Substance Use Disorders in Adolescent and Young Adult Relatives of Probands with Bipolar Disorder: What Drives the Increased Risk?

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Abstract

Background: Adults with bipolar disorder (BD) have higher rates of substance use disorders (SUDs) compared to the general population. SUD rates in young offspring/relatives of BD probands, as well as factors which drive those rates, are not as well-characterized.

Methods: We aimed to examine SUD prevalence among adolescent/young adult offspring and relatives of probands with and without BD. Data were collected from five sites in the US and Australia during 2006-2011. Youth offspring/relatives ("Relatives of BD probands;" n=267; mean age = 16.8 years; ± 2.9 S.D.), identified through a proband family member with DSM-IV BD (Type I or II), were compared to offspring/relatives of control probands ("relatives of control probands;" n=149; mean age= 17.4 years; ± 2.9 S.D.). Logistic regression with generalized estimating equations was used to compare the groups across a range of substance use and SUD variables. Odds ratios were calculated for lifetime prevalence of substance outcomes.

Results: Bivariate analyses showed DSM-IV SUDs were more prevalent among relatives of BD probands than among relatives of control probands (29% vs. 18%; p=0.01). Generalized estimating equation models showed BD mood and childhood-onset externalizing disorders in adolescent and young adult relatives to each significantly increase the odds (OR=2.80-3.17; p<0.02) for the development of several substance variables among all relatives, whereas the risk of SUDs in relatives was not increased when the relatives had no mood or externalizing disorders themselves.

Conclusion: Relatives of BD probands with lifetime mood and externalizing disorders report more substance use/SUDs than relatives of control probands. In contrast, SUD outcomes in relatives of BD probands without mood or externalizing disorders were no different from control relatives without psychopathology. Early recognition and treatment of psychiatric disorders may lead to less substance use in this highly vulnerable population.

1. Introduction

The association between substance use disorders (SUDs) and mood disorders, particularly bipolar disorder (BD), has been well documented [1-4]. Estimates of lifetime comorbidity of BD and SUDs range from 16-54% [5, 6], with a recent meta-analysis finding a mean prevalence of 33% for comorbid BD and SUDs [7]. This comorbidity is particularly important from a prognostic standpoint, with multiple studies documenting significantly worse mental and physical health outcomes in individuals afflicted by both SUDs and BD [8, 9]. SUDs complicate treatment and course of BD, and vice versa. Co-occurring SUDs have been shown to be particularly associated with increased frequency and duration of mood episodes, increased preoccupation with suicide, decreased treatment compliance and more severe cognitive impairment in individuals with BD [3, 10]. Tobacco is the most commonly used drug of abuse among individuals with BD and is used 1.5-3 times more often than in the general population [11-14]. Tobacco use is of particular interest given recent evidence of earlier death rates in both men and women with BD, driven partly by tobacco-related illnesses [15]. Alcohol, cannabis, and cocaine are the next most commonly misused substances among individuals with BD [3]. Explanatory models postulate that substance use is elevated among individuals with BD, compared to the general population, because of common risk factors. These common risk factors may increase expression of a range of self-regulatory deficits which may manifest in symptoms of mood disorders or SUDs [16].

Prominent models of addiction liability have largely focused on trajectories toward SUDs from childhood externalizing disorders [17-20]. Pathways toward SUDs among youth with BD diagnoses are also becoming increasingly well characterized [21-24]. In youth, the combination of conduct disorder and BD has been associated with especially high rates of SUDs in relatives [21], indicating an overlap between the risk factors for BD and SUDs. Genome-wide association analysis has provided evidence of a significant genetic overlap in the risk factors of BD and

SUDs [25]. However, the relative influence of a family history of BD and other risk factors (e.g., adolescent psychopathology, parental SUDs, etc.) on SUD development in BD remain unclear, as does information pertaining to relative age of onset of each disorder category. Understanding mechanisms leading to an underlying SUD in BD are essential to the development of appropriate preventive and treatment interventions. For example, if parenting practices associated with having BD are driving the effect, modifying parental behavior should become the focus of intervention development. If adolescent psychopathology is driving the effect, preventing or treating youth disorders should become the focus of study.

Examination of adolescent/young adult relatives of BD probands provides an opportunity to study SUD/substance use and psychiatric disorders as they develop. Increased risk for SUDs in relatives of individuals with BD are hypothetically attributed to several factors. First, the occurrence of high rates of psychopathology in offspring of BD probands [26] may increase risk, as higher rates of SUDs have been associated with a range of mental disorders. Second, shared genetic loading for BD as well as SUDs is higher in relatives of BD probands. Identified genes likely influence affective and reward brain circuitry abnormalities linked with both SUD and BD [27]. Third, stressors associated with having relatives with BD may also increase risk for SUDs [28].

Several recent studies have reported on rates of SUDs in offspring of BD probands. In a Canadian sample, 24% of prospectively followed adolescent and young adult offspring of BD probands (aged 12-25) were found to have lifetime SUD, with cannabis being the most common substance abused [29]. Being male and having a prior mood disorder were risk factors for offspring developing a SUD [29]. Similarly, in the Dutch Bipolar Offspring Study, lifetime prevalence of a SUD was 28% in offspring of BD probands, when assessed at follow up during young adulthood [30]. BD in parental probands has also been shown to predict offspring SUD, while MDD in parental probands in the same sample did not [31]. SUDs and substance use are

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relatively common in the general adolescent population [32]; thus, comparisons with relatives of control proband parents are warranted in order to determine if their SUD rates differ from relatives of control probands whose families do not have identified BD. The Pittsburg Bipolar Offspring Study (BIOS) reported that 20% of relatives of BD probands had SUDs at follow up at mean age of 18.1 years, compared to only 10% of community control relatives of control probands [33]. In sum, SUD rates in young adult relatives of BD probands range from 20-28% and appear to be greater than those in relatives of control probands. However, while high rates of comorbid psychiatric and SUDs have been established, the relative influence of proband SUDs/psychopathology and relatives own psychopathology on SUD outcomes in relatives of probands with BD has not been well characterized in prior studies.

The relationship between parental/relative BD and SUDs and adolescent psychopathology and SUDs remains poorly defined. We hypothesize, for our primary research question, that offspring/relatives of probands with BD ("relatives of BD probands") will be more likely to manifest SUDs, compared to youth offspring/relatives of control probands ("relatives of control probands "), even after adjusting for relative mental health diagnoses. We also report three exploratory analyses, hypothesizing that: (1) Parental SUDs, Parental BD and relative psychopathology will all be associated with increased odds for adolescent substance outcomes (2) Given the controversy surrounding the ages of onset of SUDs vs BD (e.g., some studies suggested that SUDs predict mood disorders [34-36] and others the reverse relationship [37-39], with most conceding that a bidirectional relationship is also likely), we plan to study the relative age of onset of each type of disorder and predict the onset of mood disorders will occur prior to the onset of SUDs in both groups, given the relatively earlier emergence of these disorders, in general. (3) Finally, we are unaware of any studies examining the relative age of onset of SUDs in BD relatives vs. control relatives. We predict that relatives of BD probands will have earlier onset of SUDs than relatives of control probands, given greater rates of child and

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adolescent onset psychopathology in BD relatives. To address these four topics, we examined the lifetime prevalence and age of onset of SUD outcomes and their relationship to parental SUDs and BD and comorbid youth psychopathology (i.e., mood, anxiety and externalizing disorders) in adolescent and young adult offspring/relatives of probands with and without BD. Given the young age of our sample, we examine the spectrum from subthreshold SUD symptoms to SUDs.

2. Material and Methods

2.1 Subjects

As detailed in prior publications [26, 40, 41], information on participants was ascertained through the research database of the Bipolar High Risk Study Group. Relatives of BD probands were 12-21 year old offspring (81%) or siblings (9%) of a proband with BD, the majority of whom had BD, type I (89%). A small number (10%) were 2nd degree relatives of a BD proband in a family with multiple cases of BD. Control participants ("relatives of control probands") were identified through proband parents with no BD or other major mood disorder or psychosis (or psychiatric hospitalization) themselves or in their first-degree relatives; Relatives of control probands were ascertained through general medicine clinics, motor vehicle records and campus advertising. Relatives of control probands were excluded only for substantial cognitive impairment, but could have psychiatric diagnoses. Only data from baseline interviews are presented here. Procedures were approved by institutional review boards at the 5 collection sites. Informed consent was acquired after an explanation of the study with the participant and parent or guardian, if the participant was less than 18 years (<16 in Australia). Adolescents assented to participate in the study. Relatives of probands with and without BD were recruited between June 2006 and June 2011.

2.2 Diagnostic Procedures

DSM-IV-TR psychiatric diagnoses and ages of onset, including SUD diagnoses, were generated per best-estimate procedures using a modified Kiddie Schedule for Affective Disorders with adolescent and parent report (K-SADS-BD; http://www.bipolargenes.org/hrdownloads.html), followed by consensus diagnosis [26]. Diagnoses and age at onset determinations were made on the basis of consensus between two clinicians, including information from direct interview, medical records, and parent interview. Clinicians were blind to the group status of the subject. Interrater reliability was established by distributing identical diagnostic packages to multiple diagnosticians at the four US sites and collating the results. Each site had between 2-5 assessors (most had 2). Each US participant was assessed twice, while each Australian participant was assessed once.

Kappa for interrater reliability for major affective disorder diagnosis was 0.82; kappa for other disorder categories ranged from 0.70 to 0.85. The best estimate process also included consensus ratings of lifetime symptom severity for three categories: mood, anxiety, and behavior, using a seven-point scale. Weighted kappa for ratings for mood symptoms was 0.77, for behavioral symptoms, 0.70 and for anxiety symptoms 0.67. Between site variability was addressed by holding joint training exercises for interviewers, regular conference calls for staff from all sites to standardize assessment methods and to exchange diagnostic packets for reliability. Also, 4/5 sites recruited their own controls to reduce site variability in case-control comparisons.

DSM-IV-TR diagnoses of **substance abuse, dependence,** and **"not otherwise specified-related"** (NOS) were obtained for alcohol, cannabis, stimulants, sedatives, cocaine, opiates, PCP, hallucinogens, and solvents. An NOS SUD diagnosis was made if a participant

did not meet the requisite 1 or greater DSM-IV-TR criteria but instead reported 1 or more subthreshold symptoms on the K-SADS assessment. The NOS category was included because, in another study with a different sample, up to 40% of participants with substance problems not meeting full DSM criteria for abuse or dependence have been reported to show problematic use at 3-year follow up [32]. To increase statistical power, in addition to traditionally defined DSM-IV-TR SUDs variables, measures of substance abuse, dependence, nicotine use variables (see below) and NOS diagnoses were aggregated to create a **"problematic substance use" (PSU)** variable for all of the previously listed substances. Participants with nicotine use, any DSM-IV use disorder or NOS use disorder criteria were coded as having PSU, while participants with none of these were coded as not having PSU. Separate variables, termed "**problem use**" were also calculated *individually* for each drug of abuse (e.g., problem cannabis use).. Problem use was coded for an individual, if any lifetime abuse, dependence or NOS diagnoses were present. Thus, with the exception of tobacco, we focus on use that was associated with reports of impairment (i.e., problem use linked to DSM-IV criteria for SUDs), rather than just cases where use alone was identified. The tobacco section of this version of the K-SADS was not designed to diagnose DSM-IV nicotine dependence; therefore, the participants were not assessed for nicotine dependence. However, **"nicotine use"** was defined here as "ever smoked" or "ever chewed" or "currently use."

DSM-IV-TR diagnoses for most non-substance psychiatric disorders (Supp. Table 1) were aggregated into 3 main categories: mood (major depression, bipolar disorders, dysthymia, mood disorder not otherwise specified, cyclothymia), anxiety (generalized anxiety disorder, post-traumatic stress disorder, separation anxiety, specific phobias and anxiety disorders, not otherwise specified) and externalizing disorders (attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder). An individual was coded as belonging to any of these categories (e.g., mood) if they met lifetime criteria for any of the disorders listed (e.g.

major depression, bipolar disorders, dysthymia, mood disorder not otherwise specified, cyclothymia). As the number of relatives with BD I or II diagnoses was very low in this adolescent/young adult sample, all mood disorders were collapsed into the 'mood disorder' variable. An individual may have qualified for membership in one or more categories. Disorders that occurred in <3 participants in any category were not presented in tables. Disorders with <10 participants in both groups were not analyzed individually, but were included in aggregated variable categories.

2.3 Statistical Analyses

Demographic and clinical characteristics in this cross-sectional analysis of an ongoing longitudinal study were compared between relatives of BD probands (n=267) and relatives of control probands (n=149) using an independent samples t-test for quantitative variables or a chi-square test for categorical variables. All analyses were completed using SPSS 21.0 (IBM). A Bonferroni corrected alpha of 0.01 was used for the primary analysis (correcting for 4 between group comparisons: SUDs, PSU, nicotine use, alcohol use disorders), while exploratory analyses utilized an uncorrected alpha of 0.05. Age, sex and ethnicity were covariates. Adjustment for the presence of non-substance psychiatric disorders was implemented, when specified.

For our primary analysis, we were interested in differences in SUDs, sub-threshold disorders and nicotine use between relatives of probands with and without BD. Substance variables were compared across the two groups with binary logistic regression models. Generalized estimating equations (GEE) were used with the regression model to account for the correlation between siblings. All comparisons were adjusted for age, sex, and ethnicity. Subsequently, differences between relatives of probands with and without BD in prevalence of drug and alcohol use disorders, PSU and nicotine use were examined using logistic regression

with GEE while also controlling for comorbid psychopathology (i.e., mood, anxiety and externalizing disorders).

The existing literature has not adequately addressed factors (i.e., parental mental health, adolescent mental health, parental SUD) that may explain increased SUDs in BD offspring and relatives. While we are underpowered for a definitive analysis, logistic regression with GEE was used for an exploratory analysis to determine the relative contribution of each of the following independent variables to the odds of relative substance misuse/SUD vs. no substance misuse/SUD, across the entire sample: gender, ethnicity, parental BD diagnosis, parental SUD diagnosis, relative's mood disorder, externalizing and/or anxiety disorder diagnoses (presented in Table 2). The substance-related outcomes were any lifetime DSM-IV SUD (excluding nicotine and NOS), PSU and nicotine use. We also report the goodness of fit of each model as independent variables were individually added, using the Corrected Quasi Likelihood under Independence Model Criterion (lower QICC implies better fit; Supp. Table 3). In addition, we report a breakdown of the frequency of diagnosis with problematic substance use in relatives of probands with BD vs. relatives of control probands, with or without psychopathology (Supp. Table 2) and the proportions of participants with PSU and/or nicotine use, according to group and the presence of the various categories of comorbid psychopathology (Figure 1).

Finally, for another exploratory analysis, we used three different methods to examine differences in age of onset of SUDs between groups. First, using earliest age of onset of the disorders, Kaplan-Meier survival curves were calculated for PSU and nicotine use, and the log rank test P values were examined. Second, the age of onset of PSU, cannabis, alcohol and nicotine use were compared across groups using linear regression with GEE. Third, t tests compared age of onset of SUDs between groups in a subset of participants that included only the oldest sibling in each family (as t tests do not control for sibling relatedness). Finally, t tests comparing age of onset of mood/anxiety and SUDs in participants with both types of disorders

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were compared within groups (relatives of probands with BD vs. without BD), but only in the subset of participants who were not related to each other (because of lack of control for sibling relatedness with t tests). We also compared the average ages of onset of BD vs PSU and, separately, age of onset of unipolar depression vs. PSU, across the entire sample. We repeated that analysis for alcohol use disorders (AUDs).

3. Results

Relatives of BD probands (mean age = 16.8 years; ±2.9 S.D.) comprised 267 adolescent/young adult participants. This sample included subjects from 183 families, 121 with a single offspring, 44 with 2 offspring, 13 with 3, 2 with 4, 1 with 5, and 1 with 6. Males comprised 49.4% of this sample. There were 149 relatives of control probands (mean age= 17.4 years; ±2.9 S.D.) ascertained from 114 families, 87 with a single offspring, 21 with 2 offspring, 5 with 3, and 1 with 5. Males made up 53% of this population. The two groups differed on ethnicity (rates of European ancestry in Relatives of BD probands =89.1%; relatives of control probands = 61.7%; χ^2=78.4; p=0.001), but not in age (t=-1.94; p=0.053), sex (χ^2=0.491; p=0.484) or socioeconomic status (paternal years of education: Relatives of BD probands: mean = 15.8 (S.D. =2.6); relatives of control probands: mean = 16.9 (S.D.=3.4); t=1.96; p=0.42). Body mass index (Relatives of BD probands: mean=24.5 (S.D. =5.7); relatives of control probands: mean =22.7 (S.D.=4.5); t=1.9, p=0.06) and ever repeating a year of schooling (Relatives of BD probands: 6.8% relatives of control probands: 10.9%; χ^2=1.41; p=0.24) also did not differ significantly between groups.

3.1 SUD rates in relatives of BD probands vs. relatives of control probands

Comparisons in rates of SUDs/substance use between relatives of probands with and without BD revealed that SUDs (non-nicotine; p=0.01), nicotine use (p=0.004) and PSU (p=0.01) were observed more often in relatives of probands with BD while controlling for

demographics and sibling relatedness (Bonferroni corrected alpha = 0.01; Table 1). For nicotine use, effects for ethnicity (highest use in multi-ethnic participants, lowest use in those of African descent; p=0.001) and age (older > younger; p=0.001) were found, but no effects of gender (Table 1). Of note, alcohol use disorders did not differ between groups. Significant effects of age (older > younger; p=0.001) but not ethnicity or gender were found for PSU. There were no differences in rates of PSU (20.1% vs 16.9%; p=0.50) or substance abuse and dependence (9.0% vs. 5.9%; p=0.3) between the US and Australian sites. Rates of SUDs reported at each site are reported in Supplementary Table 4.

When the effects of mood, anxiety and externalizing disorders were controlled for, the prevalence of SUDs, PSU, nicotine use and alcohol use disorders were no different in relatives of probands with and without BD (all p>0.05; findings not presented in a table). Thus, non-psychiatrically ill relatives of probands with BD were no different than relatives of control probands in terms of SUDs/substance use.

3.2 Non-substance psychopathology in relatives of probands with and without BD

Relatives of probands with BD had higher rates of any BD disorder (p=0.030), social phobia (p=0.004), GAD (p=0.006) and enuresis (p=0.014), after accounting for demographics and sibling relatedness (Supp. eTable 1). Total mood (p=0.001) and total anxiety (p=0.001) disorder diagnoses were more prevalent in relatives of probands with BD, with a trend toward higher rates of externalizing disorders (p=0.053). Rates of mood, externalizing and anxiety disorders across the 5 recruitment sites are presented in Supplementary Table 4.

3.3 Relationship of offspring psychopathology with BD and SUD family history

Participants (%) with PSU and/or nicotine use, according to group and co-morbid mental health concerns, are displayed in Figure 1. Aggregated psychiatric diagnoses can be found in Supplemental Table 2.

The odds ratios for relative assignment to PSU, nicotine use, or SUD categories, after accounting for demographic factors, parental BD and SUD and offspring psychiatric disorders, are also presented in Table 2. Increased age significantly increased the odds of developing each substance variable, as would be expected (OR range: 1.48-1.5; p<0.0001). Ethnicity and gender did not impact the odds of diagnosis of any substance outcome, after accounting for all other variables in the model. Surprisingly, neither proband BD nor SUD increased the odds of relative drug use, after accounting for all other variables in the model (Table 2). Relative's own psychopathology, however, did increase the odds of development of drug use, as follows: (1) PSU was 2.8 times more likely (p=0.003) in youth with externalizing disorders. For all models, only the addition of demographic factors and the presence of offspring psychiatric disorders improved model fit (Supplemental Table 3). (2) Nicotine use was 3.17 times more likely (p=0.017) in youth with mood disorders and (3) DSM-IV drug and alcohol use disorders (SUDs) were 3.00 times more likely (p=0.020) in youth with mood disorders.

3.5 Age of onset for psychopathology and substance use

Kaplan-Meier survival curves demonstrated no significant differences in age of onset or course of PSU or nicotine use between groups (p=0.562 and 0.221 respectively; Supp. Figures 1 & 2). Similarly, neither whole sample regression findings (PSU: p=0.707, Cannabis: p=0.264, Alcohol: p=0.711, Nicotine: p=0.816), nor direct t-test comparisons of ages of onset of PSU (p=0.290) or nicotine use (p=0.447) differed between groups (Table 3). However, mood disorders occurred significantly earlier (p<0.007) in the BD relative (siblings removed; 13.1 years) vs. control (15.6 years) sample. In this subset, on average, the first onset of mood disorders occurred significantly earlier than the earliest onset of any SUD for both groups (13.1 years vs.15.3 years for the Relatives of BD probands , p<0.0001; 15.6 years vs. 16.1 years for relatives of control probands , p<0.0001; Figure 2). The age of PSU onset occurred around the same time as the onset of BD (10.4 vs. 12.4 years; p=0.49; n=7) and unipolar depression (14.3

vs. 14.8 years; p=0.40; n=51), across the entire sample. When we examined the onset of AUDs compared to types of mood disorders, we found that BD (12.4 vs. 16.8 years; p=0.001, n=9) and unipolar depression (14.8 vs. 16.8 years, p=0.0001; n= 43) occurred significantly earlier than the onset of AUDs.

4.   Discussion

This study compared SUD development in young adult and adolescent relatives of probands with and without BD. Our primary finding was that rates of SUDs and substance use, except alcohol, were higher in relatives of BD probands compared to relatives of control probands, with offspring psychopathology appearing to partly account for such group differences in SUDs. We also found similar rates of SUDs compared to other studies on the offspring of BD probands [29-31, 33], with a lifetime DSM-IV SUD rate of 28% in the relatives of BD probands. In sum, this analysis suggests that the presence of parental BD is significantly associated with adolescent SUDs, as hypothesized, although this effect appears to be influenced by the presence of other psychiatric diagnoses. Youth psychopathology was the most important contributor to the studied substance outcomes in this high-risk adolescent sample. When non-substance psychopathology in offspring was accounted for, parental BD or SUD was no longer a significant contributor to risk for SUDs. This suggests that substance use outcomes among those with a family history of BD or SUD are influenced by the presence of psychiatric diagnoses. This finding is consistent with results from the National Comorbidity Survey Replication Adolescent Supplement (NCS-A) demonstrating that youth psychopathology is the most important predictor of SUD development, across the general population [42]. Previous research in adolescents has demonstrated that individuals with a family history of BD have more than three times the prevalence of mood disorders than those without such a family history [26]. Therefore, we speculate that youth psychopathology, related to the family history of BD, is likely the primary risk factor for the development of an SUD in our sample [26, 43]. We

fail to find independent effects of gender or ethnicity in our analyses, perhaps because offspring/relative psychopathology primarily accounted for demographic effects.

Given that nicotine variables were included in the PSU variable and appeared to be contributing to the PSU findings, we examined these separately. Relatives of BD probands were more than twice as likely to have used nicotine than relatives of control probands. Nicotine users (who may have been using multiple other substances as well) accounted for the overall difference in prevalence of SUDs among relatives of BD probands. Heavier and earlier use of inhaled substances such as nicotine and cannabis may partly explain increased death and medical comorbidity rates [15] among individuals who may eventually develop BD or other major psychiatric disorders.

For our first exploratory analysis, we found that nicotine use and SUDs were related only to youth mood disorders, but not externalizing or anxiety disorders, a surprising finding given prior links of SUDs to childhood externalizing disorders [44, 45]. However, this finding parallels our previous report showing that externalizing disorders (and anxiety disorders) among relatives of BD probands were primarily seen in subjects with mood disorders [26]. PSU, however, was associated with youth externalizing disorders, consistent with a large, existing literature relating these two clinical presentations [46, 47]. Future longitudinal work with larger samples is needed to substantiate the specific psychopathology/SUD relationships.

We also examined the chronological order of psychiatric disorders in relation to SUDs, hypothesizing that youth who have already developed mood disorders will have developed these prior to substance misuse and SUDs. Notably, the retrospective report of the age of onset was earlier for mood disorders than PSU in both groups, but mood disorders occurred earlier in relatives of BD probands vs. relatives of control probands . While the availability of substances is relevant here, these findings also speak to the link between mood disorders and SUDs across

development. As described earlier, some studies have suggested that SUDs predict mood disorders [34-36] and others the reverse relationship [37-39], with a bidirectional relationship also possible. Preisig et al [48] distinguished unipolar from bipolar depression, finding that alcohol use disorders (AUDs) occurred after the onset of BD. In contrast, unipolar depression tended to occur after the onset of AUD. Less is known of this relationship with regard to other drugs of abuse. Ours is the first study to directly examine the order of emergence of mood symptoms vs. substance use/SUDs in a sample at high risk for BD; and we found that mood disorders appeared first. When we examined ages of onset of BD and unipolar depression vs. PSU separately, we found that the average age of onset of PSU was approximately the same as the age of both forms of depression. However, we found both types of mood disorders to occur before the onset of AUDs, replicating Preisig's findings in BD, but contradicting their findings in unipolar depression. We note our small sample size with available age of onset data, particularly in comparisons involving youth with BD.

Our last exploratory hypothesis was that relatives of BD probands would have an earlier age of onset of SUDs than relatives of control probands; however, our survival analysis showed no group differences. It is possible that our analysis was underpowered, given the relatively small number of individuals who became problematic substance users by late adolescence. It is also worth noting that substance use in early adolescence is closely linked to the opportunities to use drugs of abuse [49].

Several limitations are noted. First, substance diagnoses were assessed with both parent and youth self-reported data, but without biological drug screening. Second, the groups were not initially matched on ethnicity, however we adjusted for these differences in our analyses. Third, as the sample has not fully passed through the period of risk, additional SUDs would be expected to emerge over time. Fourth, given the exploratory nature of several of our research questions, we did not correct for multiple comparisons in those analyses. Fifth, we

acknowledge that the risk for SUDs conferred by non-offspring relatives (i.e., siblings, nieces) may differ from that conveyed by offspring and these findings may therefore differ from those of other samples comprised exclusively of offspring. Finally, we cannot exclude the possibility that factors other than those that were measured and reported (e.g., cognitive traits, peer group, stressful life events, severity of illness) may account for differences between the groups.

5. Conclusions

In summary, SUDs, PSU, SUDs and nicotine use were more common in relatives of probands with BD, with these differences largely accounted for by co-existing mood or externalizing disorders. These findings suggest that prevention and treatment of psychiatric disorders in adolescents may modify the course or prevent the development of SUDs, particularly in youth with a family history of BD.

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Figure 1. Problematic Substance Use Prevalence Percentage of individuals with problematic substance use (PSU; top) and nicotine use (bottom), divided relatives of bipolar disorder (BD) probands and relatives of control probands, according to categories of psychopathology: anxiety (n=108), mood (n=104), externalizing (n=83), none (n=279). Error bars represent the standard error.

Figure 2. Age of Onset Average age of onset of mood disorder vs. problematic substance use in relatives of bipolar disorder (BD) probands and relatives of control probands. *Difference at p<0.0001.

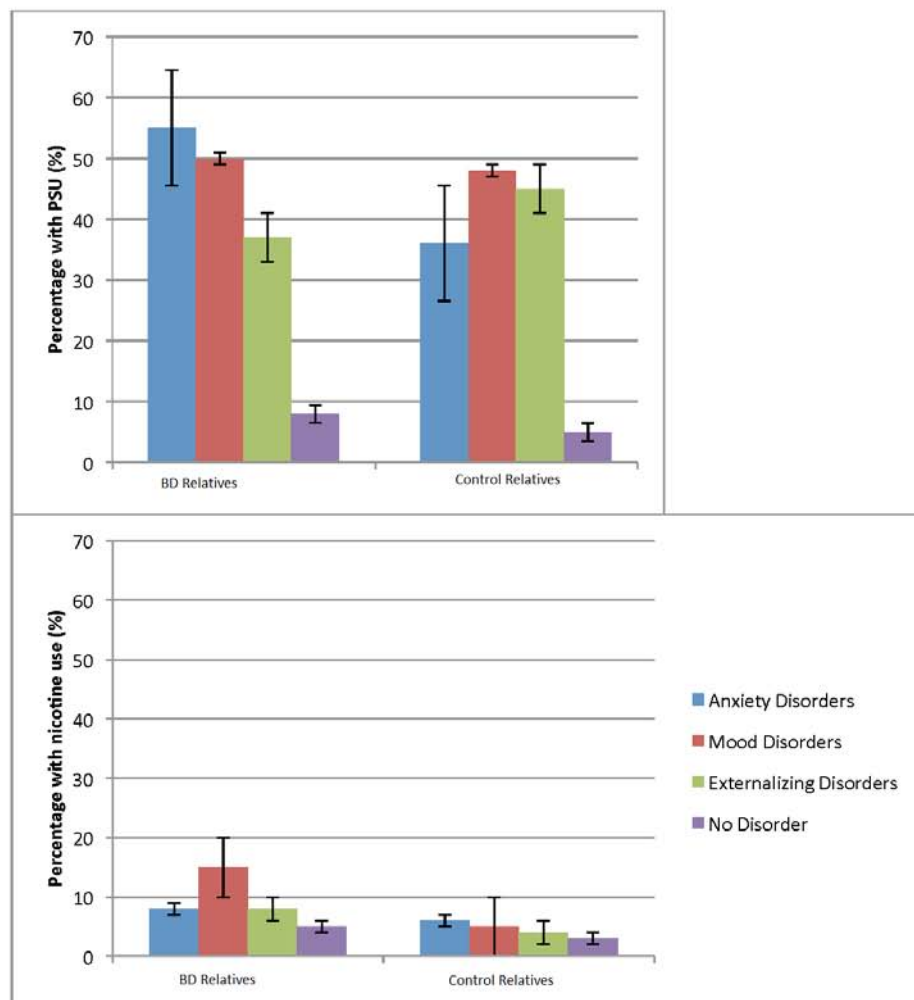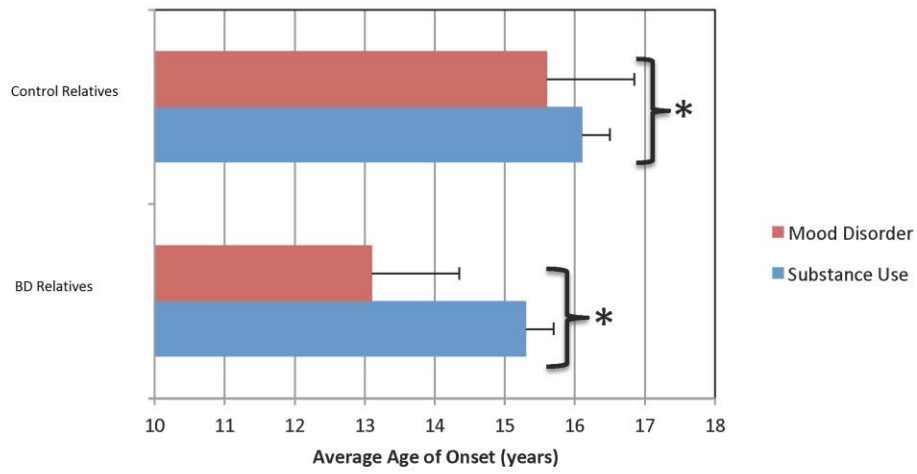Fig. 1

Fig. 2

	Relatives of BD n= 267	Relatives of Controls n= 149	Odds Ratio [95%CI]	P value
Any substance use disorder, excluding nicotine	77 28.8%	27 18.1%	1.8 [1.1-3.0]	0.011*
Alcohol abuse or dependence	20 7.5%	6 4.0%	1.0 [0.7-6.0]	0.208
Problematic substance use	88 33.0%	31 20.8%	2.0 [1.2-3.5]	0.01*
Cannabis problems	20 7.5%	6 4.0%	1.9 [0.75-4.9]	0.184
Stimulant problems	6 2.2%	4 2.7%	-	-
Sedative problems	3 1.1%	2 1.3%	-	-
Cocaine problems	6 2.2%	2 1.3%	-	-
Opiate problems	2 0.7%	1 0.7%	-	-
PCP problems	1 0.4%	1 0.7%	-	-
Hallucinogen problems	3 1.1%	1 0.7%	-	-
Solvent problems	4 1.5%	2 1.3%	-	-
Other drug problems	5 1.9%	4 2.7%	-	-
Ever smoked tobacco	63 23.6%	16 10.7%	2.6 [1.4-4.6]	0.005*
Ever chewed tobacco	15 5.6%	1 0.7%	8.8 [1.2-67.4]	0.014*
Current tobacco use	17 6.4%	2 1.3%	5.0 [1.1-21.9]	0.026*
Nicotine use	63 23.6%	16 10.7%	2.6 [1.4-4.6]	0.004*

Table 1 Substance use outcomes in relatives of BD probands vs. relatives of control probands.

Group differences were derived using GEE with logistic regression to address sibling relatedness, controlling for age, gender and ethnicity. Primary substance-related variables are bolded. Percentages represent the subset of the relative of BD proband or relative of control proband sample that met criteria for each substance variable. Odds ratios represent the odds a relative of a BD proband is more likely to meet criteria for a given substance outcome than a relative of a control proband. *p value of less than or equal to 0.05. BD=Bipolar Disorder

	Wald Chi-square	p-value	OR [95% CI]
Problematic Substance Use			
Presence of Parental Bipolar Disorder	1.66	0.198	2.42 [0.6-9.3]
Presence of Parental SUD	2.34	0.126	0.39 [0.1-1.3]
Presence of Relative Mood Disorder	3.78	0.052	1.17 [1.0-3.2]
Presence of Relative Externalizing Disorder	9.02	0.003*	2.80 [1.4-5.5]
Presence of Relative Anxiety Disorder	1.31	0.13	3.27 [.8-2.6]
Nicotine Use			
Presence of Parental Bipolar Disorder	0.02	0.889	0.92 [0.3-3.1]
Presence of Parental SUD	1.63	0.201	2.23 [0.7-7.7]
Presence of Relative Mood Disorder	5.67	0.017*	3.17 [1.2-8.2]
Presence of Relative Externalizing Disorder	0.54	0.538	1.43 [0.5-3.7]
Presence of Relative Anxiety Disorder	0.01	0.922	0.95 [0.4-2.5]
DSM-IV Drug and Alcohol Use Disorders (excluding nicotine)			
Presence of Parental Bipolar	0.08	0.779	1.19 [0.4-3.9]
Presence of Parental SUD	0.36	0.549	1.47 [0.4-5.1]
Presence of Relative Mood Disorder	5.40	0.020*	3.00 [1.2-7.6]
Presence of Relative Externalizing Disorder	0.38	0.537	1.35 [0.5-3.5]
Presence of Relative Anxiety Disorder	0.46	0.489	1.40 [0.5-3.7]

Table 2. Odds ratios of relatives of probands with and without BD for developing a lifetime diagnosis of problematic substance use, nicotine use or drug and alcohol use disorders (vs. reference category of no disorder). Results from logistic regression with GEE, accounting for demographics, proband bipolar disorder or substance use disorder (SUD) and relative's own psychiatric disorders. * p value of less than or equal to 0.05; Disorders included under mood disorders were: Bipolar (BD) type I, BD type II, BD NOS, schizoaffective disorder-bipolar or depressed type, single episode unipolar depression, unipolar recurrent depression, adjustment disorder with depressed mood, depressive disorder NOS, mood disorder secondary to a medical condition, dysthymic disorder, and cyclothymic disorder. Anxiety disorders included: obsessive compulsive disorder (OCD), panic disorder with and without agoraphobia, social anxiety disorder, specific phobia, generalized anxiety disorder (GAD), separation anxiety disorder, acute stress disorder, adjustment disorder with anxious mood, and PTSD. Externalizing disorders were defined as conduct disorder, oppositional defiant disorder (ODD) and ADHD (all subtypes).
Abbreviations: SUD=substance use disorder; OR=odds ratio; CI=confidence interval; BD=bipolar disorder

	Excluding siblings			
	Relatives of BD	**Relatives of Controls**	**t**	**P value**
AOO SUD, yrs (SD)	15.33 (2.05)	16.07 (1.88)	1.082	0.290
AOO NU, yrs (SD)	13.90 (1.51)	15.10 (2.15)	0.877	0.447

Table 3. Independent samples t-test comparison of the average age of onset (AAO) of first lifetime substance use disorder (SUD) diagnosis or nicotine use (NU) between relatives of BD probands and relatives of control probands, in the sample excluding siblings. (BD=Bipolar Disorder)