The Impact of Substance Abuse on the Course of Bipolar Disorder

Stephen M. Strakowski, Melissa P. DelBello, David E. Fleck, and Stephan Arndt

Background: Substance abuse occurs at high rates in bipolar disorder. The reasons for this co-occurrence are unknown. Alcohol use disorders have been associated with both earlier and later age of onset of bipolar disorder, in part based on the temporal associations of the two conditions. Both drug and alcohol use disorders are associated with impaired outcome of bipolar illness. This influence may involve both direct effects of alcohol or drugs on the initiation of affective symptoms and indirect effects on treatment compliance. To extend these previous findings we examined the temporal associations of substance abuse and affective symptoms in patients with new onset bipolar disorder.

Methods: Associations between affective symptoms and alcohol and cannabis use disorder symptoms were evaluated using regression and time-series correlative methods in 50 new-onset bipolar patients.

Results: The duration of alcohol abuse during follow-up was associated with the time patients experienced depression. The duration of cannabis abuse was associated with the duration of mania. Several subgroups could be identified with different temporal relationships among these disorders.

Conclusions: Although the relationships among substance use and bipolar disorders are complex, systematic study of the courses of the disorders might clarify how these conditions interact longitudinally. As the numbers of subjects in specific subgroups are relatively small in this study, these results should be considered preliminary.


Key Words: Bipolar disorder, alcohol abuse, cannabis abuse, outcome, review

Introduction

The Prevalence of Substance Abuse in Bipolar Disorder

Substance abuse is exceptionally common during the course of bipolar disorder. For example, the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study found that over 60% of patients with type-I bipolar disorder developed a substance use disorder during their lifetime (Regier et al 1990). In fact, in that study, co-occurring alcohol or drug abuse or dependence was more common in bipolar disorder than any other Axis I syndrome. These elevated rates of substance use disorders do not simply reflect the effects of chronic mental illness, since rates of substance use disorders are elevated in bipolar patients even at the time of their first manic episode (Strakowski et al 1993, 1998a,b). Moreover, high rates of substance abuse in bipolar disorder have been reported from many different countries, treatment settings, and clinical and research samples (Fogarty et al 1994; Strakowski et al 1994; Verdoux et al 1996; Winokur et al 1995). Recent reports from Taiwan, however, in which the lifetime rate of substance abuse in bipolar patients appeared to be quite low (<10%; Tsai et al 1996; Tsai et al, in press), suggest that this co-occurrence may be primarily restricted to Western societies. Additional reports from other non-Western countries are needed to replicate this observation.

The reasons substance abuse is so common in bipolar patients are unknown (Strakowski and DelBello 2000). One explanation is that patients with both bipolar and substance use disorders are more likely to seek psychiatric treatment than patients with only one of the two conditions (the so-called “Berkson’s bias”; Berkson 1946). This explanation fails, however, because studies using population survey methods found elevated rates of substance use disorders in bipolar disorder that were as high or higher than those reported in clinical samples (Kessler et al 1997; Regier et al 1990). Alternatively, because one of the criteria for mania is an “excessive involvement in pleasurable activities that have a high potential for painful consequences” (American Psychiatric Association 1994), which could be interpreted to include substance abuse,
increased rates of substance abuse in bipolar disorder might result simply by definition. In our previous work, however, substance abuse alone was not considered adequate to meet this criterion, and yet rates of substance use disorders were elevated in our bipolar samples (Strakowski et al 1993, 1996a, 1998a, 1998b). Moreover, unlike the general population, bipolar patients are more likely to exhibit substance dependence than substance abuse (Regier et al 1990). A diagnosis of substance dependence requires evidence of sustained drug and alcohol misuse that imparts significant social and functional consequences. A bipolar patient who abuses drugs or alcohol simply as part of the pleasurable seeking of mania is unlikely to exhibit these longitudinal characteristics.

Therefore, the high rate of substance use disorders in patients with bipolar disorder is not explained by ascertainment or diagnostic bias. Recently, we and others suggested that the co-occurrence of bipolar and substance use disorders results from a combination of patients with different types of associations among these two conditions (DelBello and Strakowski, in press; Mueser et al 1998; Strakowski and DelBello 2000). Specifically, one subgroup of patients includes subjects in whom bipolar illness initiates substance abuse, either as an attempt at self-medication or as a direct result of affective symptoms (e.g., the increased pleasure seeking of mania); however, evidence supporting this relationship between bipolar and substance use disorders is sparse (DelBello and Strakowski, in press; Strakowski and DelBello 2000), suggesting this subgroup is only a small fraction of the total patients. A second subgroup includes subjects in whom substance abuse has initiated affective episodes, perhaps through behavioral sensitization or kindling mechanisms (Sonne et al 1994). Clinical data suggest that this subgroup may be relatively common, as many patients have the onset of substance abuse prior to the onset of affective illness (Strakowski and DelBello 2000; Strakowski et al 1996a) and patients with co-occurring substance abuse may have lower familial rates of affective illness (DelBello et al 1999) suggesting an additional risk factor (i.e., substance abuse) is needed to precipitate bipolar disorder in those individuals (Winokur et al 1995). A third subgroup consists of subjects who share a common risk factor for both disorders. One such risk factor could be a gene or genes associated with both disorders; however, family studies have not supported this suggestion (reviewed in Strakowski and DelBello 2000). A shared vulnerability toward behavioral sensitization or kindling, which might underlie both disorders, can also be hypothesized, although this has not been studied in any detail (Post 1992; Strakowski et al 1996b). Alternatively, psychosocial stress might precipitate both conditions (reviewed in Strakowski and DelBello 2000). Finally, because substance use disorders are common in the general population, then a portion of the bipolar patients would be expected to develop substance abuse or dependence simply by chance. Unfortunately few published studies have specifically attempted to identify subgroups of patients with co-occurring bipolar and substance use disorders to clarify these relationships.

**Substance Abuse and the Age of Onset of Bipolar Disorder**

Although the specific reasons for the common co-occurrence of bipolar and substance use disorders has remained elusive, nonetheless, substance abuse appears to influence the age of onset and subsequent course and outcome of bipolar disorder. In order for substance abuse to impact the age of onset of bipolar disorder, it must begin prior to the onset of affective symptoms. Previous studies suggest that this occurs in approximately 60% of patients with both conditions (reviewed in Strakowski and DelBello 2000). In one of the earliest studies to examine whether alcohol abuse influenced the age of bipolar disorder onset, Morrison (1974) reported that affective illness was first identified at age 23 years in nonalcoholic bipolar patients but not until age 28 in alcoholic bipolar patients. Similarly, Strakowski and colleagues (Strakowski et al 1996a, 1998b) found that patients hospitalized with first-episode mania and an antecedent alcohol use disorder (i.e., beginning at least 1 year prior to the affective illness) had a significantly later age of onset (mean of 27 years) than those without alcoholism (mean of 21 years). In contrast, Winokur et al (1996) found that bipolar patients with alcoholism had a significantly younger age of onset (mean of 23 years) than those without (mean of 27 years). These conflicting results are difficult to reconcile. One explanation was suggested in a separate study by Winokur et al (1995). They found that bipolar patients with alcoholism that predated the affective illness (i.e., antecedent alcoholism) had a later age of onset (27 years) than those patients whose alcoholism began after the onset of bipolar disorder (20 years). They suggested that the early onset group had a more severe bipolar illness that included the development of alcohol abuse, whereas the patients with antecedent alcohol abuse had a less severe illness that required the presence of alcoholism to initiate the bipolar disorder. By identifying specific subgroups (e.g., early onset bipolar patients with antecedent alcohol abuse) it may be possible to better define these relationships among alcohol use and bipolar disorders.

There are few studies of associations between drug use disorders (other than alcohol) and the age of bipolar disorder onset. Strakowski et al (1996a) did not find any difference in the age of bipolar onset in patients with or
without antecedent drug (mostly cannabis) abuse or dependence; however, Sonne et al (1994) found patients with substance abuse had an earlier age of onset of bipolar illness, but they combined drug and alcohol abuse into a single category so that the effects of specific substances could not be determined. The converse relationship of how bipolar disorder might influence the onset of substance abuse has not been studied systematically to our knowledge. The study by Winokur et al (1995), however, suggests that early onset bipolar disorder may place patients at risk for developing substance abuse.

**Substance Abuse Impacts Outcome of Bipolar Disorder**

A number of investigators reported that substance abuse has negative effects on outcome in bipolar patients. In 1974, Reich and colleagues observed that patients with bipolar disorder who required hospitalization were significantly more likely to have a history of excessive alcohol use compared to patients who did not require hospitalization (Reich et al 1974). Shortly thereafter, Himmelhoch et al (1976) observed that alcohol and drug abuse was associated with mixed states that are associated with poor outcome themselves. In a regression analysis, they noted that both mixed states and drug abuse were associated with poor treatment outcome, but that the effects of drug abuse were “more profound” than those of the mixed symptoms. In a 4-year prospective outcome study of 75 bipolar patients following hospital discharge, Tohen et al (1990) examined a number of variables in a Cox regression model to identify independent predictors of outcome. A history of alcoholism was associated with poor occupational status at 6 and 48 months after hospital discharge, even after controlling for a number of other variables. Feinman and Dunner (1996) noted that substance abuse was associated with truncated daily (episodes of 1–3 days) and hourly (episodes of <24 hours) cycling, particularly in patients in whom substance abuse began prior to the onset of the bipolar disorder. Recently, Goldberg et al (1999) also found that a history of substance abuse was associated with lower rates of remission during hospitalization, as well as poor lithium treatment response.

A significant confound in many of these studies is the inclusion of patients with different histories of past affective episodes. Since the number of previous affective episodes becomes a strong predictor of future affective course, this may make it difficult to identify other course predictors (Strakowski et al 1998a). Studies of first-episode patients address this problem by removing the confound of illness chronicity. Strakowski et al (1993) studied the effects of psychiatric comorbidity in a sample of 60 bipolar patients with a first-episode of psychotic mania. They observed that psychiatric comorbidity was associated with poorer rates of recovery during hospitalization; this finding was limited by including a number of substance use and psychiatric disorders in the definition of psychiatric comorbidity. Subsequently, in a 2-year follow-up of these patients (plus additional subjects recruited later) with first-episode affective psychosis (n = 219), substance abuse was not significantly associated with outcome after controlling for other variables (e.g., index depression score, brief initial hospitalization, age of onset after age 30 years) (Tohen et al 2000). These results were confounded, however, by the combination of patients with first-episode (unipolar) psychotic depression and those with bipolar disorder.

Strakowski et al (1998a) extended prior work by prospectively examining the effects of interval substance abuse, i.e., substance abuse during the follow-up period, rather than a lifetime history of substance abuse in 109 patients with first-episode affective psychoses including 83 patients with bipolar disorder. Most prior studies combined patients with any lifetime history of substance abuse into a single group, thereby including patients actively abusing drugs and alcohol with those that had not used substances for many years. In this study, interval substance abuse was associated with impaired symptom-atic recovery (i.e., resolution of essentially all affective symptoms for at least 8 weeks) in a Cox regression model controlling for other relevant clinical variables. Although interval substance use did not also predict impaired syndromic recovery (i.e., the resolution of enough symptoms that criteria for a DSM-III-R affective syndrome were no longer met), it was associated with treatment compliance, which was the strongest predictor of syndromic recovery. Therefore, the authors concluded that interval substance abuse had both direct and indirect effects on the course of new onset bipolar and psychotic depressive disorders. Namely, substance abuse was associated with a failure of affective symptoms to resolve, which appeared to be a direct effect, and also contributed to poor treatment compliance, leading indirectly to impaired recovery. Similar findings were observed in a multiple-episode bipolar sample from the same research group (Keck et al 1998).

Other investigators examined interactions between the courses of substance use and bipolar disorders in more detail, looking at variables other than simple recovery and outcome. Young et al (1981) followed 15 bipolar patients with alcohol abuse in a lithium treatment trial for 1 year. They found that symptoms of alcoholism tended to appear before affective symptoms in those patients with relapse of their bipolar illness. The NIMH Collaborative Study on the Psychobiology of Depression (CDS) recruited 231 patients with bipolar or schizoaffective mania and followed them every 6 months for 5 years then annually after...
that using the Longitudinal Follow-up Evaluation (LIFE; Keller et al. 1987). Seventy (30%) of these patients had a lifetime history of alcoholism defined by Research Diagnostic Criteria (RDC; Endicott and Spitzer 1978), including 34 patients in whom the alcoholism developed first ("primary alcoholism"), 30 in whom the bipolar disorder developed first ("primary bipolar disorder"), and six in whom these temporal relationships could not be determined. In this study, Winoku et al. (1994, 1995) found that patients with primary bipolar disorder had significantly more affective episodes after the initial recovery, and the median time to their first affective relapse was shorter as compared to the bipolar patients with primary alcoholism. The patients with primary bipolar disorder were also less likely to recover during follow-up. Notably, the types of symptoms of alcoholism did not differ between these two groups of bipolar patients. Additionally, in contrast to a comparison group of patients with primary alcoholism and secondary depression, the bipolar patients with alcoholism (primary, secondary, or undefined) were significantly less likely to exhibit persistent symptoms of alcohol abuse during the first five years of follow-up. Specifically, by the 5-year follow-up only 5% of the bipolar patients, compared to 25% of unipolar patients, continued to exhibit RDC alcoholism.

Recently, we extended these findings by prospectively examining associations between substance use and bipolar disorders during the 12 months after a first psychiatric hospitalization for psychotic mania (Strakowski et al. 1998b). In these 77 patients, 26 (34%) patients had a history of alcohol use disorders and 28 (36%) had a drug use disorder. During the follow-up interval, 54% of the patients with an alcohol use disorder and 39% of patients with a drug use disorder experienced affective episodes in the absence of ongoing alcohol or drug abuse. Therefore, patients whose bipolar illness co-occurs with substance abuse do not necessarily require ongoing substance abuse to initiate new affective episodes; however, whenever present, alcohol abuse was associated with a current affective syndrome. In contrast, 21% of these patients continued to abuse drugs (cannabis in all cases) and yet maintained remission of their bipolar symptoms. This observation suggests that the interactions between different substances of abuse and bipolar disorder may differ. Specifically, alcohol appeared to be strongly associated with maintaining or developing affective symptoms, whereas this may be less true with cannabis. Clearly, these results need to be replicated in larger patient samples over longer periods of time. Finally, only one patient with no prior history of an alcohol use disorder developed a new alcohol abuse syndrome during the follow-up interval and no patients developed a new drug abuse syndrome. Therefore, at least in this relatively short follow-up period, developing new cases of substance use disorders after the first manic episode were rare. Coupled with the findings from Winokur et al. (1995), these results suggest that once patients are in treatment (or at least in follow-up studies) their risk of developing new substance abuse syndromes or maintaining substance use disorders appears to decrease over time.

**Bipolar Disorder May Impact the Course of Substance Abuse**

In addition to the effects of substance abuse on the course of bipolar disorder, there are a few studies that have examined how bipolar disorder may influence substance abuse syndromes (reviewed in Strakowski and DelBello 2000). For example, in a sample of 59 bipolar patients, Mayfield and Coleman (1968) found that 32% increased their alcohol use when manic, whereas only 10% increased their drinking when depressed. More commonly, patients decreased their drinking when depressed (17%), although, in most cases, alcohol consumption did not change with affective state. A number of other authors have reported similar findings (Bernadt and Murray 1986; Dunner et al. 1979; Hensel et al. 1979; Reich et al. 1974; Winokur et al. 1969). Taken together, these studies suggest that most patients (approximately three fourths) do not change their alcohol consumption during a manic episode, although some patients increase their alcohol use over baseline and only rarely do patients decrease their drinking in this affective state. In contrast, during depression, patients are as likely to decrease as to increase their drinking (approximately 15% of each), although, again, most do not change their alcohol use. There are no quantitative studies of changes in drug use (other than alcohol) during affective episodes in bipolar patients. Notably, none of these studies provided comparison groups (e.g., patients with primary substance use disorders) to control for the changes over similar time intervals that occur in alcohol or drug use in persons without bipolar disorder.

Despite these previous studies, many aspects of the relationships between the courses of substance use and bipolar disorders remain unknown. For example, it has not been clarified whether alcohol or drug use disorders are specifically associated with more time spent in manic or depressive episodes during the course of bipolar illness. Additionally, as noted, methods for defining subgroups of bipolar patients with different types of associations between the courses of substance use and bipolar disorders have not been developed. With these considerations in mind, we initiated the University of Cincinnati First Episode Mania study in June 1996. The aims of this ongoing study are to prospectively examine the relative courses of bipolar and substance use disorders in patients.
recruited at the time of their first psychiatric hospitalization for mania. By incorporating the methodology of the NIMH CDS, we generate week-by-week course of affective and substance abuse symptoms. We examined our data in order to address two questions relevant to this review:

1. Is the duration of time with alcohol or cannabis use disorders associated with the time spent in manic or depressive episodes during the course of bipolar disorder?
2. Can correlations in the courses of substance use and bipolar disorders define subgroups of patients with differing relationships between these co-occurring conditions?

Methods and Materials

The methods of this study have been described in detail elsewhere (Strakowski et al, in press), but they are presented briefly here.

Subjects

Recruitment for this study began June 1, 1996. Inclusion criteria include: 1) meets DSM-IV criteria for bipolar disorder, manic or mixed; 2) age 16–45 years; 3) no prior psychiatric hospitalizations; 4) less than 1 month prior psychotropic medication; 5) able to communicate in English; 6) lives within 50 miles of Cincinnati; and 7) provision of written informed consent after study procedures have been fully explained and understood. Patients are excluded if psychiatric symptoms: 1) are entirely due to acute medical illness as determined by examination; 2) result from acute intoxication or withdrawal from drugs or alcohol as determined by symptom resolution within the expected period of acute intoxication or withdrawal; or 3) if patients had diagnosed mental retardation (i.e., IQ < 70). This article evaluates the first 50 consecutively enrolled subjects who had at least 16 weeks of follow-up. We plan to recruit 150–200 total subjects for this study. Patients both with and without lifetime histories of substance use disorders are included. A lifetime alcohol or drug use disorder was present in 66% (n = 33) of this sample, and 23 (46%) met criteria for an alcohol or drug use disorder during the month prior to the index hospitalization.

Index Clinical Assessment

The diagnosis of DSM-IV bipolar disorder (manic or mixed) was established by psychiatrists or psychologists using the Structured Clinical Interview for DSM-IV, Patient versions (SCID-P; k > .90) (First et al 1995). Psychiatric symptoms were assessed using the Young Mania rating scale (YMRS; Young et al 1978), the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton 1960), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984). Substance use disorder assessments were made by trained research assistants supervised by a psychiatrist using the Substance Use Disorders module of the SCID-P in conjunction with completing the Addictions Severity Index (ASI; McClellan et al 1992). The investigators demonstrate good interrater reliability for symptom measures (intraclass correlation coefficient > .70).

Demographic Variables

Demographic information was obtained from direct patient interviews and review of medical records. This included gender, race, years of education, current age, and employment status prior to the onset of the current affective episode.

Follow-Up Assessments

After hospital discharge, patients are evaluated at 1 month and 4 months, then every 4 months for as long as this study remains funded. For this analysis, the maximal follow-up period analyzed was 24 months (104 weeks). For the subjects used in this analysis, the mean length of follow-up was 66 (SD = 32) weeks (range 16–104 weeks).

At each follow-up visit, investigators review, week-by-week, the prior interval. Particular attention is paid to times of symptom change as with the CDS (Keller et al 1987) and our previous work (Keck et al 1998; Strakowski et al 1998a). This follow-up review includes each item of the affective and substance abuse symptom ratings scales (YMRS, HDRS, SAPS, and ASI) in conjunction with the SCID-P for that interval. From these ratings, week-by-week six-point ratings are made of the severity of affective and substance abuse syndromes (Table 1). Then the percent of weeks with full affective or substance abuse syndromes (scores of 5 or 6) or significant symptoms (scores of 3 or 4) was calculated. Random urine toxicology and alcohol breathalyzer screens are obtained to verify self-reports of substance abuse.

Treatment Assessments

Although this is a naturalistic study, the treatments patient receive during follow-up are recorded. Using these data, treatment compliance was assessed as 1) full compliance, in which pharmacologic treatment was taken more than 75% as prescribed; 2) total noncompliance, in which pharmacologic treatment was taken less than 25% of the time as prescribed; and 3) partial noncompliance, in which pharmacologic treatment was taken between these two extremes (Keck et al 1998; Strakowski et al 1998a). This rating was obtained by reviewing interval medication use with each patient, family members and clinicians, when indicated (i.e., if a patient’s reliability is suspect). From this review, the percent of follow-up in which patients exhibited each category of compliance was determined for each prescribed psychotropic medication and an average score across medications was then used for analysis.

Statistical Analysis

To answer question 1, a regression model was evaluated examining associations between the fraction of time during follow-up in which patients experienced full affective syndromes or signif-
abuse may have precipitated the affective episode. In contrast, if the maximum correlation occurred with the substance abuse time series shifted to the right, then this relationship suggests that substance abuse occurred as a consequence of the affective relapse. A \( r-b = .20 \) was defined as having a clinically meaningful association. Finally, paired \( t \) tests were used to determine whether the overall group cross-correlations significantly deviated from zero.

**Results**

Demographic and clinical characteristics of this sample are listed in Table 2. During follow-up, the patients spent a mean of 33% (SD = 36%) of the time totally noncompliant with treatment. They experienced full affective syndromes 25% (SD = 25%) of follow-up, including 10% (SD = 18%) of the time with mania, 12% (SD = 22%) with depression, and 3% (SD = 9%) in a mixed state. An additional 27% (SD = 28%) of follow-up was spent with significant affective symptoms that did not meet full syndrome criteria. The sample exhibited symptoms or a full syndrome of an alcohol use disorder 11% (SD = 32%) of follow-up. Similarly, they exhibited cannabis abuse symptoms or syndromes for 13% (SD = 31%) of the time.

Index affective state (i.e., mixed or manic), gender, and

**Table 1. Psychiatric Status Ratings—Determination of Symptomatic Recovery**

<table>
<thead>
<tr>
<th>Code</th>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Full syndrome, severe</td>
<td>Meets DSM-IV criteria for severe syndrome</td>
</tr>
<tr>
<td>5</td>
<td>Full syndrome</td>
<td>Meets DSM-IV criteria for mild to moderate syndrome</td>
</tr>
<tr>
<td>4</td>
<td>Marked symptoms</td>
<td>Does not meet DSM-IV criteria for syndrome, but one or more DSM-IV syndrome criterion items are scored greater than “mild”</td>
</tr>
<tr>
<td>3</td>
<td>Partial remission</td>
<td>No DSM-IV syndrome criterion item scored greater than “mild” but: For affective disorder: YMRS total score &gt; 5, HAM-D total score &gt; 7, or any SAPS global item scores &gt; 2 For substance abuse disorder: ASI substance use score &gt; 2</td>
</tr>
<tr>
<td>2</td>
<td>Residual symptoms</td>
<td>Has no DSM-IV syndrome criterion item scored greater than “mild” and: For affective disorder: YMRS total score ( \leq 5 ), HAM-D total score ( \leq 7 ), and SAPS global scores all ( \leq 2 ) For substance abuse disorder: ASI substance use score &lt; 2</td>
</tr>
<tr>
<td>1</td>
<td>Usual self</td>
<td>No affective, psychotic or substance abuse symptoms</td>
</tr>
</tbody>
</table>

YMRS, Young Mania Rating Scale; HAM-D, Hamilton Depression Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; ASI, Addictions Severity Index.

To answer question 2, cross-correlations using Kendall \( r-b \) were used to compare the weekly time series of severity of affective symptom/syndrome ratings with cannabis and alcohol symptom/syndrome ratings for each patient. The time series were right- or left-shifted (from 1 to 8 weeks) relative to each other to identify whether the maximal correlation between time series demonstrated a temporal delay or advance. Specifically, if the maximum correlation occurred with the cannabis or alcohol time-series shifted to the left, then that suggested that substance

**Table 2. Demographic and Clinical Characteristic of 50 Patients with Bipolar Disorder Following a First Psychiatric Hospitalization According to Whether They Exhibited Alcohol or Cannabis Abuse during the Follow-Up Interval**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Interval abuser ((n = 21))</th>
<th>Interval nonabuser ((n = 29))</th>
<th>Total ((n = 50))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>25 (7)</td>
<td>25 (9)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Race [n (% nonwhite)]</td>
<td>10 (48)</td>
<td>12 (41)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Gender [n (% women)]</td>
<td>5 (24)</td>
<td>13 (45)</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12 (2)</td>
<td>12 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Unemployed [n (%)]</td>
<td>6 (29)</td>
<td>11 (38)</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Index mixed state [n (%)]</td>
<td>6 (29)</td>
<td>14 (48)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Age at bipolar onset (years)</td>
<td>22 (7)</td>
<td>22 (8)</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Duration of index episode (weeks)</td>
<td>7 (7)</td>
<td>15 (23)</td>
<td>12 (19)</td>
</tr>
</tbody>
</table>

\( ^a \)One subject had a history of cannabis use that did not meet abuse or dependence criteria before the index hospitalization that worsened during follow-up.

\( ^b \)Significant difference from interval nonabusers: \( \chi^2(1) = 13.8, p < .001 \).

\( ^c \)Significant difference from interval nonabusers: \( \chi^2(1) = 8.0, p < .005 \).

\( ^d \)Significant difference from interval nonabusers: \( \chi^2(1) = 8.5, p < .004 \).
fraction of time with noncompliance were associated with either interval cannabis or alcohol ratings (at $p < .2$) and so were entered as potential confounds in the regression model. In this model, the fraction of time with alcohol abuse symptoms/syndromes was significantly associated with the fraction of time with any affective syndrome (adjusted partial $R = .37, p = .01$) after controlling for the fraction of time with cannabis abuse symptoms/syndromes and the confounds. (All subsequent $R$ values reported in this section are likewise partial scores adjusted for confounds and the other substance use disorder.) Most of this association was due to correlations between the fraction of time with alcohol symptoms/syndromes and the fraction of time spent in depression ($R = .33, p = .025$) rather than mania ($R = .17, p > .2$) or mixed states ($R = .11, p > .4$). In contrast, the fraction of time with cannabis abuse symptoms/syndromes was not significantly associated with the fraction of time in depression ($R = .21, p > .1$) nor in mixed states ($R < .02, p > .9$), but was significantly associated with the fraction of time with mania ($R = .42, p = .004$). The fraction of time with alcohol abuse symptoms/syndromes was significantly correlated with the time with cannabis abuse symptoms/syndromes ($R = .49, p = .0005$).

Sixteen patients exhibited changes in both alcohol use and affective symptom/syndrome ratings scores during follow-up to permit evaluation of associations between changes in these two disorders using the correlative analysis of the respective time series. As illustrated in Table 3, the most common association was with the alcohol use series left-shifted 1–8 weeks ($n = 7, 44\%$). Only a single patient exhibited the opposite pattern with affective symptoms preceding increased alcohol use by 1 week. Similarly, 19 patients exhibited changes in both cannabis use and affective ratings to evaluate these temporal relationships. In contrast to alcohol use, similar numbers of subjects exhibited both left- and right-shifted maximal associations between affective symptoms and cannabis abuse. For both alcohol and cannabis abuse, negative associations with affective symptoms were also common (Table 3); however, at none of the time shifts did the sample, as a whole, exhibit a statistically significant overall pattern of association between alcohol use or cannabis use and affective symptoms/syndromes. In contrast, alcohol and cannabis use exhibited significant associations with each other, with the strongest relationship present when alcohol was left-shifted 4 weeks ($t = .31, SD = .32, t = 3.2, p = .009$), suggesting alcohol use increases prior to increases in cannabis use in these patients.

### Discussion

From this review, it appears that alcohol use disorders may affect the age of bipolar disorder onset. In particular, bipolar patients with antecedent alcohol abuse appear to have a later age of onset of bipolar illness, which suggests that affective episodes in those patients are not precipitated until after several years of alcohol abuse. This subgroup of patients may have a lower familial risk of developing bipolar disorder than bipolar patients without alcohol abuse (DelBello et al 1999), and may therefore “require” the alcohol abuse to initiate the illness (Winokur et al 1995); however, many patients with alcohol abuse, even when it is antecedent to the bipolar disorder, will continue to experience affective episodes even after achieving sobriety (Strakowski et al 1998b), suggesting ongoing alcohol abuse is not required to maintain the affective symptoms. Nevertheless, once the courses of bipolar and alcohol use disorders are established, the longer term prognosis suggests a resolution of the alcohol problems in most patients. Once sobriety is achieved, patients with a past history of both a substance use and bipolar disorder may subsequently experience a better course of illness than patients without such a history of co-occurrence (Winokur et al 1995). Nonetheless, alcohol and drug abuse are associated with impaired treatment response, and symptomatic and functional recovery in bipolar disorder. These effects may be direct, because alcohol abuse may specifically precipitate affective symptoms (Strakowski et al 1998a, 1998b) or indirect by interfering with treatment compliance (Strakowski et al 1998a). The new results we present here suggest that alcohol abuse is primarily associated with depression, whereas cannabis abuse may be more commonly associated with mania. Additionally, these associations do not exhibit a single, common pattern in all patients, but instead, there appear to be subgroups of patients who exhibit different temporal relationships among affective symptomatology and cannabis and alcohol abuse. Moreover, different substances of abuse may be associated with

<table>
<thead>
<tr>
<th>Substance</th>
<th>Left shifted</th>
<th>Right shifted</th>
<th>Negative</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol [n (%)]</td>
<td>7 (44)</td>
<td>1 (6)</td>
<td>6 (38)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Mean t-b (SD)</td>
<td>.39 (.21)</td>
<td>.88 (0)</td>
<td>.35 (.08)</td>
<td>.03 (.23)</td>
</tr>
<tr>
<td>Cannabis [n (%)]</td>
<td>5 (26)</td>
<td>4 (21)</td>
<td>7 (37)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Mean t-b (SD)</td>
<td>.52 (.13)</td>
<td>.53 (.17)</td>
<td>.51 (.23)</td>
<td>.08 (.14)</td>
</tr>
</tbody>
</table>

Listed are the number of subjects exhibiting maximal correlations with substance abuse left-shifted relative to affective symptoms (increased substance abuse leads to increased affective symptoms), with substance abuse right-shifted (increased substance abuse follows increased affective symptoms), with negative associations (changes in substance abuse occur inversely to changes in affective symptoms) and with no association (defined as t-b < 0.20).
different patterns. The common finding that affective symptoms and alcohol and cannabis abuse are inversely associated suggests that either substance use masks or decreases affective symptoms or, conversely, that affective symptoms may result from substance withdrawal. These suggestions required additional study as, clearly, these new data should be viewed as preliminary, since the number of subjects is still relatively small.

Most previous studies examining the common co-occurrence between substance use and bipolar disorders have been limited to simply reporting elevated rates of substance abuse or have been post-hoc analyses examining outcome associations. Few studies have been designed specifically to detail the relationships among these conditions. Although these relationships are complex, the results we present here suggest they can be examined systematically and, hopefully, clarified. Understanding the relationships between substance use and bipolar disorders may lead to new treatment approaches for patients with both conditions (Strakowski and DelBello 2000). Moreover, clarifying how different substances of abuse differentially impact the course of bipolar disorder might help define the neurophysiology of bipolar disorder.

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References


