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

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Abstract

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 six predictors: 54.7% of subjects with ≥3 predictors developed SUD vs. 14.1% of those with <3 predictors (Hazard Ratio 5.41 95% CI 2.7–11.0 p<0.0001). Greater hypo/manic

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Clinical guidance is available at the end of this article.

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 which, if replicated, may suggest targets of 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 employed.

Keywords

bipolar; predictors; prevention; prospective; substance use disorder

Introduction

Bipolar disorder (BP) among adults is the axis I disorder most strongly associated with substance use disorders (SUD; i.e., abuse or dependence of 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]

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 one 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 prior to 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 over 400 children and adolescents with BP, 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 12 years and above 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 ages 7 to 17 years 11 months at intake, with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*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 enrolled independent of current mood state or treatment status. There were 16 drop-outs who did not return for a follow-up assessment. Except for higher rates of ADHD (75% vs. 48%, p=0.06) and of anxiety disorders (69% vs. 42%, p=0.06) 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, ages 12–17 years 11 months at intake, who did not have SUD at intake, and who had at least one 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 that are operationally linked to *DSM-IV* criteria; *DSM-IV* criteria information is gathered in the interview and then translated into ratings for each week of the follow-up period. This is done for depression, hypomania, mania, psychosis, and each of the comorbidities listed in Table 2. Adolescents and parents were interviewed separately by the same interviewer who then generated consensus scores on the basis of these interviews in combination with medical records when available. Confidentiality was maintained based on the adolescent's preference.

All assessments were conducted by research staff trained to reliably administer the interviews; interview results were presented to child psychiatrists or psychologists, who confirmed the diagnoses and the PSR scores. The overall KSADS-PL kappa coefficients for psychiatric disorders were ≥0.8. Further detail regarding the reliability of these assessments has been previously reported.[16] PSR reliability was $\kappa = 0.62$ for manic, mixed, or hypomanic episode and for major depressive episode occurrence. PSR reliability was $\kappa = 0.71$ for SUD, 0.69 for alcohol abuse or dependence, and 0.64 for drug abuse or dependence. Kendall's W statistic for reliability of percentage of weeks of follow-up euthymic, full syndromal, and subsyndromal was ≥0.75.[24] Age at onset of BP was defined as the age at onset of a *DSM-IV* mood episode or an episode fulfilling the COBY's modified *DSM-IV* criteria for BP-NOS. The minimum age at onset was arbitrarily set at age 4. Age of onset of mania/hypomania/BP-NOS was also computed.

Substance use disorders—SUD at intake was determined using consensus diagnoses from the KSADS-PL.[17, 18] First-onset SUD diagnoses were determined based on the first week in which the subject fulfilled full-threshold *DSM-IV* criteria for abuse or dependence of alcohol or drugs based on the LIFE consensus ratings (see above). The confidentiality parameters involved were separately interviewing adolescents and maintaining confidentiality depending on the adolescent's preference. Nicotine dependence was not included among SUD. Time to onset of SUD was computed from the intake assessment, and data were censored at the week of SUD onset.

Other variables—Several other variables were ascertained at the intake assessment. Those variables that were ascertained prospectively as well as at intake are listed in Table 2. Family psychiatric history was ascertained at intake using the Family History Screen.[25] Socioeconomic status was ascertained at intake using the 4-factor Hollingshead scale.[26] Lifetime and current pharmacological treatment exposure were obtained at the intake assessment. In addition, the Psychotropic Treatment Record and the Psychosocial Treatment Schedule of the LIFE were used to ascertain prospective treatment exposure on a week-by-week basis. Exposure was determined by querying the prescribed dosage for each medication and multiplying that by the percentage of reported adherence to yield an mg/day value for each medication for each week. However, for the purpose of the current study, weekly exposure was considered a dichotomous variable (yes/no; i.e., specific dosage exposure within the week were not examined). For subjects taking multiple medications, exposure was ascertained separately for each medication. Data regarding antimanic medications are presented separately by subtype: antimanic anticonvulsants (valproate or carbamazepine), lithium, and second generation antipsychotics. Other medications were grouped by class. Psychosocial treatments were examined as a dichotomous variable (yes/no) together, as well as divided into 3 categories of intensity that were coded separately for each week: inpatient hospitalization/residential treatment, specialized intensive services (e.g. in-home services, partial hospitalization), and standard outpatient services. As part of the K-SADS-PL, all subjects answered questions that ascertain lifetime cigarette smoking, lifetime cannabis use, and lifetime repeated alcohol use (specific timing is not ascertained) at intake. The latter was defined based on the K-SADS-PL screen for the alcohol use disorders section, which queries whether there have been at least 4 lifetime weeks during which the participant consumed 2 or more alcoholic beverages during that week. Global functioning was assessed at intake using the Children's Global Assessment Scale (C-GAS; [27]; scores were assigned for most severe past functioning, as well as current functioning.

Each participant and a parent/guardian completed the Conflict Behavior Questionnaire (CBQ) to assess family conflict.[28, 29] The adolescent completed separate forms to rate his/her conflict with mother and father. For the present analyses, because of greater data completeness, we examined the subject's ratings about mother only. Familial functioning

was assessed with the self- and parent-report Family Adaptability and Cohesion Evaluation Scale–II (FACES-II).[30] The Life Events Checklist (LEC), assessed for the presence of negative (e.g. death of relative) and positive (e.g. academic or athletic success) life events over the year preceding intake, as well as their impact on the subject's well-being.[31]

Statistical Analyses

Past and intake risk factors were screened for their association with first-onset SUD using logrank tests for categorical variables and Cox proportional hazards regression for continuous variables. Factors associated with first-onset SUD in the univariate analyses ($p \leq 0.10$) were then entered into a stepwise Cox proportional hazards survival model controlling for significant demographic differences between groups.

To identify time-varying factors that occurred during follow-up that were associated with prospective risk for SUD, we used Cox proportional hazards regression with time-varying covariates. Data for time-varying covariates were ascertained using the LIFE. Eleven subjects developed SUD within less than 12 weeks of intake and are not included in the analyses regarding prospectively ascertained time-varying covariates, leaving 156 subjects for these analyses. Weekly values on the PSR for symptom severity and treatment exposure were aggregated over 12-week intervals in 2 ways: 1) percent of weeks over the 12-week follow-up period during which the factor was present (e.g., percent of weeks during the 12-week period 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 12-week period (e.g., maximum PSR depression severity score of 6, reflecting severe full threshold depression). Since this is the first prospective analysis of time-varying risk factors associated with SUD in youth with BP, limited information was available to guide the most preferred prospective time period for analysis. We selected 12-week intervals because these reflect a plausible window during which factors potentially associated with SUD may be exerting their effects. We examined 4- and 8-week follow-up intervals in sensitivity analyses, and found similar results. We examined both percentage of time in different mood states, and maximum severity of symptoms for each type of mood state. We compared these 2 approaches and found highly significant correlations for both depression ($r=0.63$, $p<0.0001$) and mania/hypomania ($r=0.47$, $p<0.0001$). Finally, analyses including age or pubertal status yielded similar results. Thus, only the results including age are presented. All p-values are based on 2-tailed tests with α set at 0.05.

We first performed univariate analyses of these factors; those with significance $p \leq 0.10$ were entered into a stepwise multivariate Cox regression analysis controlling for significant between-group differences in demographic variables. Hazard ratios (HR) and confidence intervals (CI) were computed. All p-values are based on 2-tailed tests with alpha=0.05.

Hazard ratios for PSR analyses examining covariates measured in percentage of weeks are interpreted as the increased risk for SUD associated with each 1% increase in the amount of the 12-week period during which the covariate was present. To calculate the increased risk for SUD associated with a k-unit increase in the percent of weeks during which the covariate was present, the HR is raised to the k-power[32] (for additional details, see[33]). HRs for maximum PSR analyses (1–6 scale) are interpreted as the increased risk for SUD associated with each one-unit increase in maximum PSR score during the 12-week period. The above equation is also used here (hazard ratio^k). For example, the HR for any psychotropic medication medication is 0.99, meaning that for every additional 1% of weeks with medication exposure within a given 12-week epoch there was a 1% decrease in the risk of SUD.

Results

During the course of 4.25±2.11 years of follow-up, 54 adolescents (32.3%) developed a first onset SUD. Cannabis use disorders were the most common (16.8% abuse, 5.4% dependence), followed by alcohol use disorders (15.6% abuse, 4.8% dependence). No other type of drug abuse/dependence (e.g., cocaine, hallucinogens) exceeded 1.2%. The mean age at SUD onset was 18.0 years, after 2.7±2.0 years of follow-up. Time to alcohol abuse or dependence was 2.9±2.1 years, and time to cannabis abuse or dependence was 2.7±2.1 years. Co-occurrence of multiple SUDs was observed in 75.9% of subjects with first-onset SUD. The following sections describe intake and follow-up variables, respectively, that were associated with incident SUD.

Intake Variables Associated With First-Onset Substance Use Disorders

Univariate analyses comparing adolescents with and without first-onset SUD with respect to intake variables are presented in Table 1. Adolescents who went on to develop SUD during follow-up were significantly ($p<0.05$) more likely to have reported lifetime cigarette smoking, cannabis use, and alcohol use at intake, and significantly more likely to have lifetime comorbid ODD. They had better overall functioning as measured by the C-GAS, lower adolescent-reported familial cohesion, and more negative life events at intake. With regard to treatment, adolescents who went on to develop SUD were less likely to have been taking antimanic or antidepressant treatment at intake. Finally, adolescents who went on to develop SUD were significantly more likely to have family history of mania/hypomania, anxiety, and SUD, compared to adolescents who did not develop SUD. History of physical or sexual abuse, comorbid panic disorder, adolescent-reported familial adaptability, positive life events, and use of any psychotropic medication were also associated with ($p\leq0.1$) first-onset SUD. All of the above variables were entered stepwise into multivariable analyses. Of note, the subtype of BP was not associated with SUD ($p=0.67$).

Exploratory univariate survival analyses examined whether the association between recreational substance use (alcohol and cannabis) reported at intake and subsequent SUD was substance-specific. Alcohol use significantly predicted the onset of alcohol use disorders ($\chi^2=11.16$, df=1, $p=0.0008$). Cannabis use also significantly but less robustly predicted alcohol use disorders ($\chi^2=3.91$, df=1, $p=0.048$). Cannabis use disorders were predicted by both alcohol use ($\chi^2=6.82$, df=1, $p=0.009$) and cannabis use ($\chi^2=5.81$, df=1, $p=0.016$).

Multivariate regression analyses demonstrated that the following intake variables were associated with increased risk of first-onset SUD: lifetime alcohol use (HR: 4.33, 95% CI 1.65–11.33, $p=0.003$), lifetime panic disorder (HR: 2.74, 95% CI 1.20–6.27, $p=0.02$), lifetime ODD (HR: 2.33, 95% CI 1.27–4.26, $p=0.01$), family history of SUD (HR: 2.54, 95% CI 1.24–5.20, $p=0.008$), low family cohesiveness (HR: 2.04, 95% CI 1.04–4.01, $p=0.04$) and absence of treatment with antidepressants (HR: 2.23, 95% CI 1.05–4.72, $p=0.04$). For the purpose of this analysis, family cohesion was dichotomized based on a median split, which allowed us to examine each of the 6 predictors categorically. We performed a Wald-test to simultaneously check the proportional hazards assumption for all 6 predictors ($p=0.69$), which confirmed that the assumptions of the model were met.

Finally, we examined the association between the number of these intake predictors and the development of SUD. Few subjects (2.2%) had none of the predictors, 22.8% had one, 27.9% had two, 32.4% had three, 12.5% had four, and 2.2% had five intake predictors. We found a significant increase in the risk of SUD with increasing number of predictors: 0–2 predictors = 14.1% SUD; 3 predictors = 45.5% SUD; 4–5 predictors = 75% SUD (χ^2 for trend = 30.89, df=2, $p<0.0001$). The risk of SUD among subjects with ≥3 predictors was

significantly greater than among subjects with <3 predictors (54.7% vs. 14.1%; HR 5.41, 95% CI 2.7–11.0, $p<0.0001$).

Follow-Up Variables Associated With First-Onset Substance Use Disorders

Univariate analyses comparing time-varying follow-up factors aggregated over 12-week intervals between those youth who exhibited first-onset SUD with those who did not are presented in Table 2. Greater maximum severity of PSR depressive and hypo/manic symptoms was associated with greater risk for SUD onset. In contrast, fewer asymptomatic weeks and less psychotropic medication exposure, specifically lithium, in the preceding 12-week period were associated with greater risk for SUD onset. All of the above variables were entered into multivariable analyses.

Multivariate regression analyses demonstrated that greater hypo/manic symptom severity in the preceding 12-week period predicted greater likelihood of SUD (HR: 1.26, 95% CI 1.03–1.56, $p=0.03$), whereas greater use of lithium during that period predicted lower likelihood of SUD (HR: 0.99, 95% CI 0.97–1.00, $p=0.02$). We then conducted a multivariable analysis controlling for all of the above-noted 6 predictors, as well as depressive and hypo/manic symptom severity during the 12-week period. This analysis therefore controlled for both intake and follow-up predictors of SUD. Despite this conservative model fitting, lithium continued to be associated with lower risk of SUD (HR 0.98, 95% CI 0.97–1.00, $p=0.05$).

Discussion

This study verifies that BP among adolescents is associated with a high incidence of SUD: one third of adolescent subjects developed at least one SUD (most commonly cannabis and/or alcohol) within 4 years of intake. The risk of incident SUD is not limited to youth with BP-I, but equally extends to adolescents with BP-II and COBY-operationalized BP-NOS as well. Experimentation with alcohol was the most robust predictor of first-onset SUD. Lifetime prevalence of ODD and of panic disorder at baseline, family history of SUD, low family cohesiveness at baseline, and absence of treatment with antidepressants at baseline were each associated with increased risk of first-onset SUD. These predictors appeared to have a compounding association; 54.7% of subjects with ≥3 predictors developed SUD, compared to 14.1% of those with <3 predictors. In terms of prospective predictors, greater proximal hypo/manic symptom severity predicted greater likelihood of SUD, whereas greater proximal use of lithium predicted lower likelihood of SUD. Therefore, familial factors, specific psychiatric comorbidity, treatment history, and symptomatic status each independently contribute to the prediction of first-onset SUD among adolescents with BP.

Several methodological limitations warrant comment. First, COBY is an observational naturalistic study. Therefore the observed associations with various pharmacological and psychosocial treatments must be considered tentatively and should not be interpreted as evidence of protective efficacy. Ultimately, randomized controlled trials will be required to examine whether treatment in general and/or specific types of treatment can be efficacious in preventing SUD among adolescents with BP. Second, assessment of SUD was based exclusively on direct interviews with the subject and their parent(s). Although reliability was good for SUD overall, it was fair for drug use disorders, which is consistent with previous findings of youth with comorbid BP and SUD.[34] Urine toxicology and self-reported substance use may have increased the reliability of the assessment of SUD. Moreover, information regarding substance-specific factors such as intentions to use substances, expectancies, and reasons for using was not collected.[35] Third, COBY did not include a comparison sample of youth without BP. As such, this study cannot compare the variables associated with first-onset SUD among youth vs. without BP. Moreover, although other studies suggest that the rate of first-onset SUD in the COBY sample is likely to be greater

than for youth without BP, the present study cannot directly undertake that comparison. Fourth, although COBY employs longitudinal methodology, the determination of onset of SUD with regard to follow-up variables such as symptomatic severity and treatment exposure was determined retrospectively within follow-up intervals that averaged over 8 months in duration. Finally, as with any observational study, causality cannot be inferred from present findings.

Despite these limitations, these findings confirm most of this study's hypotheses and converge with prior studies. Geller *et al.* also reported 32% SUD incidence during eight years of follow-up of their sample of children and early adolescents with BP-I.[36] The longer follow-up and younger mean age of subjects in that study likely offset each other. In the Oregon Adolescent Depression Project, the incidence of alcohol abuse or dependence (26.7%) and drug abuse or dependence (13.3%) among community adolescents with BP (primarily BP-II and cyclothymia) who were followed-up during early adulthood was numerically greater than among subjects with no psychiatric diagnosis (15.0% and 5.5%, respectively).[37] German epidemiologic findings indicate that adolescents with BP have significantly greater 10-year incidence of cannabis and alcohol use disorders as compared to adolescents with no mental disorder.[38, 39] Based on recent estimates of lifetime SUD prevalence among adolescents (11.7%)[40] and young adults (14.6%)[41], present findings suggest markedly increased risk of SUD in a clinical sample of adolescents and young adults with BP. These findings are not necessarily specific to BP, as recent studies have found high SUD incidence (25.5%–37.2%) among adolescents with major depressive disorder (MDD) over 5–7 years of follow-up.[42, 43]

Present findings suggest that the risk of incident SUD is not limited to youth with BP-I, but rather extends to adolescents with BP-II and COBY-operationalized BP-NOS as well. Most previous epidemiologic findings similarly suggest that sub-threshold BP is also associated with increased prevalence of SUD[3, 38, 44], although exceptions exist.[37] The finding that family history of SUD is contributory converges with previous findings regarding the familiality of BP and SUD.[45, 46] Finally, present findings are consistent with recent evidence that cannabis and alcohol comprise the most common SUD among adolescents.[47]

The finding that experimentation with alcohol and cannabis predicted first-onset SUD is consistent with previous findings regarding adolescents in general, adolescents with MDD, and adults with BP.[10, 43, 48] Cannabis use was associated with first-onset SUD in univariate but not multivariate analyses. A previous German epidemiologic study found that whereas 33% of adolescents with BP-spectrum with any history of cannabis use met criteria for cannabis abuse or dependence, the proportion among adolescents with any psychiatric disorder (18%) and with no psychiatric disorder (6%) was substantially lower.[38] Adolescents with BP may be especially susceptible to developing SUD once they have initiated even infrequent experimentation with substances.

Significant medication-related findings warrant discussion, however it is important to underscore the naturalistic and observational nature of these data, as well as the lack of objective information about medication prescriptions, adherence and dosage (e.g. medical records, prescription records, drug levels). As such, findings regarding medications should be interpreted very tentatively. For example, absence of antidepressants at intake was significantly associated with first-onset SUD in univariate and multivariate analyses. One could speculate that the presence of antidepressants is a proxy for assertive treatment, however the mechanism linking anti-depressants at intake with lower incidence of first-onset SUD over a period of several years remains uncertain. Greater hypo/manic symptoms and less exposure to psychotropic medications (particularly lithium) in the preceding 12 weeks were independently (i.e. controlling for one another) associated with first-onset SUD.

Although these findings imply that inadequate pharmacologic treatment exposure may proximally precede the onset of SUD, COBY methodology does not allow for parsing of suboptimal prescribing from suboptimal adherence. Previous studies suggest that it is common for adolescents and adults with BP to report using substances purposefully to alleviate mood symptoms [35, 49] and that SUD is associated with poor medication adherence in BP.[2, 50] Taken together, this suggests the possibility that medication nonadherence and the use of substances to manage mood symptoms may contribute, independently and/or in combination, to the development of SUD. However, gold-standard randomized controlled trials would be required to confirm these associations.

Greater exposure to lithium, whether analyzed during the overall follow-up duration or during the proximal 12-week period, was specifically associated with lower risk of first-onset SUD. Previous studies suggest that lithium may reduce excessive substance use in adults in general[51], and among adolescents with BP specifically.[6] However, it is also possible that this association is confounded by other factors that may be associated with lithium exposure, such as greater familial oversight and/or involvement in treatment, or greater investment of the adolescent him/herself in treatment. Taken together with previous findings from a small placebo-controlled trial of lithium for adolescents with BP and SUD [6], present findings suggest that additional research regarding the potential preventative role of lithium with regard to SUD among youth with BP is warranted. Nonetheless, as acknowledged above, the naturalistic design of COBY precludes any definitive conclusions regarding the observed associations between medications and SUD. Moreover, previous findings regarding lithium pertain to the treatment of SUD, and these findings cannot as yet be extrapolated to the prevention of SUD.

ODD and CD among adolescents are well-known predictors of SUD among adolescents in general, and previous cross-sectional findings from COBY provided a signal that ODD/CD might predict first-onset SUD among adolescents with BP specifically.[5] A previous cross-sectional study which found that CD did not antedate SUD among youth with BP was likely constrained by cross-sectional retrospective design and insufficient statistical power for subgroup analyses.[7] Whereas anxiety disorders overall did not independently predict first-onset SUD in this study, panic disorder specifically did predict SUD. We examined panic disorder separately because the association between anxiety and SUD among adults with BP may be most robust for panic disorder.[52]

Family history of SUD is a well-known risk factor for SUD, and it appears that comorbid SUD is among the most highly heritable aspects of familial BP.[9, 46] Although family history of SUD was not associated with SUD among COBY adolescents at intake, present findings confirm that a familial diathesis toward SUD may indeed contribute to the development of SUD among adolescents with BP. The finding that greater family cohesiveness appears to mitigate the risk for first-onset SUD among youth with BP converges with previous findings indicating that coercive parenting practices, family conflict, low parental involvement, and low family bonding are associated with initiation of substance use among adolescents.[53, 54]

Taken together with our previous finding that 16% of adolescents in COBY already had lifetime SUD at intake, present findings suggest that approximately 50% of youth with BP will experience full-threshold SUD by early adulthood. Clinical and epidemiologic studies indicate that onset of BP prior to adulthood is associated with increased risk of SUD in comparison to adult-onset BP.[55, 56] Therefore, despite the high prevalence of SUD already observed in COBY and in other early-onset BP cohorts, an estimated additional 10–20% of subjects are likely to develop first-onset SUD in the years ahead. Prevention of SUD in this population is a matter of tremendous clinical and public health importance. Strategies for prevention of SUD in this population include assertive treatment of adolescents with BP,

early identification of substance use via repeated screening beginning in late childhood, family-focused preventive interventions, and motivation-enhancing interventions targeting subthreshold substance use.[57]

Present findings suggest that mood symptoms, inadequate treatment, recreational alcohol use and familial factors may be important variables to examine in future studies regarding first-onset SUD among adolescents with BP. These findings, albeit tentative, further suggest that treatment of psychiatric comorbidity, both internalizing and externalizing, and incorporating family therapy may confer benefits with regard to SUD. Mood exacerbations, particularly those of hypo/manic polarity, may comprise an interval of risk for escalating substance use, and in such circumstances increased vigilance for excessive substance use appears warranted. Experimentation with substances is often viewed as normative and developmentally appropriate, and clinicians and parents are often ambivalent about the risks of experimentation and therefore reluctant to promote abstinence. Similar to the literature in adolescents with MDD (40, 55), the strength of the association between experimentation with substances and subsequent development of SUD in the adolescents may help to resolve ambivalence among some clinicians, parents, and perhaps adolescents. Despite the fact that present findings do not demonstrate cause, deferring the initiation of substance use is a low-risk strategy that could potentially mitigate the risk of SUD in this population. In addition to yielding a greater understanding of why the prevalence of SUD in BP is so high, advances regarding the neurobiological underpinnings of comorbid SUD in BP [42, 58] may identify novel treatment strategies that may ameliorate the substantial psychiatric burden experienced by these doubly affected patients.

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Clinical Guidance

- The risk of incident substance use disorders (SUD) is not limited to youth with bipolar I disorder (BP-I), but equally extends to adolescents with bipolar II disorder (BP-II) and Course and Outcome of Bipolar Youth (COBY)–operationalized bipolar disorder not otherwise specified (BP-NOS) as well.
- Adolescents with BP may be especially susceptible to developing SUD once they have initiated even infrequent experimentation with substances.
- The presence of multiple predictors of SUD is associated with exceedingly high risk of SUD.
- For most adolescents with BP, there is a substantial window of opportunity during which preventive strategies may be employed.

Table 1
Intake Variables Associated With First-Onset Substance Use Disorders (SUD)

	No SUD (n=113)	Developed SUD (n=54)	Statistics	
			X^2	*p*-value
Demographics/Illness Characteristics				
Age, m±SD	15.5 ± 1.5	15.3 ± 1.3	0.00	0.97
Socioeconomic status, m±SD	3.7 ± 1.2	3.5 ± 1.2	1.52	0.22
Race (White), %	76.1	87.0	0.92	0.34
Sex (Male), %	41.6	50.0	0.28	0.60
Bipolar Subtype, %			0.79	0.67
BP-I	67.3	61.1		
BP-II	11.5	13.0		
BP-NOS	21.2	25.9		
Living with both natural parents, %	53.1	44.4	0.87	0.35
Adolescent-onset (vs. Child-onset) BP, %	53.1	38.9	1.57	0.21
Adolescent-onset (vs. Child-onset) Mania/hypomania, %	67.0	57.4	0.31	0.58
Clinical Variables				
Psychiatric Hospitalization, %	62.8	66.7	0.00	0.98
Suicidality, %				
Self-Injurious behavior	32.4	40.7	0.98	0.32
Suicidal Ideation	76.1	79.6	0.05	0.83
Suicide Attempt	32.7	37.0	0.01	0.92
Mixed State, %	28.3	29.6	0.12	0.73
Psychosis, %	23.9	22.2	0.08	0.78
Physical/Sexual Abuse, %	15.9	27.8	3.28	0.07
Substance use, %				
Cigarettes	23.9	45.1	8.54	0.004
Alcohol	4.8	16.3	12.76	<0.001
Cannabis	25.0	44.2	10.09	0.002
C-GAS[1] (m±SD)				
Most Severe Lifetime	36.3 ± 9.9	35.2 ± 11.8	0.12	0.73
Current	52.0 ± 13.3	58.1 ± 11.6	3.95	0.047
Depression Symptoms, m±SD				
Most Severe Lifetime	26.2 ± 12.7	27.1 ± 9.1	0.09	0.77
Current	16.9 ± 12.3	15.8 ± 11.1	0.42	0.51
Mania/hypomania Symptoms, m±SD				
Most Severe Lifetime	36.9 ± 8.7	36.1 ± 6.9	0.010	0.75
Current	22.3 ± 13.6	22.7 ± 12.2	0.06	0.81
Comorbid Diagnoses, %				
ADHD[2]	45.1	53.7	0.64	0.42

	No SUD (n=113)	Developed SUD (n=54)	Statistics	
			X^2	*p*-value
CD/ODD[3]	31.0	61.1	10.37	0.001
ODD	26.0	51.9	13.89	0.0002
CD	12.3	14.8	0.19	0.66
Any Anxiety	43.4	38.9	0.72	0.40
Panic Disorder	8.9	16.7	2.69	0.10
Family Adaptability and Cohesion, m±SD				
Cohesion, Adolescent	55.8 ± 13.4	50.0 ± 11.6	7.99	0.005
Cohesion, Parent	57.4 ± 12.1	55.7 ± 9.9	1.77	0.18
Adaptability, Adolescent	45.0 ± 9.8	41.9 ± 10.0	2.90	0.09
Adaptability, Parent	45.7 ± 8.0	45.3 ± 7.5	0.32	0.57
Conflict Behavior Questionnaire, m±SD				
Adolescent	8.9 ± 6.0	8.0 ± 5.5	0.48	0.49
Parent	10.6 ± 6.7	11.4 ± 5.5	1.56	0.21
Life Events Checklist. m±SD				
Negative, Adolescent	4.7 ± 4.3	6.7 ± 5.1	6.50	0.01
Positive, Adolescent	2.9 ± 4.1	4.3 ± 3.3	2.82	0.09
Negative, Parent	4.8 ± 4.5	5.7 ± 3.4	1.63	0.20
Positive, Parent	2.7 ± 4.2	2.8 ± 2.2	0.21	0.65
Lifetime Medication, %				
Any Psychotropic	97.4	94.4	1.62	0.20
Antimanic Anticonvulsant	88.5	87.0	0.59	0.44
Antidepressant	62.0	59.3	0.54	0.46
Stimulant	37.2	48.2	0.54	0.46
Current Medication, %				
Any psychotropic	89.4	85.2	2.78	0.10
Antimanic	77.9	68.5	4.85	0.03
Antidepressant	36.3	20.4	4.57	0.03
Stimulant	15.0	18.5	0.001	0.97
Family Psychiatric History (1st or 2nd degree), %				
Depression	74.3	88.9	2.83	0.09
Mania/Hypomania	38.9	57.4	4.11	0.04
ADHD	28.3	37.0	2.00	0.16
CD	25.7	38.9	3.12	0.08
Anxiety	50.4	70.4	5.43	0.02
SUD	58.4	79.6	9.12	0.003
Suicide Attempt	30.1	37.0	0.34	0.56
Comorbid Mania/Hypomania and SUD	26.6	40.7	4.72	0.03

Note: ADHD=attention-deficit/hyperactivity disorder; BP=bipolar disorder; BP-I=type one bipolar disorder; BP-II=type two bipolar disorder; BP-NOS=bipolar disorder not otherwise specified; CD=conduct disorder; C-GAS = Children's Global Assessment Scale; ODD=oppositional defiant disorder.

Table 2

Follow-Up Variables Associated With First-Onset Substance Use Disorders (SUD)

	Developed SUD (n=43)		No SUD (n=113)	Statistics		
	12 weeks prior to onset	Earlier 12 week intervals		x^2	*p*-value	HR
% Weeks in Mood State, m±SD						
No significant mood symptoms	40.5 ± 42.1	46.1 ± 29.3	54.7 ± 30.8	5.93	0.02	0.99
Any sub-threshold mood state	38.8 ± 40.2	36.9 ± 26.1	30.7 ± 23.5	2.47	0.12	
Full-threshold depression	13.8 ± 26.9	13.1 ± 16.4	10.7 ± 16.2	0.67	0.42	
Full-threshold mania/hypomania	7.0 ± 18.2	3.9 ± 8.7	3.9 ± 8.5	3.22	0.07	
Any full-threshold mood state	20.7 ± 30.0	17.0 ± 18.3	14.5 ± 20.0	2.46	0.12	
Maximum Severity (Psychiatric Status Rating [PSR]), m±SD						
Depression	3.2 ± 1.6	3.1 ± 1.3	2.7 ± 1.1	4.54	0.03	1.23
Mania/Hypomania	2.9 ± 1.6	2.7 ± 1.1	2.4 ± 0.9	8.47	0.004	1.33
Psychosis, % weeks	3.1 ± 15.6	3.3 ± 11.2	3.4 ± 12.2	0.04	0.85	
Comorbid Disorders, % weeks meeting full diagnos tic criteria, m±SD						
Any Comorbid Disorder	61.6 ± 48.0	60.3 ± 40.4	48.6 ± 40.9	2.93	0.09	
ADHD	34.7 ± 47.2	33.5 ± 39.1	31.2 ± 40.0	0.40	0.53	
CD/ODD	18.6 ± 38.9	23.6 ± 35.2	15.2 ± 29.2	0.89	0.35	
CD	10.7 ± 29.1	8.4 ± 23.9	4.4 ± 17.2	6.52	0.01	1.03
ODD	8.1 ± 25.6	15.2 ± 28.7	11.5 ± 25.0	0.27	0.60	
Any Anxiety	30.8 ± 45.1	28.4 ± 40.1	27.2 ± 35.2	0.21	0.65	
Panic Disorder	7.4 ± 22.8	5.1 ± 13.9	3.9 ± 13.7	2.86	0.09	
Medication Treatment, % Weeks Receiving Medication over follow-up, m±SD						
Any Psychotropic Medication	49.8 ± 48.7	72.7 ± 33.9	69.9 ± 35.0	5.58	0.02	0.99
Antimanic Anticonvulsant	12.6 ± 32.4	18.5 ± 34.6	21.1 ± 33.2	2.30	0.13	
Lithium	6.2 ± 21.8	11.8 ± 22.8	26.2 ± 37.4	5.59	0.02	0.99
Second Generation Antipsychotic	28.9 ± 44.4	37.1 ± 41.2	35.3 ± 37.8	0.67	0.41	
Antidepressant	14.7 ± 34.5	18.0 ± 31.9	27.2 ± 35.7	3.04	0.08	
Stimulants	14.9 ± 35.1	19.2 ± 34.3	12.7 ± 28.2	0.18	0.67	
Psychosocial Treatment, % Weeks Receiving Treatment over follow-up, m±SD						

	Developed SUD (n=43)		No SUD (n=113)	Statistics		
	12 weeks prior to onset	Earlier 12 week intervals		x^2	*p*-value	HR
Any Psychosocial	32.2 ± 37.3	39.8 ± 27.2	33.9 ± 26.4	0.06	0.80	
Inpatient/Residential Treatment	5.2 ± 15.9	6.0 ± 18.0	2.9 ± 7.9	0.72	0.40	
Specialized Psychosocial Services	4.7 ± 20.4	8.5 ± 17.0	9.1 ± 20.6	0.82	0.37	
Outpatient Services	26.9 ± 33.8	31.5 ± 20.7	25.7 ± 21.7	0.63	0.43	

Note: Data for subjects who developed substance use disorders (SUD) are depicted here in 2 categories for illustrative purposes. Analyses were undertaken as described in the Method, and were not dichotomous. Subjects who developed SUD within the first 12 weeks of follow-up (N=11) are not included in these analyses. ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; HR=hazard ratio; ODD=oppositional defiant disorder.