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Brief report

Comorbid disorders in patients with bipolar disorder and concomitant substance dependence

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Abstract

Objective: Substance dependence is common in bipolar disorder and is associated with an increase in Axis I and II comorbidity. Little research has compared the relative rates of comorbidity among bipolar patients with dependence on different substances.
Methods: The Mini International Neuropsychiatric Interview (MINI) was used to assess 166 outpatients involved in one of three clinical trials of medications for bipolar disorder and substance dependence. Patients had concurrent alcohol dependence, cocaine dependence, or both conditions.
Results: Generalized anxiety disorder and current depressed mood were significantly more common in bipolar patients with alcohol dependence than bipolar patients with cocaine dependence. Those with cocaine dependence had significantly higher rates of post-traumatic stress disorder and antisocial personality disorder and were more likely to present in a mixed mood state than patients dependent on alcohol. Cocaine ENC dependent patients were more likely than alcohol dependent patients to have Bipolar I relative to Bipolar II.
Limitations: This is a retrospective, cross-sectional data analysis using the MINI for diagnosis.
Conclusions: Cocaine dependence and alcohol dependence were associated with different clinical features and comorbid disorders in bipolar patients. The results may help confirm the validity of integrative models of mood, behavioral, anxiety, and personality disorders. Further studies on the causal relationship between substance dependence and concurrent and lifetime Axis I disorders for patients with bipolar disorders are indicated.

Keywords: Alcohol dependence; Anxiety disorder; Bipolar disorder; Cocaine dependence; Comorbidity; Personality disorder

1. Introduction

Substance use in patients with bipolar disorder is a common and significant health concern. The National Epidemiological Catchment Area Study (ECA) found a 56% lifetime prevalence of substance abuse or dependence among persons with bipolar disorder (Regier et al., 1990). These dual-diagnosed patients are an important population for research given their high rates of denial and poor insight (Salloum and Thase, 2000), cognitive impairment (van Gorp et al., 1998), suicidality (Black et al., 1987), and treatment non-adherence (Keck et al., 1998).

The detrimental effects of each disorder are compounded by the presence of the other. Patients are more likely to relapse following treatment of their substance

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disorder if they have a comorbid psychiatric disorder (Pettinati et al., 1999; Kranzler et al., 1996). In turn, concurrent substance disorder increases the chronicity, disability, and mortality of bipolar disorder (Salloum and Thase, 2000).

Substance use may further complicate the management of bipolar disorder because of the presence of additional Axis I and Axis II disorders. Bipolar disorder patients with substance-use disorders are over three times more likely than patients without substance-use disorders to have comorbid lifetime anxiety disorders (Sonne et al., 1994), and they are more likely to have comorbid Axis II disorders (Kay et al., 1999). While studies have found a link between substance use and increased comorbidity, the relevance of the type of substance abuse to the type of Axis I comorbidity in bipolar disorder has not been well studied.

Large studies of the general population have shown that different substances, such as alcohol and cocaine, are associated with contrasting rates of lifetime comorbid anxiety and personality disorders (Regier et al., 1990; Kessler et al., 1996). The ECA Study, for example, found a prevalence of 33% for any anxiety disorder among people with cocaine abuse or dependence, compared to 19% for alcohol abuse or dependence (Regier et al., 1990). Antisocial personality disorder also occurred much more frequently in cocaine abuse/dependence (43%) than in those with alcohol abuse/dependence (14%) (Regier et al., 1990).

There is very little literature comparing specific substance and anxiety disorder relationships in bipolar populations. One study of participants with severe affective disorders looked at the association between lifetime anxiety disorders and lifetime substance-use disorders, including both abuse and dependence (Goodwin et al., 2002). In a subanalysis of 33 patients with bipolar disorder, they found bipolar patients with panic attacks were more likely to have disorders of cocaine use, sedative use, and stimulant use compared to bipolar patients without panic attacks. No other significant relationships were found, possibly due to the small sample size.

Another study of patients with co-occurring bipolar and substance-use disorders ($N=87$) found a higher prevalence of lifetime cocaine use disorder and lifetime amphetamine use disorder in patients with lifetime Post-traumatic stress disorder (PTSD) compared to those without lifetime PTSD (Kolodziej et al., 2005). They did not find an association with lifetime alcohol use disorder and presence or absence of lifetime PTSD and did not report associations between any other anxiety disorders and substance-use disorders.

The objective of the present study was to compare the prevalence of antisocial personality disorder and anxiety disorders in outpatients with bipolar disorder and alcohol dependence, bipolar disorder and cocaine dependence, and bipolar disorder and both cocaine and alcohol dependence. The study compared the clinical and demographic features of these three groups, defined by the type of substance dependence. We hypothesized that those with cocaine dependence would have higher rates of concurrent Axis I disorders and antisocial personality disorder than those with alcohol dependence. We also expected that the group dependent on both alcohol and cocaine would have the highest rates of concurrent Axis I disorders of the three groups.

2. Materials and methods

Participants ($N=166$) were drawn from three clinical trials of bipolar disorder and cocaine or alcohol related disorders. All participants were part of a research clinic at UT Southwestern Medical Center in Dallas, Texas. Prior to enrollment, all participants signed an informed consent form, approved by the Institutional Review Board. All participants were evaluated at their baseline visit with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), a structured interview conducted by a trained research assistant, followed by an unstructured interview by a psychiatrist to confirm the diagnosis. The MINI uses DSM-IV criteria to diagnose bipolar disorder, substance-use disorders, social phobia (current, i.e. in the last month), panic disorder (current and lifetime), post-traumatic stress disorder (current), obsessive–compulsive disorder (current), generalized anxiety disorder (current), and antisocial personality disorder (lifetime). It also assesses the participant's current mood state (i.e., manic, mixed, depressed, etc.). Before conducting study interviews, all research assistants received two days of formal training on the MINI by a psychologist who had conducted similar training for large clinical trials.

The inclusion criteria for the three clinical trials were DSM-IV diagnoses of Bipolar I, Bipolar II, or Bipolar NOS and of substance dependence in the last six months. The trials excluded pregnant or nursing women, those with current and active suicidal or homicidal ideations, and those with life-threatening or unstable medical conditions such as terminal cancer or severe cirrhosis. Participants were recruited through referrals from substance abuse treatment centers, psychiatric outpatient treatment facilities, flyers, and classifieds. Participants were not followed past study participation.

2.1. Statistical analyses

We divided the participants into three groups consisting of alcohol dependence (ETOH), cocaine dependence (COC), and alcohol and cocaine dependence (ETOH+COC). The three groups were compared in terms of demographic data, rates of comorbidity, types of bipolar disorder, and baseline mood states. Some of the mood states were combined in the latter analysis to avoid an invalid chi-squared test. Manic mood states were combined with hypomanic, depressed+hypomanic states were combined with mixed, and all subjects with euthymia were excluded due to its small numbers and fairly even distribution across the three groups.

One-way between-groups analysis of variance followed by post-hoc Tukey HSD tests was used to contrast the three groups with age and education level. Categorical variables were tested by Pearson chi-squared tests, which were considered valid if more than 80% of the cells had expected counts more than five. Fisher's Exact Tests were used for comparing two dichotomous variables. Where applicable, all tests were two-tailed. All statistics were computed using SAS Version 9.1, and $p<0.05$ determined significance.

3. Results

3.1. Demographics

Participants ($N=166$) had a mean age of 36.2±8.8 years (range from 19 to 57), a mean education level of 12.7±2.2 years, and were mostly men ($N=98$, 59%) and 68% Caucasian ($N=112$, 68%) but also included 24% African–American ($N=39$), 7% Hispanic ($N=12$), and 2% Native American ($N=3$) participants. Of 164 patients with data on marital status, most patients were single ($N=80$, 49%) or either separated or divorced ($N=62$, 38%). A minority of patients were married ($N=21$, 13%) or widowed ($N=1$, 1%). There was no significant difference between the three groups in gender, ethnicity, or marital status.

The only significant difference in age was between the ETOH and the ETOH+COC groups (34.6±8.9 and 38.4±8.0, respectively, $p<0.05$). This comparison had a small effect size (eta squared=0.4). The mean age of the COC group (35.5±9.6) did not differ from the other two groups. There was a significant difference ($p=0.003$) in education level between the ETOH group (Mean Years of Education=13.3±1.9) and the COC group (11.6±2.6) with a moderate effect size (eta squared=0.8). The educational level of the ETOH+COC group (12.6±2.2) was not different from the other two groups.

3.2. Mood and diagnosis

Baseline mood state was significantly associated with the type of substance dependence ($p=.001$). The ETOH group was more likely to be in the depressed phase ($N=46$, 70.8%) than either the COC ($N=10$, 27.8%; $p<.001$) or ETOH+COC groups ($N=31$, 47.7%; $p=.012$). The depressed phase was somewhat more frequent in the ETOH+COC group than in the COC group, although the difference was merely a trend ($p=.059$). Conversely, the COC group was significantly more likely than the ETOH group to present in the mixed or depressed+hypomanic mood state ($p=.002$). The

Table 1
Comparative diagnoses and mood states for the three substance-dependent groups with bipolar disorder

	Entire sample ($N=166$)	Alcohol dependence ($N=65$)	Cocaine dependence ($N=36$)	Alcohol and cocaine dependence ($N=65$)	p value
Diagnosis					
% Bipolar I (total)	96 (57.8%)	34 (52.3%)	24 (66.7%)	38 (58.5%)	.088 [a]
% Bipolar I w/ current psychotic features	28 (16.9%)	9 (13.8%)	8 (22.2%)	11 (16.9%)	
% Bipolar II	61 (36.7%)	31 (47.7%)	8 (22.2%)	22 (33.8%)	
% Bipolar NOS	9 (5.4%)	0 (0%)	4 (11.1%)	5 (7.7%)	
Mood state					
% manic	14 (8.4%)	2 (3.1%)	4 (11.1%)	8 (12.3%)	.001 [b]
% hypomanic	8 (4.8%)	3 (4.6%)	3 (8.3%)	2 (3.1%)	
% mixed	31 (18.7%)	8 (12.3%)	12 (33.3%)	11 (16.9%)	
% depressed+hypomanic	17 (10.2%)	3 (4.6%)	5 (13.9%)	9 (13.8%)	
% depressed	87 (52.4%)	46 (70.8%)	10 (27.8%)	31 (47.7%)	
% euthymic	9 (5.4%)	3 (4.6%)	2 (5.6%)	4 (6.2%)	

[a] Compares Bipolar I versus Bipolar II diagnosis among three groups. Bipolar NOS was removed from analysis due to invalid chi-squared test.
[b] In order to obtain a valid chi-square analysis, manic was combined with hypomanic, mixed was combined with depressed+hypomanic, and euthymic patients were discounted due to their relatively low numbers and equal distribution.

ETOH+COC group tended to exhibit these mixed states more than the ETOH group ($p=.099$) (see Table 1).

In comparing the types of diagnoses (Bipolar I, Bipolar II, or Bipolar NOS) among the substance-dependent groups, Bipolar NOS patients were removed from the analysis since the small group size ($N=9$) caused an invalid chi-squared test. The difference in prevalence of Bipolar I and Bipolar II among the three substance-dependent groups showed a trend toward significance ($p=.088$). The COC group was significantly more likely than the ETOH group to be diagnosed with Bipolar I compared to Bipolar II ($p=.047$) (see Table 1).

3.3. Comorbid disorders

The three groups did not differ ($p=0.880$) in the probability of having at least one comorbid anxiety disorder, which were diagnosed in 79.7% of the ETOH group, 82.9% of the COC group, and 82.8% of the ETOH+COC group.

Looking at individual comorbid disorders, the ETOH group had the highest prevalence rates of generalized anxiety disorder. Post-traumatic stress disorder was more prevalent in both the COC and COC+ETOH groups than in the ETOH group. Antisocial personality disorder was most prevalent in the COC+ETOH group. Rates of social phobia, obsessive–compulsive disorder, and panic disorder (current and lifetime), did not differ between the three groups (see Table 2).

To examine the hypothesis that different types of substance abuse are associated with different comorbid conditions, the three groups were combined and an analysis was conducted to see if alcohol or cocaine dependence was related to specific anxiety disorders or antisocial personality disorder (ASPD) in our study population. Combining all three groups, COC dependence was linked to both ASPD ($p=.016$) and PTSD ($p=.008$) independent of alcohol dependence. Alcohol dependence was linked to GAD ($p=.011$) independent of cocaine dependence.

4. Discussion

On the whole, the rates of comorbid anxiety disorder in our substance-dependent bipolar population were nearly three times those reported in the general bipolar population (McElroy et al., 2001). These results are supported by previous findings showing that bipolar patients with substance dependence are up to four times more likely to be diagnosed with Axis I disorders (Sonne et al., 1994), but they are the first (to our knowledge) to show that these comorbid disorders are related to the type of substance on which a bipolar patient is dependent.

Alcohol dependent participants were significantly more likely to have comorbid generalized anxiety disorder than the cocaine dependent participants, while cocaine dependence was associated with significantly higher prevalence rates of ASPD and PTSD. In addition

Table 2
Prevalence rates of comorbid disorders in bipolar disorder with substance dependence

	Post-traumatic stress disorder[a]	Generalized anxiety disorder[b]	Antisocial personality disorder[c]	Obsessive–compulsive disorder[a]	Panic disorder lifetime[a]	Panic disorder current[a]	Social phobia[a]
Bipolar patients with alcohol dependence	11 (16.9%)	36 (57.1%)	24 (37.5%)	21 (32.3%)	35 (53.8%)	20 (30.8%)	26 (40.0%)
Bipolar patients with cocaine dependence	13 (36.1%) OR=2.77[d] (1.08–7.10)	8 (24.2%) OR=0.24[d] (0.09–0.61)	19 (52.8%) OR=1.86 (0.81–4.26)	6 (16.7%) OR=0.42 (0.15–1.16)	15 (41.7%) OR=0.61 (0.27–1.39)	7 (19.4%) OR=0.54 (0.20–1.45)	16 (44.4%) OR=1.20 (0.53–2.73)
Bipolar patients with alcohol and cocaine dependence	23 (35.9%) OR=2.75[d] (1.21–6.29)	25 (41.0%) OR=0.52 (0.26–1.06)	39 (60.0%) OR=2.50[d] (1.23–5.08)	19 (29.7%) OR=0.88 (0.42–1.87)	26 (40.6%) OR=0.59 (0.29–1.18)	16 (25.0%) OR=0.75 (0.35–1.62)	28 (43.8%) OR=1.17 (0.58–2.35)
Chi-squared statistics	$\chi^2=7.038$ $p=0.030$ $df=2$	$\chi^2=9.872$ $p=0.007$ $df=2$	$\chi^2=6.705$ $p=0.035$ $df=2$	$\chi^2=2.989$ $p=0.224$ $df=2$	$\chi^2=2.627$ $p=0.269$ $df=2$	$\chi^2=1.603$ $p=0.449$ $df=2$	$\chi^2=0.263$ $p=0.877$ $df=2$

95% confidence intervals are listed in parentheses after each odds-ratio. OR are computed relative to ETOH group.

[a] Datum missing for one patient in the ETOH+COC group.

[b] Data missing for 9 patients: 2 ETOH patients, 4 ETOH+COC patients, and 3 COC patients.

[c] Data missing for one ETOH patient.

[d] Odds-ratios are significantly different from 1 at the $p<0.05$ level.

to the type of comorbid Axis I and Axis II disorders, clinical features of the bipolar patients were also related to the type of substance dependence in our study population. Alcohol dependence was associated with the depressed mood state, while cocaine dependent participants were more likely to have a mixed mood state and Bipolar I diagnosis than alcohol dependent participants.

The association between cocaine dependence and both ASPD and PTSD in bipolar disorder is consistent with previous research (Regier et al., 1990; Kolodziej et al., 2005). Since cocaine induces anxiety, a link between cocaine dependence and anxiety disorders is not unexpected. In addition, PTSD has been shown to develop in cocaine use disorder perhaps due to trauma associated with the use and procurement of cocaine, although cocaine use disorder can occur secondary to PTSD (Brady et al., 1998). ASPD is also congruent with the adverse behavior associated with cocaine use.

In contrast to ASPD and PTSD, GAD was more prevalent in bipolar disorder with alcohol dependence than in bipolar disorder with cocaine dependence. The National Comorbidity Survey also found a significantly higher 12-month co-occurrence of GAD with alcohol dependence than GAD with drug (other than alcohol) dependence (Kessler et al., 1996). This association may arise from the notion that alcohol can be "therapeutic" for anxiety. Some studies have suggested that substance dependence can originate from an attempt to treat a mental disorder (Sonne et al., 1994; Weiss et al., 2004).

Conversely, while substance dependence may begin in an effort to self-medicate, Maremmani has suggested in a recent review that bipolar patients with substance use often continue to use substances even after the substance fails to continue to provide symptom relief (Maremmani et al., 2006). He suggests that dependence in individuals with bipolar spectrum disorders may be better explained by (hypo)manic excitement, which leads to both sensation seeking behavior and a failure to appreciate its consequences (Maremmani et al., 2006). (Hypo)mania – the core trait of the bipolar spectrum – also becomes the driving force behind the addiction. This idea suggests that substance abuse and bipolar disorder may be more than simply comorbid disorders, and may actually arise from a common diathesis. Similarly, GAD and alcohol dependence or ASPD, PTSD and cocaine dependence may be linked clinically simply because they arise from common temperament or personality traits.

Lara et al. (2006) recently proposed a bidimensional model based on fear and anger traits to explain the comorbidity of mood, behavior, and personality disorders. Fear was used to encompass pessimism, fear of uncertainty, timidity and low energy, while anger included goal-directed exploration and appetitive impulsivity. They proposed that fear was the basis of depression and anxiety disorders, while both ASPD and PTSD were linked to high levels of anger. This hypothesis could be extended to suggest that alcohol dependence is linked to high fear traits, and cocaine dependence derives from high anger traits.

In our study, those with alcohol dependence were more likely to present in the depressed phase (high fear) of bipolar illness. Cocaine dependence was in turn associated with higher rates of mania (high anger) and mixed states. Alcohol has long been linked to depression, and it has even been found that a past diagnosis of alcohol dependence was associated with more than a 4-fold increase in risk of current or recent (last 12 months) major depressive disorder (Hasin and Grant, 2002). The association between cocaine dependence and mania is more complex, since cocaine can induce mania. Conversely, Camacho and Akiskal have suggested that the temperamental inclination to bipolar disorder, and the social stressors related to that temperament, may be the driving factors leading to stimulant use and abuse (Camacho and Akiskal, 2005). Bipolar patients have also been reported to increase stimulant use during mania in order to accentuate the manic high (Strakowski and Delbello, 2000). Regardless of the primary etiology, it is possible that a state of high anger leads to both stimulant abuse and mania.

An advantage of the bidimensional model is that the basic fear and anger traits are mostly independent of each other. By design, this tenet accounts for the observation that apparently paradoxical states, such as depression and mania, can coexist (Lara et al., 2006). It also suggest that a person with both alcohol and cocaine dependence would be susceptible to the combined set of comorbid disorders. Indeed, those in the ETOH+COC group were significantly more likely to be diagnosed with PTSD and ASPD than those in the ETOH group. The ETOH+COC group tended towards a higher prevalence of GAD than the COC group, although the result was not significantly different. This comparison was likely hampered by the small size of the COC group.

The study has several limitations. Data was initially collected for the purpose of clinical trials and not for the purpose of a well-designed epidemiological study. Temperament was not assessed, and the MINI diagnostic interview does not assess for lifetime comorbidities except for panic disorder and antisocial personality disorder. Lifetime rates would better reveal long-term relationships among the disorders. Medication being taken by patients at baseline could have also affected the rates of comorbidity found. Participants were drawn from those entering three clinical trials instead of just

one study, though the research assistants from all three trials received the same training in conducting the MINI, and a secondary interview with a certified psychiatrist was always used. Relative to the local demographics, our patient sample over-represented Caucasians and under-represented Asians and Hispanics. Thus, the generalizability of the findings may be limited.

The study reinforces the previous finding of a high prevalence of personality and anxiety comorbidity in the substance-dependent, bipolar population. Such an association is noteworthy, since comorbid personality and anxiety disorders exacerbate bipolar disorder even without the negative effects of substance abuse (Young et al., 1993; Carpenter et al., 1995; Ucok et al., 1998; Dunayevich et al., 2000; Feske et al., 2000; George et al., 2003). Given the implications for the management of patients with bipolar disorder and concurrent substance, anxiety, and/or personality disorder, care should be taken to identify comorbid psychiatric illness in any patient population. Unfortunately, bipolar disorder is itself frequently underdiagnosed in the substance-dependent population (Albanese et al., 2006).

This study helps support the theory that a person's expression of comorbid personality, anxiety, mood, or behavior disorders may result from a common, underlying diathesis. Further studies to define the order of development of these comorbid disorders are needed to elucidate any causal relationships and common susceptibilities.

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