Brief Report

Aggression and substance abuse in bipolar disorder

Persons suffering from bipolar disorder have rates of comorbid substance use disorders (SUD) as high as 60% (1, 2). Among mood and anxiety disorders in a recent nationally representative survey, the highest odds of co-occurring SUD was associated with bipolar disorder (3). Compared to non-depressed persons, those with depression have a more than threefold risk of being alcohol dependent (4) and mania is associated with a sixfold risk of SUD (5). Further understanding of the clinical profile of persons with bipolar disorder who are at higher risk of developing comorbid SUD could aid prevention and shed light on the interplay between mood and SUD.

Studies have identified a number of correlates of SUD in mood disorder samples. These include: psychosocial impairment (6); anxiety traits and elevated cortisol near sleep onset (6); neuroticism and novelty seeking (7); perceived stress (4); ‘self-medication’ of unpleasant mood symptoms (5), and sociodemographic factors such as minority status (8), younger age (9), male gender and being divorced or never married (10).

Bipolar subtypes such as rapid cycling and mixed states (5, 11) are reported to be associated with comorbid SUD. One study found the bipolar symptoms most associated with comorbid SUD were depressive symptoms and racing thoughts (12). Studies have reported that an earlier age of onset of bipolar disorder (13, 14), particularly in adolescence (15), is associated with a higher risk of SUD. This could be mediated by increased impulsivity, which has been postulated as a link between

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bipolar disorder and SUD (16). One study found that mania complicated by comorbid alcohol misuse was associated with greater impulsivity, violence and other drug abuse (17). Trait aggression has been associated with poor outcome in bipolar disorder, specifically, a greater risk of attempted suicide (18). In this hypothesis-generating study, we searched for clinical correlates of the development of comorbid SUD in a sample of persons with bipolar disorder.

Methods

Subjects
A total of 146 consecutively enrolled subjects with bipolar disorder (types I, II and not otherwise specified) presenting for treatment of manic, hypomanic, mixed or depressed episodes at two university hospitals were included in the study. Patients with significant neurological or unstable medical conditions were not enrolled. The study group (mean age 35 years, SD = 10.9, range 17–67 years), was 57% female, 72% Caucasian, 15% Hispanic, 10% African-American and 2% Asian. A total of 27% of subjects were married and 62% were inpatients. After the studies had been described to them, subjects gave written informed consent as approved by the Institutional Review Boards.

Measures

Consensus Axis I and II diagnoses were made using the Structured Clinical Interview for DSM-IIIR/DSM-IV (SCID-P) (19, 20). As subjects were in manic, hypomanic, mixed or depressed episodes at baseline assessment, we excluded ‘state’ measures (e.g., depression and mania rating scales) from this analysis. Sociodemographic information was collected using our research clinic’s baseline demographic form. Lifetime aggression was measured with the Brown–Goodwin Aggression Inventory (BGAI), a clinician-rated measure that surveys aggression traits separately for childhood (≤ 12 years), adolescence (13–18 years) and adulthood (≥ 19 years) (21). The BGAI has been used in published studies measuring aggression in the context of mood disorders (18, 22). Reliability for the measure is high (r = 0.96) (21), and it has demonstrated evidence of construct validity (23). Hostility and impulsivity were rated with the Buss–Durkee Hostility Inventory (BDHI) (24) and the Barratt Impulsivity Scale (BIS) (25). Global psychopathology was measured with the Brief Psychiatric Rating Scale (BPRS) (26) and global functioning was measured with the Global Assessment Scale (GAS) (27). Raters were at least masters-level psychologists or nurses. Interrater agreement and intraclass coefficients were good to excellent (22).

Statistical methods

The primary outcome variable was a lifetime diagnosis of SUD. Continuous and quantitative variables were analyzed using t-tests or Mann–Whitney tests, as appropriate. We truncated the numbers of manic episodes at 10, depressive episodes at 40, suicide attempts at 5, hospitalizations at 20 and length of the current mood episode at 60 days. Categorical variables were analyzed using chi-squared tests. We used the age categories of the BGAI to compare rates of SUD in individuals with child (≤ 12 years), adolescent (13–18 years) and adult (≥ 19 years) onset of bipolar disorder.

We used multiple logistic regression analysis of lifetime SUD to test the relative association of variables significant on bivariate tests, with a focus on the effect of age at onset of mood disorder. We also analyzed the time-course of psychopathology onset and associations with aggressive traits, using subscores for the three life stages measured by the BGAI. We used paired samples t-tests to compare the age of onset of major depression with that of mania/hypomania and that of SUD.

Results

We compared proportions of subjects with child, adolescent and adult onset bipolar disorder with respect to rates of alcohol use disorder, drug use disorder, and mixed alcohol/drug use disorder (Table 1). The child/adolescent onset group was more likely to have a comorbid SUD of any kind (65.4% versus 48.5%; χ² = 4.18, df = 1, p = 0.04) and more likely to have any alcohol use disorder (pure or combined with drug misuse) (55.3% versus 36.9%; χ² = 4.73, df = 1, p = 0.03) than the adult onset bipolar group. Child onset bipolar subjects were more likely to have a lifetime alcohol use disorder (pure or combined with drugs) compared to those with onset of bipolar disorder in adolescence or adulthood (63% versus 42%; χ² = 4.82, df = 1, p = 0.03). There was a trend towards a higher proportion of child/adolescent onset bipolar subjects having comorbid drug use disorder (pure or combined with alcohol) (42.1% versus 27.7%; χ² = 3.18, df = 1, p = 0.075). The proportion of those with drug use only disorder was highest among those with adolescent onset bipolar disorder, but the proportion of adolescent onset
bipolar subjects with any drug use disorder (pure or combined with alcohol) was not significantly higher than among those with child or adult onset bipolar disorder (44% versus 32%: \( \chi^2 = 1.80, df = 1, p = 0.18 \)).

Results for demographic and clinical variables are summarized in Table 2. Bipolar patients with comorbid lifetime SUD were more likely to be male \( (p = 0.002) \) and to report higher lifetime aggression traits \( (p < 0.001) \). Aggression scores did not differ with respect to whether subjects were in a manic/hypomanic, depressed or mixed episode at baseline assessment \( (F = 2, 1.19, df = 117, p = 0.27) \). Lifetime SUD was associated with greater aggression during childhood \((0–12 \text{ years}) (t = -3.3, df = 99.9, p = 0.001), \) adolescence \((13–18 \text{ years}) (t = -3.5, df = 99, p < 0.001) \) and adulthood \((\geq 19) (t = -4.3, df = 95.9, p < 0.001) \).

Compared to those without lifetime SUD, those with lifetime SUD reported more impulsivity \( (p = 0.01) \), an earlier age of onset of the first major depressive episode \( (p = 0.009) \) and manic/hypomanic episodes \( (p = 0.004) \). Subjects with comorbid SUD made more frequent suicide attempts \( \text{Table 3} \), but there was no between-group difference in the maximum lethality of the attempts \( (Z = -0.72, p = 0.47) \). Subjects with and without SUD did not differ in terms of age, race, marital status, history of physical or sexual abuse, or family history of SUD \( \text{Table 2} \). They did not differ with respect to inpatient/outpatient status \( \text{Table 2} \), global psychopathology \( (t = -1.51, df = 93, p = 0.14) \) or global functioning \( (t = 1.30, df = 133, p = 0.19) \). Subjects with SUD were more likely to have a comorbid lifetime conduct disorder \( \text{Table 2} \). However, when subjects were stratified by type of substance, conduct disorder comorbidity was more likely among those with an alcohol use disorder \( (12\% \text{ versus } 3\% \text{; Fisher’s Exact Test \( [FET] p = 0.047 \)}) \), but not among those with a drug use disorder \( \text{data available on request} \). Those with and without SUD did not differ in proportion to those with lifetime attention-deficit hyperactivity disorder, nor with any other lifetime anxiety disorder \( \text{Table 2} \). They also did not differ in total

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With SUD (n = 85 (58%))</th>
<th>Without SUD (n = 61 (42%))</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.3 (10.8)</td>
<td>36.3 (10.9)</td>
<td>1.11 (143) 0.27</td>
</tr>
<tr>
<td>Male sex</td>
<td>46 (54)</td>
<td>17 (28)</td>
<td>(9.98) 1 0.002</td>
</tr>
<tr>
<td>Inpatient</td>
<td>50 (59)</td>
<td>40 (66)</td>
<td>(0.92) 1 0.34</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64 (74)</td>
<td>41 (67)</td>
<td>(1.15) 1 0.29</td>
</tr>
<tr>
<td>Married</td>
<td>18 (21)</td>
<td>21 (34)</td>
<td>(3.19) 1 0.07</td>
</tr>
<tr>
<td>Past physical or sexual abuse</td>
<td>42 (49)</td>
<td>24 (39)</td>
<td>(1.94) 1 0.17</td>
</tr>
<tr>
<td>First degree relatives with alcoholism</td>
<td>0.61 (0.85)</td>
<td>0.55 (0.99)</td>
<td>[-0.99] 0.32</td>
</tr>
<tr>
<td>First degree relatives with substance abuse</td>
<td>0.32 (0.77)</td>
<td>0.16 (0.45)</td>
<td>[-1.4] 0.16</td>
</tr>
<tr>
<td>Comorbid lifetime anxiety disorder</td>
<td>31 (36)</td>
<td>24 (39)</td>
<td>(0.13) 1 0.72</td>
</tr>
<tr>
<td>Comorbid lifetime conduct disorder</td>
<td>9 (11)</td>
<td>1 (2)</td>
<td>FET 0.046</td>
</tr>
<tr>
<td>Comorbid lifetime ADHD</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>FET 1.0</td>
</tr>
<tr>
<td>Comorbid Cluster B personality disorder</td>
<td>39 (46)</td>
<td>19 (31)</td>
<td>(4.03) 1 0.05</td>
</tr>
<tr>
<td>Barratt Impulsivity Scale</td>
<td>64.1 (20.0)</td>
<td>55.3 (16.4)</td>
<td>-2.63 113.2 0.01</td>
</tr>
<tr>
<td>Brown–Goodwin Aggression</td>
<td>23.0 (6.8)</td>
<td>17.6 (5.0)</td>
<td>-5.25 127.5 &lt;0.001</td>
</tr>
<tr>
<td>Buss–Durkee Hostility Inventory</td>
<td>41.2 (12.6)</td>
<td>38.0 (12.7)</td>
<td>-1.39 120 0.166</td>
</tr>
</tbody>
</table>

ADHD = Attention-Deficit Hyperactivity Disorder; FET = Fisher’s Exact Test.
number of lifetime anxiety disorder diagnoses; these results were comparable when the tests were performed separately for alcohol or drug use disorders (data available on request). There was a trend for subjects with SUD to be more likely to have a Cluster B personality disorder (Table 2).

Subjects with and without SUD did not differ in numbers of past depressive episodes, manic episodes, hospitalizations or the length of the current mood episode (Tables 2 and 3). Subjects with and without drug use disorders and with and without alcohol use disorders did not differ with respect to numbers of depressive episodes, manic episodes or hospitalizations (data available on request). There was a trend for subjects with lifetime alcohol use disorders, but not drug use disorders, to have a shorter current mood episode (19.3 days (SD 19.1) versus 25.3 days (SD 21.6); \( Z = 1.9 \), \( p = 0.055 \)).

Logistic regression analysis

We used independent variables associated with SUD on bivariate tests to conduct a logistic regression analysis with lifetime SUD as the dependent variable. The independent variables were sex, aggression, impulsivity, age of onset of depression, age of onset of mania/hypomania, Cluster B personality disorder, conduct disorder, and number of suicide attempts. When all variables were entered into a model simultaneously, the only variable associated with SUD was aggression (Wald coefficient = 5.44, \( p = 0.02 \), odds ratio = 1.15, 95% confidence interval = 1.02–1.29). Exploratory models showed that aggression was more strongly associated with SUD than impulsivity, Cluster B diagnosis, or conduct disorder (data available on request). Age at onset of the first major depressive episode and age at onset of the first manic or hypomanic episode were highly correlated (\( r = 0.69 \), \( p < 0.001 \)). Therefore, we tested two final exploratory regression models with SUD as the dependent variable. The two models included sex and aggression in addition to each of the bipolar onset age variables, separately, as predictor variables (Table 4). In both models, males were three times more likely to have SUD and scoring five points higher on the aggression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With SUD</th>
<th>Without SUD</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age at first major depressive episode</td>
<td>18.2</td>
<td>10.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Age at first manic/hypomanic episode</td>
<td>22.3</td>
<td>9.6</td>
<td>27.6</td>
</tr>
<tr>
<td>Number of depressive episodes(^a)</td>
<td>12.3</td>
<td>13.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Number of manic episodes(^b)</td>
<td>4.4</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Number of hospitalizations(^c)</td>
<td>3.1</td>
<td>4.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Length of current episode(^d)</td>
<td>19.9</td>
<td>19.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Number of suicide attempts(^e)</td>
<td>1.9</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Age of first suicide attempt</td>
<td>22.9</td>
<td>11.7</td>
<td>25.6</td>
</tr>
</tbody>
</table>

\(^a\)Truncated at 40.
\(^b\)Truncated at 10.
\(^c\)Truncated at 20.
\(^d\)Truncated at 60 days.
\(^e\)Truncated at 5.

Aggression and SUD in bipolar disorder

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald coefficient</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of first manic/hypomanic episode</td>
<td>2.4</td>
<td>0.12</td>
<td>0.97</td>
<td>0.93–1.01</td>
</tr>
<tr>
<td>Aggression</td>
<td>11.7</td>
<td>0.001</td>
<td>1.15</td>
<td>1.06–1.24</td>
</tr>
<tr>
<td>Sex</td>
<td>5.3</td>
<td>0.02</td>
<td>2.79</td>
<td>1.17–6.64</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of first depressive episode</td>
<td>2.3</td>
<td>0.13</td>
<td>0.97</td>
<td>0.93–1.01</td>
</tr>
<tr>
<td>Aggression</td>
<td>11.8</td>
<td>0.001</td>
<td>1.16</td>
<td>1.07–1.26</td>
</tr>
<tr>
<td>Sex</td>
<td>5.7</td>
<td>0.02</td>
<td>3.03</td>
<td>1.22–7.48</td>
</tr>
</tbody>
</table>

\( df = 1 \) for all tests; 95% CI = 95% confidence interval.
inventory (BGAI) was associated with doubling the odds of having SUD. In both models, there was a trend suggesting that a 10 year earlier onset of a first episode of depression or mania/hypomania was associated with 36% greater odds of having SUD.

Time-course analyses

The mean age of onset of major depression predated the mean age of onset of mania/hypomania in subjects with lifetime SUD [17.6 years (SD 10.3) versus 22 years (SD 9.5); t = -4.3, df = 68, p < 0.001] and without lifetime SUD [23.8 years (SD 11.7) versus 28.3 years (SD 11.4); t = -3.6, df = 49, p = 0.001]. We found no difference between the mean age of onset of SUD and mania/hypomania [20.4 years (SD 8.6) versus 22.0 years (SD 9.1); t = 1.2, df = 67, p = 0.22]. However, in those with lifetime SUD, the mean age of onset of major depression preceeded the mean age of onset of SUD [17.6 years (SD 9.2) versus 21.2 years (SD 9.2); t = -2.7, df = 67, p = 0.009].

Discussion

The main findings of this study are that SUD in persons with bipolar disorder is associated with male sex and impulsive-aggressive comorbidity, including both dimensional traits and categorical DSM diagnoses such as conduct disorder and Cluster B personality disorder. Earlier age of bipolar disorder onset appeared to be associated, although less strongly, with SUD comorbidity. Irrespective of SUD, the first mood episode tended to be depressive and on average preceded the development of the SUD.

Those with lifetime SUD experienced the onset of a first mood episode at approximately 18 years of age, whereas those without lifetime SUD did at around 24 years of age. These ages are similar to those reported in the study by Dalton et al. (14). Our finding regarding male sex is consistent with a report from the Stanley Foundation Bipolar Network on alcoholism comorbidity (28).

Aggressive behavior in childhood – which may be more common among males – may predict the future development of SUD in persons with bipolar disorder. Behavioral disinhibition in children, which overlaps with aggressive traits, has been associated with affective symptoms and family history of bipolar disorder (29), as well as with the development of SUD (30). In the present study, lifetime SUD was associated with aggressive traits during childhood (0–12 years) and the mean age of onset of SUD was 21.3 years (SD 9.2) in the full sample. While we cannot infer causality from these retrospectively obtained chronological data, the results suggest that aggressive traits were less likely to have occurred as a consequence of SUD and more likely to represent predictors of SUD in this bipolar sample. A prospective design would be required to confirm this. The results are consistent with general population studies that have found SUD to be associated with aggressive behavior (31, 32).

In the dually diagnosed persons in our sample, onset of the initial (usually depressive) episode of bipolar disorder appeared to occur on average 3.5 years earlier than the SUD, in the late teens, compared with the early to mid-20s among those without SUD. The late teenage years may be a more vulnerable period when a life-disrupting, first mood episode may raise the risk for development of comorbid SUD.

One explanation for our findings is that childhood and adolescent aggression, in some persons, may be a prodrome to a bipolar phenotype with earlier onset and higher risk for SUD. Alternatively, earlier onset of mood disorder may lead to less ability to regulate aggression, impulsivity or risk-taking behavior, which in turn may heighten the risk for SUD. In monkeys, low cerebrospinal fluid 5-hydroxyindoleacetic acid, the major serotonin metabolite, is associated with aggression and higher alcohol consumption (33). Mice lacking the serotonin-1B receptor have been reported to be more aggressive and cocaine preferring (34). Persons with a bipolar diathesis and more trait aggression, possibly associated with serotonin dysregulation, may be prone to earlier onset of illness and to self-medication with alcohol and/or drugs. In general, our results are consistent with other studies in suggesting that correlates of comorbid SUD in bipolar disorder are similar to those reported in non-psychiatric samples, with behavioral disinhibition (30, 35) and externalizing traits appearing to predominate (36). A logical next step would be to compare persons with bipolar disorder and SUD to a control group with SUD but not bipolar disorder.

Limitations of this retrospective study include potential recall bias. Another limitation is that Axis II pathology was assessed when patients were in the midst of a mood episode. However, the SCID-II, a clinician-administered assessment, was utilized by experienced raters. The validity of clinician-administered diagnostic measures has been demonstrated for Axis II diagnoses in depressed patients (37). Furthermore, only Cluster B traits were examined in this study. These traits have been found to be stable even after the
remission of depression in patients diagnosed with Cluster B personality disorders during major depressive episodes (38, 39). It is also possible that the assessment of aggression traits may be affected by current mood state, as has been reported for impulsivity (40). Further research is needed to confirm the sequence of onset of psychopathology using prospective designs with high-risk samples.

Individuals with aggressive traits and the onset of a depressive disorder in the late teenage years may merit closer follow-up to monitor for the onset of bipolarity and prevention of SUD. Treatments designed to help patients manage aggressive affects more effectively may also be worth investigation.

Acknowledgements

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References

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