduct disorder (ODD/CD), psychosis, family history of SUD, and previous alcohol experimentation.[5,7,9-11] There are no prospective studies evaluating predictors of first-onset SUD among youth with BP, and only 1 study has examined predictors of first-onset SUD among adults with BP. Strakowski *et al.* found that 17.5% of adults with BP-I developed first-onset cannabis use disorders after a first hospitalization for mania (mean follow-up interval, 2.6 years), predicted by younger age, lower education, and greater substance use before hospitalization.[10] The same proportion of subjects developed first-onset alcohol use disorders, predicted by psychosis.[11]

Determining risk factors for comorbid SUD among adolescents with BP could potentially help to identify patients for whom preventive interventions are most strongly indicated, and could inform initial medication selection. For example, lithium and anticonvulsants have been associated with attenuation of SUD in BP in placebo-controlled trials, whereas second-generation antipsychotics have not.[6,12-15]

The Course and Outcome of Bipolar Youth (COBY) is a long-term naturalistic study of more than 400 children and adolescents with BP, which is funded by the National Institute of Mental Health.[16] The purpose of this report is to examine which factors evident at the baseline assessment, and which prospectively ascertained intervening factors, predict first onset of SUD among adolescent subjects. We include only subjects at least 12 years or more of age in this analysis because earlier cases of SUD were not identified in COBY,[5] and to ensure follow-up into at least midadolescence.

We set out to examine factors that can help to identify adolescents with BP who are at particularly increased risk of developing first-onset SUD. Based on prior COBY cross-sectional findings and longitudinal predictors of SUD among adults with BP, we predicted that greater severity of hypo/manic, depressive, panic, psychotic, and ODD/CD symptoms would predict incident SUD, whereas greater proximal treatment exposure would be protective. To our knowledge, this is the first longitudinal study that examines predictors of first-onset SUD among adolescents with BP. This is also the first study in any age group that examines predictors of SUD that occur during the course of follow-up in BP. Future analyses will compare COBY participants who entered the study with SUD to those who developed SUD during prospective follow-up.

METHOD

Participants

The methods for COBY have been described in detail elsewhere.[17,18] Briefly, the study included youths aged 7 through 17 years 11 months at intake, with *DSM-IV* BP-I or -II or operationally defined BP not otherwise specified (BP-NOS).[16] Youths with schizophrenia, mental retardation, autism, and mood disorders secondary to substances, medications, or medical conditions were excluded from the study. Participants were recruited from outpatient clinics (67.6%), inpatient units (14.3%), advertisements (13.3%), and referrals from other physicians (4.8%), and were enrolled independent of current mood state or treatment status. There were 16 individuals who dropped out and did not return for a follow-up assessment. Except for higher rates of ADHD (75% versus 48%, $p = .06$) and of anxiety disorders (69% versus 42%, $p = .06$) in youths who dropped out of the study, there were no other demographic or clinical differences between those who continued in the study and those who withdrew.

Analyses including intake variables in this study are based on the prospective evaluation of 167 subjects, aged 12 through 17 years 11 months at intake, who did not have SUD at intake, and who had at least 1 follow-up assessment. Forty adolescents who had SUD at intake were excluded. Participants were prospectively interviewed every 38.5 ± 22.2 weeks (target of 26-week intervals; range, 18–337 weeks) for an average of 4.25 ± 2.11 years. During this interval, participants were interviewed 7.2 ± 2.9 times.

Procedures

Each participating university's institutional review board approved the study, and consent was obtained from the participating youths and their parents. At intake, adolescents and parents were directly interviewed for the presence of current and lifetime psychiatric disorders in the adolescents.

Psychiatric Diagnoses and Symptoms. The instruments used at intake were the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL),[19] the Kiddie Mania Rating Scale (K-MRS),[20] and the depression section of the K-SADS-P.[21] Intake demographic and clinical variables are listed in Table 1. Longitudinal changes in psychiatric symptoms since the previous evaluation were assessed using the Longitudinal Interval Follow-Up Evaluation (LIFE)[22] and tracked on a week-by-week basis using this instrument's Psychiatric Status Rating (PSR) scales.[23] These scales use numeric values