Parsing the Association between Bipolar, Conduct, and Substance Use Disorders: A Familial Risk Analysis

Joseph Biederman, Stephen V. Faraone, Janet Wozniak, and Michael C. Monuteaux

Background: Bipolar disorder has emerged as a risk factor for substance use disorders (alcohol or drug abuse or dependence) in youth; however, the association between bipolar disorder and substance use disorders is complicated by comorbidity with conduct disorder. We used familial risk analysis to disentangle the association between the three disorders.

Methods: We compared relatives of four proband groups: 1) conduct disorder + bipolar disorder, 2) bipolar disorder without conduct disorder, 3) conduct disorder without bipolar disorder, and 4) control subjects without bipolar disorder or conduct disorder. All subjects were evaluated with structured diagnostic interviews. For the analysis of substance use disorders, Cox proportional hazard survival models were utilized to compare age-at-onset distributions.

Results: Bipolar disorder in probands was a risk factor for both drug and alcohol addiction in relatives, independent of conduct disorder in probands, which was a risk factor for alcohol dependence in relatives independent of bipolar disorder in probands, but not for drug dependence. The effects of bipolar disorder and conduct disorder in probands combined additively to predict the risk for substance use disorders in relatives.

Conclusions: The combination of conduct disorder + bipolar disorder in youth predicts especially high rates of substance use disorders in relatives. These findings support previous results documenting that when bipolar disorder and conduct disorder occur comorbidly, both are validly diagnosed disorders. Biol Psychiatry 2000;48:1037–1044 © 2000 Society of Biological Psychiatry

Key Words: Bipolar disorder, conduct disorder, substance use, familial risk

Introduction

In recent years, a focus on bipolar disorder (BPD) as a risk factor for substance use disorders (SUDs; alcohol or drug abuse or dependence) in youth has emerged as a clinical and public health concern. A prospective study of children and adolescents with and without attention-deficit/hyperactivity disorder (ADHD) found that early-onset BPD predicted subsequent SUD independently of ADHD (Biederman et al 1997). Similarly, an excess of SUDs has been reported in studies of adolescents with BPD or prominent mood lability and dyscontrol (Biederman et al 1997; West et al 1996; Wilens et al 1997a; Wills et al 1995; Young et al 1995). West et al (1996) reported that 40% of inpatient adolescents with BPD suffered from SUDs. Likewise, we reported that psychiatrically referred adolescent outpatients with SUDs were more likely than those without SUDs to have comorbid BPD (Wilens et al 1997a).

But understanding the association between BPD and SUDs is complicated by the fact that BPD is frequently comorbid with conduct disorder (CD; Biederman et al 1998b; Faraone et al 1997b; Geller et al 1994; Kovacs and Pollock 1995; Kutcher et al 1989; Wozniak et al 1995a) and CD is a well-documented risk factor for SUDs in youth (Bukstein et al 1989, 1992; DeMilio 1989; Hovens et al 1994; Kaminer 1991; McKay et al 1991, 1992; West et al 1996; Wilens et al 1997a).

One approach to addressing this issue is the use of data from families (Faraone et al 1999). Since BPD, CD, and SUD are known to be familial conditions, examining their familial patterns of aggregation and coaggregation can disentangle the associations among them. Although several studies have shown a familial association between BPD and SUD and between CD and SUD (Dunner et al 1979; Maier and Merikangas 1996; Morrison 1975; Penick et al 1978; Raskin and Miller 1993), no studies examined the three-way associations between BPD, CD, and SUD.

A better understanding of the links among SUDs, CD, and BPD is of high scientific, clinical, and public health relevance. Clinically, the identification of BPD in SUD youth may permit the use of appropriate treatments targeting the underlying mood disorder. Scientifically, the delineation of a subtype of SUDs linked to mood disorders in the young may lead to the identification of a more
The purpose of this study was to disentangle the association between BPD, CD, and SUD using familial risk analysis (Faraone et al. 1999). We tested three hypotheses: 1) BPD in probands is a risk factor for SUD in relatives, independent of comorbid CD in probands; 2) CD in probands is a risk factor for SUD in relatives, independent of comorbid BPD in the probands; and 3) in comorbid cases, the effects of BPD and CD in probands combine additively to predict the risk for SUDs in relatives (i.e., relatives in the comorbid proband group are at greatest risk for SUDs, but no more than what we would expect from the risks imparted by the individual disorders in the probands).

Methods and Materials

Subjects

We pooled data from two samples of youth with DSM-III-R BPD and their first-degree relatives. The first sample comprised 29 youths with BPD and their 99 first-degree relatives ascertained through a longitudinal study of ADHD that had assessed 128 ADHD probands and their 434 relatives as well as 107 non-ADHD probands (control subjects) and their 354 relatives (Biederman et al. 1996; Faraone et al. 1997a). The second sample comprised 16 consecutively referred BPD children and their 46 first-degree relatives ascertained through consecutive outpatient referrals to a pediatric psychopharmacology program (Biederman et al. 1995; Wozniak et al. 1995b). In a prior report (Biederman et al. 1998b) we concluded that pooling these samples was reasonable because 1) all subjects were evaluated using the same assessment methodology; 2) patterns of comorbidity and functioning did not differ between the two samples; and 3) we found no differences in rates of ADHD, major depression, BPD, antisocial personality disorder, conduct disorder, or SUDs (all \( p > .05 \)) in first-degree relatives of BPD probands from the two ascertainment sources.

The pooled sample contained 45 BPD probands and their 145 first-degree relatives. We stratified these into two proband groups defined by the presence or absence of CD and BPD: 1) CD+/BPD (\( N = 26 \) probands, 92 relatives) and 2) BPD without CD (BPD; \( N = 19 \) probands, 53 relatives). We compared these with two additional groups: 1) children from our family study of ADHD who had CD without BPD (CD; \( N = 16 \) probands, 58 relatives) and 2) control subjects from our family study of ADHD without ADHD, CD, or BPD (\( N = 102 \) probands, 338 relatives).

Assessment Procedures

As previously described (Biederman et al. 1992; Wozniak et al. 1995b), all children were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia, epidemiologic version (SADS-E; Orvaschel and Puig-Antich 1987) administered to the mother by raters who had been trained and supervised by the senior investigator (JB). We directly interviewed children older than 12 with the Kiddie SADS-E. The approach taken by the Kiddie SADS to evaluate diagnostic criteria for bipolar disorder is similar to that taken by the original SADS. First, a period of time characterized by the features in section A are established, then each of the criteria in B are addressed. For example, to assess B1 in the mania module the interviewer would ask the parent, “During this period did [child’s name] feel especially self-confident? Like he/she could do anything? Was special? In what way? Special powers? Stronger? Smarter?” For parents and adult siblings, we collected self-reports of symptoms using the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1990) supplemented with modules from the Kiddie SADS-E covering childhood diagnoses.

For every diagnosis in children and adults, information was gathered regarding the ages at onset and end of symptoms, number of episodes, and treatment history. All diagnoses were reviewed by a diagnostic sign-off committee chaired by the service chief (JB) that reviewed both the items endorsed during the interview and detailed notes taken by the interviewer. We computed \( \kappa \) coefficients of diagnostic agreement by having three experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff. From 173 interviews, the median \( \kappa \) was .86. We attained a kappa of 1.0 for CD and ADHD, and .91 for BPD.

To be given the lifetime diagnosis of BPD, the child had to meet full DSM-III-R criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period of extreme and persistently elevated, expansive, or irritable mood, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance, plus criterion C, associated impairment. To be given the diagnosis of CD, the child had to meet full DSM-III-R diagnostic criteria for CD. In addition, all diagnoses of BPD and CD were presented for review and were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. By “clinically meaningful” we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. A key point is that these diagnoses were made as part of the clinical assessment procedures for our clinic; they were not simply research diagnoses computed by counting symptoms endorsed and applying an algorithm. We consider these diagnoses clinically meaningful because they are routinely used in planning the treatment of children in our clinic.

As in our previous work, we diagnosed major depression only if the depressive episode was associated with severe impairment. To define our diagnostic SUD outcomes, we included subjects who satisfied full DSM-III-R criteria for alcohol dependence or
Table 1. Demographic Characteristics of Sample

<table>
<thead>
<tr>
<th></th>
<th>Proband diagnostic status</th>
<th>Control subjects</th>
<th>Omnibus analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD+BPD</td>
<td>BPD</td>
<td>CD</td>
</tr>
<tr>
<td>Number of probands</td>
<td>26</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Number of relatives</td>
<td>92</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>13.3 (4.1)</td>
<td>10.9 (4.4)</td>
<td>16.6 (4.0)</td>
</tr>
<tr>
<td>Parents</td>
<td>39.2 (6.2)</td>
<td>40.2 (4.6)</td>
<td>42.4 (5.8)</td>
</tr>
<tr>
<td>Siblings</td>
<td>14.2 (4.6)</td>
<td>11.4 (4.1)</td>
<td>18.4 (7.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>26 (100)</td>
<td>18 (95)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Parents</td>
<td>25 (49)</td>
<td>18 (49)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Siblings</td>
<td>27 (69)</td>
<td>8 (62)</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>2.2 (1.2)</td>
<td>1.9 (1.0)</td>
<td>1.7 (1.1)</td>
</tr>
<tr>
<td>Intactness of families</td>
<td>14 (54)</td>
<td>13 (68)</td>
<td>11 (69)</td>
</tr>
</tbody>
</table>

Values represent mean (sd) or frequency (percent). Gender represents the proportion of the group that is male. CD, conduct disorder; BPD, bipolar disorder.

\[<.05 \text{ vs. CD only.} \]

\[<.05 \text{ vs. BPD only.} \]

\[<.05 \text{ vs. control subjects.} \]

drug dependence, with information derived from the structured interviews. We also defined a broad category of SUD, which included subjects meeting DSM-III-R criteria for either drug or alcohol abuse or dependence.

All subjects older than 12 gave written informed consent for participation. Parents gave written informed consent for participation of children under 12, and these children participated only if they assented to the study procedures. All subjects older than 12 were considered competent to give consent, having understood the study procedures and potential risks. The Subcommittee on Human Studies of the Massachusetts General Hospital approved this study.

**Statistical Analyses**

For the analysis of demographic features, binary outcomes were examined using logistic regression, whereas ordinal outcomes were analyzed with ordinal logistic regression and continuous outcomes with linear regression. Where sparse data made the fitting of a logistic regression model difficult (i.e., the comparison of gender for probands), analyses were conducted using the Fisher exact test. Omnibus tests found to be statistically significant were followed by pairwise comparisons to tease out differences.

For the analysis of SUDs, Cox proportional hazard survival models were utilized to compare age-at-onset distributions. These models correct for age differences among relative groups by using age at onset as survival time for SUD cases and age at interview as the time of censoring for non-SUD cases. To test our hypotheses, the CD and BPD diagnoses of probands were independent variables and the SUD outcomes in relatives were the dependent variables. From these models we report the main effect of CD (statistically controlling for BPD), the main effect of BPD (statistically controlling for CD), and the interaction between CD and BPD. The two main effects test our first two hypotheses (i.e., they show whether each disorder predicts SUD after taking the other into account). The interaction tests our third hypothesis. A significant interaction indicates that the effects of BPD and CD do not combine additively to predict the risk for SUDs (i.e., it shows that the risk for SUDs in the comorbid group is different from what we would expect from the risks imparted by the individual disorders). To show the nature of these effects, we used graphs that stratified family members based on four proband groups (CD only, BPD only, CD+BPD, and neither).

We handled the effects of nonindependence of observations among family members by adjusting the variance estimates of regression coefficients using Huber’s formula (Huber 1967), a “theoretical bootstrap” that produces robust statistical tests. The method involves entering the cluster scores (i.e., the sum of scores within families) into the formula for the estimate of variance. The resulting p values are robust to distributional assumptions and to misspecification of the linear predictors in the model. All statistical tests were two tailed and used the .05 level of statistical significance.

**Results**

**Sociodemographic Characteristics**

Table 1 shows the sociodemographic characteristics of the sample. The mean ages of probands with CD+BPD (13.3 years) and probands with BPD (10.9 years) were significantly lower than those of the CD probands and control subjects (16.6 and 15.3 years, respectively). Consequently, the mean age of parents of CD+BPD probands (39.2 years) was significantly lower than the mean age of parents of the control probands (42.2 years). Also, the mean ages of the siblings of probands with CD+BPD (14.2 years) and siblings of probands with BPD (11.4 years) were significantly lower than that of siblings of the CD probands (18.4 years). Furthermore, there were significant differences in age between the siblings of pro-
bands with CD+BP and siblings of probands with BP, as well as between the siblings of probands with BP and siblings of control probands (15.7 years). In addition, CD+BP probands and BP probands came from significantly lower social class strata, as compared with control subjects. Finally, CD+BP probands had a smaller proportion of intact families than control probands (54% vs. 83%). No differences were found in the gender distributions of the sample. The Cox model analyses corrected for age differences by using age at onset as survival time for SUD cases and age at interview as the time of censoring for non-SUD cases. We corrected for other sociodemographic differences by entering them as covariates.

Disorders in Relatives
Because SUD typically begins in adolescence, analyses of SUD outcomes were restricted to relatives older than 14. Figure 1A gives the age-at-onset curves for alcohol dependence in relatives stratified by proband group. This figure plots the cumulative probability of developing alcohol dependence as a function of age. As the statistics in the figure indicate, both proband BP and CD predicted alcohol dependence in relatives independently of one another. This can be seen by the fact that the curves for subjects having only one of these disorders each rise above the curve for the control subjects. We also see that the curve for the families of BP+CD subjects rises above the curves for the BP and CD groups. Because the interaction between BP and CD was not significant, we know that the effect of the two disorders combined is a simple additive sum of the effects of the individual disorders. In Figure 1A, this is seen by the fact that the cumulative probability of onset of alcohol dependence for the BP+CD group is approximately equal to the sum of these probabilities for the BP and CD groups.

Figure 1A also shows that the pattern of onset over time

Figure 1. Kaplan–Meier survival estimates in relatives older than 14 years, stratified by proband diagnosis.
differs for the BPD and CD groups. For families of BPD and BPD+CD probands, we see a sharp rise in the onset of alcohol dependence that differentiates these groups from control subjects during the teenage years. In contrast, the curve for families of CD probands does not diverge from the control curve until adulthood.

The data for drug dependence show a different pattern of results (Figure 1B). Although the BPD curve rises above the control curve, the CD curve does not. As this suggests, there is a significant effect of proband BPD on drug dependence in relatives after taking proband CD into account. But there is not a significant effect of CD when BPD is taken into account. Notably, the curve for CD families is nearly identical to that of control families. The figure clearly shows that proband CD is associated with drug dependence in relatives only when it co-occurs with BPD. Because the interaction is not significant, we must conclude that the effects of CD and BPD are additive. As we saw for alcohol dependence, the BPD and BPD+CD curves for drug dependence show a sharp rise in onset that differentiates these groups from control subjects during the teenage years.

Because proband BPD and CD were associated with lower social class and more divorce and separation among parents (Table 1), we used these variables as covariates in our analyses to see if the effects of CD and BPD could be accounted for by these demographic variables. After making these corrections, the effect of proband BPD as a predictor of relative drug dependence remained significant \(z = 2.9, p = .004\), but the effect of proband BPD as a predictor of relative alcohol dependence was only marginally significant \(z = 1.7, p = .088\). The effect of proband CD as a predictor of relative alcohol dependence lost significance \(z = 1.1, p = .281\).

Discussion

Using familial risk analysis we examined the three-way association between CD, BPD, and SUD. We found strong support for hypothesis one: after accounting for CD in probands, BPD in probands was a risk factor for SUDs in relatives, including both drug and alcohol addiction. We found weaker support for hypothesis two: after accounting for BPD in probands, CD in probands was a risk factor for alcohol dependence in relatives but not for drug dependence, independent of comorbid BPD in the probands. Our third hypothesis was supported for all SUD outcomes: the effects of BPD and CD in probands combined additively to predict the risk for SUDs in relatives. The relatives in the comorbid proband group were at greatest risk for SUDs, but no more than what we would expect from the risks imparted by the individual disorders in the probands.

The finding that the proband diagnosis of BPD increases the risk for SUD in relatives is consistent with much prior work showing a significant overlap between BPD and SUDs in both youth and adults (Biederman et al 1997; Brady and Sonne 1995; Dunner and Feinman 1995; Gawin and Kleber 1986; Himmelhoch 1979; Regier et al 1990; Reich et al 1974; Rounsaville et al 1982, 1991; Strakowski et al 1998; Weiss et al 1988; West et al 1996; Wilens et al 1997a, 1997b; Wills et al 1995; Winokur et al 1995; Young et al 1995). These studies suggest that about half of clinically referred and epidemiologically derived persons with BPD have a lifetime history of an SUD. Our current finding expands upon this prior work by showing not only that BPD in youth predicts SUD in relatives, but also that the familial link cannot be accounted for by comorbid CD.

In contrast to the effect of proband BPD, which significantly increased the risk for both drug and alcohol dependence in relatives, the effect of proband CD was only significantly associated with alcohol dependence in relatives. The differential effect of CD on drug and alcohol dependence in relatives is clearly seen by comparing Figures 1A and 1B. Figure 1A shows that, in the absence of BPD, CD imparts a twofold risk for alcohol dependence in relatives, as compared with control subjects. But Figure 1B shows that the risk for drug dependence is identical in control relatives and relatives of youth who have CD without BPD. This latter point is remarkable because, if replicated by other studies, it would suggest that BPD, but not CD, is a risk factor for the familial transmission of drug dependence.

Our data show that regardless of the presence of CD in BPD probands, relatives of these probands are at risk for substance dependence onset in their teenage years. In contrast, the risk for alcohol dependence imparted by CD probands only becomes evident during adulthood. These data suggest that the familial disposition to BPD is associated with early-onset SUDs, making it especially relevant for prevention programs aimed at adolescents.

Notably, the ability of proband BPD to predict drug dependence in the relatives remained significant even after correcting for social class and divorce and separation among parents. In contrast, the effects of proband BPD and CD on alcohol dependence lost statistical significance. This provides further evidence that BPD is a potent predictor of drug dependence. Our findings for alcohol dependence, however, caution that further work is needed to clarify the joint effects of family history, social class, and family intactness on the familial transmission of substance use disorders.

As predicted by our third hypothesis, relatives of youths who had both BPD and CD had the greatest risk for SUDs. Our results also showed that this risk was additive (i.e., it was not greater than expected given the separate risks
imparted by proband BPD and proband CD). The significance of BPD+CD as a risk for SUDs is consistent with prior studies. For example, a meta-analysis of population-based epidemiologic data from the Epidemiological Catchment Area project found that a subset of earlier onset BPD patients had comorbid CD, which resulted in a course more likely to be complicated by substance abuse (Carlson et al. 1998).

These findings are consistent with the idea that when BPD and CD occur comorbidly, both are validly diagnosed disorders. Although CD and BPD are clearly different clinical conditions, the differential diagnosis can be complex when youth present with a complicated clinical picture of symptoms suggestive of both CD and BPD. When a disinhibited and aggressive youth with BPD steals, lies, assaults, or vandalizes, are these behaviors a complication of the BPD? Or are they symptoms of an antisocial tendency? When a juvenile is arrested for antisocial acts, and presents with a high degree of irritability, does he or she suffer from BPD?

If among BPD youth CD were a pseudodisorder, then we would not expect this pseudo-CD to impart the same familial risks as “true” CD. But our results support the rejection of this idea by finding that CD imparts an increased risk for alcohol dependence regardless of its comorbidity of BPD. Thus, one could interpret these results as further supporting the idea that CD occurring in the presence of BPD is true CD.

If confirmed, our findings may have important clinical and public health implications. Since BPD is one of the most severe forms of psychopathology in both children (Carlson and Kashani 1988; Geller et al. 1995; Strober et al. 1995; Wozniak et al. 1993), the treatment of BPD in comorbid cases may result in reduced risk for SUDs (Brady et al. 1998; Donovan et al. 1996; Geller et al. 1998). For example, in a small open trial of valproate in adolescent marijuana abusers with prominent mood lability, reductions in both marijuana use and mood lability were observed (Donovan et al. 1996). In addition, a recent 6-week, controlled clinical trial demonstrated that lithium treatment resulted in both significant reductions in substance use and improvement in global functioning in adolescents with comorbid BPD and SUDs (Geller et al. 1998).

In light of the large overlap between CD and BPD, it is reasonable to expect that a substantial number of CD youth may have affective dysregulation suggestive of BPD. Thus, identifying those CD children with comorbid BPD may permit the introduction of appropriate treatments to treat these aggressive antisocial youth. Treatment data from extensive chart reviews of youths with BPD suggest that antimanic agents are important for the clinical stabilization of these difficult-to-treat patients (Biederman et al. 1998a). Thus, identifying a subtype of CD patients with comorbid BPD may offer some hope of improving the highly compromised lives of these youth and possibly diverting them from the criminal justice system.

Our findings should be seen in light of certain methodological limitations. We pooled data from two data sets for greater statistical power. Although all subjects were evaluated with the same assessment methodology in the same institution by the same-trained staff, they were not evaluated at the same time. We also do not know if our results will generalize to DSM-IV criteria. Thus, these results should be viewed as preliminary until replicated in larger samples assessed concurrently with DSM-IV-based measures. Because we studied children who were clinically referred, our findings may not generalize to community samples; however, they should generalize to other referred samples.

The lack of direct psychiatric interviews with children younger than 12 may have decreased the sensitivity of some diagnoses; however, while these concerns apply to probands younger than 12 years, it is noteworthy that in this familial risk analysis we used data from relatives older than 14 years who had been directly interviewed.

Despite these limitations, our results suggest that CD cannot account for the familial link between BPD and SUDs. In contrast, although the familial link between CD and alcohol dependence cannot be accounted for by BPD, we could not demonstrate a specific familial link between CD and drug dependence. In addition, the combination of CD and BPD in youth predicts especially high rates of SUDs in relatives, suggesting that this subgroup deserves further attention in future research.

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