Published in final edited form as:
Am J Addict. 2014 September ; 23(5): 440–446. doi:10.1111/j.1521-0391.2014.12125.x.

Parental History of Substance Use Disorders (SUD) and SUD in Offspring: A Controlled Family Study of Bipolar Disorder

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Abstract

Background and Objectives—Adolescents with bipolar disorder (BPD) have been previously shown to be at very high risk for substance use disorders (SUD). We now examine the influence of a parental history of substance use disorders on SUD risk in offspring with and without BPD.

Methods—We studied 190 parents ascertained through 104 adolescent BPD probands and 189 parents ascertained through 98 control probands using structured interviews. We compared the prevalence of SUD using logistic regression.

Results—While adjusting for BPD in our combined sample, probands with a parental history of SUD were more likely to have an alcohol use disorder compared to probands without a parental history. Probands with a parental history of SUD were not more likely to have a drug use disorder or overall SUD compared to probands without a parental history. BPD in the offspring did not pose any additional risk between parental history of SUD and offspring SUD.

Conclusion—Alcohol use disorders were more common in the offspring of parents with a SUD history compared to parents without SUD and the risk was not influenced by offspring BPD.

Scientific Significance—Clarifying the mechanisms linking parental SUD to offspring SUD, particularly in children and adolescents with BPD, would help clinicians to educate and monitor

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Declaration of Interest:

Dr. Timothy Wilens in the past 3 years received grant support from the following sources: National Institute on Drug Abuse (NIDA) and Shire Laboratories Inc; and has been a consultant for Eli Lilly, Euthymics, Shire, Theravance, and Tris.

Dr. Amy Yule received grant support from the American Academy of Child and Adolescent Psychiatry Pilot Research Award for Junior Faculty supported by Lilly USA, LLC.

In the past year, Dr. Faraone received consulting income and/or research support from Shire, Otsuka and Alcobra and research support from the National Institutes of Health (NIH). He is also on the Clinical Advisory Board for Akili Interactive Labs. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health and Oxford University Press: Schizophrenia: The Facts.

MaryKate Martelon, MPH and Courtney Zulauf, BA report no conflicts of interest.

high-risk families, which would facilitate strategies to mitigate risks associated with parental substance abuse.

Introduction

Studies of adults indicate an important relationship between bipolar disorder (BPD) and substance use disorders (SUD: including drug and alcohol abuse or dependence)[1,2]. Data has indicated that childhood or early onset BPD is particularly related to a high risk for SUD[3]. A growing body of literature also shows a strong association between SUD and BPD in adolescents[4–6]. For example, Goldstein et al.[5] in a systematic review showed that adolescent-onset BPD had a higher risk for SUD than adult-onset BPD.

Likewise, in a series of studies we have demonstrated that BPD in adolescence is a major risk factor for SUD independent of conduct disorder[4]. Adolescents with BPD have been shown to be five times more likely to manifest a SUD compared to non-mood disordered youth[4]. High SUD rates are constantly reported in samples of adolescents and young adults with BPD with environmental and psychological issues such as self-medication shown to play a role[7,8]. However, the influence of parental SUD in samples of adolescents with BPD remains unclear. For instance, does a parental history of SUD further increase the risk for early-onset SUD in adolescents with BPD?

Family, twin, and adoption studies indicate that genes and environment have etiologic roles in the development of alcohol and drug use disorders[9–13]. However, the family-study literature linking BPD and SUD has produced conflicting findings[14]. Several adult-based studies have shown a familial association between BPD and SUD[15,16], raising the question that their comorbidity is caused by genes or familial environmental etiologic factors. Conversely, Winokur et al.[14] found a higher than expected rate of alcoholism in BPD, but noted that BPD plus alcoholism was not accounted for by familial alcoholism.

There has been a paucity of family studies of BPD and SUD in children. We have previously shown an increased risk for BPD and SUD in the first-degree relatives of BPD adolescents, and that BPD and SUD were transmitted together in families[17]. These findings suggested that the two disorders share familial etiologic risk factors. We also reported that the parents of adolescents with BPD were more likely than relatives of controls to have SUD and found a higher risk for SUD in parents with BPD than in those without BPD[17]. Despite this work, some basic questions remain unanswered. For instance, it remains unclear if a parent with SUD increases the likelihood of SUD in their offspring, particularly in early-onset BPD. If parental SUD increases the risk for SUD in BPD youth, for instance, how much greater risk does parental history of SUD have on SUD in these vulnerable youth?

An improved understanding of familial risk factors for SUD would have clinical, scientific, and public health implications. Clarifying the mechanisms linking parental SUD to offspring SUD, particularly in children and adolescents with BPD, would help clinicians to educate and monitor high-risk families, which would facilitate strategies to mitigate risks associated with parental substance abuse for “vulnerable” individuals. Thus, in the present work, we sought to examine the impact of parental SUD history on a combined sample of adolescents

with and without BPD from an ongoing, longitudinal, case controlled, family-based study of BPD[4]. Based on the literature, we hypothesized that parental SUD would increase their offspring's risk for SUD and that these findings would be accentuated among 'vulnerable' individuals with BPD.

Methods

Subjects

The current analysis is based on our assessments of our controlled, longitudinal, family-based study of BPD adolescents[4]. The methods of the study are described in our preliminary report on this sample[18]. The age range of subjects was directed at adolescents but included youth 10–18 years of age. Subjects were recruited through advertisements, referrals to our program (BPD only), internet postings, and postings within the Partners HealthCare system (including Massachusetts General Hospital, McLean, and Brigham Women's Hospital). No ethnic or racial groups were excluded.

Potential subjects were excluded if they had been adopted, or if their nuclear family was not available to participate in the study. We excluded youth if they had major sensorimotor handicaps (paralysis, deafness, blindness), autism, inadequate command of the English language, or a Full Scale IQ less than 70. Parents provided written informed consent for their children and children provided written assent to participate. The institutional review board at Massachusetts General Hospital approved the study and a federal release of confidentiality was obtained.

As described previously[18], a two-stage ascertainment procedure selected subjects. For BPD probands, the first stage was a systematic phone screening. This first stage confirmed the diagnosis of BPD by screening all children using a telephone questionnaire with their mother (or primary caregiver). The questionnaire asked about symptoms of BPD and questions regarding study exclusion criteria. The second stage was the psychiatric interview as described below. Only subjects who received a positive diagnosis at both stages were included in the sample. We also screened potential controls without mood disorder in two stages. We eliminated any mood disorder from our ascertainment of controls secondary to concerns of "manic switching" from dysthymia or unipolar depression to BPD[19–21]. First, the control mothers responded to the telephone questionnaire. Eligible controls meeting study entry criteria were recruited for the study and received the diagnostic assessment with a semi-structured interview. Only subjects classified as not having any mood disorder at both stages were included in the control group.

Assessments

All diagnostic assessments of probands and their first-degree relatives were made using DSM-IV-based structured interviews by raters with bachelor's degrees in psychology that had been trained and supervised by senior investigators. Raters were blind to the ascertainment status of the probands. Psychiatric assessments relied on the Schedule for Affective Disorder and Schizophrenia for Children (Kiddie SADS-E; Epidemiologic Version)[22] and were based on independent interviews with mothers and direct interviews of

probands. Subjects, including first-degree family members (parents), aged 18 years and older, received psychiatric diagnoses in the semi-structured Clinical Interview for the DSM-IV (SCID)[23] (supplemented with modules from the Schedule for Affective Disorder and Schizophrenia for Children (K-SADS-E)[24] to assess childhood diagnoses). For every diagnosis, we gathered data regarding the ages at onset and offset of full DSM-IV criteria and treatment history. The onset of psychopathology was defined as *child onset* if it occurred before the age of 13 years and *adolescent onset* if it occurred at age 13 or beyond.

Substance use disorders (SUD) in our analyses included any alcohol or drug (excluding nicotine) abuse or dependence. SUD was diagnosed based on DSM-IV criteria using the Kiddie SADS-E. To be given a diagnosis of drug or alcohol abuse, the subject must have met *DSM-IV* criteria without meeting criteria for dependence. All subjects who had clinically meaningful subthreshold alcohol or drug dependence were included in the abuse category. Rates of disorders reported are lifetime prevalence.

All cases were presented to a committee composed of board-certified child psychiatrists and psychologists. Diagnoses presented for review were considered positive only if the diagnosis would be considered clinically meaningful. By clinically meaningful, we mean that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. Because self-report of psychopathology by juvenile probands may be discrepant form their parents' reports, and data suggest the utility of report from both youth and parent for BPD[25–27], the diagnostic board assessed the information provided by each respondent based on interviewer notes, the responses to the semi-structured interview, and a review of the audiotaped interview. Using these data, the rule for combining discrepant reports was to use the most severe diagnosis from any source unless the diagnosticians suspected that the source was unreliable. In addition, all cases of suspected substance use were reviewed with a child and adult psychiatrist with addiction credentials.

To assess the reliability of our diagnostic procedures, we computed kappa coefficients of agreement by having three experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 independent assessments from interviews of children and adults from the current study and other ongoing family studies in our laboratory, the median kappa coefficeient was 0.98. Kappa coefficients for individual diagnoses included; major depression (MDD; 1.0), mania (0.95), attention deficit hyperactivity disorder (ADHD; 0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; 0.90), antisocial personality disorder (ASPD; 0.80), and SUD (1.0).

Data Analysis

We evaluated whether a parental history of SUD increased the risk for SUD in offspring and if this risk could be accounted for by BPD in the offspring. *A priori*, one family was removed from analyses because both parents lacked diagnostic information. As a result, our analyses were conducted using 202 probands. In these analyses, we examined probands with and without a family (parental) history of SUD.

We compared demographic factors between groups using t tests for continuous outcomes, the Wilcoxon Rank Sum test for SES, and the Pearson χ^2 tests for binary outcomes. We used logistic regression to assess the effect of parental SUD history on offspring SUD.

Due to the nature of this sample (BPD vs. Controls) and because BPD has been linked previously with SUD[4,5], we incorporated offspring BPD into our statistical models. Therefore, we examined the association between family SUD history and offspring SUD in three different analyses. We first tested the interaction between offspring BPD and parental SUD history on offspring SUD. We then examined the independent effects of BPD and parental SUD history on offspring SUD. Lastly, we examined the effects of both offspring BPD and parental SUD on offspring SUD when both were included in the model (the conditional effects).

An alpha-level of 0.05 was used to assert statistical significance; all statistical tests are two-tailed. We calculated all statistics using STATA 12.0.

Results

As previously reported, the mean age of our sample was: 13.6 ± 2.8 years[4]. We found no significant differences between participants with and without parental SUD in age, sex, socioeconomic status, intactness (divorced/separated versus married) of parents, ADHD status, and conduct disorder status (Table 1). We did, however, find a significant difference in BPD status; probands with a parental history of SUD were more likely to have BPD than probands without a parental history of SUD ($\chi^2(2)=8.4$, p=0.004). As shown in Table 2, we found that probands with parental SUD were more likely to have alcohol use disorders, substance use disorders, and any SUD than probands without parental SUD (Table 2, all p values <0.05).

In models predicting offspring SUD from offspring BPD, parental SUD and their interaction, we found no significant interactions. This indicates that the effect of parental SUD on offspring SUD is not moderated by offspring BPD (Table 3). Similar to our previous report[4], overall analysis revealed offspring BPD was a significant predictor of offspring SUD (Table 3).

Independent Effects of Parental SUD History on Offspring SUD

Any Parental SUD History and Offspring SUD—Any parental SUD was significantly related to the endorsement of offspring SUD (Table 3, OR: 2.8; 95% CI: 1.1, 6.7; p=0.03), alcohol use disorders (OR: 5.2, 95% CI: 1.5, 18.1; p=0.01), and drug use disorders (OR: 3.00; 95% CI: 1.1, 8.3; p=0.04). We found a significant association between parental alcohol use disorders and offspring alcohol use disorders (OR: 4.3; 95% CI: 1.5, 11.9; p=0.006). We did not find a significant association between parental drug use disorders and offspring drug use disorders (OR: 2.2; 95% CI: 0.9, 5.0; p=0.07).

Any Maternal SUD History and Offspring SUD—Any maternal SUD was significantly related to the endorsement of offspring alcohol use disorders (OR: 2.4; 95% CI: 1.0; 5.7; p=0.04). We did not find significant associations between maternal SUD and

offspring SUD (OR: 1.9; 95% CI: 0.91, 4.1; p=0.09) or between maternal SUD and offspring drug use disorders (OR: 2; 95% CI: 0.9, 4.6; p=0.1). For individual disorders, we did not find a significant association between maternal alcohol use disorders and offspring alcohol use disorders (OR: 2.1; 95% CI: 0.8, 5.0; p=0.1) or between maternal drug use disorders and offspring drug use disorders (OR: 1.5; 95% CI: 0.6, 3.9; p=0.4).

Any Paternal SUD History and Offspring SUD—Any paternal SUD was significantly related to the endorsement of offspring SUD (OR: 3.2; 95% CI: 1.2, 8.4; p=0.02), any offspring alcohol use disorders (OR: 4.9, 95% CI: 1.4, 17.8; p=0.02), and any offspring drug use disorders (OR: 3.6; 95% CI: 1.2, 11.5; p=0.03). For individual disorders, we found significant associations between paternal alcohol use disorders and offspring alcohol use disorders (OR: 3.4; 95% CI: 1.2, 10.2; p=0.03). For paternal drug use disorders and offspring drug use disorders we did not find a significant association (OR: 2.8; 95% CI: 1.1, 7.5; p=0.4).

The Conditional Effects of Parental SUD History and Offspring BPD on Offspring SUD

Any Parental SUD History, Parental BPD, Offspring BPD, and Offspring SUD—In order to examine the effects of offspring BPD separate from the potential effects of parental SUD, we included both in the model. We report the effects of offspring BPD adjusting for parental SUD and the effects of parental SUD adjusting for offspring BPD. In these analyses, we also adjusted for parental BPD to control for the potential effects that this factor may have on offspring SUD. When we included offspring BPD, parental BPD, and parental SUD history in the model, we found a significant effect of offspring BPD and parental SUD for any offspring alcohol use disorders (Table 3, parental SUD: OR: 3.9; 95% CI: 1.1, 14.3; p=0.04 and offspring BPD: OR: 6.4; 95% CI: 2.0, 20.5; p=0.002). For any offspring SUD and any offspring drug use disorders, family history lost significance (family history: OR: 2.3; 95% CI: 0.9, 5.9; p=0.1 and OR: 2.4; 95% CI: 0.8, 7.1; p=0.1, respectively), while offspring BPD remained significant (OR: 4.8; 95% CI: 2.0, 11.6; p=0.001 and OR: 3.6; 95% CI: 1.4, 9.5; p=0.01).

When we looked at parental alcohol use disorders and offspring alcohol use disorders, offspring BPD (OR: 6.2; 95% CI: 2.0, 19.8; p=0.002) remained significant, while parental alcohol use disorders lost significance (OR: 2.9; 95% CI: 0.96, 8.7; p=0.06). When we looked at parental drug use disorders and offspring drug use disorders, parental drug use history remained not significant (OR: 2.0; 95% CI: 0.8, 4.9; p=0.1), while offspring BPD remained significant (OR: 4.0; 95% CI: 1.5, 10.5; p=0.005).

Any Maternal SUD History, Maternal BPD, Offspring BPD, and Offspring SUD—When we included both offspring BPD and maternal SUD history in the model, the association between maternal SUD history and offspring alcohol use disorders lost significance (OR: 2.3; 95% CI: 0.9, 5.7; p=0.1). The associations between maternal SUD history and any SUD (OR: 1.9; 95% CI: 0.8, 4.2; p=0.3) and any drug use disorders remained not significant (OR: 1.9; 95% CI: 0.8, 4.5; p=0.2). BPD however remained significant for any offspring SUD (OR: 5.5; 95% CI: 2.3, 13.1; p<0.001), any offspring

alcohol use disorders (OR: 8.2, 95% CI: 2.7, 25.3; p<0.001), and any drug use disorders (OR: 4.3; 95% CI: 1.8, 11.0; p=0.002).

When we looked at maternal alcohol use disorders and offspring alcohol use disorders, maternal alcohol use disorders remained not significant (OR: 1.8; 95% CI: 0.7, 4.7; p=0.2), while BPD remained significant (OR: 8.2; 95% CI: 2.7, 25.4; p<0.001). We found similar results between maternal drug use and offspring drug use (maternal history: OR: 1.4; 95% CI: 0.5, 3.6; p=0.5; BPD: OR: 4.5; 95% CI: 1.8, 11.3; p=0.002).

Any Paternal SUD History, Offspring BPD, and Offspring SUD—When we included offspring BPD, paternal BPD, and paternal SUD history in the model, all associations lost significance. We did not find a significant association for paternal SUD history and any SUD (OR: 2.1; 95% CI: 0.7, 6.0; p=0.2), any alcohol use disorders (OR: 2.8; 95% CI: 0.7, 10.8; p=0.14), and any drug use disorders (OR: 2.6; 95% CI: 0.8, 8.8; p=0.13). BPD remained significant for any offspring SUD (OR: 2.9; 95% CI: 1.1, 7.5; p=0.03), and any offspring alcohol use disorders (OR: 4.1, 95% CI: 1.2, 13.8; p=0.03). For any paternal drug use disorder and offspring drug use disorders, BPD lost significance (OR: 1.9; 95% CI: 0.7, 5.6; p=0.13).

When we looked at paternal alcohol use disorders and offspring alcohol use disorders, paternal alcohol use disorders lost significance (OR: 1.6; 95% CI: 0.5, 5.5; p=0.4), while BPD remained significant (OR: 4.3; 95% CI: 1.3, 14.8; p=0.02). For paternal drug use and offspring drug use both paternal drug use history and BPD lost significance (paternal history: OR: 2.2; 95% CI: 0.79, 6.4; p=0.13; BPD: OR: 2.2; 95% CI: 0.76, 6.3; p=0.15).

Discussion

These analyses support our hypothesis showing that parental SUD would increase their offspring's risk for SUD. These findings were strongest for predicting offspring alcohol use from parental alcohol use. We did not find significant effects of parental drug use on offspring drug use.

Our current findings indicating an overall increase in SUD in offspring of parents with SUD are consistent with a large body of literature[10,28,29]. The current data extends these findings into high-risk adolescents. Heightened risk for early-onset SUD has been shown to be associated with family history of SUD[10,30]. For instance, Hill et al.[31] using a prospective longitudinal design of offspring from three-generation alcohol dependent families, showed that parental alcohol and drug dependence significantly increased the odds that offspring would experience alcohol and drug use disorders; as well as other psychopathology during adolescence.

Surprisingly, we found no interaction between parental SUD and offspring BPD in predicting offspring SUD. In other words, the risk for offspring SUD imparted by parental SUD is the same for offspring with and without BPD. It also means that the risk for offspring SUD imparted by offspring BPD is the same for offspring who do and do not have a parental history of SUD. This finding is of particular interest given that it was speculated that, due to deficits in self-regulation of mood[8,32], youth with BPD would moderate that

risk. Although the lack of interactions show that parental SUD does not moderate the risk for SUD imparted by BPD, our conditional analyses show that, for alcohol use, there are additive effects of parental SUD and offspring BPD. This means that having a parent with SUD increases the offspring's risk for an alcohol use disorder, which is already increased if that offspring also has BPD.

The clinical implications of this data are that a parental history of SUD increases the overall risk for an alcohol use disorder in the offspring, and that risk is already noted in adolescence. In adolescents with BPD, having a parental history of SUD does not preferentially increase the risk for developing an SUD compared to adolescents without BPD. This is important as BPD has been shown to be a potent risk factor for SUD in adolescents[4,5], and these data are reassuring in that parental SUD does not further increase this risk.

The findings in the current study need to be tempered against some methodological limitations. Because the sample was mostly Caucasian and ascertained from outpatient clinical referrals and advertisements, it may not generalize to community or minority samples. Although our sample was large, the subgroup of adolescents in the control group and those with SUD was relatively small limiting our statistical power. Furthermore, we had a relatively young overall age of participants with the average age of the sample being just over 13 years of age. Probands in our study were not through the full risk of SUD, probably producing an under-representation of the full SUD risk and may only be applicable for early-onset SUD. Despite the use of semi-structured diagnostic interviews in this study, the diagnostic criteria for juvenile BPD remain controversial[33]. While collecting data prospectively as part of a family-study of BPD, our assessments relied on retrospective reporting of past symptoms and impairment to detail BPD, SUD, and other psychiatric comorbidity. We reported on results derived from psychiatric interviews for psychopathology and SUD. Subjects meeting full DSM criteria for abuse or dependence by either parent or youth report during structured interview and not by urine toxicology screens or autonomous self-reports defined SUD categorically. Using these definitions, use and misuse of substances as well as subthreshold psychopathology or substance abuse was not captured. Further studies should integrate parent report, youth self-report, youth report during a structured interview, as well as urine toxicology testing to more accurately identify substance use both categorically and dimensionally in youth[34]. Further studies should also examine whether there are "critical periods" of development at which youth are at heightened risk for the development of SUD if exposed to a parent with active SUD.

Despite these limitations, the current data derived from an ongoing, longitudinal study of BPD add to the clinical literature by further demonstrating that parental SUD places adolescent offspring at a heightened risk of developing an alcohol use disorder. However, having juvenile BPD does not preferentially increase the risk associated with a parental history of SUD.

Acknowledgments

Research was supported by the NIH R01 DA12945 awarded to Dr. Timothy Wilens.

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Table 1

Demographics and Clinical Features of Subjects from the Ongoing, Controlled, Longitudinal, Family-Based Study (N=202)

	No Parental SUD History (N=79)	Parental SUD History (N=123)	Test statistic, p-value
Age	13.8 ± 2.2	13.6 ± 2.4	t=0.7, p=0.5
Socioeconomic Status (SES)	1.6 ± 1.0	1.9 ± 1.1	z=−1.8, p=0.7
	N(%)	N(%)	
Sex (% male)	46 (58)	86 (70)	$\chi^2(2)=2.9$, p=0.09
Intactness (% married)	49 (62)	62 (50)	$\chi^2(2)=2.6$, p=0.1
Bipolar Disorder	**25 (32)**	**65 (52)**	**$\chi^2(2)=8.4$, p=0.004****
Attention Deficit/Hyperactivity Disorder	31 (39)	61 (50)	$\chi^2(2)=2.1$, p=0.1
Conduct Disorder	19 (24)	47 (38)	$\chi^2(2)=4.4$, p=0.04*

* $p < 0.05$

** $p < 0.005$

Table 2

Substance Use Disorders among Offspring (N=202)

	No Parental SUD History (N=79)	Parental SUD History (N=123)	Test statistic, p-value
	N (%)	N (%)	
Any Alcohol Use Disorder	3 (4)	21 (17)	$\chi^2(2)=8.1$, p=0.004**
Any Drug Use Disorder	5 (6)	21 (17)	$\chi^2(2)=4.8$; p=0.03*
Any Substance Use Disorder	7 (9)	26 (21)	$\chi^2(2)=5.3$, p=0.02*

* $p < 0.05$

** $p < 0.005$

Table 3

Effects of Parental History and Offspring BPD on Offspring SUD (N=202)

		Independent Effects		Conditional Effects	
	Interaction Effect	**Parental History**	**BPD**	**Parental History**	**BPD**
Parental SUD					
Offspring Alcohol Use	p=0.8	**p=0.01**	**p<0.001**	**p=0.04**	**p=0.002**
Offspring Drug Use	p=1.0	**p=0.04**	**p=0.002**	p=0.1	**p=0.01**
Offspring SUD	p=0.6	**p=0.03**	**p<0.001**	p=0.1	**p=0.001**
Parental Alcohol Use					
Offspring Alcohol Use	p=0.4	**p=0.006**	*	p=0.06	**p=0.002**
Parental Drug Use					
Offspring Drug Use	p=0.6	p=0.07	*	p=0.1	**p=0.005**
Maternal SUD					
Any Alcohol Use	p=0.8	**p=0.04**	*	p=0.1	**p<0.001**
Any Drug Use	p=0.8	p=0.1	*	p=0.2	**p=0.002**
Any SUD	p=0.4	p=0.09	*	p=0.3	**p<0.001**
Maternal Alcohol Use					
Offspring Alcohol Use	p=0.9	p=0.1	*	p=0.2	**p<0.001**
Maternal Drug Use					
Offspring Drug Use	p=0.7	p=0.4	*	p=0.5	**p=0.002**
Paternal SUD					
Any Alcohol Use	p=0.8	**p=0.02**	*	p=0.14	**p=0.03**
Any Drug Use	p=0.7	**p=0.03**	*	p=0.13	p=0.2
Any SUD	p=0.3	**p=0.02**	*	p=0.2	**p=0.03**
Paternal Alcohol Use					
Offspring Alcohol Use	p=1.0	**p=0.03**	*	p=0.4	**p=0.02**
Paternal Drug Use					
Offspring Drug Use	p=0.4	p=0.4	*	p=0.13	p=0.15

* The association between family SUD history and offspring SUD was studied in three different ways: the interaction of offspring BPD and parental SUD history, the independent effects of parental SUD history and offspring BPD (for this analysis, the relationship between offspring BPD and offspring SUD did not pertain to parental SUD, therefore, it was only studied once); the conditional effects of both offspring BPD and parental SUD history (both were in the model) on offspring SUD.