

Anxiety disorders among patients with co-occurring bipolar and substance use disorders[☆]

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Abstract

Bipolar and substance use disorders are known to co-occur frequently, but limited attention has been paid to anxiety disorders that may accompany this dual diagnosis. Therefore, we examined the prevalence and nature of anxiety disorders among treatment-seeking patients diagnosed with current bipolar and substance use disorders, and investigated the association between anxiety disorders and substance use. Among 90 participants diagnosed with bipolar disorder I ($n = 75$, 78%) or II ($n = 15$, 22%), 43 (48%) had a lifetime anxiety disorder, with post-traumatic stress disorder (PTSD) occurring most frequently ($n = 21$, 23%). We found that those with PTSD, but not with the other anxiety disorders assessed, began using drugs at an earlier age and had more lifetime substance use disorders, particularly cocaine and amphetamine use disorders, than those without PTSD. Further examination revealed that (1) most participants with PTSD were women, (2) sexual abuse was the most frequently reported index trauma, and (3) the mean age of the earliest index trauma occurred before the mean age of initiation of drug use. Our findings point to the importance of further investigating the ramifications of a trauma history among those who are dually diagnosed with bipolar and substance use disorders.

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1. Introduction

Substance use and bipolar disorders co-occur at a high rate (Chengappa et al., 2000; Kessler et al., 1996; Regier et al., 1990; Sloan et al., 2000). Epidemiologic evidence shows that, among all mood or anxiety disorders, a history of mania is associated with the highest lifetime probability of drug dependence (Kessler et al., 1996); in patients diagnosed with bipolar I disorder, there is a 61% lifetime prevalence of substance use disorder (Regier et al., 1990). Clinical studies demonstrate that patients with this combination of disorders are prone to poor treatment outcomes (Dalton et al.,

2003; Keck et al., 1998; Feinman and Dunner, 1996) and to considerable severity of substance use disorders (Lambert et al., 1996; Winokur et al., 1998). However, in examining the co-occurrence between bipolar and substance use disorders, limited attention has been given to other categories of psychiatric disorders that may accompany this dual diagnosis (Weiss et al., 1992). Among diagnoses that deserve further attention are anxiety disorders, because these frequently co-occur with bipolar disorder (Boylan et al., 2004; Freeman et al., 2002; Perugi et al., 2001; Simon et al., 2003) and with substance use disorders (Kessler et al., 1996; Skinstad and Swain, 2001).

The associations between bipolar, anxiety, and substance use disorders have been examined in studies conducted with small and large samples of patients-seeking treatment for bipolar disorder. In an initial, small-sample study, Sonne et al. (1994) found that 30 of 44 patients had either current or past

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substance use disorders. These patients were more likely than those without substance use disorders to have other lifetime axis I disorders, with post-traumatic stress disorder (PTSD) occurring most frequently. More recently, Goodwin et al. (2002) examined the association between anxiety disorders and substance use disorders among 108 patients with affective disorders, including 33 patients diagnosed with bipolar disorder. Patients with bipolar disorder exhibited a general association between lifetime anxiety disorders and lifetime substance use disorders, and specific associations between lifetime panic disorder and lifetime cocaine, sedative, and stimulant use disorders. However, PTSD was not investigated in this study, and participants had to have at least 6 months of abstinence to be eligible for study participation. Neither one of these two small sample studies specified whether patients were diagnosed predominantly with the more severe bipolar I disorder marked by history of at least one manic episode or the less severe bipolar II disorder marked solely by hypomanic episodes.

Authors of larger-sample studies have provided more detailed analyses of participants' sociodemographic and diagnostic characteristics. For example, in a study of 267 patients, Frye et al. (2003) examined gender-specific relationships between current bipolar disorder, a history of alcohol use disorder, and lifetime anxiety disorders. Compared to women without a history of alcohol use disorder, women with a history of alcohol use disorder were more likely to have lifetime diagnoses of panic disorder and social phobia, but not PTSD. In contrast, Henry et al. (2003) did not find a significant association between anxiety disorder co-occurrence and substance misuse in a sample of 318 patients with bipolar disorder. However, PTSD and generalized anxiety disorder were not included in the analyses, and "substance misuse" (alternatively referred to as "addictive behavior") was ambiguously defined. More recently, in a study of 475 patients with bipolar disorder, Simon et al. (2004) found approximately twice the rate of substance dependence among those with co-occurring anxiety disorders. The majority of participants in these three studies were diagnosed with bipolar I disorder. Comparisons between those with bipolar I and bipolar II disorders were significant only in the study by Simon et al., who found that current anxiety disorder co-occurrence, and current PTSD in particular, was greater among patients with bipolar I disorder than among those with bipolar II disorder.

Most of the studies listed above show that substance use and anxiety disorders frequently co-occur in samples of patients with bipolar disorder. However, these studies differ in their assessment of anxiety and substance use disorders. Moreover, because a diagnosis of bipolar disorder was the sole entry criterion in these studies, they have not systematically examined the prevalence of lifetime anxiety disorders among patients dually diagnosed with bipolar and substance use disorders. The goals of our study therefore were to (1) investigate the lifetime prevalence of anxiety disorders in a sample of patients-seeking treatment for both bipolar and substance use disorders; (2) examine whether certain anxiety

disorders were associated with specific types of substance use disorders; if so, (3) examine the profiles of patients diagnosed with these anxiety disorders. Our analyses were conducted in consideration of participants' characteristics, including the subtype of bipolar disorder.

2. Method

2.1. Participants

Ninety-six participants with current bipolar disorder and substance dependence were recruited for an outpatient group treatment study at a psychiatric hospital in the suburban Boston area. Participants, recruited from the hospital setting and from the community at large, were seeking group treatment for co-occurring bipolar and substance use disorders but not for anxiety disorders. Each person gave written informed consent. Inclusion criteria were (1) current diagnoses of bipolar disorder (any subtype) and substance dependence, (2) substance use within 60 days prior to assessment, (3) ongoing pharmacotherapy with a mood stabilizer, and (4) permission to contact the treating psychopharmacologist. Exclusion criteria included (1) presence of medical disorders or neurocognitive deficits that would preclude study participation, (2) psychotic disorders such as schizophrenia, and (3) residence in a setting in which substance use was controlled. Because of the small number of patients diagnosed with bipolar disorder not otherwise specified (NOS; $n = 6$), only patients with bipolar disorder I ($n = 75$) or II ($n = 15$) are included in the current analyses.

2.2. Measures

The analyses are based primarily on the initial diagnostic assessment using the Structured Clinical Interview for DSM-IV, Research Version (SCID-IV) (First et al., 1996). The following SCID-IV modules were administered: module A, mood episodes; modules B and C, psychotic symptoms and disorders; module D, mood disorders; module E, substance use disorders, and module F, anxiety disorders except for specific phobias. Module E inquiries about all the major classes of substances listed in the DSM-IV except for nicotine use disorders, which were not assessed. As specified in module F, generalized anxiety disorder was assessed solely for the past 6 months. For all other disorders, information was obtained about lifetime and current (i.e., past 30 days) diagnoses. In addition, we used the Drug and Alcohol Questionnaire to obtain information about the age of initiation of substance use. This questionnaire is a self-report measure that has been developed by our group and used in previous studies (e.g., Weiss et al., 2000).

2.3. Procedures

Participants completed the study measures after detoxification and stabilization of mood symptoms. The SCID was

administered immediately following the signing of the consent form. All of the SCID modules except module E were administered by a trained psychologist. Module E and the Drug and Alcohol Questionnaire were administered by a trained and supervised research assistant, who also administered other measures related to the treatment study. The psychologist reviewed the Module E diagnoses obtained by the research assistant, and any diagnostic uncertainties were resolved during team meetings with the study's principal investigator (RDW).

2.4. Data analysis

Data analyses were performed with SPSS (SPSS Inc., 2001). Continuous variables (e.g., number of anxiety and substance use disorder diagnoses, age of initiation of substance use) were analyzed using one-way analyses of variance (ANOVAs) and paired *t*-tests. Categorical variables (e.g., presence of anxiety disorder by subtype of bipolar disorder) were analyzed using the chi-square test when the expected cell frequency was more than five and the Fisher Exact Probability Test when the expected cell frequency was less than five (Siegel and Castellan, 1988). Diagnostic variables derived from the SCID-IV were simplified to minimize the possibility of type II error. Specifically, current and past diagnoses of anxiety and substance use disorders were collapsed into their respective lifetime diagnoses. Moreover, lifetime substance dependence and substance abuse diagnoses were collapsed into specific substance use disorder variables.

3. Results

3.1. Sociodemographic characteristics

Table 1 shows sociodemographic characteristics for the entire sample. Comparisons were conducted first between patients with bipolar I and bipolar II disorders and second between patients with and without lifetime anxiety disorders. There were no sociodemographic differences between those with bipolar I and bipolar II disorders. Forty-three participants (48%) had a lifetime anxiety disorder, which was significantly more common among women ($n=28$, 65%) than men ($n=15$, 35%; $\chi^2(1)=4.59$, $p=0.032$). There were no other significant differences between those with and without a lifetime anxiety disorder.

3.2. Diagnostic characteristics

Table 2 shows substance use and anxiety disorder characteristics as well as ages of initial alcohol and drug use based on subtype of bipolar disorder diagnosis. There were no significant differences between those with bipolar I and bipolar II disorders.

Table 1
Sociodemographic characteristics for the total sample

Characteristic	$n=90$
Gender, n (%)	
Female	48 (53)
Male	42 (47)
Age, M (S.D.)	39.0 (9.9)
Race, n (%)	
White	81 (90)
African-American	5 (6)
Other	4 (4)
Marital status, n (%)	
Single, never married	37 (41)
Married or cohabiting	26 (29)
Separated or divorced	25 (28)
Widowed	2 (2)
Education ^a , n (%)	
High school or less	11 (12)
Some college	34 (38)
College graduate	24 (27)
Postgraduate degree	20 (22)
Occupational status ^a , n (%)	
Employed full-time	22 (25)
Employed part-time	17 (19)
Disabled or retired	24 (27)
Unemployed	16 (18)
Homemaker	5 (5)
Student	5 (5)

^a This information is missing for one person.

3.3. Associations between anxiety disorders and substance use

Table 3 shows the following substance use characteristics examined in association with lifetime history of any anxiety disorder, as well as each of the assessed anxiety disorders: number of lifetime substance use disorders, age of initial alcohol use, and age of initial drug use. Lifetime PTSD was associated with a greater number of lifetime substance use disorders and a significantly earlier age of initial drug use.

3.3.1. Profiles of participants with PTSD

In view of our findings showing more substance use disorders and earlier age of initial drug use among participants with lifetime PTSD, we further examined the profiles of those with PTSD. First, we compared participants with and without PTSD on sociodemographic variables listed in Table 1. The only significant difference was that lifetime PTSD was more prevalent among women ($n=18$, 86%) than men ($n=3$, 14%; $\chi^2(1)=11.54$, $p=0.001$).

We then compared patients with and without PTSD on the diagnoses of substance use disorders listed in Table 2. These comparisons are shown in Fig. 1. Lifetime cocaine use disorder was more prevalent among participants with lifetime PTSD ($n=14$, 67%) than those without lifetime PTSD ($n=25$, 36%; $\chi^2(1)=6.07$, $p=0.014$). Lifetime amphetamine use disorder was also more prevalent among

Table 2
Lifetime substance use and anxiety disorders based on subtype of bipolar disorder

Diagnosis	Total (<i>n</i> = 90)	Bipolar I (<i>n</i> = 75)	Bipolar II (<i>n</i> = 15)
Lifetime alcohol use disorder, <i>n</i> (%)	82 (91)	69 (92)	13 (87)
Lifetime drug use disorder, <i>n</i> (%)	71 (79)	57 (76)	14 (93)
Cannabis	55 (61)	43 (57)	12 (80)
Cocaine	39 (43)	30 (40)	9 (60)
Sedatives/hypnotics/anxiolytics	30 (33)	26 (35)	4 (27)
Hallucinogens	26 (29)	19 (25)	7 (47)
Amphetamines	26 (29)	20 (27)	6 (40)
Opioids	23 (25)	21 (28)	2 (13)
Inhalants	3 (3)	1 (1)	2 (13)
Number of lifetime substance use disorders, <i>M</i> (S.D.)	3.2 (2.0)	3.1 (1.9)	3.8 (2.1)
Age of initial alcohol use, <i>M</i> (S.D.)	14.7 (5.5)	14.8 (5.9)	14.1 (2.4)
Age of initial drug use, <i>M</i> (S.D.)	15.8 (5.0)	15.8 (5.2)	15.6 (3.9)
Lifetime anxiety disorder, <i>n</i> (%)	43 (48)	34 (45)	9 (60)
PTSD	21 (23)	17 (23)	4 (27)
Panic disorder	15 (17)	12 (16)	3 (20)
Obsessive–compulsive disorder	12 (13)	8 (11)	4 (27)
Social phobia	10 (11)	7 (9)	3 (20)
Generalized anxiety disorder	6 (7)	5 (7)	1 (7)
Number of lifetime anxiety disorders, <i>M</i> (S.D.)	0.7 (0.9)	0.7 (0.8)	1.0 (1.0)

participants with PTSD (*n* = 10, 48%) than those without PTSD (*n* = 16, 23%); $\chi^2(1) = 4.68, p = 0.031$.

Subsequently, we examined features of PTSD that can be obtained from SCID-IV data: type of trauma that participants reported to have affected them the most (the index trauma), experience of multiple types of traumas, and the earliest age

of index trauma occurrence. The following types of trauma were reported as index traumas: (1) sexual abuse (*n* = 11, 52%), (2) physical abuse (*n* = 4, 19%), (3) co-occurring sexual and physical abuse (*n* = 1, 5%), and (4) other types of trauma, which consisted of a parent's death, a life-threatening car accident, and having had one's home destroyed by fire (*n* = 4,

Table 3
Association between lifetime anxiety disorders and lifetime substance use

Lifetime anxiety disorder	<i>n</i>	Number of lifetime substance use disorders <i>M</i> (S.D.)	Age of initial alcohol use <i>M</i> (S.D.)	Age of initial drug use <i>M</i> (S.D.)
Any anxiety disorder				
Yes	43	3.4 (2.1)	14.9 (6.2)	15.0 (3.6)
No	47	3.1 (1.9)	14.6 (4.7)	16.4 (5.9)
PTSD				
Yes	21	4.2 (2.1) ^a	13.0 (2.5)	13.6 (3.6) ^b
No	69	2.9 (1.8)	15.3 (6.0)	16.4 (5.2)
Panic disorder				
Yes	15	3.1 (1.9)	14.8 (6.7)	15.4 (3.5)
No	75	3.3 (2.0)	14.7 (5.2)	15.8 (5.3)
Obsessive–compulsive disorder				
Yes	12	2.6 (1.4)	14.2 (2.1)	16.1 (2.5)
No	78	3.3 (2.0)	14.8 (5.8)	15.7 (5.3)
Social phobia				
Yes	10	4.2 (2.0)	18.6 (11.0) ^c	14.6 (4.5)
No	80	3.1 (1.9)	14.2 (4.2)	15.9 (5.1)
Generalized anxiety disorder ^d				
Yes	6	2.8 (1.9)	14.7 (1.4)	16.2 (2.8)
No	84	3.3 (2.0)	14.7 (5.6)	15.7 (5.1)

^a $F(1, 88) = 6.84, p = 0.011$.

^b $F(1, 81) = 4.89, p = 0.030$.

^c Participants with lifetime social phobia were older than those without social phobia at the time of initial alcohol use, $F(1, 88) = 5.95, p = 0.017$. However, this statistical significance disappeared upon removal of participant who had the initial drink at the age of 43, $F(1, 87) = 1.03, p = 0.312$. Removal of this participant did not affect statistical significance of the other "age of initial use" analyses.

^d Generalized anxiety disorder was assessed for the past 6 months only.

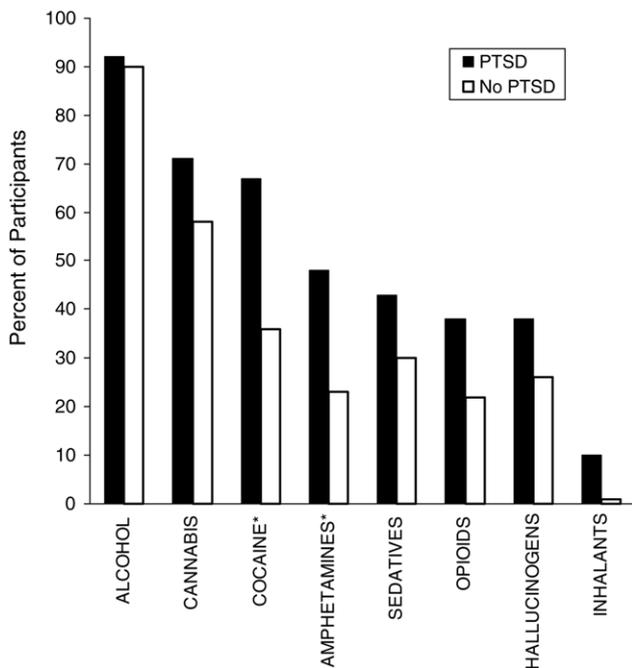


Fig. 1. Substance use disorders among participants with and without PTSD; * $p < 0.05$.

19%). One participant (5%) did not disclose the nature of the trauma experience. Nine participants (43%) reported that they experienced other types of traumas in addition to the index trauma.

To explore how trauma may be linked to initial drug use, we used a paired t -test to compare the earliest age of the index trauma to the age of initiation of drug use. For the 16 out of 21 patients with PTSD who recalled both the age of their earliest index trauma and their age of initial drug use, we found that their mean age of index trauma ($M = 9.4$, $S.D. = 7.3$) occurred earlier than the mean age of their initial drug use ($M = 13.7$, $S.D. = 3.8$; $t(15) = 2.36$, $p = 0.032$).

4. Discussion

The goals of this study were to examine the prevalence of lifetime anxiety disorders among patients with current bipolar and substance use disorders, to investigate whether any anxiety disorders were associated with specific types of substance use disorders, and if so, to examine profiles of patients diagnosed with these anxiety disorders. Of 90 participants, 48% had a lifetime history of an anxiety disorder. This rate is similar to the rates reported in studies examining the associations between bipolar disorder and anxiety disorders in treatment-seeking patients with bipolar disorder without specific consideration of substance use disorders. For example, McElroy et al. (2001) reported a 42% lifetime prevalence of anxiety disorders in a sample of 288 patients. Boylan et al. (2004) found that 56% of 108 patients had at least one co-occurring anxiety disorder. Similarly, in a sample of 475

patients, Simon et al. (2004) found that 51% had a lifetime history of an anxiety disorder.

In our study, the majority of patients (78%) were diagnosed with bipolar I disorder. A greater prevalence of bipolar I disorder than bipolar II disorder is typical in studies of patients-seeking treatment primarily for bipolar disorder (Frye et al., 2003; Henry et al., 2003; Simon et al., 2004) but not necessarily in studies of patients-seeking treatment primarily for substance use disorders (for a review, see Brown et al., 2001). Patients in this study were recruited for treatment of both disorders, which may be related to the high level of severity of bipolar illness in our sample. Although a trend is evident in Table 2 indicating greater lifetime prevalence of anxiety and drug disorders among patients with bipolar II disorder relative to patients with bipolar I disorder, this trend did not reach statistical significance. The relatively small number of patients with bipolar II disorder prevents us from making definitive conclusions about lifetime diagnostic co-occurrence based on subtype of bipolar disorder.

Among the assessed lifetime anxiety disorders, PTSD was most common, having been reported by 23% of participants. Our findings support those of Sonne et al. (1994) who found that 30% of patients with bipolar and substance use disorders had PTSD. Our findings differ from those of Frye et al. (2003), who found no association between a history of alcohol use disorder and PTSD among bipolar patients. In that study, however, patients with current alcohol or other substance use dependence were typically excluded, whereas all of our participants had current substance dependence; lifetime PTSD may be more commonly diagnosed among bipolar patients with current rather than past substance use disorders.

The diagnosis of PTSD, but not other anxiety disorders, was associated with earlier age of drug use and greater number of lifetime substance use disorders, particularly cocaine and amphetamine use disorders. Further examination of profiles of patients with PTSD revealed that most of these patients were women. A greater prevalence rate of PTSD among women than men with substance use disorders has been reported elsewhere (Back et al., 2000; Kessler et al., 1995; Najavits et al., 1998). It is also notable that in our study, 52% of those with lifetime PTSD reported sexual abuse as the index trauma, and that trauma occurred at a significantly younger age than initial drug use. This suggests that childhood sexual abuse may be especially important to assess in this dually diagnosed population. Indeed, studies have found significant associations between PTSD marked by childhood sexual abuse and use of drugs among women with co-occurring psychiatric disorders in particular (Back et al., 2000; Cottler et al., 1992).

In addition to PTSD, 41% of participants were also diagnosed with panic disorder, obsessive-compulsive disorder, or social phobia. Complex neurobiological mechanisms have been suggested to explain the associations between bipolar disorder and these anxiety disorders without consideration of co-occurring substance use (Freeman et al., 2002; Himmelhoch, 1998; Perugi et al., 2001). These anxiety

disorders have also been examined among patients with substance use disorders (Kessler et al., 1996; Skinstad and Swain, 2001; Zimmermann et al., 2004). Identification of panic disorder, obsessive–compulsive disorder, and social phobia in this study provides further justification to evaluate these anxiety disorders among patients diagnosed with both bipolar and substance use disorders.

Our results need to be interpreted in light of study limitations. Importantly, the degree to which our results generalize to other samples is limited by participant characteristics. Specifically, the participants were mostly white, treatment-seeking patients, who, by virtue of the current nature of their bipolar and substance use disorders, had a high severity of illness. The fact that these patients were knowingly seeking treatment for both bipolar and substance use disorders speaks to their heightened awareness of these co-occurring diagnoses and further distinguishes them from patients described in all of the other cited studies, which were conducted primarily with patients-seeking treatment for bipolar disorder alone. It is also notable that the participants were seeking group treatment. Thus, our sample may be under-representative of patients with current anxiety disorders, especially those with social phobia, as such disorders may preclude willingness to engage in group therapy. Finally, all of the patients were prescribed mood stabilizers, which have been speculated to attenuate the experience of some anxiety disorders (e.g., Cassano et al., 2000).

The relatively small sample size further limits the interpretation of findings. For example, we simplified some diagnostic variables, which prevented us from distinguishing between current and past diagnoses as well as between substance dependence and substance abuse. These simplifications limit our understanding of temporal and severity aspects of the relationship between anxiety, substance use, and bipolar disorders. Second, despite finding gender differences in the prevalence of anxiety disorders in general and PTSD in particular, we did not conduct analyses controlling for gender because of a small number of men diagnosed with various anxiety disorders (e.g., only three men had PTSD). Third, it is possible that the failure to find a link between substance use disorders and anxiety disorders other than PTSD is attributable to low statistical power, i.e., a type II error, for anxiety disorders occurring at a lower rate. For example, while social phobia, like PTSD, was associated with approximately 4 lifetime substance use disorders, this association did not reach statistical significance.

Other limitations relate to assessment methods used in this study. Specifically, data relied heavily on patient report and recall of some events that occurred long ago, with the biases inherent in that process. Also, all of the results are based on the SCID-IV (First et al., 1996), the primary purpose of which was to ascertain the presence of current bipolar and substance use disorders. Hence, in our assessment of anxiety disorders, we did not obtain information about lifetime generalized anxiety disorder or specific phobias. Moreover, assessment of certain anxiety disorders, such as PTSD, benefits from using

an assortment of measures to collect data about the diagnostic and historical nature of the disorder (Newman et al., 1996). Therefore, it is possible that we did not obtain complete information about trauma history of some participants who may have been reluctant to share this information in the context of a diagnostic interview alone. This is suggested by our examination of profiles of participants with PTSD showing a relatively low prevalence of multiple trauma exposure. In contrast, studies of patients with substance use disorders and PTSD that have relied on other trauma history assessments in addition to the SCID, have shown higher rates of multiple trauma exposure (e.g., Back et al., 2000; Najavits et al., 1999).

In conclusion, our findings show that PTSD is associated with greater severity of substance use disorders among treatment-seeking individuals diagnosed with current bipolar disorder and substance dependence. Despite the limitations listed above, these findings highlight the heterogeneity of dually diagnosed patients (Weiss et al., 1992) and point to the importance of obtaining further diagnostic information from those with a dual diagnosis.

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