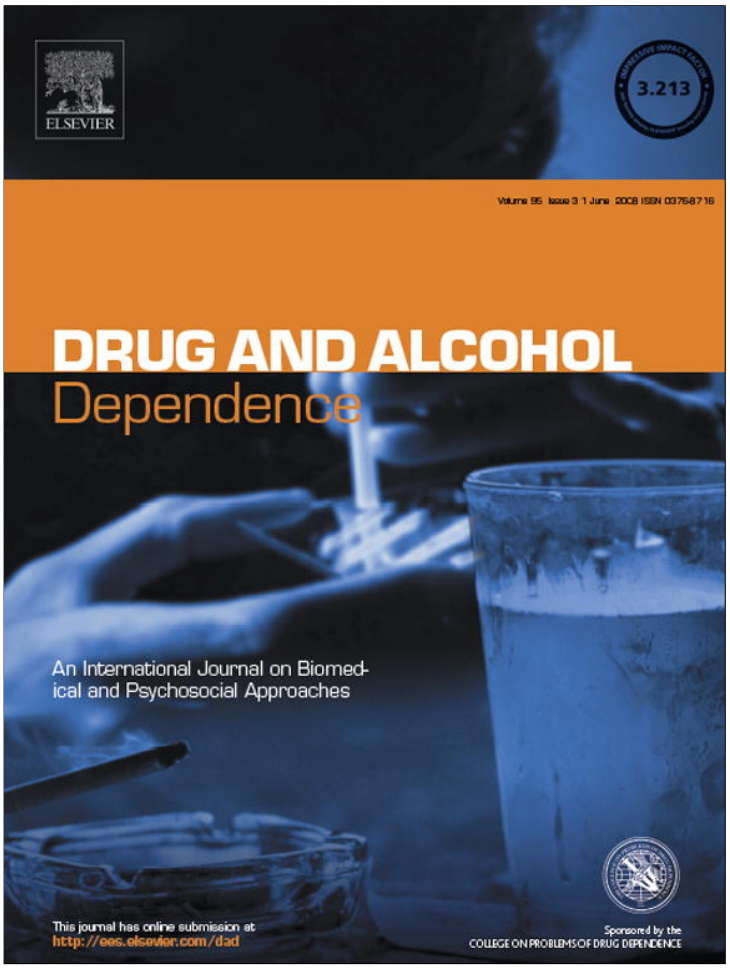

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Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: A controlled study☆

Timothy E. Wilens[a,b,*], Joseph Biederman[a,b], Joel J. Adamson[a], Aude Henin[a], Stephanie Sgambati[a], Martin Gignac[c], Robert Sawtelle[a], Alison Santry[a], Michael C. Monuteaux[a,b]

[a] *Massachusetts General Hospital, Pediatric Psychopharmacology Unit, Boston, MA 02114, USA*
[b] *Harvard Medical School, Department of Psychiatry, Cambridge, MA 02115, USA*
[c] *Institute Philippe Pinel, Université de Montréal, Montréal, Qc H3C 3J7, Canada*

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Abstract

Although previous work suggests that juvenile onset bipolar disorder increases risk for substance use disorders and cigarette smoking, the literature on the subject is limited. We evaluated the association of risk for substance use disorders and cigarette smoking with bipolar disorder in adolescents in a case–control study of adolescents with bipolar disorder ($n = 105$, age 13.6 ± 2.5 years [mean]; 70% male) and without bipolar disorder ("controls"; $n = 98$, age 13.7 ± 2.1 years; 60% male). Rates of substance use and other disorders were assessed with structured interviews (KSADS-E for subjects younger than 18, SCID for 18-year-old subjects). Bipolar disorder was associated with a significant age-adjusted risk for any substance use disorder (hazard ratio[95% confidence interval] = 8.68[3.02 25.0], $\chi^2 = 16.06$, $p < 0.001$, df = 1), alcohol abuse (7.66 [2.20 26.7], $\chi^2 = 10.2$, $p = 0.001$, df = 1), drug abuse (18.5 [2.46 139.10], $\chi^2 = 8.03$, $p = 0.005$, df = 1) and dependence (12.1 [1.54 95.50], $\chi^2 = 5.61$, $p = 0.02$, df = 1), and cigarette smoking (12.3 [2.83 53.69], $\chi^2 = 11.2$, $p < 0.001$, df = 1), independently of attention deficit/hyperactivity disorder, multiple anxiety, and conduct disorder (CD). The primary predictor of substance use disorders in bipolar youth was older age (BPD − SUD versus BPD + SUD, logistic regression: $\chi^2 = 89.37$, $p < 0.001$). Adolescent bipolar disorder is a significant risk factor for substance use disorders and cigarette smoking, independent of psychiatric comorbidity. Clinicians should carefully screen adolescents with bipolar disorder for substance and cigarette use.

Keywords: Adolescent; Mania; Bipolar disorder; Substance abuse

1. Introduction

A growing literature documents that many seriously disturbed children are afflicted with bipolar disorder (BPD) (Birmaher and Axelson, 2006). Juvenile BPD in its various forms affects from 1 to 4% of pediatric groups (Lewinsohn et al., 1995) with up to one-fifth of psychiatrically referred children and adolescent psychiatric outpatients manifesting BPD (Weller et al., 1986; Wozniak et al., 1995). The literature also documents the concurrent, face, and predictive validity of BPD in childhood (Biederman et al., 2003). Recent work suggests that pediatric onset BPD may represent a unique developmental type of BPD characterized by a chronic course, mixed presentations, and high levels of severe irritability (Carlson, 1984; Wozniak et al., 1995; Biederman et al., 2003; Geller et al., 2004; Axelson et al., 2006; Birmaher and Axelson, 2006; Birmaher et al., 2006; Geller et al., 2006). For instance, two ongoing multisite, National Institute of Mental Health (NIMH) funded studies show that children and adolescents with BPD maintain a functionally impaired status characterized by a highly relapsing and remitting course (Birmaher, 2004; Geller et al., 2004; Birmaher et al., 2006; Geller et al., 2006). BPD is a substantial cause of psychiatric morbidity among youth including high rates of hospitalization,

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* Corresponding author at: Massachusetts General Hospital, Pediatric Psychopharmacology Unit, 32 Fruit Street, YAW 6A, Boston, MA 02114, USA. Tel.: +1 617 726 1731; fax: +1 617 724 3742.
E-mail address: twilens@partners.org (T.E. Wilens).

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disruption of the family environment, and psychosocial disability (Akiskal et al., 1985; Wozniak et al., 1993; Weller et al., 1995; West et al., 1996; Geller et al., 2002a,b; Birmaher and Axelson, 2006).

Systematic studies of BPD children have found high rates of attention deficit/hyperactivity disorder (ADHD), anxiety disorders (panic, and obsessive-compulsive disorder) (Strober et al., 1998; Geller et al., 1995; Wozniak et al., 1995; West et al., 1996; Geller et al., 1998a,b; Geller et al., 2000; Geller et al., 2006), and conduct disorder (CD) (Geller et al., 1995; Kovacs and Pollock, 1995; Biederman et al., 1997a; Carlson et al., 1998; Geller et al., 2000). Among the most concerning comorbidities in juvenile onset BPD is the link with cigarette smoking and substance use disorders (SUD; including drug or alcohol abuse or dependence). Recent epidemiological data suggests that SUD occurs in up to 15% of the adult population (Kessler et al., 2005) with a 1-year prevalence of 1.4% and 0.6% for drug abuse and dependence (Compton et al., 2007); and 4.7% and 3.8% for alcohol abuse and dependence (Grant et al., 2004). These data also show the frequent onset of both alcohol and drug use disorders during adolescence (Grant et al., 2004; Kessler et al., 2005; Compton et al., 2007).

Emerging data suggest a bi-directional over-representation of BPD and SUD across the lifecycle. About half of referred and community samples of adults with BPD have a lifetime history of SUD (Reich et al., 1974; Himmelhoch, 1979; Winokur et al., 1995; Strakowski et al., 1998; Merikangas et al., 2007). Likewise, an excess of BPD has also been reported in SUD samples (Rounsaville et al., 1982; Gawin and Kleber, 1986; Weiss et al., 1988; Regier et al., 1990; Rounsaville et al., 1991). Data from studies of BPD adults also suggest that the risk for SUD is particularly high in those adults who had the onset of their BPD prior to age 18 years (Dunner and Feinman, 1995; Perlis et al., 2004; Fleck et al., 2006; Goldstein and Levitt, 2006; Lin et al., 2006). For instance, Lin et al. (2006) showed that earlier onset BPD was associated with a higher risk for SUD in adults than later onset (e.g. adult onset) BPD. Similarly, McElroy and colleagues showed an association between early onset BPD, mixed mood symptoms and SUD (McElroy et al., 2001).

A limited literature exists suggesting that juvenile onset BPD may be a major risk factor for SUD. For instance, an excess of SUD has been reported in adolescents with BPD (Wills et al., 1995; Young et al., 1995; West et al., 1996; Biederman et al., 1997a; Wilens et al., 1997a; Wilens et al., 2004; Birmaher and Axelson, 2006) and BPD appears over-represented in youth with SUD (Wills et al., 1995; Young et al., 1995; West et al., 1996; Wilens et al., 1997a,b; Biederman et al., 1997b; Weinberg and Glantz, 1999; Deas and Brown, 2006). However, the lack of controls, retrospective nature of the adult studies, and small sample sizes in some of these studies limits their interpretabilty.

One important potential confound in disentangling the relationship of BPD and SUD is psychiatric comorbidity. One of the most frequent comorbidities in BPD is conduct disorder (CD) (Kovacs and Pollock, 1995; Wozniak et al., 1995; Faraone et al., 1997) (Birmaher and Axelson, 2006). Since CD is a well-known risk factor for early onset SUD (Tarter et al., 1990; Brook et al., 1995; Whitmore et al., 1997; Carlson et al., 1998), a thorough examination of putative associations between BPD and SUD requires careful evaluation of the influence of comorbid CD. For instance, while some work has suggested that CD accounts for SUD in BPD adults (Carlson et al., 1998) we previously reported that the association between BPD and SUD in youth was independent of CD (Wilens et al., 1999). Another potential confounder in evaluating SUD risk in BPD is ADHD. High rates of ADHD have consistently been reported in samples of children and adolescents with BPD (Wozniak et al., 1995; Geller et al., 2002a,b); and ADHD has been reported to be a risk factor for SUD in young adults (Wilens et al., 1997a; Molina and Pelham, 2001). Similarly, anxiety disorders within BPD have also been reported to be linked independently to an elevated risk for SUD (Dilsaver et al., 2006). Examination of specific psychiatric comorbidities in the manifestation of SUD will provide useful information as to the contribution of BPD itself and potential mechanism(s) of SUD risk.

Characterizing the risk and nature of the relationship between BPD and SUD in the young is of particular clinical scientific and public health importance. BPD is an increasingly recognized prevalent and persistent disorder affecting children and adolescence (Weller et al., 1995; Wozniak et al., 1995; Geller and Luby, 1997; Brady et al., 1998; Geller et al., 1998a,b; Geller et al., 2004; Birmaher et al., 2006), that commonly onsets prior to SUD (Stowell and Estroff, 1992; West et al., 1996; Biederman et al., 1997b; Wilens et al., 1999). Also, persistent BPD into adulthood is associated with SUD (Dunner and Feinman, 1995; Strakowski et al., 1998) and BPD is treatable (Pavuluri et al., 2004; Kowatch et al., 2005). Thus, efforts at improving the understanding of the nature of the association between BPD and SUD in the young can lead to further refinements in efforts aimed at mitigating this risk.

To this end, this study's main aim was to re-examine the association between BPD and SUD in adolescents. To this end we examined findings from an ongoing, controlled, longitudinal family-based study of adolescents with BPD attending to developmental factors, correlates of BPD, and psychiatric comorbidity. Based on our previous findings, we hypothesized that adolescents with BPD will be at higher risk for SUD than non-mood disordered adolescents, and that the association between BPD and SUD would be independent of psychiatric comorbidity with ADHD, conduct and multiple anxiety disorders.

2. Methods

2.1. Subjects

The current study is based on our baseline assessments of our ongoing, controlled, family-based study of BPD adolescents. The methods of the study are described in a preliminary report on this sample (Wilens et al., 2004). We ascertained 105 bipolar adolescent probands and 98 non-mood disordered control subjects and their first-degree relatives. Subjects from both groups were recruited through newspaper advertisements, Internet postings, clinical referrals to our program (BPD only), and internal postings within the Partners/Massachusetts General Hospital (MGH) system.

Potential subjects were excluded if they had been adopted, or if their nuclear family was not available for study. We excluded any youth with major sensori-

motor handicaps, 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 MGH approved this study and a federal certificate of confidentiality was obtained for the study.

A two-stage ascertainment procedure selected subjects. For BPD probands, the first stage assessed the diagnosis of BPD by screening all children using a telephone questionnaire conducted with their primary caregiver, which queried about symptoms of BPD and study exclusion criteria. The second stage confirmed the diagnosis of BPD using a structured psychiatric interview, as described below. Only subjects who received a positive diagnosis at both stages were included in the study sample. We also screened non-mood disordered controls in two stages. First, control primary caregivers responded to the telephone questionnaire, then eligible controls meeting study entry criteria were recruited for the study and received the diagnostic assessment with a structured interview. Only subjects classified as not having any mood disorder at both stages were included in the control group. We excluded controls with any mood disorder because of concerns about potential "manic switching" from dysthymia or unipolar depression to BPD (Geller et al., 1994).

2.2. Assessments

All diagnostic assessments were made using DSM-IV-based structured interviews, by raters with bachelor's or master's degrees in psychology who had been extensively trained and supervised by the senior investigators (TW, JB). Raters were blind to the ascertainment status of the probands. Psychiatric assessments relied on the DSM-IV Kiddie Schedule for Affective Disorders-Epidemiologic Version (KSADS-E) (Ambrosini, 2000) and were based on independent interviews with the primary caregivers and direct interviews of probands and siblings. For every diagnosis, information was gathered regarding the ages at onset and offset of full syndromatic criteria, and treatment history.

Substance use disorders (SUD) in our analyses included any alcohol or drug (excluding nicotine) abuse or dependence. Alcohol or drug abuse or dependence was diagnosed based on DSM-IV criteria using the Kiddie SADS-E. Recent evidence suggests the utility of structured interview data compared to objective data for "lifetime" SUD determination (Gignac et al., 2005). Rates of disorders reported are lifetime prevalence. Duration of disorders is expressed in years based on ages of onset and offset.

All cases were presented to a committee composed of board certified child psychiatrists and licensed psychologists. Diagnoses presented for review were considered positive only if the diagnosis would be considered clinically meaningful—of clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. Discrepant reports were reconciled using the most severe diagnosis from any source unless the diagnosticians suspected that the source was not supplying reliable information. Subjects were queried for any use of illicit drugs during the SUD module of the structured interview, in addition to assessment of abuse and dependence. Early use of drugs or alcohol was not included in establishing diagnoses of conduct disorder. All cases of suspected drug or alcohol abuse or dependence were further reviewed with a child and adult psychiatrist with additional 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 assessments from interviews of children and adults, the median kappa coefficient 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).

The Hollingshead Four-Factor Index was used to assess socioeconomic status (SES). The Social Adjustment Inventory for Children and Adolescents (SAICA), a semi-structured interview administered to the child or parent was used to measure social functioning in children 6–18 years old. Content areas assessed include activities, peer relations, family relations, and academic performance. We present the total SAICA score as a summary measure.

2.3. Statistical analysis

We used Student's *t*-test or linear regression for continuous outcomes (age, duration of disorders, mean annual manic episodes), Wilcoxon rank-sum tests for ordinal outcomes, and Pearson tests for dichotomous outcomes. We used logistic regression for dichotomous outcomes when controlling for other clinical characteristics, and negative binomial regression for count outcomes. We used Cox proportional hazards regression to model age-dependent onset ("failure") in all SUD diagnoses and all psychiatric diagnoses. Since kernel estimators used in Kaplan-Meier failure curves may be biased at the upper end-points of age-range, failure curve figures are truncated at age 16. Few subjects experienced onset after age 16 in any SUD [overall SUD: 1 (3% of cases); alcohol abuse: 4 (15%); alcohol dependence: 1 (17%); drug abuse: 0 (0%); drug dependence: 0 (0%)]. Independent variables in all regression analyses were dummy variables denoting group membership (Control versus BPD, BPD − SUD versus BPD + SUD) and any confounding demographic or psychiatric variables (e.g., parental SUD, parental BPD). We conducted all statistical analyses using Stata 9.2 (Stata Corporation, 2005).

3. Results

3.1. Clinical characteristics of sample

Table 1 shows the demographic characteristics of our sample. We found no significant differences in age between BPD and control subjects (overall mean of 13.7 ± 2.3 years; range 10–18 years). BPD subjects had significantly lower SES (higher Hollingshead scores) compared to control subjects. BPD subjects also tended to have significantly more parents with a SUD, as previously reported (Wilens et al., 2007). We found no differences in sex or family intactness between BPD and control subjects. All further comparisons of BPD and control subjects control for SES. Our sample contained 47 subjects diagnosed with BPD I and 58 subjects diagnosed with BPD II (55% and 45%, respectively).

3.2. Disorders comorbid with BPD

We assessed age-adjusted rate of comorbid psychiatric disorders in subjects with BPD compared to control subjects using Cox proportional hazards models controlling for SES (Table 2). We found higher age-adjusted rates of attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD),

Table 1
Demographic variables for control and BPD subjects

	Control ($N=98$) Mean ± S.D.	BPD ($N=105$) Mean ± S.D.	Test statistic	p
Age[a]	13.69 ± 2.10	13.64 ± 2.47	$t=0.16$	0.9
SES[b]	1.67 ± 0.95	2.03 ± 1.16	$z=2.25$	0.02
	N(%)	N(%)	χ^{2c}	p
Any parental SUD	55(56)	81(77)	10.13	0.001
Sex (% male)	59(60)	73(70)	1.94	0.2
Family intactness	55(56)	57(54)	0.07	0.8

[a] *t*-test.
[b] Wilcoxon rank-sum test.
[c] Pearson X^2 test.

Table 2
Psychiatric disorders in non-mood disordered control and BPD subjects

	Control ($N=98$) $N(\%)$	BPD ($N=105$) $N(\%)$	HR[a]	[95% CI]	χ^2	p[b,c]
Attention deficit/hyperactivity disorder	16(16)	77(73)	7.222	[3.927, 13.283]	40.45	<0.001
Conduct disorder	8(8)	58(55)	10.873	[4.571, 25.861]	29.13	<0.001
Oppositional	14(14)	93(89)	14.747	[7.515, 28.940]	61.21	<0.001
Multiple anxiety (≥2)	15(15)	69(66)	5.747	[3.094, 10.674]	30.65	<0.001
Panic disorder	3(3)	17(16)	8.541	[1.899, 38.426]	7.81	0.0050
Agoraphobia	11(11)	36(34)	4.144	[1.937, 8.867]	13.42	<0.001
Social phobia	3(3)	39(37)	13.111	[3.936, 43.672]	17.57	<0.001
Simple phobia	21(21)	46(44)	2.211	[1.231, 3.972]	7.04	0.0080
Obsessive-compulsive disorder	2(2)	21(20)	10.257	[2.307, 45.601]	9.35	0.0020
Generalized anxiety disorder	5(5)	40(38)	8.004	[3.053, 20.985]	17.89	<0.001
Separation	13(13)	52(50)	3.656	[1.878, 7.119]	14.54	<0.001
Avoidant disorder	1(1)	10(10)	6.929	[0.813, 59.062]	3.14	0.080
Post-traumatic stress disorder	0(0)	10(10)	–	–	–	0.002[d]
Speech language	9(9)	14(14)	1.601	[0.601, 4.261]	0.89	0.30
Stuttering	4(4)	1(1)	0.234	[0.026, 2.124]	1.67	0.20
Enuresis	9(9)	28(27)	2.864	[1.277, 6.421]	6.52	0.010
Encopresis	1(1)	9(9)	7.873	[0.933, 66.441]	3.60	0.060
Tourette's syndrome	1(1)	9(9)	5.340	[0.625, 45.653]	2.34	0.10
Tics disorder	11(11)	23(22)	1.917	[0.802, 4.585]	2.14	0.10
Sleep disorder	17(17)	54(51)	3.377	[1.843, 6.188]	15.52	<0.001

[a] Hazard ratio; Cox proportional hazards model controlling for parental BPD, parental SUD, and SES.
[b] Significant results shaded in gray.
[c] Bonferroni-adjusted $\alpha = 0.0025$.
[d] Fisher's exact test.

oppositional defiant disorder (ODD), multiple (more than 2) anxiety disorders, agoraphobia, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder, separation anxiety, post-traumatic stress disorder (PTSD) and sleep disorders compared to control subjects at a Bonferroni-adjusted level of $\alpha = 0.0025$. We found higher age-adjusted rates of panic disorder, simple phobia, and enuresis, although these did not reach our adjusted α-level.

3.3. SUD in BPD youth

BPD subjects, compared to controls, had significantly higher age-adjusted rates of any SUD (lifetime prevalence: controls 4% and BPD 34%; HR[95% CI] = 8.68[3.02 25.0], $\chi^2 = 16.06$, $p < 0.001$, df = 1; Fig. 1a), as well as higher rates of alcohol abuse (controls 3%, BPD 23%; HR[95% CI] = 7.66[2.20 26.7], $\chi^2 = 10.2$, $p = 0.001$, df = 1; Fig. 1b), alcohol dependence

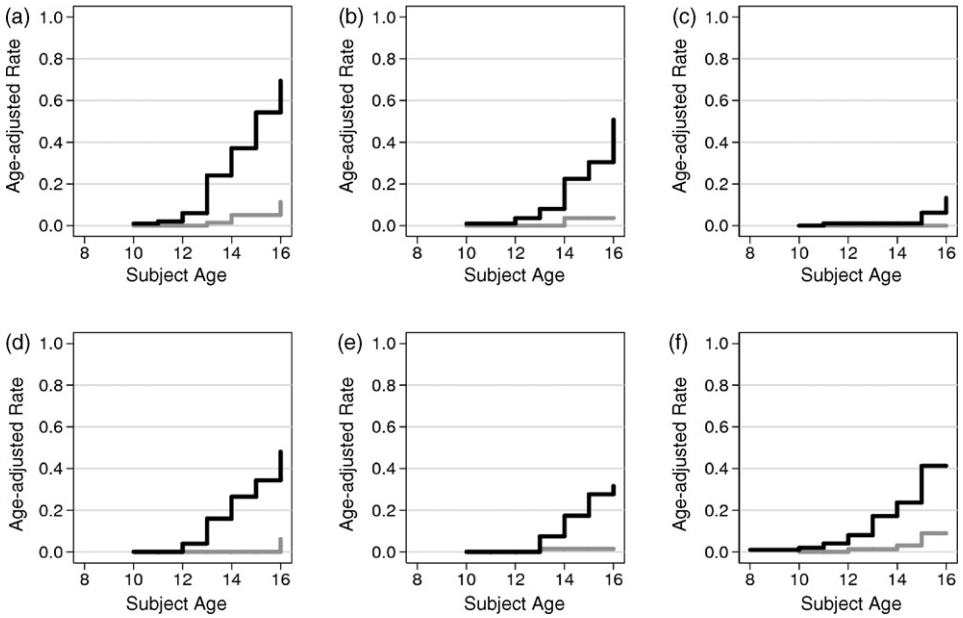

Fig. 1. Failure curves for (a) overall SUD, (b) alcohol abuse, (c) alcohol dependence, (d) drug abuse, (e) drug dependence, and (f) smoking in adolescent non-mood disordered control ($N = 98$; grey line) and BPD ($N = 105$; black line) probands stratified by BPD status, controlling for number of parents with a SUD and SES.

(controls 0%, BPD 6%; Fig. 1c; Fisher's exact test: $p = 0.05$), drug abuse (controls 1%, BPD 22%; HR[95% CI] = 18.5[2.46 139.10], $\chi^2 = 8.03$, $p = 0.005$, df = 1; Fig. 1d), drug dependence (controls 1%, BPD 14%; HR[95% CI] = 12.1[1.54 95.50], $\chi^2 = 5.61$, $p = 0.02$, df = 1; Fig. 1e) and cigarette smoking (controls 4%, BPD 22%; HR[95% CI] = 12.3[2.83 53.69], $\chi^2 = 11.2$, $p < 0.001$, df = 1; Fig. 1f); all of these models controlled for number of parents with a SUD and SES. Fourteen percent of probands with BPD had a combined alcohol and drug use disorder compared to none of the controls (Fisher's exact test $p < 0.001$).

3.3.1. The effect of comorbid disorders on SUD. We assessed the effect of CD, ADHD and multiple anxiety disorders on SUD, alcohol abuse, drug abuse, drug dependence and smoking by repeating the above survival analyses including each of these disorders as an additional covariate, again controlling for number of parents with a SUD and SES. We first entered each disorder into a model with an interaction term with proband status; we found no significant interactions terms and re-fitted the models with only main effects. When we accounted for CD, we found a significant effect of BPD on age-adjusted risk of any SUD ($X^2 = 6.22$, $p = 0.01$), and the effect of CD was also significant ($X^2 = 7.95$, $p = 0.005$); we found a significant effect of BPD status on age-adjusted risk of alcohol abuse ($X^2 = 4.5$, $p = 0.03$), and the effect of CD was also significant ($X^2 = 4.16$, $p = 0.04$). When we included the effect of CD, the effect of BPD status on age-adjusted risk of drug abuse remained significant ($X^2 = 4.38$, $p = 0.04$), and the effect of CD was also significant ($X^2 = 4.3$, $p = 0.04$); the effect of BPD status on risk of drug dependence was not significant ($X^2 = 1.48$, $p = 0.22$), nor was the effect of CD ($X^2 = 3.72$, $p = 0.54$). The effect of BPD status on risk of smoking remained significant ($X^2 = 4.67$, $p = 0.03$), and the effect of CD was significant ($X^2 = 7.03$, $p = 0.008$).

We found a significant effect of BPD status on age-adjusted risk of any SUD, alcohol abuse, drug abuse, drug dependence and smoking when we added ADHD to the model and in each case the effect of ADHD was not significant. Similarly, we found a significant effect of BPD status on age-adjusted risk of any SUD, alcohol abuse, drug abuse and drug dependence when we added multiple anxiety disorders to the model, and in each case the effect of multiple anxiety disorders was not significant.

3.4. BPD characteristics associated with SUD

Table 3 shows the results of comparisons of BPD subjects with a SUD and BPD subjects without a SUD, for age-adjusted models and non-adjusted models. We found that subjects with a SUD were significantly older than subjects without a SUD. BPD − SUD subjects were significantly younger at BPD onset; this result lost significance when we included the effect of age in the prediction of BPD onset. We found no significant differences between BPD + SUD and BPD − SUD subjects in duration of BPD, nor in mean annual number of manic episodes.

BPD + SUD subjects were no more likely than BPD − SUD subjects to have a parent with MDD, BPD, or SUD. We found no significant effect of SUD on the probability of rapid cycling (more than four manic episodes per year) or the onset of mania before any depressive disorder (dysthymia or MDD). BPD − SUD subjects were more likely to develop mania in childhood (younger than 12 years); this result lost significance when we included the effect of subject age. We found no significant difference in the likelihood of experiencing trauma between BPD − SUD and BPD + SUD subjects. We found BPD − SUD subjects significantly more likely to have had onset of any depressive disorder in childhood than BPD + SUD subjects; this result lost significance when we included the effect of subject age.

We found no significant difference in number of manic symptoms or manic episodes between BPD − SUD and BPD + SUD subjects with BPD. We found no differences in number of MDD symptoms or lifetime number of depressive episodes between BPD − SUD and BPD + SUD subjects with BPD and MDD. When we restricted our analysis to subjects with ADHD, we found no differences in ADHD symptoms between BPD − SUD and BPD + SUD subjects with BPD. When we limited our analysis to subjects with conduct disorder, we found that BPD + SUD subjects had more CD symptoms at the 0.05 level; this result lost significance when we included age in the model.

We found no significant difference in total SAICA score between BPD − SUD (mean ± S.D.: 30.1 ± 10.3) and BPD + SUD subjects (30.4 ± 12.1; *t*-test: $t = 0.093$, $p = 0.93$). We found no difference in the frequency of medical treatment (hospitalization, medication, or a combination of medication with counseling) versus no treatment or counseling alone between BPD − SUD and BPD + SUD subjects ($X^2 = 0.13$, $p = 0.7$); frequency of medical treatment was high (92 subjects, or 89% of the sample of BPD subjects), thereby limiting our ability to make this conclusion. We found no association between SUD and BPD subtype: we found no significant difference in the frequency of Bipolar I disorder between BPD + SUD (19 subjects, 56%) and BPD − SUD (28 subjects, 39%; $X^2 = 2.5$, $p = 0.1$).

3.5. Characteristics of SUD in BPD subjects

The duration of substance use disorders in BPD subjects ranged from 1 to 7 years, with average duration of any SUD no greater than 1.91 years (alcohol abuse: 1.91 ± 1.53 years; alcohol dependence 1.32 ± 0.52 years; drug abuse 1.82 ± 1.44 years; substance dependence 1.86 ± 1.36 years). Out of 33 subjects with both a SUD and BPD, 22 subjects (67%) experienced onset of BPD before the onset of their SUD; 8 subjects (24%) experienced onset of BPD and SUD within the same year, and 3 subjects (9%) experienced BPD onset after SUD onset. In 27 BPD subjects with SUD and CD, 15 (56%) experienced CD onset before SUD onset, 7 subjects (26%) experienced CD onset within 1 year of SUD onset and 5 subjects (19%) experienced CD onset 1 year after SUD onset.

4. Discussion

The results of this controlled, family-based study of adolescents with and without BPD support our hypotheses that adolescents with BPD manifest an increased risk for cigarette smoking and SUD compared to their non-mood disordered

Table 3
Characteristics of BPD in all BPD subjects, BPD subjects with BPD − SUD and BPD subjects with SUD

	Whole sample ($N=105$)	BPD − SUD ($N=71$)	BPD + SUD ($N=34$)	Omnibus statistic[a]		Age-adjusted model[b]	
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	F[c]	p	F[d]	p
Subject's age	13.64 ± 2.47	12.48 ± 1.96	16.06 ± 1.46	89.37	<0.001		
BPD onset	8.45 ± 3.79	7.49 ± 3.34	10.48 ± 3.92	16.12	<0.001	0.22	0.6
BPD duration	3.53 ± 2.61	3.17 ± 2.95	4.11 ± 1.97	0.63	0.4	0.40	0.5
Mean annual episodes	5.29 ± 10.71	4.99 ± 11.49	5.91 ± 8.99	0.15	0.7	0.81	0.4
	N(%)	N(%)	N(%)	X^{2}[e]	p	X^{2}[f]	p
Parental MDD	36(35)	23(32)	13(40)	0.49	0.5	1.11	0.3
Parental BPD	26(25)	18(25)	8(24)	0.04	0.8	2.19	0.1
Parental SUD	81(77)	53(75)	28(82)	0.77	0.4	1.56	0.2
Rapid cycling	28(29)	16(25)	12(39)	2.00	0.2	0.16	0.7
Mania before depression[g]	46(44)	31(44)	15(44)	0.00	1.0	1.66	0.2
Mania childhood onset	78(74)	60(85)	18(53)	11.05	<0.001	0.04	0.8
Trauma (lifetime)	23(22)	15(21)	8(24)	0.08	0.8	0.00	1.0
Depression childhood onset[h]	67(71)	52(83)	15(47)	11.96	<0.001	0.17	0.7
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	X^{2}[i]	p	X^{2}[j]	p
Manic symptoms	6.40 ± 1.64	6.23 ± 1.64	6.76 ± 1.62	1.04	0.3	0.93	0.3
Manic episodes	21.58 ± 52.19	19.18 ± 54.28	26.69 ± 47.87	0.92	0.3	0.50	0.5
MDD symptoms[k]	6.20 ± 0.99	6.02 ± 1.12	6.52 ± 0.58	0.69	0.4	1.0	0.3
Depressive episodes[l]	11.05 ± 22.43	8.81 ± 14.27	15.19 ± 32.55	2.58	0.1	0.00	1.0
ADHD symptoms[m]	12.94 ± 3.52	13.22 ± 3.27	12.08 ± 4.17	1.45	0.2	3.0	0.09
Conduct disorder symptoms[n]	4.78 ± 1.77	4.24 ± 1.34	5.41 ± 2.01	4.08	0.04	0.95	0.3

[a] Comparison of No SUD vs. SUD groups.
[b] t-test.
[c] Linear regression.
[d] Linear regression.
[e] Logistic regression.
[f] Logistic regression.
[g] Any depressive disorder.
[h] Bonferroni-adjusted $\alpha = 0.0025$.
[i] Negative binomial regression.
[j] Negative binomial regression.
[k] Lifetime MDD subjects only: $N=75$, 48 No SUD, 27 SUD.
[l] Lifetime MDD subjects only: $N=75$, 48 No SUD, 27 SUD.
[m] Lifetime ADHD subjects only: $N=77$, 58 No SUD, 19 SUD.
[n] Lifetime CD subjects only: $N=58$, 31 No SUD, 27 SUD.

peers. The increased risk for SUD in our sample was independent of conduct disorder, ADHD, or multiple anxiety disorders. We also found evidence that the onset of mood episodes (mania or depression) occurring during adolescence was associated with a specifically elevated risk for SUD compared to mood arising prepubertally. Few intrinsic characteristics of BPD distinguished those with and without SUD. These results further support that BPD in adolescence confers a very high risk for the development of cigarette smoking and SUD.

In the current study, we found that BPD in youth with a mean age of 14 years was associated with a clinically and statistically significant higher risk of SUD (31%) compared to a group of similarly aged non-mood disordered controls (4%). Compared to controls, elevations in all categories of substance use were evident including cigarette smoking, drug and alcohol abuse and dependence, and drug abuse and dependence in mainly young adolescents with BPD. Our findings that juvenile BPD increased the risk for cigarette smoking and SUD provides compelling support for a growing literature documenting this risk in pediatric and adult samples. For instance, West et al. (1996) reported that 40% of inpatient adolescents with BPD suffered from SUD. In a controlled longitudinal sample of ADHD youth, adolescents with comorbid BPD were at risk for early initiation and higher rates of cigarette smoking (Wilens et al., 2000) and SUD (Wilens et al., 1997a,b) independently of ADHD. Likewise, outpatient adolescents with BPD were previously found to be at heightened risk for the development of SUD relative to non-BPD psychiatric controls (Wilens et al., 1999). Strober et al. (1995) reported that 5 years after hospitalization, 22% of adolescents with BPD had SUD, though no further description of the SUD or comparison with controls were available. More recently, Axelson et al. (2006) reported a 10% rate of SUD in a younger sample of BPD although no control groups were available for comparison.

The high risk of SUD in adults with BPD has been demonstrated soundly in the literature in both epidemiological and clinically based studies (Reich et al., 1974; Regier et al., 1990; Winokur et al., 1993; McElroy et al., 1995; Winokur et al., 1995; Strakowski et al., 1998; Goldstein and Levitt, 2006; Merikangas

et al., 2007). For instance, McElroy et al. (1995) reported that drug and alcohol use disorders were found in 39% and 32% of BPD adults, respectively. Similarly, epidemiologically derived data shows the lifetime prevalence of co-occurring SUD in BPD in excess of 60% (Regier et al., 1990; Merikangas et al., 2007).

Adult-based studies provide further evidence linking age at onset of BPD with the risk for SUD (Goldstein and Levitt, 2006). For instance, Lin et al. (2006) reported that early onset BPD was associated with a higher risk for SUD. Similarly, McElroy and colleagues showed a retrospective association between early onset BPD, mixed symptoms, other psychiatric comorbidity and SUD (McElroy et al., 2001). Perlis et al. (2006) reporting on 1000 BPD adults in the STEP-BD program found that childhood onset BPD (e.g., <18 years) was more likely to be associated with SUD than BPD that emerged in adulthood (Perlis et al., 2006). Interestingly, this group observed that half of adults who had the onset of their BPD prior to age 18 years manifested SUD (Perlis et al., 2006). Given that early onset BPD is associated with SUD, and early onset SUD is associated with a pernicious SUD course and ongoing impairment (Kandel and Logan, 1984; Brook et al., 2002), BPD youth appear at risk for SUD-related difficulties in addition to a chronic BPD course (Geller et al., 2004; Birmaher and Axelson, 2006). These data highlight the need for careful screening of cigarette and substance use in adolescents with BPD.

In the current study, we found consistently higher rates of psychiatric comorbidity with BPD compared to our non-mood disordered controls. Our rates of co-occurring ADHD, disruptive and anxiety disorders were similar to other studies of prepubertal and adolescent BPD (Wozniak et al., 1995; Geller et al., 2000; Geller et al., 2004; Kowatch et al., 2005; Birmaher et al., 2006) as well as supporting epidemiological evidence of heightened risk for anxiety and disruptive disorders associated with BPD (Lewinsohn et al., 1995). An important finding in the current study was that the higher risk of cigarette smoking and SUD in BPD youth was independent of other psychiatric comorbidity (ADHD, CD, multiple anxiety); disorders that have been associated independently with SUD (Weinberg et al., 1998).

Of particular note, we found that conduct disorder (CD) did not account for cigarette smoking or SUD in our BPD sample. Consistent with the well-known association of CD and SUD (Robins, 1966; Crowley et al., 1998), a higher number of conduct symptoms were associated with SUD within youth with BPD. The current study supports findings from a separate group of clinically referred adolescents with BPD in which adolescents with BPD were at heightened risk for the development of SUD relative to non-BPD psychiatric controls not accounted by CD (Wilens et al., 1999). It is noteworthy that we previously found that the risk for SUD associated with adolescent onset BPD (9-fold) was reminiscent of the risk for SUD associated with CD (6-fold) highlighting the importance of BPD as a separate and major risk factor for SUD (Wilens et al., 1999). Recent epidemiological work in adults also suggests a similar risk for SUD associated with BPD (adjusted risk odds ratio of 2.3) compared to CD/antisocial personality disorder (OR 2.9) (Compton et al., 2007). Our current findings along with the literature support the importance of both CD and BPD as independent risk factors for adolescent onset SUD.

We found equal rates of alcohol and drug abuse with lower rates of more severe alcohol or drug dependence in our BPD youth. There was no evidence of specificity in classes of agents (drug versus alcohol), or specific drugs of abuse that were preferentially abused in our BPD youth although interpretation of these data is limited by the low rates of SUD in our controls. There was the disturbing trend of both an alcohol and drug use disorder simultaneously in 14% of BPD youth (compared to no controls), most likely a proxy of more severe SUD.

In the current study we found that 63% of youth with BPD and SUD experienced the full syndromatic onset of their BPD prior to SUD while a minority had the onset of their BPD after the onset of SUD. Carefully conducted work by Winokur et al. (1995), Strakowski et al. (1992, 1995, 1998) and Lin et al. (2006) have helped elucidate the developmental timing of SUD as it pertains to BPD in adults. These research teams have found that in retrospective reports of adult samples, BPD preceded SUD in 30%–47% of cases (Winokur et al., 1995; Strakowski et al., 1998). Lin et al. (2006) showed that early onset BPD precedes and is associated with SUD; and Winokur has reported that a subgroup of BPD + SUD have evidence of alcoholism *secondary* to BPD (Winokur et al., 1995). Strakowski has noted that active SUD was associated with unstable BPD; however unstable BPD was not associated with SUD (Strakowski et al., 1998). Recent work also shows that, whereas the course of alcohol use disorders and BPD symptoms is complex in adults, in younger BPD subjects, alcohol use and BPD symptoms tended to cycle in unison (Fleck et al., 2006). Of note, our current findings are similar to other work from our group in outpatient adolescents, in which BPD preceded SUD in 55% of the cases, onset was within 1 year of SUD onset in 9%, and onset after SUD in 36% (Biederman et al., 1997b). Similar distribution of onsets of mood disorders and SUD have been reported in other mood-disordered youth with SUD (Kashani et al., 1985; Deykin et al., 1986; Mezzich et al., 1992; Stowell and Estroff, 1992). Though BPD precedes or is simultaneous with the onset of SUD in pediatric groups in the majority of cases, no clear mechanistic relationship between BPD and SUD clearly transpires.

In evaluating specific characteristics of BPD that are related to non-nicotine SUD in BPD youth, we had some intriguing findings. Compared to BPD youth without SUD, those with SUD had an older age at assessment, older age of BPD onset, adolescent onset of their mania, higher number of yearly episodes and more conduct symptoms. In the current study the vast majority of subjects were deemed to manifest highly mixed presentations and rapid cycling-characteristics that had been putatively linked with SUD in adults with BPD (McElroy et al., 2001; Perlis et al., 2004). However, unlike in adults where mixed and highly comorbid BPD have been associated with SUD (McElroy et al., 2001), in the current study, BPD youth with and without SUD did not differ significantly in the number of manic symptoms, BPD type, or mixed status. In the Axelson study (2006), albeit limited by small samples developing SUD, youth with BPD I were more likely to have SUD than those with BPD II. Similarly, adult epidemiological studies suggest higher risk for SUD in BPD I

compared to BPD II or subthreshold BPD (Merikangas et al., 2007; Compton et al., 2007). While it remains unclear if our youth with BPD II or subthreshold BPD will ultimately develop BPD I, more work evaluating the intrinsic characteristics of BPD and SUD risk overtime need be undertaken. Understanding features of BPD related to SUD may assist mechanistically in understanding SUD risk as well as predicting SUD in at-risk youth with BPD.

Similar to previous findings (Wilens et al., 1999; Biederman et al., 2000), probands in whom the onset of their BPD was in adolescence had higher risk for SUD relative to those who had the onset of their BPD prepubertally. The reasons why adolescent and child onset BPD may confer a differential risk for SUD in adolescence remain unclear. Considering that adolescence is a time of high risk for the development of SUD, we speculate that BPD through poor judgment, limited self control, disinhibition (Tarter et al., 2003), or a combination may be particularly noxious for the development of SUD during adolescence (Wilens et al., 1999; Biederman et al., 2000). It may be that adolescents self medicate their irritable mood, aggressivity, and "affective storms" with substances of abuse or alcohol (Reich et al., 1974; Khantzian, 1997; Brady et al., 1998). Another possibility is that child and adolescent onset BPD may be etiologically distinct with important developmental variation based on the timing of the onset of the BPD (Faraone et al., 1997) as well as a variable course and outcome including the risk for SUD. Alternatively, adolescent onset BPD and adolescent onset SUD may represent variable expressivity of a shared risk factor (Ebstein et al., 1996).

The findings in the current study need to be tempered against their methodological limitations. The sample was ascertained from outpatient clinical referrals and advertisements and was mostly Caucasian and may not generalize to community or minority samples. Given the lengthy burden of the assessments, it may have been that more disturbed youth with BPD were recruited for the study than may be representative in the community. Although our sample was large, the subgroup of adolescents in the control group and those with adolescent onset BPD with SUD was relatively small limiting our statistical power. Our sample includes a range of ages and although we conducted an age-adjusted analysis, our analysis of characteristics associated with SUD is highly dependent on subject age. Future studies of potential SUD-promoting characteristics in BPD adolescents should use age-matched designs to isolate the effects of other factors. Despite the use of structured diagnostic interviews in this study, the diagnostic criteria for juvenile BPD remain controversial (Leibenluft et al., 2003). 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 structured psychiatric interviews for psychopathology and SUD. SUD was defined categorically by 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. Using these definitions, use and misuse of substances as well as subthreshold psychopathology or substance abuse was not captured. Further studies should integrate parent, youth self-report, youth report during structured interview, as well as urine toxicology testing to more accurately identify substance use both categorically and dimensionally in youth (Gignac et al., 2005).

Despite these limitations, the current data derived from an ongoing longitudinal study of BPD add to a growing literature indicating that BPD in adolescents is associated with clinically and statistically significant risk for cigarette smoking and SUD independent of ADHD, multiple anxiety, and conduct disorder. Our data also support findings in generally younger samples (Wozniak et al., 1995; Geller et al., 2006) of the substantial clinical impairment in adolescents with BPD in terms of other cognitive and psychiatric comorbidities (Birmaher and Axelson, 2006) Adolescent onset BPD, more conduct symptoms and higher rates of cycling distinguished BPD youth with and without SUD. Adolescents with BPD should be carefully screened for cigarette smoking and SUD. Further studies examining the course and mechanism(s) of SUD risk in juvenile onset BPD are warranted.

Potential conflicts of interest/financial disclosure

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