Does Conduct Disorder Mediate the Development of Substance Use Disorders in Adolescents With Bipolar Disorder? A Case-Control Family Study

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Supported by National Institutes of Health grants RO1 DA12945 and K24 DA016264 (Dr. Wilens).

Presented at the Pediatric Bipolar Conference, March 28–29, 2008, Boston, Mass.

Financial disclosure appears at the end of this article.

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Background: Recent work has highlighted important relationships among conduct disorder (CD), substance use disorders (SUD), and bipolar disorder in youth. However, because bipolar disorder and CD are frequently comorbid in the young, the impact of CD in mediating SUD in bipolar disorder youth remains unclear.

Method: 105 adolescents with DSM-IV bipolar disorder (mean ± SD age = 13.6 ± 2.50 years) and 98 controls (mean ± SD age = 13.7 ± 2.10 years) were comprehensively assessed with a structured psychiatric diagnostic interview for psychopathology and SUD. The study was conducted from January 2000 through December 2004.

Results: Among bipolar disorder youth, those with CD were more likely to report cigarette smoking and/or SUD than youth without CD. However, CD preceding SUD or cigarette smoking did not significantly increase the subsequent risk of SUD or cigarette smoking. Adolescents with bipolar disorder and CD were significantly more likely to manifest a combined alcohol plus drug use disorder compared to subjects with bipolar disorder without CD ($\chi^2 = 11.99$, $p < .001$).

Conclusions: While bipolar disorder is a risk factor for SUD and cigarette smoking in a sample of adolescents, comorbidity with preexisting CD does not increase the risk for SUD. Further follow-up of this sample through the full risk of SUD into adulthood is necessary to confirm these findings.

J Clin Psychiatry 2009;70(2):259–265

Juvenile bipolar disorder in its various forms affects from 1%–4% of pediatric groups,[1] with up to one fifth of psychiatrically referred children and adolescent psychiatric outpatients manifesting bipolar disorder.[2,3] Convergent evidence documents that bipolar disorder is a substantial cause of morbidity and disability among youth, including high rates of hospitalization, disruption of the family environment, and severe psychosocial disability.[4–10] Systematic studies of bipolar disorder youth have found high rates of psychiatric comorbidity.[3,10–16] Among the most concerning comorbidities in juvenile onset bipolar disorder is the link with cigarette smoking and substance use disorders (SUDs, including drug or alcohol abuse or dependence).[17–20]

In independent samples, we have shown that juvenile bipolar disorder is a risk for cigarette smoking and SUD[17–20]; however, the role of conduct disorder (CD) in accounting for these findings has not been fully explored. This issue is important considering the high comorbidity between bipolar disorder and CD[3,11,21–27] and the well-documented association between CD and SUD, particularly in the context of mood dysregulation.[28–33] Further understanding of the nature of the associations between bipolar disorder, CD, and SUD is of high relevance. For example, since heterogeneity exists in SUD, it may be that CD in bipolar disorder predicts a different risk, onset, severity, or course of SUD. The delineation of SUD risk in bipolar disorder attending to CD is of great clinical and public health interest. If targeted, child-based

psychopathology can be identified early with heightened surveillance and intervention, which may result in reduced SUD. Also, scientifically parsing out the heterogeneity of bipolar disorder and SUD may provide important data on developmental etiologies and subtypes of SUD.[34] The main aim of this study was to evaluate the associations between bipolar disorder and SUD attending to the comorbidity with CD. To this end, we examined the risk for SUD associated with CD, bipolar disorder, and the combination of both in a large sample of adolescents with and without bipolar disorder. On the basis of the literature, we hypothesized that CD will mediate the association between bipolar disorder and SUD.

METHOD

Subjects

The current study is based on assessments of our ongoing, controlled, family-based study of adolescents with bipolar disorder. The methods of the study are described in detail elsewhere.[20] Briefly, we ascertained 105 bipolar adolescent probands and 98 non–mood disordered control subjects and their first-degree relatives. Subjects from both groups were recruited from the same catchment area through newspaper advertisements, Internet postings, clinical referrals to our program (bipolar disorder only), and internal postings within the Partners Healthcare/Massachusetts General Hospital system. These methods were used to collect controls that would also use the Partners/Massachusetts General Hospital system if they had bipolar disorder, representing the same source population as the cases. The study was conducted from January 2000 through December 2004.

We included families with a child (designated the proband) aged 10 to 18 years and at least 1 parent available to complete interviews about the children. We also recruited the probands' biologic siblings, as young as age 6 years. We excluded potential probands if they had been adopted or if their nuclear family was not available for study. We also excluded any youth with major sensorimotor handicaps that would impede the testing process, such as paralysis, deafness, or blindness; those with profound disorders of language, including autism and inadequate command of the English language; and those with 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 this study, and a federal certificate of confidentiality was obtained for the study.

A 2-stage ascertainment procedure selected subjects. For bipolar disorder probands, the first stage assessed the diagnosis of bipolar disorder by screening all children using a telephone questionnaire conducted with their primary caregiver that queried about symptoms of bipolar disorder and study exclusion criteria. The second stage confirmed the diagnosis of bipolar disorder using a structured psychiatric interview, as described in Assessments. Only subjects who received a positive diagnosis at both stages were included in the study sample. Also, we screened non–mood disordered controls in 2 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 dysthymic disorder or unipolar depression to bipolar disorder.[23]

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 (T.W., J.B.). Raters were blind to the ascertainment status of the probands. Psychiatric assessments for subjects under 18 years old relied on the DSM-IV Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (KSADS-E)[35] and were based on independent interviews with the primary caregivers and direct interviews of probands and siblings. Psychiatric assessments for subjects aged 18 years or older relied on the Structured Clinical Interview for DSM-IV (SCID). For every diagnosis, information was gathered regarding the ages at onset and offset of full syndromatic criteria, and treatment history.

Substance use disorder in our analyses included any alcohol or drug (excluding nicotine) abuse or dependence. SUD, conduct disorder, and smoking dependence were diagnosed on the basis of DSM-IV criteria using the KSADS-E and SCID. All CD and smoking diagnoses used age-appropriate criteria to ensure accurate diagnosis. All cases of CD were reviewed by clinicians to determine accurate diagnosis. To meet a positive diagnosis of smoking dependence, subjects under 18 years of age needed to endorse any amount of smoking daily, whereas subjects over 18 needed to endorse smoking at least a pack of cigarettes per day. Recent evidence suggests the utility of structured interview data compared to objective data for "lifetime" SUD determination.[36] Rates of disorders reported are lifetime prevalence. Duration of disorders is expressed in years based on ages at 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 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. In addition to assessment of abuse and dependence, subjects were queried for any use of illicit drugs during the SUD module of the structured interview. 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 κ coefficients of agreement by having 3 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 κ coefficient was 0.98. Kappa coefficients for individual diagnoses included major depressive disorder (1.0), manic episode (0.95), attention-deficit/hyperactivity disorder (ADHD; 0.88), conduct disorder (1.0), oppositional defiant disorder (0.90), antisocial personality disorder (0.80), and substance use disorder (1.0). The Hollingshead Four-Factor Index was used to assess socioeconomic status.[37] As a measure of overall lifetime functioning, we used the DSM-IV Global Assessment of Functioning (GAF).[38]

Statistical Analysis

To examine the full relationship between bipolar disorder, CD, and SUD, we conducted 2 separate analyses. We compared the demographic factors between those bipolar disorder subjects with and without lifetime history of CD who were in our primary analysis (Cox model). We used t tests for meristic outcomes, Wilcoxon rank sum tests for socioeconomic status, and Pearson χ^2 tests for binary outcomes.

We used the Cox proportional hazards models to assess the risk of SUD between bipolar disorder subjects with and without lifetime history of CD. Subjects who reported an onset of CD prior to or within 1 year of the bipolar disorder onset were dropped from all Cox analyses (N = 17). Subjects were considered exposed if they reported a CD onset prior to the substance-use onset and were considered unexposed if they did not have CD or reported a CD onset following the substance-use onset. Subjects whose CD and substance-use onset were at the same time (within 1 year) were dropped from the Cox analysis for that outcome. Because we assessed multiple outcomes, each with its own age at onset, the number of dropped subjects varied across the different outcomes ranging from 2 for cigarette smoking to 4 for alcohol abuse and any substance use. Further information regarding this method was reported previously.[39]

We also compared subjects with bipolar disorder and no CD, bipolar disorder and late-onset CD, and bipolar disorder and early-onset CD, defined as onset before or after age 10 years using Cox proportional hazards models. Time to onset of a SUD or cigarette smoking was the primary outcome, and group membership (bipolar disorder–CD, early-onset CD, late-onset CD) was the primary covariate.

In our secondary analysis, we used all bipolar disorder subjects in linear and logistic regression models to assess the overall association between bipolar disorder, CD, and SUD and the influence of CD on the severity of SUD. No subjects were dropped in this analysis. An α-level of .05 was used to assert statistical significance; all statistical tests are 2-tailed. We calculated all statistics using Stata, version 10.0 (StataCorp LP, College Station, Tex.).

RESULTS

Sample Characteristics

We ascertained 105 adolescents with bipolar disorder (mean ± SD age = 13.6 ± 2.50 years) and 98 controls (mean ± SD age = 13.7 ± 2.10 years). Among bipolar subjects, 58 (55%) met lifetime criteria for CD; 47 subjects (45%) met criteria for subthreshold CD or had no CD.[20] Among controls, 8 subjects (8%) met lifetime criteria for CD and 4 subjects (4%) met lifetime criteria for SUD. In order to test our main hypothesis, we stratified our subjects with preexisting bipolar disorder by the presence and absence of CD. We found that subjects with bipolar disorder plus CD (N = 41) were significantly younger at bipolar disorder onset than bipolar disorder subjects without CD (N = 47, see Table 1). We found no significant differences in age, socioeconomic status, gender, family intactness, or frequency of lifetime ADHD diagnosis (Table 1). We found a higher frequency of multiple anxiety disorders (2 or more in a lifetime) in subjects with bipolar disorder plus CD.

We also found that most bipolar disorder plus CD subjects had their CD onset prior to any SUD or cigarette-smoking onset. For all categories of SUD and cigarette smoking, at least 50% of subjects had CD before SUD (Figure 1).

Risk of SUD

We examined the risk that preexisting CD begets on subsequent SUD in adolescents with bipolar disorder using Cox proportional hazards models to control for age, socioeconomic status, family history of bipolar disorder, and family history of SUD. Specifically, stratifying our youth with bipolar disorder by the presence or absence of CD preexisting SUD, we did not find any significant difference in risk between the 2 groups (Table 2). When we repeated this analysis controlling for the presence of multiple anxiety disorders, no result gained significance.

As an exploratory analysis, we also looked to see whether preexisting SUD mediates the risk of CD among

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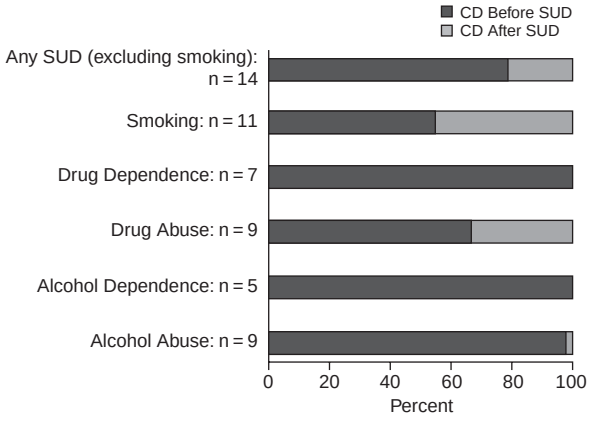
Table 1. Demographic Variables for Adolescents With Bipolar Disorder Stratified by Conduct Disorder (N = 88)

Variable	Bipolar Disorder Without CD (N = 47)	Bipolar Disorder With CD (N = 41)[a]	Statistic	p Value
Age, mean ± SD, y	13.11 ± 2.25	14.05 ± 2.47	t = –1.87	.06
Age at onset of bipolar disorder, mean ± SD, y	8.76 ± 3.57	7.10 ± 3.64	t = 2.15	.03
Socioeconomic status, mean ± SD[b]	2.20 ± 1.26	1.88 ± 1.04	z = 0.93	.35
Gender, male, N (%)	30 (64)	29 (71)	$\chi^2 = 0.47$	.50
Family intact, N (%)	30 (64)	20 (49)	$\chi^2 = 2.02$	.16
DSM-IV ADHD (lifetime history), N (%)	37 (79)	28 (68)	$\chi^2 = 4.43$	.11
Multiple anxiety disorders, N (%)	26 (55)	32 (78)	$\chi^2 = 5.04$	.03

[a]Bipolar disorder preceded CD for all subjects with bipolar disorder plus CD.
[b]Assessed with Hollingshead Four-Factor Index.[37]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder.

Figure 1. Subjects With Bipolar Disorder Classified by Onset of Conduct Disorder (CD) With Respect to Substance Use Disorder (SUD) (n = 41)



bipolar disorder youth using Cox proportional hazards models (N = 94). When we conducted this analysis between bipolar disorder with SUD youth (N = 23, 24%) and bipolar disorder without SUD youth (N = 71, 76%), we did not find any significant difference in risk of CD between the 2 groups.

Age at CD Onset and SUD

We further assessed the influence of the age at onset of CD on the onset of SUD with Cox proportional hazards models. These models predict time of onset of SUD and cigarette smoking in subjects with bipolar disorder without CD compared to subjects with early CD onset (before age 10 years, N = 14) and late CD onset (onset at age 10 years or older, N = 27). All subjects with early CD onset reported CD before any SUD onset. For subjects with late CD onset, 20 subjects reported CD prior to cigarette smoking and substance abuse onsets, 23 subjects reported CD prior to an alcohol abuse onset, 27 reported CD prior to an alcohol dependence onset, and 24 reported CD prior to a substance dependence onset.

Since we found significant variance in mean age across groups ($F = 11.93$, $df = 2,88$; $p < .0001$), we corrected all analyses for age: subjects with late-onset CD were significantly older than subjects with early-onset CD ($F = 22.50$, $df = 1,88$; $p < .0001$) and subjects with bipolar disorder without CD ($F = 14.13$, $df = 1,88$; $p < .001$). When we compared the 3 groups with each SUD onset, we did not find any significant differences in the ages at SUD onset. We also did not find any differences in the ages at SUD onset between those with early CD onset or late CD onset.

Overall Association

Using logistic regression to control for age, socioeconomic status, family history of bipolar disorder, and family history of SUD, we first examined the overall relationship between bipolar disorder, CD, and SUD among all subjects. As previously reported,[20] there were significant differences between bipolar disorder subjects with and without CD and controls in rates of overall SUD ($\chi^2 = 20.52$, $p < .001$), alcohol abuse ($\chi^2 = 11.45$, $p < .005$), drug abuse ($\chi^2 = 11.84$, $p < .005$), drug dependence ($\chi^2 = 6.26$, $p < .05$), and cigarette smoking ($\chi^2 = 14.88$, $p < .001$). When we repeated this analysis controlling for the presence of multiple anxiety disorders, alcohol abuse was the only outcome to lose significance.

Rates of SUD were significantly lower in bipolar disorder subjects without CD (N = 7, 15%) compared to bipolar disorder with CD (N = 27, 47%; $\chi^2 = 5.91$, $p = .009$). Similar trends were seen for alcohol and drug use disorders.[20] When we compared bipolar disorder subjects without CD and controls, overall SUD and cigarette smoking remained significant ($p < .05$).

Clinical Characteristics of SUD

We also evaluated the influence of CD on severity of SUD and smoking in individuals with SUD and smoking, using linear regression controlling for age. Comparing subjects with bipolar disorder plus CD to those without CD, we found no significant difference in the duration of cigarette smoking or SUD. We found a significant effect of CD on the frequency of the nonnicotine simultaneous abuse or dependence of more than 1 drug or alcohol across all subjects: bipolar disorder plus CD subjects were significantly more likely to manifest a combined alcohol

Table 2. Substance Use Disorders in Adolescents With Bipolar Disorder by the Presence or Absence of Conduct Disorder (CD) (N = 88)[a]

	Bipolar Disorder Without CD		Bipolar Disorder With CD					
Outcome	N	N (%) With Outcome	N	N (%) With Outcome	Hazard Ratio	95% CI	χ^2	p Value
Substance use disorder	50	10 (20)	34	11 (32)	1.46	0.62 to 3.43	0.74	.39
Alcohol abuse	48	6 (13)	37	8 (22)	1.24	0.43 to 3.58	0.16	.69
Alcohol dependence	47	1 (2)	41	5 (12)	3.23	0.37 to 28.08	1.13	.29
Drug abuse	50	7 (14)	33	6 (18)	1.12	0.38 to 3.33	0.04	.84
Drug dependence	47	2 (4)	37	7 (19)	3.45	0.71 to 16.83	2.34	.13
Cigarette smoking	52	9 (17)	34	6 (18)	0.94	0.33 to 2.63	0.02	.89

[a]CD preceded outcome for all subjects with both CD and outcome; Cox proportional hazards models controlling for subjects' age.

plus drug use disorder (23 subjects or 40% of 58 cases with bipolar disorder plus CD) compared to subjects with bipolar disorder without CD (3 subjects or 6% of 47 subjects; by logistic regression, $\chi^2 = 11.99$, $p < .001$).

Subjects with bipolar disorder plus CD had significantly lower current GAF scores (mean ± SD = 45.4 ± 5.8) than subjects with bipolar disorder without CD (mean ± SD = 50.3 ± 7.0; $F = 16.39$, $df = 1,102$; $p < .001$). We also found that subjects with bipolar disorder plus CD had significantly lower lifetime GAF scores (mean ± SD = 37.7 ± 5.1 vs. 40.0 ± 5.7; linear regression: $F = 3.97$, $df = 1,102$; $p = .05$).

DISCUSSION

The results of these analyses of adolescents with bipolar disorder show that CD commonly has onset prior to SUD. Contrary to our hypothesis, CD that precedes SUD does not significantly increase the risk for a subsequent SUD or earlier-onset SUD. Compared to adolescents with bipolar disorder without CD, CD is associated overall with a more complicated SUD (combined drug plus alcohol use disorders) and poorer overall functioning.

These findings are reminiscent of our previous work in juvenile bipolar disorder and SUD. In 3 pediatric samples, we have reported that adolescents with bipolar disorder are at a 2- to 4-fold higher risk for SUD relative to prepubescent-onset bipolar disorder[18,20,40] independent of CD. In these studies, however, the sequential relationship of CD onset to SUD onset was not examined.

Our current data partially replicate previous studies that have shown an increased risk for SUD associated with CD in bipolar disorder.[28–33] In some of these studies, CD plus other psychopathology incrementally increased the risk for SUD and/or resulted in earlier onset of SUD. In the Course and Outcome of Bipolar Illness in Youth (COBY) study, for example, Goldstein et al.[41] reported that among 12- to 17-year-old adolescents with bipolar disorder, CD was associated with a 5.6-fold increased likelihood of developing SUD. Carlson et al.[13] reported that young adults with bipolar disorder (< 30 years of age) and SUD had a significant overrepresentation of CD as youth and that the presence of comorbid CD, not bipolar disorder, accounted for the increased risk for SUD. In our current data, overall bipolar disorder plus CD was associated with a more complicated SUD; however, controlling for CD, bipolar disorder was associated with SUD. Moreover, if one examined only those cases with CD prior to SUD, CD did not increase incrementally the risk for subsequent SUD over that observed with bipolar disorder. Differences in the findings may be accounted for by age at follow-up (adolescents vs. young adults), study design (prospective vs. retrospective), and definitions of CD (exclusion vs. inclusion of SUD in CD criteria).

Our data show some differences in the associations for drug compared to alcohol use disorders in our bipolar disorder sample. Despite alcohol being the most common substance misused in our sample of adolescents with bipolar disorder, subjects with CD plus bipolar disorder, specifically, were more likely to have cigarette smoking and drug use disorders. It is of interest that similar findings have been reported recently,[42] in which conduct mediated drug but not alcohol use disorders in first-degree relatives of ADHD youth. While our current finding may be due to relatively small sample sizes in specific analyses, further work needs to be completed to examine more carefully the role of CD in mediating specific classes of agents that are misused or abused.

Why CD is more likely to occur with drug use disorders than with alcohol use disorder remains unclear. It may be that drug use is considered more delinquent, and given the nature of CD, these youth preferentially use cigarettes and drugs. Alternatively, given familial specificity in SUD,[43,44] CD may be linked to specific forms of SUD, such as cigarette or drug use disorders. It may also be related to the increased risk for cigarette use that precedes SUD, which in turn may kindle specific subsequent drug use disorders.[39] Clinically, youth with bipolar disorder plus CD need to be carefully monitored for the onset of cigarette smoking as well as SUD, in particular, marijuana.

The reported association between bipolar disorder, CD, and SUD is not surprising considering that juvenile mania is frequently associated with prolonged and

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aggressive outbursts[45,46] that may predispose these youth to develop SUD.[47–49] Although these aberrant behaviors are consistent with the diagnosis of CD, they may be due to the behavioral disinhibition that characterizes bipolar disorder that may lead to SUD.[4,21,50] Considering that adolescence is a time of high risk for the development of SUD, we have speculated that bipolar disorder (and CD), through poor judgment, limited self-control, and/or disinhibition,[51] may be particularly noxious for the development of SUD during adolescence, the time of heightened risk for SUD.[18,20,52] It may be that adolescents self-medicate their irritable mood, aggressivity, and "affective storms" with substances of abuse or alcohol.[49,53] It may also be that there is a synergistic familial/genetic or other biologic predisposition to SUD in bipolar disorder (with or without CD),[50] such that a synergistic relationship exists placing youth simultaneously at risk for bipolar disorder, CD, or the combination. Our findings continue to support our previous work on the independence of bipolar disorder as a risk factor for adolescent-onset SUD.[18–20] What remains to be further delineated are the magnitude of the ultimate risk associated with CD in the development of SUD, the interactions of CD with bipolar disorder, the roles of additional psychosocial stressors and family functioning, and the mediating roles of mood-related CD and treatment as our sample passes through the full age of risk for SUD.

There are a number of methodological limitations in the current study. Data for the current study are derived from the baseline assessment and are, hence, cross-sectional in nature. Follow-up of this sample through the full age of risk for SUD is necessary. The sample size is limited, particularly in groups such as those with SUD and CD. Substance use disorder was determined by aggregating direct and indirect report via structured interview, as opposed to urine toxicology screens. However, we have found in separate samples that such interviews may provide a more sensitive method of detecting historical SUD that may be missed by urine testing.[36] Additionally, while differences in ages existed between groups such as those with early versus later onset of CD, we utilized modeling to correct for these differences. Furthermore, we were unable to assess the magnitude of the ultimate risk associated with CD or the interaction of CD with bipolar disorder due to the lack of individuals with CD without bipolar disorder. Given the racial and ethnic composition of our sample, it is unclear if these findings will generalize to other settings. Also, our results may not generalize to bipolar disorder cases in the community.

Despite these limitations, the results of these analyses show that bipolar disorder in adolescence confers an elevated risk for SUD and that CD is associated with a more complex presentation of SUD in this group. However, early-onset CD does not appear to increase incrementally the risk for cigarette smoking or SUD over that created by bipolar disorder alone. Clinicians need to be mindful of the association between CD and SUD and the role this association may play in the risk of SUD among bipolar disorder youth. Further study of this group as they pass fully through the age of risk is necessary.

Financial disclosure: **Dr. Wilens** receives research support from, is a speaker for, or is on the advisory board of Abbott, McNeil, Eli Lilly, National Institutes of Health National Institute on Drug Abuse (NIH NIDA), Novartis, Merck, and Shire. **Dr. Biederman** receives research support from Alza, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, McNeil, Merck, Organon, Otsuka, Shire, National Institute of Mental Health, and National Institute of Child Health and Human Development; is a consultant/advisory board member for Janssen, McNeil, Novartis, and Shire; is a member of the speakers bureaus for Janssen, McNeil, Novartis, Shire, and UCB Pharma; and in previous years, has received research support, consultation fees, or speaker's fees from Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly, Esai, Forest, Glaxo, Gliatech, NARSAD, NIDA, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, The Stanley Foundation, and Wyeth. **Dr. Kreusi** receives research support from or is a consultant for Select Health and Eli Lilly. **Dr. Gignac** receives research support from, is a speaker for, or is on the advisory board for Janssen Ortho, Shire, and Eli Lilly. **Mss. Martelon**, **Parcell**, **Westerberg**, and **Schillinger** report no additional financial or other relationships relevant to the subject of this article.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, M.D., Ph.D., at kwagner@psychiatrist.com.

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