



Published in final edited form as:

*Bipolar Disord.* 2008 June ; 10(4): 469–478. doi:10.1111/j.1399-5618.2008.00584.x.

## Substance Use Disorders among Adolescents with Bipolar Spectrum Disorders

Benjamin I. Goldstein, MD, PhD<sup>1</sup>, Michael A. Strober, PhD<sup>2</sup>, Boris Birmaher, MD<sup>1</sup>, David A. Axelson, MD<sup>1</sup>, Christianne Esposito-Smythers, PhD<sup>3</sup>, Henrietta Leonard, MD<sup>3</sup>, Jeffrey Hunt, MD<sup>3</sup>, Mary Kay Gill, RN, MSN<sup>1</sup>, Satish Iyengar, PhD<sup>4</sup>, Colleen Grimm, BA<sup>1</sup>, Mei Yang, MSc<sup>1</sup>, Neal D. Ryan, MD<sup>1</sup>, and Martin B. Keller, MD<sup>3</sup>

<sup>1</sup>Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA

<sup>2</sup>Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA

<sup>3</sup>Department of Psychiatry and Butler Hospital, Brown University School of Medicine, Providence, RI

<sup>4</sup>Department of Statistics, University of Pittsburgh, Pittsburgh, PA

### Abstract

**Objective**—We set out to examine the prevalence and correlates of substance use disorders (SUD) in a large sample of adolescents with bipolar disorder (BP).

**Methods**—Subjects were 249 adolescents ages 12 to 17 years old, who fulfilled DSM-IV criteria for BPI (n = 154) or BPII (n = 25), or operationalized criteria for BP not otherwise specified (BP NOS; n = 70) via the K-SADS. As part of the multi-site Course and Outcome of Bipolar Youth study, demographic, clinical, and family history variables were measured via intake clinical interview with the subject and a parent/guardian.

**Results**—The lifetime prevalence of SUD among adolescents with BP was 16% (40/249). Results from univariate analyses indicated that subjects with, as compared to without, SUD were significantly less likely to be living with both biological parents, and that there was significantly greater lifetime prevalence of physical abuse, sexual abuse, suicide attempts, conduct disorder, and post-traumatic stress disorder among subjects with SUD. Subjects with SUD reported significantly greater 12-month prevalence of trouble with police, and females with SUD reported significantly greater 12-month prevalence of pregnancy and abortion. Significant predictors of SUD in a logistic regression model included living with both biological parents (lower prevalence), conduct disorder and suicide attempts (increased prevalence). In logistic regression analyses controlling for demographic differences and conduct disorder, SUD remained significantly associated with trouble with police, whereas the association of SUD with pregnancy and abortion was reduced to a statistical trend. The prevalence of SUD was not significantly different among child- versus adolescent-onset BP subjects.

**Conclusions**—SUD among adolescents with BP is associated with profound hazards including suicide attempts, trouble with police, and teenage pregnancy and abortion.

### Keywords

bipolar disorder; adolescent; alcohol; drug; substance; pregnancy; forensic

## BACKGROUND

The comorbidity of bipolar disorders (BP) and substance use disorders (SUD; defined as abuse or dependence of alcohol or drugs) has been well documented in the adult BP literature. When SUD occur in BP there is dramatically increased illness severity across a broad spectrum of parameters including delayed recovery, hastened relapse, increased number and inter-episode persistence of symptoms, increased functional disability, and mortality (1). SUD in BP have also been implicated in increased impulsivity (2), treatment-emergent mania (3), forensic problems (4), suicidality (5), and nonadherence (6).

Recent years have seen the development of a body of literature regarding comorbid SUD among youth with BP. While empirical data remain scant, epidemiologic and clinical findings demonstrate a significantly greater prevalence of SUD among adolescents with BP spectrum disorders as compared to non-BP adolescents (7-9). Previous studies in youth with BP have been subject to two primary limitations. First, small sample sizes (largest with N=18) preclude adequately-powered examination of demographic variables and clinical characteristics and comorbidities. Second, despite the known association of SUD with increased disease severity among adults, no study to date has tested for these associations among youth with BP.

The Course and Outcome of Bipolar Youth (COBY) (10,11) is a long-term naturalistic study of youth with BP, funded by the National Institute of Mental Health. The COBY sample comprises 446 children and adolescents. The purpose of this report is to document the prevalence of SUD in this cohort at the time of the intake assessment, and to identify clinical and demographic factors associated with SUD. Based on the extant literature it was hypothesized that: 1) SUD would be associated with conduct disorder (12); 2) its prevalence would be significantly greater among those with adolescent-onset as compared to childhood-onset (<12 years) BP (8,9); 3) subjects with SUD would demonstrate greater severity of illness as compared to subjects without SUD, reflected in suicide attempts (5), psychiatric hospitalizations, mixed episodes (1), and trouble with police (4). On the basis of findings from adolescents with SUD, we also hypothesized that SUD would be associated with pregnancy and abortion among females with BP (13,14).

## METHOD

### Participants

The COBY study enrolled 446 subjects, ages 7-17 years. However, present analyses are restricted to adolescents (ages 12-17; N=249) due to the absence of SUD among children. Subject assent and parental informed consent was provided for participation in the COBY study. Subjects were primarily recruited through clinical referrals within three academic medical centers (University of Pittsburgh, n = 113 Brown, n = 75; and UCLA, n = 61); community referrals and print advertisements were also utilized to recruit subjects. Institutional Review Board approval was obtained at each site prior to subject enrollment.

The sample comprised 110 (44%) males and 139 (56%) females, mean age 12.7 years (SD = 3.3). Subjects were, on average, middle class (mean SES = 3.4, SD = 1.2; 15). Demographic and clinical characteristics are reported in Tables 1 and 2.

### Inclusion Criteria

Subjects met the following criteria: 1) DSM-IV bipolar I disorder (BPI), bipolar II disorder (BPII), or study-operationalized criteria for bipolar disorder not otherwise specified (BP NOS, see *Diagnosis* below) via the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version (K-SADS-PL; 16) Depression Rating Scale (K-

SADS-DRS; 17) and Mania Rating Scale (K-SADS-MRS; 18); 2) determined to have a primary bipolar disorder (not induced by substance use, medications, or a medical condition); and 3) intellectual functioning within normal limits.

## Procedures

Procedures for the COBY study have been previously reported (10,11), and are presented here in summarized format. All of the information described below was ascertained at the intake assessment.

**Diagnosis**—All COBY diagnosticians have a bachelor's, master's or Ph.D. degree in a mental health field, and attended K-SADS training sessions. Parents were interviewed about their adolescents, and adolescents were directly interviewed for the presence of mood disorders using the K-SADS-DRS (17) and K-SADS-MRS, and for the presence of non-mood psychiatric disorders using the K-SADS-PL (16). K-SADS symptom ratings and diagnoses were based on consensus ratings incorporating all available data; in the event of conflicting information, summary ratings were guided by clinical judgment. Diagnoses were confirmed by a consensus conference with a child psychiatrist or psychologist following the interview. To maintain reliability, bimonthly conference calls between sites addressed assessment questions and concerns. Based on ratings of 13 study interviews (4-7 raters per case), inter-rater reliabilities for mood disorders were  $\geq 0.75$  (kappa); kappas for non-mood disorders were  $\geq 0.80$ . The intraclass coefficient (ICC) for the K-SADS-MRS (12 cases) was 0.96, and the DRS (12 cases) was 0.98.

Given that the DSM-IV criteria for BP NOS are not specific and there are no other available criteria for this BP subtype, for COBY BP NOS was operationalized as follows: elevated and/or irritable mood, plus: 1) two associated DSM-IV manic symptoms (three if only irritable mood), 2) change in functioning, 3) mood and symptom duration of at least four hours within a 24-hour period, and 4) episode frequency of at least four cumulative 24-hour periods meeting the mood, symptom, and functional change criteria over the subject's lifetime. COBY data on clinical course and outcome provide preliminary validation for these operationalized BP NOS criteria (10,11).

Subjects were considered to have lifetime SUD if they met DSM-IV criteria (see *Diagnosis*, above) for abuse or dependence of alcohol or any drug other than nicotine.

**Other Clinical Information**—Basic demographic information was obtained at intake. History of sexual and physical abuse was systematically obtained using an interviewer-administered medical history questionnaire. Information on subjects' comorbid diagnoses and clinical characteristics were discerned from summary scores from the K-SADS interview with the adolescent and the parent. The age of onset for a subject's BP illness was considered to be when the subject first met DSM-IV criteria for a manic, mixed, hypomanic, or major depressive episode, or when he/she first met COBY criteria for BP NOS. Given that the validity of DSM-IV diagnostic criteria for preschool-aged children has not been established, the minimum age of onset for BP-spectrum illness was set at 4 years.

Suicide attempt was defined by self-injurious behavior that met one of the following criteria: a seriousness or lethality score of 3 on the K-SADS-P depression section (0-6 scale); a seriousness or lethality score of 2 on the K-SADS-PL depressive disorders section (0-3 scale); a lifetime suicide attempt rated as clinically significant on the K-SADS summary lifetime diagnostic checklist (19).

The parent(s) who attended the interview were interviewed at intake about their personal psychiatric history using the Schedule for Clinical Interview of DSM-IV (SCID; 20). The

parent(s) were also interviewed regarding the psychiatric status of all first- and second-degree relatives using the Family History Screen, which has demonstrated adequate reliability and validity (21).

Study participants completed the Life Events Checklist (22) which ascertains the 12-month prevalence of a variety of life events, as well as the perceived quality of the event (positive versus negative) and degree of perceived impact on the adolescent. For the purpose of the present study, only the 12-month prevalence trouble with police, and pregnancy and abortion (females only) was examined.

### Statistical Analysis

Variables were screened for their association with lifetime SUD using chi-square tests for categorical variables and t-tests for continuous variables. Next, demographic and clinical characteristics and comorbidities that were significantly associated with SUD in the univariate analyses were entered into a logistic regression model in order to examine the unique contribution to variance in SUD associated with each predictor, controlling for the effects of other predictors. A second logistic regression model was created to examine the unique contribution of SUD to the variance in life events for which between-group differences emerged. In addition to controlling for demographic differences (i.e., age, living with both biological parents), this model also controlled for conduct disorder. All P values are based on 2-tailed tests with  $\alpha = 0.05$ . Given the paucity of information on the correlates of SUD in this population, particularly given the inclusion of youth with BP-II and -NOS, we did not apply statistical correction for multiple comparisons. Statistical analyses were performed using the Statistical Package for the Social Sciences Version 14 (SPSS).

## RESULTS

### Demographic characteristics

Demographic characteristics are depicted in Table 1. Subjects with SUD were significantly older at intake ( $p < 0.001$ ) and were significantly less likely to be living with both natural parents ( $p = 0.001$ ). Subsequent regression analyses controlled for these two variables. There were no significant differences in sex, race, SES, or pubertal status.

### Prevalence of SUD

The lifetime prevalence of SUD was 16% among the subset of 249 adolescent subjects (40/249). Eighteen of these subjects (45%) met full criteria for an active SUD at the time of intake. Cannabis use disorders (5% dependence, 7% abuse) were the most common SUD, with a lifetime prevalence of 12% among all adolescents and 73% among adolescents with an SUD. Eight percent of all adolescents had a lifetime alcohol use disorder (5% dependence, 3% abuse), corresponding with 50% of subjects with any SUD. The prevalence of other types of drug abuse/dependence (e.g., cocaine, hallucinogens) did not exceed 3%. Five percent ( $N = 12$ ) of all adolescents and 30% of adolescents with SUD had both lifetime cannabis and alcohol use disorders. There was a trend toward increased SUD prevalence among adolescents with adolescent-onset (20%; 26/129) as compared to adolescents with childhood-onset (<12 years) BP (12%; 14/120) ( $\chi^2 = 3.3$ ,  $df = 1$ ,  $p = 0.07$ ). The mean duration since SUD symptom onset was 2.4 years ( $SD = 1.4$ ).

### Clinical characteristics, comorbidities, and life events

Clinical characteristics, comorbidities, and life events associated with SUD are summarized in Table 2. Subjects with SUD, as compared to those without SUD, demonstrated significantly greater lifetime prevalence of suicide attempts ( $p = 0.007$ ), physical abuse ( $p < 0.001$ ), sexual

abuse ( $p<0.001$ ), conduct disorder ( $p<0.001$ ), and PTSD ( $p<0.02$ ). However, there were no significant differences in terms of BP subtype or BP onset age, and no significant differences in terms of lifetime prevalence of psychosis, mixed episodes, and psychiatric hospitalizations. There were no significant differences in the prevalence of anxiety disorders, ODD, or ADHD. Subjects with SUD were significantly more likely to report 12-month history of trouble with police as compared to subjects without SUD (all  $p$ -values  $<0.05$ ). Twelve-month prevalences of pregnancy and of abortion were significantly greater among females with versus without SUD ( $p\leq 0.001$ ).

### Family history

The prevalence of ADHD, anxiety, conduct disorder, depression, mania, and SUD among first and second degree family members of subjects is presented in Table 3. There were no significant between-group differences in the prevalence of any of these conditions among either first or second degree relatives.

### Logistic regression analyses

The clinical characteristics and comorbidities that differed significantly based on the presence or absence of SUD were included in logistic regression analyses to examine their unique contribution to variance in SUD. These factors included: age, living with both biological parents, lifetime suicide attempt, conduct disorder, physical abuse, sexual abuse, and PTSD. These analyses included SUD as the dependent variable.

Separate logistic regression models were created to examine the unique contribution of SUD to the variance in 12-month history of trouble with police and pregnancy (females only). These models controlled for age, living with both biological parents, and conduct disorder.

**Predictors of SUD**—Conduct disorder was a significant positive predictor of SUD (OR 5.6, 95% CI 2.4-13.2;  $p<0.001$ ), as was suicide attempt history (OR 2.8, 95% CI 1.3-6.2;  $p=0.01$ ) and age ( $\chi^2=16.3$ ,  $df=1$ ,  $p<0.001$ ). Living with both biological parents was a significant negative predictor of SUD (OR 0.2, 95% CI 0.1-0.5;  $p=0.001$ ). The association of sexual abuse, physical abuse, and PTSD with SUD was no longer significant. The data could not elucidate whether SUD onset was antecedent or consequent to physical/sexual abuse or to the onset of not living with both parents. Among subjects with both conduct disorder and SUD, onset of conduct disorder occurred prior to or in the same year as SUD in 81% (13/16; age of conduct disorder onset missing for one subject). Although these variables were included in the logistic regression as putative risk factors for SUD, the direction of the association could not be ascertained definitively.

**Age of BP onset**—Due to the fact that the mean age of adolescent subjects with adolescent-onset BP was significantly greater than adolescent subjects with child-onset BP (16.0 $\pm$ 1.4 years vs. 14.3 $\pm$ 1.5 years,  $t=9.3$ ,  $p<0.001$ ), age was included as a covariate in a logistic regression examining the impact of adolescent-onset versus child-onset BP on SUD prevalence. The initial trend toward increased SUD prevalence among adolescent-onset versus child-onset BP among COBY adolescents was no longer evident ( $p=0.76$ ).

**Negative life events**—Logistic regression analyses were also calculated for the negative life events examined, which were found to be significantly more prevalent among subjects with SUD: trouble with police, and pregnancy or abortion (among females). Conduct disorder was included in these analyses as a covariate due to the possibility that this might confound the association between SUD and the negative life events. The analyses also controlled for age and living with both biological parents. SUD was significantly associated with trouble with police (OR 2.5, 95% CI 1.1-6.0,  $p=0.04$ ). Among females, the association of SUD with greater



12-month prevalence of pregnancy was reduced to a statistical trend (OR 7.6, 95% CI 0.6-89.6,  $p=0.11$ ). Odds ratio estimates could not be generated for abortion due to zero prevalence in the non-SUD group. However, SUD accounted for a nearly-significant proportion of the variance in abortion ( $\chi^2=3.0$ ,  $df=1$ ,  $p=0.08$ ).

### Exploratory analyses

Analyses were repeated for BP-I subjects only in order to explore whether the above findings differed if BP-II and BP-NOS subjects were excluded. In univariate analyses, with the exception of PTSD, the same variables for which there were significant between-group differences in the overall analyses were also significant when only BP-I subjects were examined. Moreover, there were no additional significant variables. The prevalence of SUD did not differ significantly if BP-I onset occurred in childhood (13%) or adolescence (18%;  $\chi^2=0.8$ ,  $df=1$ ,  $p=0.36$ ). The logistic regression analyses were repeated as well. Again, the same variables remained significant. Family history variables were also examined among BP-I subjects only, and there were several differences from the overall sample. Subjects with SUD had significantly greater prevalence of mania in first-degree relatives as compared to subjects without SUD (57% vs 31%;  $\chi^2=5.7$ ,  $df=1$ ,  $p=0.02$ ), and a trend was observed among second-degree relatives (48% vs 28%;  $\chi^2=3.1$ ,  $df=1$ ,  $p=0.08$ ). Subjects with SUD also had significantly greater prevalence of comorbid mania and SUD among first-degree relatives (35% vs 13%;  $\chi^2=7.1$ ,  $df=1$ ,  $p=0.008$ ).

Finally, logistic regression analyses were repeated for the overall sample in order to examine the contribution of baseline manic and depressive symptoms to variance in SUD. Neither baseline manic ( $\chi^2=0.0$ ,  $df=1$ ,  $p=0.97$ ) nor depressive ( $\chi^2=0.1$ ,  $df=1$ ,  $p=0.74$ ) symptoms were significant predictors, and their inclusion in the model did not impact the significance of the other predictors.

## DISCUSSION

To our knowledge, this is the largest study to date examining SUD among adolescents with BP spectrum disorders, and the first to examine with adequate power the association of SUD with psychiatric comorbidities and the putative sequelae of SUD in this population. The lifetime prevalence of SUD among adolescents with BP was 16%, and did not differ significantly based on whether these adolescents experienced onset of BP in childhood or adolescence. Subjects with SUD were significantly older as compared to subjects without SUD. The most common substance of abuse/dependence was cannabis, followed by alcohol.

Compared to subjects without SUD, those with SUD were significantly less likely to be living with both biological parents. They had greater lifetime prevalence of suicide attempts and of sexual and physical abuse, although the latter findings were reduced to statistical trends after controlling for confounders. Twelve-month prevalence of self-reported trouble with police was significantly greater among subjects with SUD, and females with SUD were significantly more likely to report past-year pregnancy and abortion as compared to females without SUD (although this was reduced to a statistical trend in regression analyses). There were no significant between-group differences in lifetime prevalence of any other clinical characteristics or comorbidities, or in family history.

The finding of zero prevalence of SUD among children in the COBY study converges with previous findings (23,24). The prevalence of SUD (16%) among adolescents with BP was in keeping with some previous studies (6,23), but lower than that of other studies (8,9). A study of adolescents hospitalized for mania reported a 39% prevalence of SUD (25), whereas figures in outpatient samples have ranged from 18% to 32% (8,23). The somewhat lower prevalence of SUD in the present study as compared to the 22% reported in a community sample of 14-18

year olds with BP (6) may be explained by the older mean age in that study (16.6 vs 15.2 years). Given that few adolescents in COBY (19%) were inpatients at the time of referral, the higher prevalence of SUD in the study of adolescents hospitalized for mania could also be expected (25).

The prevalence of SUD among adolescents in this study did not differ based on whether BP onset occurred in childhood or adolescence, contrary to two previous studies (8,9). This discrepancy may relate to differences in ascertainment. Whereas COBY was designed to examine BP specifically, one previous study was derived from a sample originally recruited based on a diagnosis of ADHD (9). Another study that specifically recruited BP subjects (8) did not control for age, which may have confounded the results. Present findings are convergent with retrospective data from adults with BP which indicate that child-onset and adolescent-onset BP confer greater risk of SUD as compared to adult-onset BP, but that adolescent-onset BP does not confer greater risk of SUD compared to child-onset BP (26,27).

One possible explanation for the differences between present and previous findings is that subjects with BP-II and BP-NOS were included in this study, whereas most previous studies include only subjects with BP-I. However, analyses were recalculated for BP-I subjects only, and both the prevalence and correlates of SUD were nearly identical to the findings for the combined sample. It is unlikely, therefore, that this methodologic difference accounts for these findings.

Only half of the SUD group (8% overall) demonstrated alcohol abuse/dependence. These findings contrast those of adults, among whom alcohol is the most common substance of abuse/dependence (1), but converge with previous findings for adolescents (6). Findings from epidemiologic studies suggest that drug abuse/dependence is more common than alcohol abuse/dependence among adolescents with BP (6), whereas alcohol abuse/dependence is more common among young adults with BP (28). This observation is important for developmentally-appropriate prevention and intervention strategies.

As hypothesized, subjects with conduct disorder had significantly increased prevalence of SUD. Previous studies have found that conduct disorder is a risk factor for SUD among adolescents in general (29), and that comorbid conduct disorder does not fully account for the association between SUD and BP among adolescents (8). However, to our knowledge, this is the first study to demonstrate that conduct disorder is associated with significantly increased prevalence of SUD among adolescents with BP.

The hypothesis that subjects with SUD would have increased BP severity was only partially supported. Suicide attempts were significantly more prevalent among subjects with versus without SUD. Ample literature attests to the increased rate of suicidality among youth with SUD (30). Similarly, previous studies have shown that SUD is a significant risk factor for suicide attempts among adults with BP (4,31). BP has been implicated as a putative risk factor for suicide among adolescents, and SUD is twice as common among suicide completers as compared to ideators/attempters (32). A previous study based on the COBY study reported that the lifetime prevalence of SUD was 17% among attempters and 5% among non-attempters (19). BP adolescents with SUD may be at increased risk for suicide attempts, as is the case among adults.

The presence of SUD was significantly associated with trouble with police, and this finding persisted after adjusting for the high prevalence of CD. These findings replicate those in studies of adults (5,33). In a previous study of youth with comorbid BP (or MDD and BP predictors) and SUD, 52% reported a lifetime history of arrest (34). Present findings demonstrate that conduct disorder does not confound the association between SUD and trouble with police. Albeit that legal difficulty may in some cases be a direct consequence of underage drinking,

or of possession or distribution of illicit substances, it is important to consider that legal difficulty is a common proximal risk factor preceding adolescent suicide (35-37).

SUD among females was associated with greater 12-month prevalence of pregnancy and abortion. Substance use among adolescent females has previously been associated with risky sexual behavior and adverse sexual/reproductive outcomes, especially when depression is present (13,14,38). Adolescent females with BP and SUD may be at risk for these outcomes as well.

The absence of significant between-group differences in family history in the present study converges with findings from adults (39) and youth (34,41) with BP. The prevalence of comorbid mania and SUD among any first-degree relative was nearly two-fold greater among BP adolescents with SUD as compared to BP adolescents without SUD. Although this difference did not reach statistical significance, it does replicate the finding by Winokur and colleagues showing a trend toward increased alcoholism among BP relatives of BP probands with alcoholism as compared to BP relatives of non-alcoholic BP probands (39). When BP-I subjects were analyzed separately, between-group differences in family history of mania and comorbid mania and SUD attained statistical significance. Future studies examining the contribution of BP-subtype to family history variables associated with proband SUD are indicated.

The methodologic limitations of this study must be considered when interpreting these findings. First, under-reporting of SUD may have occurred. Although adolescent subjects were interviewed separately from parents, at least one parent was closely involved in this study which may have lead to under-reporting of SUD. Urine toxicology was not collected to address possible duplicity. Such false negative cases would serve to diminish the between-group differences examined, and this may have decreased the apparent impact of SUD on youth with BP. Second, this naturalistic study did not examine certain treatment-related details such as dosage and adherence, and did not systematically collect data regarding SUD treatment. Third, this study focused on the association between lifetime SUD and other lifetime variables (e.g., hospitalization, suicidality), and therefore present findings likely under-estimate the impact of concurrent SUD on BD severity. Fourth, trouble with police was ascertained via self-report, and details regarding the nature of or reason for this trouble could not be determined. Finally, this study employed cross-sectional and retrospective methodology. As such, it could not be determined whether SUD onset antecedent or consequent to physical/sexual abuse and/or not living with both parents. Although these variables are considered here as putative risk factors for SUD, the direction of causality is uncertain as SUD could also potentially predispose to sexual/physical abuse and/or not living with both parents. Similarly, temporal priority of SUD with suicide attempts or hospitalizations could not be determined.

Despite the acknowledged limitations, the results of the present study may have important clinical implications. Adolescents with comorbid BP and SUD have an elevated risk of suicide attempts, trouble with police, and teenage pregnancy and abortion. These risks exceed what would be expected from other predictors such as conduct disorder and non-intact families. Although these findings require replication, extreme vigilance is warranted in the monitoring and management of SUD among adolescents with BP. The finding of relatively low alcoholism as compared to adults with BP is important because clinical and epidemiologic data suggest that the prevalence of alcoholism among these adolescents will increase approximately 7-fold by middle-adulthood (1,26-27). Clearly this presents an important opportunity for secondary prevention and early intervention that cannot be ignored. Future large-scale studies are needed to examine the dynamic relationship between substance use and BP among adolescents longitudinally, in order to elaborate on previous findings based on smaller sample sizes (42).



Reports examining these topics in the COBY sample will be forthcoming. Targeted preventative strategies for averting SUD among adolescents with BP are urgently needed.

## Acknowledgments

This research was supported by National Institute of Mental Health Grants MH59929 (Dr. Birmaher), MH59977 (Dr. Strober), and MH59691 (Dr. Keller). The authors wish to acknowledge the contributions of COBY faculty: Kristin Bruning MD, Jennifer Dyl PhD, Sylvia Valeri, PhD. Raters: Mathew Arruda BA, Mark Celio BA, Jennifer Fretwell BA, Michael Henry BS, Risha Henry PhD, Norman Kim PhD, Marguerite Lee BA, Marilyn Matzko EdD, Heather Schwickrath MA, Anna Van Meter BA, Matthew Young BA. Data personnel: Amy Broz AS, Nicole Ryan BA.

## REFERENCES

1. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. *Bipolar Disord* 2001;3:181–188. [PubMed: 11552957]
2. Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. Impulsivity: a link between bipolar disorder and substance abuse. *Bipolar Disord* 2004;6:204–212. [PubMed: 15117399]
3. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. *J Clin Psychiatry* 2002;63:791–795. [PubMed: 12363119]
4. Quanbeck CD, Stone DC, Scott CL, McDermott BE, Altshuler LL, Frye MA. Clinical and legal correlates of inmates with bipolar disorder at time of criminal arrest. *J Clin Psychiatry* 2004;65:198–203. [PubMed: 15003073]
5. Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord* 2003;5:58–61. [PubMed: 12656940]
6. Weiss RD, Greenfield SF, Najavits LM, Soto JA, Wyner D, Tohen M, Griffin ML. Medication compliance among patients with bipolar disorder and substance use disorder. *J Clin Psychiatry* 1998;59:172–174. [PubMed: 9590667]
7. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry* 1995;34:454–463. [PubMed: 7751259]
8. Wilens TE, Biederman J, Kwon A, Ditterline J, Forkner P, Moore H, Swezey A, Snyder L, Henin A, Wozniak J, Faraone SV. Risk of substance use disorders in adolescents bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2004;43:1380–1386. [PubMed: 15502597]
9. Wilens TE, Biederman J, Millstein RB, Wozniak J, Hahealy AL, Spencer TJ. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 1999;38:680–685. [PubMed: 10361785]
10. Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63:175–183. [PubMed: 16461861]
11. Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 2006;63:1139–1148. [PubMed: 17015816]
12. Carlson GA, Bromet EJ, Jandorf L. Conduct disorder and mania: what does it mean in adults? *J Affect Disord* 1998;48:199–205. [PubMed: 9543210]
13. Waller MW, Hallfors DD, Halpern CT, Iritani BJ, Ford CA, Guo G. Gender differences in associations between depressive symptoms and patterns of substance use and risk sexual behavior among a nationally representative sample of U.S. adolescents. *Arch Womens Ment Health* 2006;9:139–150. [PubMed: 16565790]
14. Shrier LA, Harris SK, Sternberg M, Beardslee WR. Associations of depression, self-esteem, and substance use with sexual risk among adolescents. *Prev Med* 2001;33:179–189. [PubMed: 11522159]
15. Hollingshead, A. Four-factor Index of Social Status. Yale University; New Haven: 1975.
16. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-

- SADS-PL): Initial Reliability and Validity Data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980–8. [PubMed: 9204677]
17. Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabizi MA, Davies M. The assessment of affective disorders in children and adolescents by semi-structured interview: test-retest reliability. *Arch Gen Psychiatry* 1985;42:696–702. [PubMed: 4015311]
  18. Axelson, DA.; Birmaher, B.; Brent, DA.; Ryan, ND. The KSADS-Mania Rating Scale for Pediatric Bipolar Disorder 10-21-1999; American Academy of Child and Adolescent Psychiatry Annual Meeting; 1999;
  19. Goldstein TR, Birmaher B, Axelson D, Ryan ND, Strober MA, Gill MK, Valeri S, Chiappetta L, Leonard H, Hunt J, Bridge JA, Brent DA, Meller M. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. *Bipolar Disord* 2005;7:525–535. [PubMed: 16403178]
  20. Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. The Structured Clinical Interview for DSM-III-R/DSM-IV. New York State Psychiatric Institute; New York: 1996.
  21. Weissman MM, Wickramatne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief Screening for Family Psychiatric History: The Family History Screen. *Arch Gen Psychiatry* 2000;57:675–82. [PubMed: 10891038]
  22. Johnson, JH.; McCutcheon, SM. Assessing life stress in older children and adolescents: Preliminary findings with the Life Events Checklist. In: Sarason, IG.; Spielberger, CD., editors. *Stress and Anxiety*. Hemisphere; Washington, DC: 1980.
  23. Findling RL, Gracious BL, McNamara NK, Youngstrom EA, Demeter CA, Branicky LA, Calabrese JR. Rapid continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord* 2001;3:202–210. [PubMed: 11552959]
  24. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Cayton GA, Clark SV. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J Psychiatr Res* 2005;39:611–622. [PubMed: 16009376]
  25. West SA, Strakowski SM, Sax KW, McElroy SL, Keck PE Jr, McConville BJ. Phenomenology and comorbidity of adolescents hospitalized for the treatment of acute mania. *Biol Psychiatry* 1996;39:458–460. [PubMed: 8679794]
  26. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden MP, Sachs GS, Nierenberg AA, for the STEP-BD investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 2004;55:875–881. [PubMed: 15110730]
  27. Goldstein BI, Levitt AJ. Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Am J Psychiatry* 2006;163:1633–1636. [PubMed: 16946191]
  28. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord* 2000;2:281–293. [PubMed: 11249806]
  29. Brook JS, Whiteman M, Cohen P, Shapiro J, Balka E. Longitudinally predicting late adolescent and young adult drug use: childhood and adolescent precursors. *J Am Acad Child Adolesc Psychiatry* 1995;34:1230–1238. [PubMed: 7559319]
  30. Esposito-Smythers C, Spirito A. Adolescent substance use and suicidal behavior: a review with implications for treatment research. *Alcohol Clin Exp Res* 2004;28:77S–88S. [PubMed: 15166639]
  31. Potash JB, Kane HS, Chiu Y, Simpson SG, MacKinnon DF, McInnis MG, McMahon FJ, DePaulo JR. Attempted suicide and alcoholism in bipolar disorder: clinical and familial relationships. *Am J Psychiatry* 2000;157:2048–2050. [PubMed: 11097977]
  32. Brent DA, Perper JA, Goldstein CE, Kolko DJ, Allan MJ, Allman CJ, Zelenak JP. Risk factors for adolescent suicide: A comparison of adolescent suicide victims with suicidal inpatients. *Arch Gen Psychiatry* 1988;45:581–588. [PubMed: 3377645]
  33. Friedman SH, Shelton MD, Elhaj O, Youngstrom EA, Rapport DJ, Packer KA, Bilali SR, Jackson KS, Sakai HE, Resnick PJ, Findling RL, Calabrese JR. Gender differences in criminality: bipolar disorder with co-occurring substance abuse. *J Am Acad Psychiatry Law* 2005;33:196–198. [PubMed: 15985662]

34. Geller B, Cooper TB, Sun K, Zimmerman B, Frazier J, Williams M, Heath J. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 1998;37:171–178. [PubMed: 9473913]
35. Shaffer D, Garland A, Gould M, Fisher P, Trautman P. Preventing teenage suicide: a critical review. *J Am Acad Child Adolesc Psychiatry* 1988;27:675–687. [PubMed: 3058676]
36. Brent DA, Perper JA, Moritz G, Baugher M, Schweers J, Roth C. Suicide in affectively ill adolescents: a case-control study. *J Affect Disord* 1994;193–202. [PubMed: 7963072]
37. Bukstein OG, Brent DA, Perper JA, Moritz G, Baugher M, Schweers J, Roth, Balach L. Risk factors for completed suicide among adolescents with a lifetime history of substance abuse: a case-control study. *Acta Psychiatr Scand* 1993;88:403–408. [PubMed: 8310846]
38. Silverman JG, Raj A, Mucci LA, Hathaway JE. Dating violence against adolescent girls and associated substance use, unhealthy weight control, sexual risk behavior, pregnancy, and suicidality. *JAMA* 2001;286:572–579. [PubMed: 11476659]
39. Winokur G, Coryell W, Akiskal HS, Maser JD, Keller MB, Endicott J, Mueller T. Alcoholism in manic-depressive (bipolar) illness: familial illness, course of illness, and the primary-secondary distinction. *Am J Psychiatry* 1995;152:365–372. [PubMed: 7864261]
40. Wilens, TE.; Adamson, J.; Sgambati, S.; Santry, A.; Wozniak, J.; Biederman, J. The familial relationship between bipolar and substance use disorders in the relatives of adolescents with bipolar disorder: a controlled family study; Proceedings of the Annual Meeting of the American Academy of Child and Adolescent Psychiatry; San Diego, CA. 2006;
41. DelBello MP, Strakowski SM, Sax KW, McElroy SL, Keck PE, West SA, Kmetz GF. Familial rates of affective and substance use disorders in patients with first-episode mania. *J Affect Disord* 1999;56:55–60. [PubMed: 10626780]
42. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry* 1995;34:724–731. [PubMed: 7608045]

Table 1

Demographic Characteristics of 249 Adolescents with Bipolar Disorders with vs. without Substance Use Disorders

	Overall Sample (N=249)	SUD Present (N=40)	SUD Absent (N=209)	Statistic	P
Age	M+/-SD 15.2+/-1.7	M+/-SD 16.1+/-1.0	M+/-SD 15.0+/-1.7	t=5.5	<0.001
SES	3.6+/-1.2 %	3.6+/-1.1 %	3.6+/-1.1 %	t=-0.19	0.85
Sex (% Male)	44	35	46	$\chi^2=1.6$	0.20
Caucasian *	80	75	80	$\chi^2=0.6$	0.44
Intact family *	44	20	49	$\chi^2=11.3$	0.001
Pubertal Status				FET**	0.46
I	2	0	2		
II/III	25	20	26		
IV/V	73	80	71		

\* Subject lives with both biological parents

\*\* Fisher's Exact Test; valid N=211

Clinical Characteristics, Comorbidities, and Life Events of 249 Adolescents with Bipolar Disorders with versus without Substance Use Disorders

	Overall (N=249)	SUD Present (N=40)	SUD Absent (N=209)	Statistic	P
<i>Clinical characteristics</i>					
BP onset age	M+/-SD 11.7+/-3.4	M+/-SD 12.5+/-3.2	M+/-SD 11.5+/-3.4	t=1.6	0.11
Baseline depression <sup>1</sup>	16.5+/-11.5	18.7+/-10.0	16.0+/-11.7	t=1.3	0.19
Baseline mania <sup>2</sup>	22.5+/-12.8	23.5+/-12.1	22.4+/-12.9	t=0.5	0.60
Baseline CGAS <sup>3</sup>	54.1+/-12.3	53.8+/-10.7	54.1+/-12.6	t=-0.2	0.86
Lifetime CGAS <sup>4</sup>	35.9+/-10.4	34.5+/-11.5	36.2+/-10.2	t=-0.9	0.34
SUD onset age	n/a	13.7+/-1.6	n/a		
	%	%	%		
BP diagnosis	61	60	61	FET	0.38
BP-I	10	5	12		
BP-II	29	35	27		
BP-NOS					
Referral source	19	25	18	FET	0.69
Inpatient	61	58	61		
Outpatient	16	12	16		
Advertisement	4	5	4		
Other	28	30	27		
Psychosis	30	33	29	$\chi^2=0.1$	0.72
Mixed	39	58	35	$\chi^2=0.2$	0.67
Suicide attempt	63	65	63	$\chi^2=7.2$	0.007
Hospitalizations	24	48	20	$\chi^2=0.1$	0.74
Any abuse	19	40	15	$\chi^2=11.9$	<0.001
Physical abuse	13	30	10	$\chi^2=13.9$	<0.001
Sexual abuse	42	33	43	$\chi^2=12.5$	<0.001
Comorbidity	8	18	6	$\chi^2=1.7$	0.20
Any anxiety	50	38	52	$\chi^2=5.8$	0.02
PTSD	36	43	34	$\chi^2=2.9$	0.09
ADHD	17	43	12	$\chi^2=0.9$	0.33
ODD	21	42	17	$\chi^2=21.2$	<0.001
Conduct disorder	3	5	3	$\chi^2=12.2$	<0.001
Life events	5	20	1	FET	0.42
Trouble with police <sup>5</sup>	2	12	0	FET	<0.001
Put in jail <sup>6</sup>				FET	0.008
Pregnancy <sup>7</sup>				FET	
Abortion <sup>8</sup>				FET	

<sup>1</sup> Baseline DEP-P, valid N=243<sup>2</sup> Baseline K-MRS, valid N=246<sup>3</sup> Baseline CGAS, valid N=245<sup>4</sup> Most serious lifetime CGAS, valid N=240<sup>5</sup> Twelve-month prevalence by self-report, valid N=223



- <sup>6</sup>Twelve-month prevalence by self-report, valid N=221
- <sup>7</sup>Twelve-month prevalence by self-report, females only, valid N=125
- <sup>8</sup>Twelve-month prevalence by self-report, females only, valid N=123

Table 3

Family History among Adolescents with Bipolar Disorders with vs. without Substance Use Disorders

	Overall (N=235) %	SUD Present (N=37) %	SUD Absent (N=198) %	Statistic	P
First Degree					
Anxiety	45	46	45	$\chi^2=0.0$	0.94
ADHD <sup>1</sup>	26	32	25	$\chi^2=0.9$	0.35
Conduct	19	24	18	$\chi^2=0.9$	0.33
Depression	72	76	71	$\chi^2=0.3$	0.59
Mania	33	41	32	$\chi^2=1.1$	0.29
SUD <sup>2</sup>	44	49	43	$\chi^2=0.4$	0.54
Mania+SUD <sup>3</sup>	14	22	13	$\chi^2=2.1$	0.15
	(N=232)	(N=35)	(N=197)		
Second Degree					
Anxiety	43	40	43	$\chi^2=0.1$	0.75
ADHD	19	14	21	$\chi^2=0.8$	0.38
Conduct	22	23	22	$\chi^2=0.0$	0.88
Depression	66	60	67	$\chi^2=0.6$	0.44
Mania	33	34	34	$\chi^2=0.1$	0.82
SUD	62	66	61	$\chi^2=0.3$	0.61
Mania+SUD	12	11	12	$\chi^2=0.0$	0.90

<sup>1</sup> ADHD = attention deficit-hyperactivity disorder<sup>2</sup> SUD = substance use disorder<sup>3</sup> Mania+SUD = a relative has both mania and SUD