Further Evidence for Smoking and Substance Use Disorders in Youth With Bipolar Disorder and Comorbid Conduct Disorder

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ABSTRACT

Objective: Bipolar disorder (BPD) is a highly morbid disorder increasingly recognized in adolescents. The aim of this study was to examine the relative risk for substance use disorders (SUDs; alcohol or drug abuse or dependence) and cigarette smoking in adolescents with BPD.

Methods: We evaluated the relative risk for SUDs and cigarette smoking in a case-controlled, 5-year prospective follow-up of adolescents with (n = 105, mean ± SD baseline age = 13.6 ± 2.5 years) and without ("controls"; n = 98, baseline age = 13.7 ± 2.1 years) BPD. Seventy-three percent of subjects were retained at follow-up (BPD: n = 68; controls: n = 81; 73% reascertainment). Our main outcomes were assessed by blinded structured interviews for *DSM-IV* criteria.

Results: Maturing adolescents with BPD, compared to controls, were more likely to endorse higher rates of SUD (49% vs 26%; hazard ratio [HR] = 2.0; 95% confidence interval (CI), 1.1–3.6; $P = .02$) and cigarette smoking (49% vs 17%; HR = 2.9; 95% CI, 1.4–6.1; $P = .004$), as well as earlier onset of SUD (14.9 ± 2.6 [SD] years vs 16.5 ± 1.6 [SD] years; $t = 2.6$; $P = .01$). Subjects with conduct disorder (CD) were more likely to have SUD and nicotine dependence than subjects with BPD alone or controls (all P values < .05). When we added conduct disorder to the model with socioeconomic status and parental SUD, all associations lost significance (all P values > .05). Subjects with the persistence of a BPD diagnosis were also more likely to endorse cigarette smoking and SUD in comparison to those who lost a BPD diagnosis or controls at follow-up.

Conclusions: The results provide further evidence that adolescents with BPD, particularly those with comorbid CD, are significantly more likely to endorse cigarette smoking and SUDs when compared to their non–mood disordered peers. These findings indicate that youth with BPD should be carefully monitored for comorbid CD and the development of cigarette smoking and SUDs.

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A growing literature documents that juvenile bipolar disorder (BPD) is a prevalent, highly morbid condition estimated to affect up to 5% of adolescents.[1,2] Longitudinal studies document that the disorder is associated with elevated levels of functional impairments including high rates of psychiatric hospitalization, academic and occupational underachievement, disruption of the family environment, psychosocial disability, and comorbid psychiatric disorders.[3–6]

Among the most concerning problems in BPD are those associated with the development of cigarette smoking and substance use disorders (SUDs; drug or alcohol abuse or dependence).[7] For instance, about one-half of referred and community samples of adults with BPD have a lifetime history of SUDs,[2] and excess BPD has been reported in SUD.[8,9] Data suggest a heightened risk for SUDs in adults who experienced BPD onset prior to 18 years of age.[7,10,11]

The literature also suggests that juvenile BPD is a major risk factor for SUDs[12–15] and is overrepresented in youth with SUDs.[15,16] For example, we previously reported that 31% of adolescents with BPD manifest a SUD at a mean age of 14 years compared to only 4% in a matched group of non–mood disordered adolescents ($P < .001$). Since the age at onset of BPD generally precedes that of SUDs (particularly juvenile-onset BPD),[12,14,17] it has been suggested that the direction of risk is from BPD to SUD.[12,14,17]

Although in independent samples (our own group and others) have shown that juvenile BPD is a risk for cigarette smoking and SUD,[12,14] the role of conduct disorder (CD) in accounting for these findings has not been fully explored longitudinally. This issue is important considering the high comorbidity between juvenile-onset BPD and CD[18–20] and the well-documented association between CD and SUD, particularly in context to mood dysregulation.[21,22]

The current study's main aim was to examine the association between BPD and SUD in developing adolescents. We examined findings from a controlled, 5-year longitudinal family study of adolescents with and without BPD attending to developmental factors, correlates of BPD, and psychiatric comorbidity. We hypothesized that adolescents with BPD would continue to 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 and CD—2 conditions known to raise the risk for SUD. Furthermore, we posited that persistence of BPD would be associated with the highest risk for SUD relative to nonpersistent cases and controls.

METHODS

Subjects

The current analysis is based on the 5-year follow-up of a case-control study, the methods of which are described in detail in the

baseline report of this sample.[12] We originally ascertained 108 bipolar adolescent probands and 98 non–mood disordered controls. 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), Boston, system. A 2-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 2 stages. We excluded controls with any mood disorder because of concerns about potential "manic switching" from dysthymia or unipolar depression to BPD.[23]

Briefly, at baseline, potential subjects were excluded if they had been adopted, if they had major sensorimotor handicaps, autism, inadequate command of the English language, or a Full Scale Intelligence Quotient less than 70. Child assent and parental consent were obtained.

Assessments

All diagnostic assessments were made using *DSM-IV*–based semistructured interviews. Raters were blinded to the (re)ascertainment status of the subjects. Psychiatric assessments for adolescents relied on the *DSM-IV* Kiddie Schedule for Affective Disorders and Schizophrenia–Epidemiologic Version (KSADS-E),[24] while for subjects 18 years or older, the Structured Clinical Interview for *DSM-III-R* (SCID)[25] was used. For each diagnosis at baseline and follow-up, information was gathered regarding the ages at onset and offset of syndromatic criteria, interval history (follow-up), and treatment history. As reported previously,[26] for a subject to be diagnosed with BPD, he or she had to meet full *DSM-IV* criteria for bipolar I or II disorder by both structured and clinical interviews.

Substance use disorders included any non-nicotine drug or alcohol abuse or dependence and was diagnosed based on *DSM-IV* criteria. To meet criteria for nicotine dependence, subjects under 18 years needed to endorse smoking daily, whereas subjects over 18 years needed to endorse smoking at least a pack of cigarettes per day. Rates of disorders reported are lifetime prevalence, and SUD data reflect moderate to severe impairment.

All cases at baseline and follow-up were presented to board-certified child psychiatrists and licensed psychologists. Diagnoses were considered positive only if the disorder was of clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. κ Coefficients of agreement were evaluated by having 3 experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interview. Based on 500 assessments from interviews of children and adults, the median κ coefficient was 0.98 and included κ coefficients for 8 individual diagnoses.

Clinical Points

- Youth with persistent bipolar disorder (BPD) or comorbid conduct disorder are more likely to develop substance use disorders (SUDs).
- Bipolar disorder is frequently associated with other psychopathology including conduct disorder, attention-deficit/hyperactivity disorder, disruptive disorders, anxiety disorders, and serious depression, compared to adolescents without a mood disorder.
- Since the onset of BPD typically occurs prior to SUD, practitioners should treat symptoms of BPD and continue to carefully monitor youth for cigarette smoking and the development of SUD.

Statistical Analysis

The baseline sample included 105 BPD probands (mean ± SD baseline age = 13.6 ± 2.5 years) and their first-degree relatives and 98 controls (mean ± SD baseline age = 13.7 ± 2.1 years) and their first-degree relatives.[12] For this analysis, we merged the baseline and follow-up data and computed lifetime rates of disorders and characteristics using the most severe diagnosis, the earliest onsets, and the latest offsets unless noted otherwise. We compared demographic and clinical characteristics between cases and controls using *t* tests for continuous outcomes, χ^2 tests for binary outcomes, and the Wilcoxon rank sum test for socioeconomic status (SES).

The Hollingshead Four-Factor Index[27] was used to assess SES. We used Kaplan-Meier curves and Cox proportional hazard models to assess the risk of SUD at follow-up between BPD subjects without SUD at baseline and control subjects as well as between subjects with persistent BPD and nonpersistent BPD. Persistence of BPD was described as full BPD at wave 1 and full or subthreshold BPD criteria at follow-up (*persistent BPD*).[5] Subjects with BPD at baseline who no longer met criteria for BPD at follow-up were considered to have *nonpersistent BPD*.[5] The age at onset was computed using the earliest age at onset between baseline and follow-up. Three subjects with BPD were dropped from the Cox proportional hazard models as they had developed an SUD prior to their BPD (alcohol abuse: 1 dropped; alcohol dependence: 0; substance abuse: 3; substance dependence: 0; any SUD: 3; cigarette smoking: 3). An α level of .05 was used to assert statistical significance; all statistical tests were 2-tailed. We calculated all statistics using Stata 12.0.[28]

RESULTS

Among the 203 probands enrolled in the study at wave 1, we had follow-up data on 149 probands (73%): 68 BPD subjects and 81 control subjects. More BPD subjects were lost to follow-up compared to controls (37 [35%] vs 17 [17%], $\chi^2 = 8.3$, $P = .004$). We found no significant differences in age ($t = -0.3$, $P = .7$), socioeconomic status ($z = -1.3$, $P = .2$), and

Table 1. Clinical Characteristics and Lifetime Comorbidities of the Follow-Up Sample: Bipolar Disorder and Controls (N = 149)

Demographic	Controls (n = 81)	Bipolar Disorder (n = 68)	Test Statistic	*P* Value
Age, mean ± SD, y	19.2 ± 2.5	20.1 ± 3.1	$t = -2.0$	.05
Socioeconomic status, mean ± SD	1.9 ± 1.0	2.5 ± 1.1	$z = -3.4$	.0006
Sex (male), n (%)	48 (59)	42 (62)	$\chi^2 = 1.0$	.76
Parental history of substance use disorder, n (%)	38 (47)	51 (75)	$\chi^2 = 12.1$	< .001
Comorbidity, n (%)				
Multiple anxiety disorders	7 (9)	22 (32)	$\chi^2 = 13.3$	< .001
Attention-deficit/ hyperactivity disorder	16 (20)	52 (76)	$\chi^2 = 47.9$	< .001
Conduct disorder	12 (15)	43 (63)	$\chi^2 = 37.2$	< .001
Oppositional defiant disorder	13 (16)	63 (93)	$\chi^2 = 86.8$	< .001

parental history of SUD (33 [61%] vs 89 [60%], $\chi^2 = 0.03$, $P = .9$) between those who were lost to follow-up and those who continued on in the study. We did however find a significant difference in sex, such that more boys were lost to follow-up than girls (42 [32%] vs 12 [17%], $\chi^2 = 5.3$, $P = .02$).

Clinical Characteristics

As shown in Table 1, we found no significant differences at follow-up for age or sex between cases and controls. BPD subjects had a lower SES (higher Hollingshead scores) and more parental history of SUD.

Disorders Comorbid With BPD

The BPD group at follow-up had higher lifetime rates of comorbid psychiatric disorders compared to controls. Significant differences were noted for conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder (ADHD), and multiple anxiety disorders (Table 1).

SUD and Cigarette Smoking in Youth With BPD

The BPD probands, compared to controls, had more *new onset* cases of SUD during the time between baseline and follow-up: alcohol abuse (14 [27%] vs 12 [15%]), alcohol dependence (14 [22%] vs 4 [5%]), drug abuse (10 [19%] vs 10 [13%]), drug dependence (13 [24%] vs 7 [9%]), any SUD (15 [31%] vs 18 [23%]), and smoking (18 [25%] vs 11 ([14%]).

At the 5-year follow-up, while adjusting for SES and parental history of SUD, probands with BPD, compared to controls, reported a significantly higher rate of lifetime SUD (32 [49%] vs 21 [26%]; hazard ratio [HR] = 2.0; 95% confidence interval [CI], 1.1–3.6; $P = .02$; Figure 1), as well as higher rates of all individual SUDs including alcohol abuse (HR = 2.4; 95% CI, 1.2–4.9; $P = .01$), alcohol dependence (HR = 5.0; 95% CI, 1.6–15.7; $P = .006$), drug abuse (HR = 2.3; 95% CI, 1.03–5.3; $P = .04$), drug dependence (HR = 3.1; 95% CI, 1.3–7.2; $P = .01$), and smoking (32 [49%] vs 14 [17%]; HR = 2.9; 95% CI, 1.4–6.1; $P = .004$). Subjects with BPD also had higher rates of an alcohol use disorder (abuse or dependence; HR = 2.5; 95% CI, 1.3–5.0; $P = .006$) and drug use disorder (HR = 2.4; 95% CI, 1.2–4.9; $P = .02$). Likewise, more BPD probands (36%; n = 24/66) had combined alcohol plus drug use disorders compared to controls (10%; n = 8/81); adjusting for SES and parental history of SUD: HR = 3.8; 95% CI, 1.6–9.3; $P = .003$.

There was more abuse or dependence of cannabis, opiates, cocaine, sedatives, stimulants, hallucinogens, and all other drugs listed (aspirin and ecstasy) among subjects with BPD compared to controls (any use disorder, adjusting for SES and parental history of SUD: 27 [40%] vs 11 [14%]; odds ratio [OR] = 3.7; 95% CI, 1.5–9.0; $P = .003$). While cannabis was the most commonly abused drug, 13% and 9% of the BPD group had an addiction to opiates or cocaine (see Table 2).

The Effect of Comorbid Disorders on SUD

We repeated our analyses on SUD and nicotine addiction controlling for ADHD and CD—2 major comorbid disorders found to independently result in SUD.[29] When we added ADHD to the model with SES and parental SUD, we found a significant effect of BPD status on age-adjusted risk of nicotine dependence (HR = 2.4; 95% CI, 1.0–5.6; $P = .049$), alcohol dependence (HR = 6.0; 95% CI, 1.5–25.0; $P = .01$), drug abuse (HR = 3.2; 95% CI, 1.2–8.4; $P = .02$), drug dependence (HR = 3.2; 95% CI, 1.2–9.0; $P = .02$), and overall SUD (HR = 2.4; 95% CI, 1.1–5.1; $P = .02$). We did not find a significant association for alcohol abuse (HR = 2.4; 95% CI, 0.95–5.6; $P = .06$). When we added CD to the model with SES and parental SUD, all associations lost significance (all *P* values > .05).

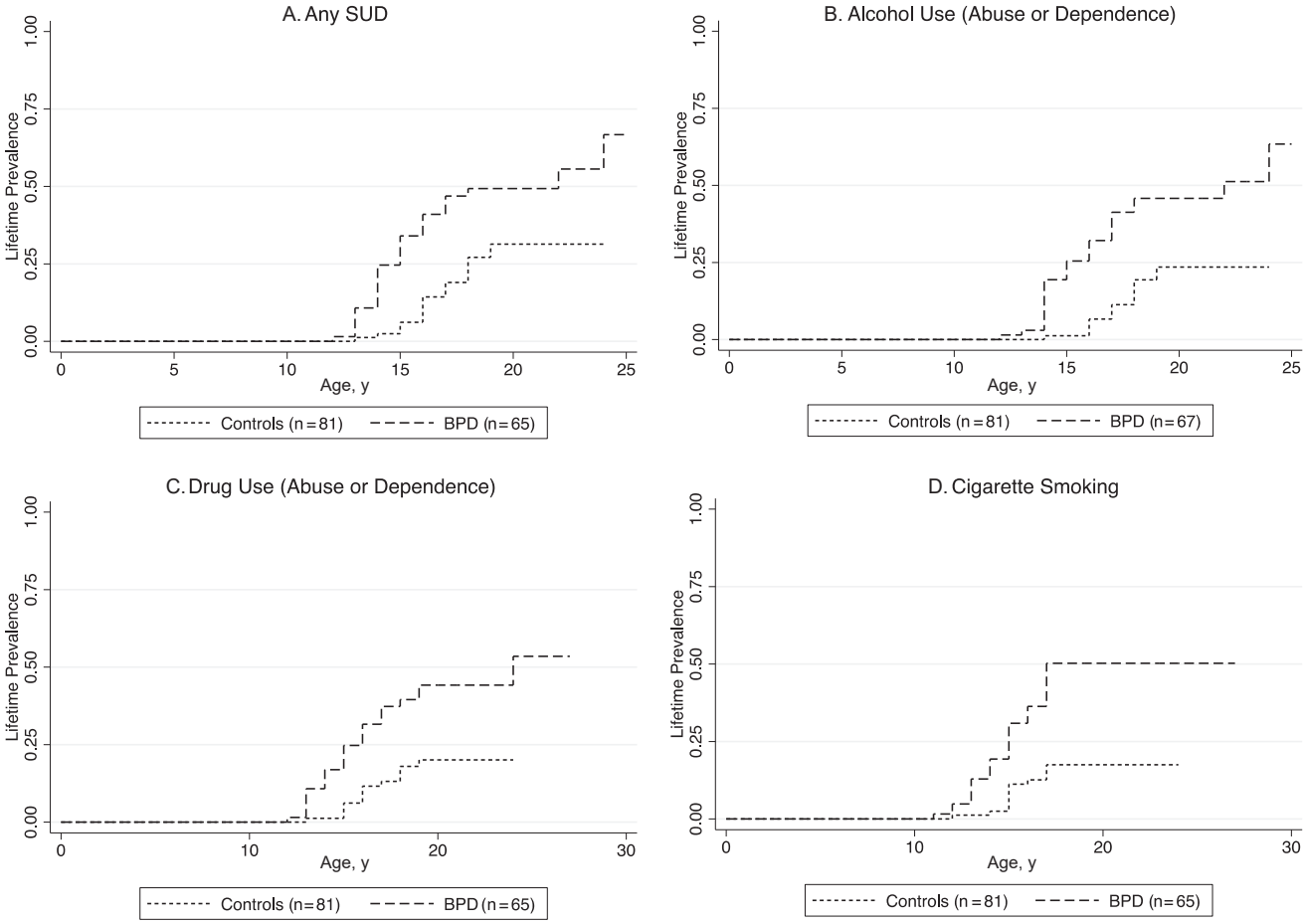
The Effect of Conduct Disorder

To further examine the relationship between BPD, CD, and SUD, we ran an additional analysis with 4 groups: controls (N = 81), BPD only (N = 25), BPD + CD (N = 29, where BPD onset < CD onset), and BPD + CD (N = 13, where BPD onset ≥ CD onset). One subject was missing age at onset for CD and was subsequently removed from this analysis. While controlling for SES and parental history of SUD, we found that subjects with CD (with an onset prior to BPD or at the same time or after BPD) were more likely to have any SUD than subjects with BPD alone or controls (all *P* values < .05; see Figure 2). We found that subjects with a BPD onset before CD onset were more likely to have nicotine dependence than subjects with BPD alone or controls (all *P* values < .05). We found no significant difference in the risk of any SUD or nicotine dependence between subjects who had a CD onset after BPD or a CD onset at the same time or before BPD (both *P* values > .05).

SUD Onset in Youth With BPD

The mean ± SD age at onset for any SUD was 15.5 ± 2.4 years and was similar for the individual ages at onset for drug use disorders (15.5 ± 2.4 years) and alcohol use disorders (16.0 ± 2.4 years). In general, BPD subjects had a > 1 year earlier onset of an SUD compared to controls: any SUD (14.9 ± 2.6 years vs 16.5 ± 1.6 years; $t = 2.6$; $P = .01$), alcohol use disorders (15.5 ± 2.7 years vs 17.1 ± 1.4 years; $t = 2.2$; $P = .03$), and any drug use disorders (15.1 ± 2.6 years vs 16.2 ± 1.6

Figure 1. Survival Curves for Substance Use and Smoking (N = 149)[a]



[a]While adjusting for SES and parental history of SUD, we found that probands with BPD, compared to controls, reported a significantly higher rate of lifetime SUD (32 [49%] vs 21 [26%]; HR] = 2.0; 95% CI, 1.1–3.6; $P = .02$), as well as higher rates of all individual SUDs including alcohol abuse (HR = 2.4; 95% CI, 1.2–4.9; $P = .01$), alcohol dependence (HR = 5.0; 95% CI, 1.6–15.7; $P = .006$), drug abuse (HR = 2.3; 95% CI, 1.03–5.3; $P = .04$), drug dependence (HR = 3.1; 95% CI, 1.3–7.2; $P = .01$), and smoking (32 [49%] vs 14 [17%]; HR = 2.9; 95% CI, 1.4–6.1; $P = .004$).
Abbreviations: BPD = bipolar disorder, CI = confidence interval, HR = hazard ratio, SES = socioeconomic status, SUD = substance use disorder.

Table 2. Specific Drugs of Abuse and Dependence in Bipolar Disorder and Controls (N = 149), n (%)

Drug Type	Controls (n = 81)	Bipolar Disorder (n = 68)	Test Statistic	*P* Value
Cannabis	10 (12)	24 (35)	$\chi^2 = 11.1$	.001
Opiates	2 (2)	9 (13)	$\chi^2 = 6.3$	.01
Cocaine	1 (1)	6 (9)	$\chi^2 = 4.8$[a]	.047
Sedatives	0 (0)	3 (4)	$\chi^2 = 3.6$[a]	.09
Stimulants	0 (0)	2 (3)	$\chi^2 = 2.4$[a]	.21
Hallucinogens	1 (1)	3 (4)	$\chi^2 = 1.4$[a]	.3
All other drugs	0 (0)	3 (4)	$\chi^2 = 3.6$[a]	.09

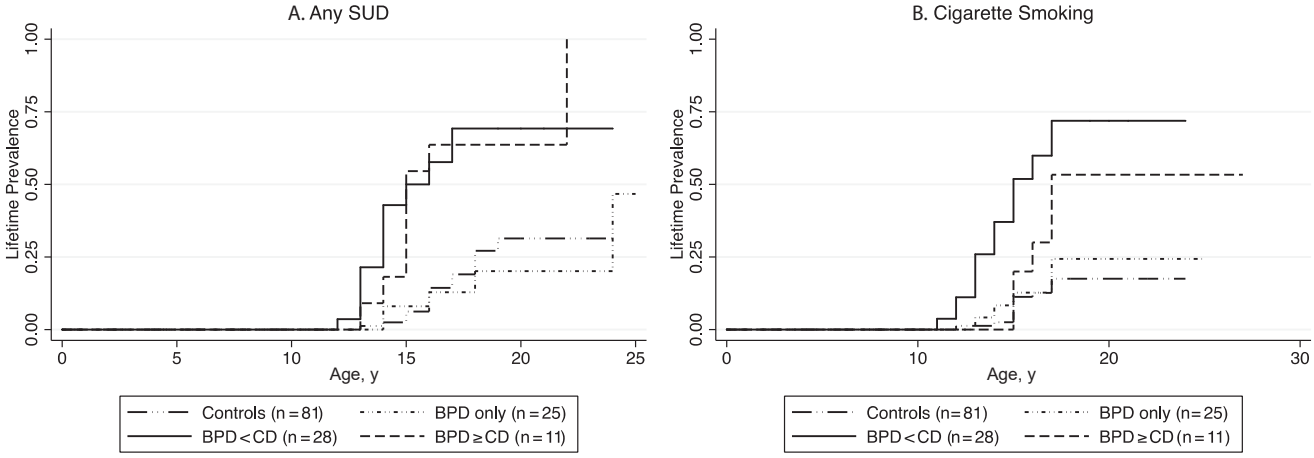
[a]Exact test was employed.

years; $t = 1.4$; $P = .16$). The mean ± SD duration of any SUD was 3.4 ± 3.1 years. We found that BPD subjects manifest a longer duration of SUD relative to controls (4.4 ± 3.2 years vs 1.6 ± 1.9 years; $P = .0007$).

SUD and Nicotine Addiction in BPD at Follow-Up: Persistent vs Nonpersistent BPD

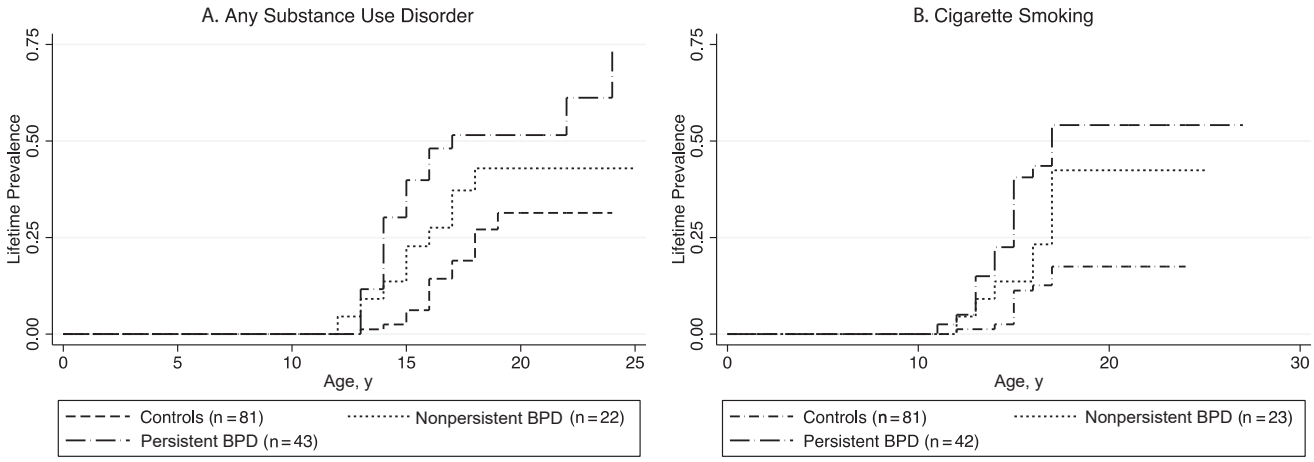
Among the 68 subjects with BPD at both baseline and wave 2 assessments, 23 (34%) reported no BPD at follow-up, 9 (13%) reported subthreshold BPD, and 36 (53%) reported having full BPD. Qualitative analysis of the data suggested that those with persistent BPD had the highest risk for SUD relative to those with nonpersistent BPD and controls. Moreover, we found a linear effect of the 3 groups (controls = 0, nonpersistent BPD = 1, and persistent BPD = 2) for any SUD (HR = 1.7; 95% CI, 1.3–2.3; $P < .001$) and for smoking (HR = 2.0, 95% CI, 1.4–2.8; $P < .001$.) However, when stratifying solely by the presence or absence of persistent BPD, we failed to find significant differences between persistent BPD and nonpersistent BPD in the percentage of any SUD or cigarette smoking (Figure 3, adjusting for SES and parental history of SUD [nonpersistent vs controls: HR = 1.5; 95% CI, 0.6–3.3; $P = .36$; persistent vs controls: HR = 2.4; 95% CI, 1.2–4.5; $P = .008$; persistent vs nonpersistent: HR = 1.6; 95% CI, 0.7–3.5; $P = .23$]). We found similar results for cigarette smoking (nonpersistent vs controls: HR = 2.1; 95% CI, 0.8–5.1; $P = .12$; persistent vs controls: HR = 4.1; 95% CI, 3.6–7.8; $P = .001$; persistent vs nonpersistent: HR = 1.7; 95% CI, 0.8–3.9; $P = .17$).

Figure 2. Substance Use and Cigarette Smoking (N = 145) Stratified by the Presence and Absence of Conduct Disorder (CD)[a]



[a]While adjusting for SES and parental history of SUD, we found that those with CD had the highest risk for SUD and cigarette smoking compared to those without CD (BPD only and controls) (SUD: BPD + CD [BPD onset ≥ CD onset] vs controls: HR = 4.6; 95% CI, 2.0–10.9; $P < .001$; BPD + CD [BPD onset < CD onset] vs controls: HR = 3.5; 95% CI, 1.8–6.8; $P < .001$; BPD + CD [BPD ≥ CD] vs BPD only: HR = 8.4; 95% CI, 2.6–26.6; $P < .001$; BPD + CD [BPD < CD] vs BPD only: HR = 6.3; 95% CI, 2.3–17.2; $P < .001$; BPD + CD [BPD ≥ CD] vs BPD + CD [BPD < CD]: HR = 1.3; 95% CI, 0.6–3.1; $P = .5$). (Cigarette smoking: BPD + CD [BPD ≥ CD] vs controls: HR = 2.8; 95% CI, 0.96–8.4; $P = .058$; BPD + CD [BPD < CD] vs controls: HR = 5.9; 95% CI, 2.8–12.8; $P < .001$; BPD + CD [BPD ≥ CD] vs BPD only: HR = 3.03; 95% CI, 0.86–10.7; $P = .09$; BPD + CD [BPD < CD] vs BPD only: HR = 6.3; 95% CI, 2.3–17.2; $P < .001$; BPD + CD [BPD ≥ CD] vs BPD + CD [BPD < CD]: HR = 0.5; 95% CI, 0.2–1.3; $P = .3$).
Abbreviations: BPD = bipolar disorder, CI = confidence interval, HR = hazard ratio, SES = socioeconomic status, SUD = substance use disorder.

Figure 3. Substance Use and Cigarette Smoking (N = 146)[a]



[a]While adjusting for SES and parental history of SUD, for any SUD: nonpersistent vs controls: HR = 1.5; 95% CI, 0.6–3.3; $P = .36$; persistent vs controls: HR = 2.4; 95% CI, 1.2–4.5; $P = .008$; persistent vs nonpersistent: HR = 1.6; 95% CI, 0.7–3.5; $P = .23$. For cigarette smoking: nonpersistent vs controls: HR = 2.1; 95% CI, 0.8–5.1; $P = .12$; persistent vs controls: HR = 4.1; 95% CI, 3.6–7.8; $P = .001$; persistent vs nonpersistent: HR = 1.7; 95% CI, 0.8–3.9; $P = .17$.
Abbreviations: BPD = bipolar disorder, CI = confidence interval, HR = hazard ratio, SES = socioeconomic status, SUD = substance use disorder.

BPD Characteristics Associated With SUD

To examine what characteristics within BPD are associated with SUD at follow-up, BPD probands with SUD (n = 35) were compared to BPD probands without SUD (n = 33) (Table 3). BPD subjects with (versus without) SUD had more lifetime hospitalizations related to psychiatric disorders or SUD (72% [n = 49] vs 4% [n = 3]; $\chi^2 = 76.0$, $P < .0001$). As expected, there were higher rates of lifetime psychopharmacology in all probands with BPD compared to controls, but these percentages did not significantly differ between those with and without SUD. At baseline or during the 5-year follow-up, we did not find any differences in rates of pharmacotherapy or psychotherapy between BPD subjects with and without SUD (all P values > .05).

We then examined the temporal relationship of BPD and SUD by examining ages at onset of both disorders. A majority of BPD subjects (n = 29 [83%]) experienced the full syndromic onset of their BPD prior to SUD, while a minority had the onset within the same year (n = 3 [9%]) or after the onset of SUD (n = 3 [9%]). We did not find a significant difference in the chronology of mania compared to depression in the sample (onset of mania prior to depression in probands with BPD with and without SUD). We also did not find a significant difference in lifetime

Table 3. Clinical Characteristics and Lifetime Comorbidities of Individuals With Bipolar Disorder (BPD) Without (–) and With (+) Substance Use Disorders (SUDs)

Demographic	BPD – SUD (n = 33)	BPD + SUD (n = 35)	Test Statistic	*P* Value
Age, mean ± SD, y	18.7 ± 2.9	21.3 ± 2.8	$t = -3.8$	.0004
Socioeconomic status, mean ± SD	2.3 ± 1.0	2.7 ± 1.2	$z = -1.5$	.14
Sex (male), n (%)	20 (61)	22 (63)	$\chi^2 = 0.04$	.85
Parental history of SUD, n (%)	24 (73)	27 (77)	$\chi^2 = 0.18$	.67
Parental history of MDD, n (%)	23 (70)	30 (86)	$\chi^2 = 1.9$	.16
Parental history of BPD, n (%)	10 (30)	10 (29)	$\chi^2 = 0.06$	.81
Total BPD symptom count, mean ± SD	5.8 ± 1.3	6.3 ± 1.2	$t = -1.4$	.16
BPD episodes, mean ± SD	24.8 ± 39.8	30.6 ± 48.6	$t = -0.6$	.60
BPD onset in adolescence, n (%)	5 (15)	9 (26)	$\chi^2 = 1.2$	.3
MDD onset in adolescence, n (%)	5 (15)	11 (31)	$\chi^2 = 2.5$	.1
Conduct disorder, n (%)	5 (15)	19 (54)	$\chi^2 = 17.0$	< .001
Oppositional defiant disorder, n (%)	14 (42)	23 (66)	$\chi^2 = 3.71$	.05
Full Scale Intelligence Quotient, mean ± SD	102.4 ± 14.3	102.1 ± 11.2	$t = 0.09$	.92
Repeated a grade, n (%)	5 (15)	10 (29)	$\chi^2 = 1.78$	.18
Special class, n (%)	22 (67)	21 (60)	$\chi^2 = 0.32$	.57
Extra help, n (%)	25 (76)	27 (77)	$\chi^2 = 0.02$	.89

Abbreviation: MDD = major depressive disorder.

SUD or cigarette smoking between BPD I and BPD II at baseline (n = 47, 58, respectively) or follow-up (n = 31, 37, respectively; all *P* values > .05).

DISCUSSION

The results of this study partially support our hypotheses that developing adolescents with BPD manifest an increased likelihood for cigarette smoking and SUDs compared to their non–mood disordered peers. While cigarette and SUD endorsement remained significant when controlling for ADHD, this significance did not remain when controlling for CD, highlighting the importance of CD in juvenile-onset BPD as a major risk for later cigarette smoking and SUD. We also found a disturbing trend of more combined and severe SUDs in adolescents with BPD compared to controls. There was a linear trend for risk of cigarette smoking and SUD such that persistent > nonpersistent > controls—although both BPD groups continued to be at higher risk than controls. These data punctuate the need for providers to carefully monitor cigarette smoking and SUD in these highly dysregulated adolescents, in particular those with persistent BPD and CD.

Our findings that adolescent BPD increases the likelihood for cigarette smoking and SUDs mirror an emerging literature documenting this risk in clinical and epidemiologic samples.[14,30–33] For instance, Goldstein et al[17] found that in 12- to 17-year-old adolescents with BPD followed for a mean of 2.7 years, 32% of subjects had their first onset of SUD, with 76% of the aforementioned group manifesting multiple SUDs. Our data also support findings noted in adult-based studies that provide further evidence linking age at onset of BPD with the risk for SUD.[7,10,12,34–36] Specifically, Lin et al[10] reported that early-onset BPD was associated with a higher risk for SUD compared to later-onset BPD.

Given that early-onset BPD is associated with SUD, and early-onset SUD is associated with a more pernicious SUD course and ongoing impairment,[37] youth with BPD are at a very high risk for severe SUD-related difficulties in addition to a chronic BPD course.[13,38] In support of this notion, Kozloff and colleagues[32] noted that individuals with BPD plus SUD were more likely to use mental health services compared to those without this comorbidity. These data highlight the need for careful, ongoing screening of cigarette and substance use in adolescents and young adults[22] with BPD.

An important finding in the current study was that the association of cigarette smoking and SUD in maturing BPD youth was independent of ADHD[29]; however, the risk for cigarette smoking and SUD did not remain significant when controlling for CD, suggesting that comorbidity with CD mediates this risk. While these findings may be confounded by the high comorbidity of CD in BPD in our and others' samples,[5,6] it may be that CD in BPD is a critical variable in linking SUD to BPD.[39]

Of interest, CD as a major risk for the development of SUD in BPD partially supports our previous findings in midadolescence in which juvenile-onset BPD plus CD conferred a greater risk for SUD than that attributable to BPD without CD.[40] In midadolescence, however, BPD was a risk for SUD independent of CD.[12,40] Our current findings support epidemiologic data published by Carlson et al[41] who reported that young adults (< 30 years of age) with BPD plus SUD had a significant overrepresentation of CD as youth and that the presence of comorbid CD was the main mediator of the SUD in the young adults with BPD.

Clinically, maturing adolescents and young adults with BPD plus CD should be aggressively monitored for the onset of cigarette smoking and SUD. From a research perspective, BPD plus CD may represent a distinct subtype of BPD[19,42,43] that is identifiable in childhood and associated with high degrees of later impairment such as SUD. For instance, Barzman et al[44] found that juveniles with later-onset BPD were more likely to be delinquent than those with early-onset BPD—an important consideration given that delinquency is strongly associated with SUD.[21] Our data add to a growing literature highlighting heterogeneity in BPD based on the comorbidity of BPD and CD. Further studies evaluating the mechanisms of SUD in BPD plus CD, such as internal self-regulatory mechanisms[22,44] and familial/genetic risks, are necessary.

While our findings are potentially confounded by treatment effects on "persistence" and limited by statistical power, we found evidence of a linear effect in that subjects with persistent BPD manifest the highest risk (and earliest onset) of cigarette smoking and SUD relative to nonpersistent BPD and controls. However, our data also suggest that even subjects with nonpersistent BPD were at elevated risk for

SUD relative to controls. Our findings are consistent with a 5-year follow-up report by Wozniak et al[5] who, using a similar definition of "persistence," reported an almost 2-fold higher risk for SUD and cigarette smoking in persistent cases. Along the same lines, Lewinsohn et al[46] reported a higher risk for alcohol and drug use in those with full BPD versus subthreshold BPD.

Similar to others, we found that the majority of adolescents (83%) with BPD and SUD experienced the full syndromic onset of their BPD prior to SUD, while a minority had the onset of their BPD after that of SUD.[47–49] Winokur et al,[50] Strakowski et al,[51,52] and Lin et al[10] have helped elucidate this developmental timing of SUD as it pertains to BPD in adults. Lin et al[10] showed that early-onset BPD precedes and is associated with SUD, and Winokur et al[50] reported that a subgroup of subjects with BPD plus SUD showed evidence of alcoholism secondary to BPD. It is possible to hypothesize that BPD-associated poor judgment, limited self-control, and emotional dysregulation and disinhibition contribute to the high risk for SUD in young adulthood.[22,53] In support of this notion, we recently reported a strong relationship between the degree of emotional dysregulation and the risk for SUD in BPD.[22]

The findings in the current study need to be tempered against methodological limitations. The sample was mostly white and may not generalize to community or minority samples. Although our sample was large, the subgroup of adolescents in the control group and those with specific disorders was relatively small, limiting our statistical power for some analyses. Our assessments at baseline and 5-year follow-up relied on retrospective reporting to detail BPD, SUD, and other psychiatric comorbidity and may have missed important interval data. Among our original probands, we reascertained 73% of probands at the 5-year follow-up. However, we had significantly more BPD subjects that were lost to follow-up compared to controls. While the current follow-up rate is similar to that in other studies of juvenile BPD,[5] we may have underestimated the severity of outcomes in the BPD group because of less power, differences in sex, and differential severity of those cases reassessed. SUD was defined categorically by subjects meeting full *DSM* criteria for abuse or dependence, and not by urine toxicology screens. Because we used these definitions, use and misuse of substances as well as subthreshold non-BPD psychopathology or substance abuse were not captured. Future studies should integrate parent report, subject self-report, and subject report during structured interview, as well as urine toxicology testing, to more accurately identify substance misuse both categorically and dimensionally in youth.[54]

Despite these limitations, our controlled findings add to the literature by demonstrating that adolescent BPD persists in 66% of adolescents into young adulthood. BPD was associated with higher rates and more severe SUD compared to controls. In particular, comorbid CD and the persistence of bipolar symptoms resulted in higher rates of SUD. As they age, adolescents with BPD have a high degree of persistence of BPD and CD symptoms that appear to be related to higher risk for cigarette smoking and SUD. These findings have important clinical considerations. Since BPD onset occurs prior to the SUD in the majority of cases, practitioners following these individuals should treat symptoms of BPD and continue to carefully monitor for cigarette smoking and the development of SUD. Finally, youth with persistent BPD and comorbid CD appear to be at the greatest risk for SUD, and it may be that CD is the primary mediator between BPD and SUD.

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REFERENCES

1. Youngstrom EA, Birmaher B, Findling RL. Pediatric bipolar disorder: validity, phenomenology, and recommendations for diagnosis. *Bipolar Disord*. 2008;10(1 pt 2):

194–214.
2. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
3. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(10):1139–1148.
4. Geller B, Tillman R, Bolhofner K, et al. Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *Arch Gen Psychiatry*. 2006;63(10):1130–1138.
5. Wozniak J, Petty CR, Schreck M, et al. High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: a four year prospective longitudinal follow-up study. *J Psychiatr Res*. 2011;45(10):1273–1282.
6. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*. 2006;18(4):1023–1035.
7. Goldstein BI, Levitt AJ. Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the national epidemiologic survey on alcohol and related conditions. *Am J Psychiatry*. 2006;163(9):1633–1636.
8. Rounsaville BJ, Anton SF, Carroll K, et al. Psychiatric diagnoses of treatment-seeking cocaine abusers. *Arch Gen Psychiatry*. 1991;48(1):43–51.
9. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264(19):2511–2518.
10. Lin PI, McInnis MG, Potash JB, et al. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *Am J Psychiatry*. 2006;163(2):240–246.
11. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1,000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875–881.
12. Wilens TE, Biederman J, Adamson JJ, et al. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. *Drug Alcohol Depend*. 2008;95(3):188–198.
13. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(2):175–183.
14. Goldstein BI, Strober MA, Birmaher B, et al. Substance use disorders among adolescents with bipolar spectrum disorders. *Bipolar Disord*. 2008;10(4):469–478.
15. Biederman J, Faraone SV, Hatch M, et al. Conduct disorder with and without mania in a referred sample of ADHD children. *J Affect Disord*. 1997;44(2–3):177–188.
16. Weinberg NZ, Glantz MD. Child psychopathology risk factors for drug abuse: overview. *J Clin Child Psychol*. 1999;28(3):290–297.
17. Goldstein BI, Strober M, Axelson D, et al. Predictors of first-onset substance use disorders during the prospective course of bipolar spectrum disorders in adolescents. *J Am Acad Child Adolesc Psychiatry*. 2013;52(10):1026–1037.
18. Kovacs M, Pollock M. Bipolar disorder and comorbid conduct disorder in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry*. 1995;34(6):715–723.
19. Biederman J, Faraone SV, Chu MP, et al. Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. *J Am Acad Child Adolesc Psychiatry*. 1999;38(4):468–476.
20. Endrass J, Vetter S, Gamma A, et al. Are behavioral problems in childhood and adolescence associated with bipolar disorder in early adulthood? *Eur Arch Psychiatry Clin Neurosci*. 2007;257(4):217–221.
21. Whitmore EA, Mikulich SK, Thompson LL, et al. Influences on adolescent substance dependence: conduct disorder, depression, attention deficit hyperactivity disorder, and gender. *Drug Alcohol Depend*. 1997;47(2):87–97.
22. Wilens TE, Martelon M, Anderson JP, et al. Difficulties in emotional regulation and substance use disorders: a controlled family study of bipolar adolescents. *Drug Alcohol Depend*. 2013;132(1–2):114–121.
23. Geller B, Fox LW, Clark KA. Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *J Am Acad Child Adolesc Psychiatry*. 1994;33(4):461–468.
24. Ambrosini PJ. Historical development and present status of the Schedule for Affective Disorders and Schizophrenia for school-age children (K-SADS). *J Am Acad Child Adolesc Psychiatry*. 2000;39(1):49–58.
25. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for *DSM-III-R* (SCID), I: history, rationale, and description. *Arch Gen Psychiatry*. 1992;49(8):624–629.
26. Wilens TE, Biederman J, Wozniak J, et al. Can adults with attention-deficit/hyperactivity disorder be distinguished from those with comorbid bipolar disorder? findings from a sample of clinically referred adults. *Biol Psychiatry*. 2003;54(1):1–8.
27. Hollingshead AB. Four factor index of social status. New Haven, CT: Yale University Press; 1975.
28. Stata Corporation. *Stata User's Guide: Release 9*. College Station, TX: Stata Corp LP; 2005.
29. Charach A, Yeung E, Climans T, et al. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry*. 2011;50(1):9–21.
30. Geller B, Tillman R, Bolhofner K, et al. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry*. 2008;65(10):1125–1133.
31. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry*. 2007;164(4):582–590.
32. Kozloff N, Cheung AH, Schaffer A, et al. Bipolar disorder among adolescents and young adults: results from an epidemiological sample. *J Affect Disord*. 2010;125(1–3):350–354.
33. Strober M, Schmidt-Lackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry*. 1995;34(6):724–731.
34. Goldstein BI, Bukstein OG. Comorbid substance use disorders among youth with bipolar disorder: opportunities for early identification and prevention. *J Clin Psychiatry*. 2010;71(3):348–358.
35. Perlis RH, Brown E, Baker RW, et al. Clinical features of bipolar depression versus major depressive disorder in large multicenter trials. *Am J Psychiatry*. 2006;163(2):225–231.
36. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry*. 2001;158(3):420–426.
37. Brook JS, Adams RE, Balka EB, et al. Early adolescent marijuana use: risks for the transition to young adulthood. *Psychol Med*. 2002;32(1):79–91.
38. Geller B, Tillman R, Craney JL, et al. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. *Arch Gen Psychiatry*. 2004;61(5):459–467.
39. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry*. 2000;157(2):213–219.
40. Wilens TE, Martelon M, Kruesi MJ, et al. Does conduct disorder mediate the development of substance use disorders in adolescents with bipolar disorder? a case-control family study. *J Clin Psychiatry*. 2009;70(2):259–265.
41. Carlson GA, Bromet EJ, Jandorf L. Conduct disorder and mania: what does it mean in adults. *J Affect Disord*. 1998;48(2–3):199–205.
42. Biederman J, Mick E, Wozniak J, et al. Can a subtype of conduct disorder linked to bipolar disorder be identified? integration of findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program. *Biol Psychiatry*. 2003;53(11):952–960.
43. Wozniak J, Biederman J, Faraone SV, et al. Heterogeneity of childhood conduct disorder: further evidence of a subtype of conduct disorder linked to bipolar disorder. *J Affect Disord*. 2001;64(2–3):121–131.
44. Barzman DH, DelBello MP, Fleck DE, et al. Rates, types, and psychosocial correlates of legal charges in adolescents with newly diagnosed bipolar disorder. *Bipolar Disord*. 2007;9(4):339–344.
45. Farrell AD, Kung EM, White KS, et al. The structure of self-reported aggression, drug use, and delinquent behaviors during early adolescence. *J Clin Child Psychol*. 2000;29(2):282–292.
46. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*. 2000;2(3 pt 2):281–293.
47. Wilens TE, Biederman J, Abrantes AM, et al. Clinical characteristics of psychiatrically referred adolescent outpatients with substance use disorder. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):941–947.
48. Mezzich AC, Tarter RE, Hsieh Y, et al. Substance abuse severity in female adolescents: association between age at menarche and chronological age. *Am J Addict*. 1992;1:217–221.
49. Stowell RJ, Estroff TW. Psychiatric disorders in substance-abusing adolescent inpatients: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 1992;31(6):1036–1040.
50. Winokur G, Coryell W, Akiskal HS, et al. Alcoholism in manic-depressive (bipolar) illness: familial illness, course of illness, and the primary-secondary distinction. *Am J Psychiatry*. 1995;152(3):365–372.
51. Strakowski SM, Tohen M, Stoll AL, et al. Comorbidity in mania at first hospitalization. *Am J Psychiatry*. 1992;149(4):554–556.
52. Strakowski SM, Sax KW, McElroy SL, et al. Course of psychiatric and substance abuse syndromes co-occurring with bipolar disorder after a first psychiatric hospitalization. *J Clin Psychiatry*. 1998;59(9):465–471.
53. Tarter RE, Kirisci L, Mezzich A, et al. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am J Psychiatry*. 2003;160(6):1078–1085.
54. Gignac M, Wilens TE, Biederman J, et al. Assessing cannabis use in adolescents and young adults: what do urine screen and parental report tell you? *J Child Adolesc Psychopharmacol*. 2005;15(5):742–750.