Effects of Co-occurring Alcohol Abuse on the Course of Bipolar Disorder Following a First Hospitalization for Mania

Stephen M. Strakowski, MD; Melissa P. DelBello, MD; David E. Fleck, PhD; Caleb M. Adler, MD; Robert M. Anthenelli, MD; Paul E. Keck, Jr, MD; Lesley M. Arnold, MD; Jennifer Amicone, MSW

Context: Alcohol-use disorders are common co-occurring conditions affecting bipolar patients, and this co-occurrence is negatively associated with outcome.

Objective: The primary goal of this study was to identify how the relative onsets of alcohol-use and bipolar disorders affect the subsequent courses of illness in patients with both conditions.

Design and Setting: Inception cohort at an academic medical center.

Patients: Patients meeting criteria for type I bipolar disorder, manic or mixed, with ages of 12 to 45 years, no prior hospitalizations, and minimal prior treatment. We enrolled 144 subjects who were followed up for up to 5 years, including 27 subjects in whom the onset of an alcohol-use disorder preceded the onset of bipolar disorder (Alcohol First), 33 subjects in whom bipolar disorder onset preceded or was concurrent with the onset of alcohol abuse (Bipolar First), and 83 subjects with bipolar disorder only (No Alcohol).

Main Outcome Measures: Symptomatic recovery and recurrence of both conditions and percentage of follow-up with affective episodes and affective and alcohol-use disorder symptoms.

Results: The Alcohol First group was older and more likely to recover and recover more quickly than the other groups. Affective symptomatic recurrence curves were similar among groups. The Bipolar First group spent more time with affective episodes and symptoms of an alcohol-use disorder during follow-up than the Alcohol First group. Hospitalization was associated with a period of decreased alcohol abuse, although recurrence of the alcohol-use disorder was common.

Conclusions: The relative age at onset of alcohol-use and bipolar disorders is associated with differences in the course of both conditions. A first hospitalization for mania is associated with a period of recovery from comorbid alcohol abuse, suggesting this posthospital time may provide an opportunity to treat this co-occurring condition.

Arch Gen Psychiatry. 2005;62:851-858

The course of bipolar disorder is frequently complicated by alcohol abuse. In the Epidemiological Catchment Area Study, 46% of bipolar type I patients had lifetime histories of alcohol-use disorders. Longitudinal studies suggest that a co-occurring alcohol-use disorder negatively impacts the course of bipolar disorder. Alcohol and drug abuse have been associated with poor symptomatic and functional recovery, more recurrences, more hospitalizations, poorer lithium response, developing mixed states, and decreased treatment adherence. Regardless, the relationship between these co-occurring conditions is relatively complex. One way to untangle these complexities is to examine temporal associations of the courses of the co-occurring conditions. For example, Winokur et al defined patients in whom bipolar disorder symptoms began prior to the onset of alcohol abuse as “primary bipolar disorder” and the converse as “primary alcoholism.” They found that this distinction predicted different courses of bipolar disorder. Namely, the primary alcoholism...
group exhibited a less severe bipolar course of illness than the primary bipolar disorder group. With these considerations in mind, we prospectively studied the course of illness for both bipolar and alcohol-use disorders in patients following a first psychiatric hospitalization for mania. We examined course-of-illness differences between patients whose bipolar illness onset preceded the development of an alcohol-use disorder and those whose alcohol-use disorder was antecedent to test 2 primary hypotheses:

1. The relative order of onset of bipolar and alcohol-use disorders will affect the subsequent course of bipolar disorder. Specifically, patients whose alcohol-use disorder precedes the onset of bipolar disorder will have a less severe course than the other groups.8

2. The relative order of onset of bipolar and alcohol-use disorders will affect the subsequent course of alcohol abuse. The specific direction of this effect could not be predicted from the literature, as it has been minimally studied previously.

We studied first-episode patients to improve the validity of age-at-onset estimates and because alcohol effects may be more likely to influence the course of bipolar disorder early in the course of illness.3,4,6,7

METHODS

SUBJECTS

Bipolar patients (n=144) were recruited within the University of Cincinnati First-Episode Mania Study.3,13,14 Inclusion criteria encompassed (1) meeting DSM-IV criteria for bipolar disorder, manic or mixed (bipolar disorder type I), with a Young Mania Rating Scale (YMRS) score greater than or equal to 20, (2) age of 12 to 45 years, (3) no prior psychiatric hospitalizations, (4) less than 1 month of cumulative lifetime exposure to psychotropic medication, (5) able to speak English, and (6) able to return for follow-up visits. Subjects were excluded if (1) psychiatric symptoms were due entirely to acute medical illnesses, (2) psychiatric symptoms were entirely due to acute drug or alcohol withdrawal as determined by symptom resolution within the expected period of acute intoxication or withdrawal,4 or (3) IQ was less than 70. Written informed consent was obtained from all adult patients and from parents or guardians of adolescent patients (with the patients’ assent) after the details of the study were explained. This protocol was approved by local institutional review boards.

Patients were recruited from consecutive hospitalizations from June 1, 1996, through October 1, 2003. We identified 271 potential subjects of whom 182 (67%) of 271 appeared to meet study criteria and 172 (95%) of 182 provided informed consent. Of these subjects, 144 (84%) of 172 had at least 4 months of follow-up at the time of this analysis and are included in this report. Four months was chosen as the minimum follow-up period because it represented the first major visit and because it is consistent with prior work.3,13,14 Thirteen subjects were in their first year of follow-up. The 28 subjects who did not attend at least 4 months of follow-up were similar to these 144 subjects in age (25 years vs 22 years), sex (50% vs 48% women), ethnicity (64% vs 70% white), education (12 years vs 11 years), index mania score (YMRS score, 34 in both groups), depression score (Hamilton Depression Rating Scale score, 17 vs 15), and rates of alcohol-use disorders (61% vs 42%; χ² = 3.2, P < .08).

INDEX CLINICAL ASSESSMENT

The diagnosis of DSM-IV bipolar disorder was established using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P),3,13 administered by trained research clinicians with established interrater reliability (κ = 0.90).3,13,14 These investigators assessed psychiatric symptoms using the YMRS17 and the 17-item Hamilton Depression Rating Scale.17 The presence or absence of psychosis was determined with the SCID-I/P and the Scale for the Assessment of Positive Symptoms.18 Patients’ index symptoms were rated for the worst period during the current episode, typically coinciding with hospital admission. The investigators established good interrater reliability for these measures (intraclass correlation coefficient > 0.70 for most individual symptoms and all total scores).3,13,14

Trained research assistants (predominantly master’s level social workers) assessed substance-use disorders using the Substance Use Disorders module of the SCID-I/P and the Addiction Severity Index (ASI).19 again with good interrater reliability (intraclass correlation coefficient > 0.70 for individual symptoms). Drug and alcohol use in the month (30 days) prior to admission was rated using the ASI integrated with Timeline Follow-Back (TLFB) methods.20 An ASI score for overall severity of use was determined for drug and alcohol use based on a 10-point scale: 0 to 1, no real problem; 2 to 3, slight problem, substance abuse treatment probably not necessary; 4 to 5 moderate problem, some treatment indicated; 6 to 7 considerable problem, treatment necessary; and 8 to 9 extreme problem, treatment absolutely necessary.

AGE AT ONSET

The age at onset of bipolar disorder was defined as the age at which the first DSM-IV affective episode began, established using the SCID-I/P. The index manic or mixed episode was the first affective episode in 89 (62%) of 144 patients. Forty-five patients (31%) had 1 (n = 20) or more (n = 25) prior depressive episodes. Twenty-three patients (16%) had 1 (n = 14) or more (n = 9) prior hypomanic or mild manic episodes. For all patients, this was the first manic or mixed episode requiring hospitalization. The age at onset of alcohol-use disorders was defined as that age at which patients first met criteria for alcohol abuse. This was determined by using information obtained from both the SCID-I/P and the ASI. Interrater reliability for age-at-onset estimates was high (intraclass correlation coefficient > 0.90).3,13,14

SUBJECT CLASSIFICATION

The study subjects were classified into 3 groups by age-at-onset information. The first group (No Alcohol) consisted of bipolar patients with no history of alcohol-use disorders (n = 84, 58% of the sample). The second group (Bipolar First) were patients in whom the onset of bipolar disorder occurred prior to or concurrently with the onset of the alcohol-use disorder (n = 33, 23%). Concurrently with was defined as occurring within 1 year (before or after) of the onset of bipolar disorder consistent with our previous work.3,14 The concurrent patients were added to the Bipolar First group because the bipolar disorder was the principal diagnosis since patients were identified for study by the presence of mania. Finally, the third group (Alcohol First) were patients in whom the onset of the alcohol-use disorder preceded the onset of bipolar disorder by more than 1 year (n = 27, 19%). Rates of study completion were 83% for the No Alcohol group, 76% for the Bipolar First group, and 63% for the Alcohol First group (χ² = 3.3, P < .08). However, patients often discontinued some time after outcome events (see Figures 1, 2, and 3). The primary reasons for drop out typi-
symptom severity were made based on these assessments and alcohol-use disorders, week-by-week 6-point ratings of included every item of the symptom ratings scales, the Affective changing drug and alcohol use. Each follow-up review in-
tendar methods were used to assist with identifying periods of
tivation was paid to times of affective symptom changes, and cal-
calffective symptoms and drug and alcohol use. Particular atten-
vestigators reviewed the prior interval, week-by-week, for both
the sample had more than 2.5 years of follow-up.

The mean±SD follow-up for the entire sample had more than 4 years of follow-up, and half the sample had more than 2.5 years of follow-up.
As described elsewhere,3,13,14 the general study design is based on previously published studies.6,9,12 At each follow-up visit, investigators reviewed the prior interval, week-by-week, for both affective symptoms and drug and alcohol use. Particular attention was paid to times of affective symptom changes, and calendar methods were used to assist with identifying periods of changing drug and alcohol use. Each follow-up review included every item of the symptom ratings scales, the Affective and Psychotic and Substance Use Disorders Modules of the SCID-I/P, the ASI, and ratings of the severity of both affective and substance-use disorder syndromes. For both the bipolar and alcohol-use disorders, week-by-week 6-point ratings of symptom severity were made based on these assessments (Table 1).3 For the alcohol and drug use disorders, we used the Timeline Follow-Back to identify change points and use patterns, but we used only the ASI overall rating coupled with the SCID-I/P module to make determinations of the week-by-
week severity ratings of Table 1. From these ratings, we identity periods of recovery and recurrence and calculated the percentage of weeks in different phases of illness.3,13,14 Rapid cycling was defined as 4 or more full affective episodes in any 52-week period. Independent raters, blind to each other’s scores, obtained the substance-use and affective symptom ratings, respectively.

**DEMOGRAPHIC VARIABLES**

Demographic information, such as age, sex, ethnicity, and years of education, was obtained from direct patient interviews and review of medical records.

**FOLLOW-UP ASSESSMENTS**

Following hospital discharge, patients were re-evaluated at 1 month, at 4 months, and then every 4 months for up to 8 years. In the current analysis, we restricted follow-up to a maximum of 5 years because the number of evaluable subjects after that time was relatively small. The mean±SD follow-up for the entire sample was 135±89 weeks (2.6 years). Twenty-five percent of the sample had more than 4 years of follow-up, and half the sample had more than 2.5 years of follow-up.

As described elsewhere,3,13,14 the general study design is based on previously published studies.6,9,12 At each follow-up visit, investigators reviewed the prior interval, week-by-week, for both affective symptoms and drug and alcohol use. Particular attention was paid to times of affective symptom changes, and calendar methods were used to assist with identifying periods of changing drug and alcohol use. Each follow-up review included every item of the symptom ratings scales, the Affective and Psychotic and Substance Use Disorders Modules of the SCID-I/P, the ASI, and ratings of the severity of both affective and substance-use disorder syndromes. For both the bipolar and alcohol-use disorders, week-by-week 6-point ratings of symptom severity were made based on these assessments (Table 1).3 For the alcohol and drug use disorders, we used the Timeline Follow-Back to identify change points and use patterns, but we used only the ASI overall rating coupled with the SCID-I/P module to make determinations of the week-by-week severity ratings of Table 1. From these ratings, we identified periods of recovery and recurrence and calculated the percentage of weeks in different phases of illness.3,13,14 Rapid cycling was defined as 4 or more full affective episodes in any 52-week period. Independent raters, blind to each other’s scores, obtained the substance-use and affective symptom ratings, respectively.

**Table 1**

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>No Alcohol</th>
<th>Bipolar First</th>
<th>Alcohol First</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Recovered, %</td>
<td>27</td>
<td>34</td>
<td>83</td>
</tr>
<tr>
<td>Patients Remaining Not Recovered from Alcohol-Use Disorder, No.</td>
<td>83</td>
<td>58</td>
<td>35</td>
</tr>
<tr>
<td>Follow-up Time, wk</td>
<td>60</td>
<td>180</td>
<td>260</td>
</tr>
</tbody>
</table>

**Figure 1.** Affective symptomatic recovery following a first manic episode in bipolar patients with no alcohol-use disorder (No Alcohol), alcohol-use disorder that began after the onset of the bipolar disorder (Bipolar First), and alcohol-use disorder that began prior to the onset of bipolar disorder (Alcohol First). The Alcohol First group survival curve significantly differs from those of the other groups (log-rank 2=16.2, P<.001). Asterisk indicates censored data (subjects dropped out of the study prior to recovery).

**Figure 2.** Affective symptomatic recurrence following a first manic episode in bipolar patients with no alcohol-use disorder (No Alcohol), alcohol-use disorder that began after the onset of the bipolar disorder (Bipolar First), and alcohol-use disorder that began prior to the onset of bipolar disorder (Alcohol First). Asterisk indicates censored data (subjects dropped out of the study prior to recurrence).

**Figure 3.** Alcohol-use disorder symptomatic recovery following a first manic episode in bipolar patients with alcohol-use disorder that began after the onset of the bipolar disorder (Bipolar First) and alcohol-use disorder that began prior to the onset of bipolar disorder (Alcohol First). Also indicated are the subgroups of the Bipolar First group: those whose alcohol-use disorder preceded hospitalization and those whose alcohol-use disorder began during follow-up. The survival curves are significantly different (log-rank 2=10.0, P<.002). Asterisk indicates censored data (subjects dropped out of the study prior to recovery).
TREATMENT ASSESSMENTS

Because this study was naturalistic, investigators did not administer treatment. The treatments that patients received during each follow-up interval were reviewed, and treatment adherence for each medication was recorded as full adherence in which the medication was taken more than 75% of the time as prescribed, total nonadherence in which the medication was taken less than 23% of the time as prescribed, or partial nonadherence in which the medication was taken at a rate between these 2 extremes. This rating was obtained by reviewing week-by-week interval medication use with patients and with family members or clinicians when necessary (ie, if the patient’s reliability was suspect). Serum levels were not obtained because many patients were taking medications without standard blood levels (eg, antipsychotics) and the investigators did not control treatment. From this review, we determined the percentage of follow-up in which patients exhibited full compliance for each prescribed medication and used an average (total compliance) score across medications as a potential covariate in analyses.

STATISTICAL ANALYSIS

All statistical analyses were performed on version 8.02 of the Statistical Analysis System for the PC (SAS Institute Inc, Cary, NC). To answer the first hypothesis about the effect on the course of bipolar disorder, we performed comparisons of outcome variables among the 3 groups (No Alcohol, Bipolar First, and Alcoholic First). Survival analysis was used to compare the groups on recovery from bipolar disorder and recurrence of significant affective symptoms using the log-rank \( \chi^2 \) test. If the omnibus comparison was significant, then we performed pairwise comparisons to further evaluate differences. Times to events (eg, recovery, relapse) were evaluated using Cox regression models in which we forced the group and bipolar age at onset into the model and then entered other covariates using stepwise selection if associated with the event at a significance level of \( P < .1 \). We used analysis-of-covariance models to compare groups on percentages of weeks spent in recovery (symptom severity scores of 1 or 2), with full affective syndromes (scores of 5 or 6), and with subsyndromal symptoms (scores of 3 or 4). We used Tukey Honestly Significant Difference post hoc procedures or least squares means protected \( t \) tests to further examine planned pairwise comparisons in these models.

To address the second hypothesis about the effect on the course of alcohol abuse, we again used survival analysis to examine rates of symptomatic recovery and recurrence of alcohol-use disorders among the groups and Cox regression models to examine time to events. We used analysis of covariance models to examine differences among the groups in percentage of time with symptoms of alcohol-use disorders during follow-up (symptom severity scores \( \geq 3 \), Table 1). Regression models evaluated associations between percentage of weeks in episodes and symptoms of alcohol-use disorders. For these planned comparisons, significance was defined as \( P < .05 \). Other analyses were performed as indicated for completeness.

RECOVERY AND RECURRENCE

Affective symptomatic recovery (referred to as recovery subsequently) from bipolar disorder was defined as at least 8 contiguous weeks with symptom severity ratings of 1 or 2 (Table 1). Affective (symptomatic) recurrence was defined as at least 1 week of several new significant subsyndromal symptoms (scores \( > 3 \), Table 1). Recovery from alcohol-use disorders was similarly defined as at least 8 contiguous weeks with symptom severity ratings of 1 or 2 (Table 1). Recurrence of alcohol-use disorders was defined as at least 1 week of new symptom severity scores greater than 3 (Table 1).

DRUG ABUSE

This article focuses on alcohol-use disorders; drug-use disorders will be discussed in future publications. However, in our sample, regular cannabis use and abuse was common, whereas abuse of other drugs was infrequent and always accompanied by cannabis use. Additionally, we previously found associations between cannabis and alcohol abuse in this population. Consequently, we used cannabis use, rather than drug use more generally, as a potential confounding variable in analyses. Week-by-week cannabis use was assessed and scored similarly to alcohol use (Table 1).

Table 1. Definitions for Week-by-Week Overall Symptom Severity Ratings for Bipolar Disorder and Alcohol-Use Disorders Following a First Hospitalization for Mania

<table>
<thead>
<tr>
<th>Rating</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Full syndrome, severe: meets several DSM-IV criteria, more than the minimum required. Bipolar disorder: for a manic, mixed, or major depressive episode. Alcohol-use disorder: for alcohol dependence.</td>
</tr>
<tr>
<td>4</td>
<td>Marked symptoms. Bipolar disorder: does not meet full affective syndrome criteria, but several DSM-IV affective syndrome criteria are scored higher than mild on the HDRS or YMRS. Alcohol-use disorder: does not meet full syndrome criteria for alcohol dependence, but 1 or more alcohol abuse or dependence criteria are met.</td>
</tr>
<tr>
<td>3</td>
<td>Partial remission. Bipolar disorder: no DSM-IV affective syndrome criteria are rated higher than mild on the HDRS or YMRS, but the total HDRS score is greater than 7, the YMRS score is greater than 5, or any SAPS global item score is greater than 2. Alcohol-use disorder: no dependence criteria, but the ASI rater severity score is greater than 3.</td>
</tr>
<tr>
<td>2*</td>
<td>Residual symptoms. Bipolar disorder: 1 or more mild symptoms, but the YMRS score is less than 5 and the HDRS score is less than 7 and SAPS global item scores are all less than 2. Alcohol-use disorder: no dependence or abuse criteria, but the ASI rater severity score is greater than 1.</td>
</tr>
<tr>
<td>1*</td>
<td>Usual self: no significant symptoms</td>
</tr>
</tbody>
</table>

Abbreviations: ASI, Addiction Severity Index; HDRS, Hamilton Depression Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; YMRS, Young Mania Rating Scale. *Scores required for remission. Eight weeks of remission required for recovery.
Despite differences in age and age at onset of bipolar disorder, the comorbid groups did not exhibit differences in the age at onset of alcohol-use disorders. However, the Alcohol First group was more likely to have alcohol dependence than abuse, relative to the Bipolar First group. Both comorbid groups exhibited more alcohol use to intoxication and higher alcohol-abuse severity (ASI) scores in the month prior to admission than the No Alcohol group but did not differ from each other. Rates of cannabis-use disorders significantly differed among the 3 groups (Table 2). Again, the Alcohol First group exhibited higher rates of cannabis dependence than abuse, relative to the other 2 groups. The Alcohol First group exhibited more cannabis use during the month prior to admission than the No Alcohol group, but not the Bipolar First group. The total drug-abuse severity score in the month prior to admission was significantly higher for the Alcohol First group than it was for both other groups. Psychosis significantly correlated with the drug-abuse severity scores at index (r = 0.20, P < .02).

### COURSE OF BIPOLAR ILLNESS

Figure 1 illustrates survival curves for (symptomatic) recovery from bipolar disorder during follow-up for the 3 groups of patients. These curves significantly differed (log-

### Table 2. Demographic Characteristics of Patients Hospitalized for a First Manic Episode According to Whether They Have No Alcohol-Use Disorder or Whether the Onset of the Alcohol-Use Disorder Occurred Before or After the Onset of the Bipolar Disorder

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Alcohol (n = 83)</th>
<th>Bipolar First (n = 34)</th>
<th>Alcohol First (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>20 ± 8</td>
<td>21 ± 7</td>
<td>28 ± 8</td>
</tr>
<tr>
<td>Women, No.</td>
<td>48 ± 58</td>
<td>13 ± 38</td>
<td>8 ± 30</td>
</tr>
<tr>
<td>White, No.</td>
<td>58 ± 70</td>
<td>24 ± 71</td>
<td>19 ± 70</td>
</tr>
<tr>
<td>Education, y</td>
<td>10.1 ± 3.3</td>
<td>11.0 ± 3.1</td>
<td>12.6 ± 1.9</td>
</tr>
<tr>
<td>Baseline YMRS score</td>
<td>34 ± 8</td>
<td>33 ± 9</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>Baseline HDRS score</td>
<td>15 ± 7</td>
<td>17 ± 7</td>
<td>14 ± 9</td>
</tr>
<tr>
<td>Mixed state, No.</td>
<td>45 ± 54</td>
<td>20 ± 59</td>
<td>7 ± 26</td>
</tr>
<tr>
<td>Psychotic, No.</td>
<td>46 ± 55</td>
<td>24 ± 71</td>
<td>6 ± 96</td>
</tr>
<tr>
<td>Age at onset of bipolar disorder, y</td>
<td>17 ± 8</td>
<td>17 ± 6</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Alcohol-use disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse, No.</td>
<td>NA</td>
<td>19 ± 56</td>
<td>7 ± 26</td>
</tr>
<tr>
<td>Dependence, No.</td>
<td>NA</td>
<td>15 ± 44</td>
<td>20 ± 74</td>
</tr>
<tr>
<td>Days alcohol was used to intoxication in the prior month, No.</td>
<td>0.5 ± 2.0</td>
<td>6.0 ± 8.8</td>
<td>4.3 ± 7.7</td>
</tr>
<tr>
<td>Age at onset of alcohol use, y</td>
<td>NA</td>
<td>19 ± 6</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Alcohol-use severity score in prior month</td>
<td>0.1 ± 0.5</td>
<td>1.5 ± 2.4</td>
<td>2.5 ± 2.9</td>
</tr>
<tr>
<td>Cannabis-use disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse, No.</td>
<td>8 ± 10</td>
<td>8 ± 24</td>
<td>2 ± 7</td>
</tr>
<tr>
<td>Dependence, No.</td>
<td>10 ± 12</td>
<td>9 ± 38</td>
<td>17 ± 63</td>
</tr>
<tr>
<td>Days cannabis used in prior month, No.</td>
<td>3.0 ± 8.1</td>
<td>6.4 ± 9.2</td>
<td>8.5 ± 12.2</td>
</tr>
<tr>
<td>Age at onset of cannabis use, y</td>
<td>16 ± 6</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Other drug abuse or dependence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine, No.</td>
<td>2 ± 2</td>
<td>2 ± 6</td>
<td>3 ± 11</td>
</tr>
<tr>
<td>Hallucinogens, No.</td>
<td>0 ± 0</td>
<td>1 ± 3</td>
<td>6 ± 22</td>
</tr>
<tr>
<td>Other, No.</td>
<td>0 ± 0</td>
<td>1 ± 3</td>
<td>3 ± 11</td>
</tr>
<tr>
<td>Drug-use severity score in prior month</td>
<td>0.5 ± 1.4</td>
<td>1.4 ± 2.0</td>
<td>2.9 ± 3.3</td>
</tr>
</tbody>
</table>

Abbreviations: HDRS, Hamilton Depression Rating Scale; NA, not applicable; YMRS, Young Mania Rating Scale.

©2005 American Medical Association. All rights reserved.
and time to recovery from the Cox regression model. In the Cox regression model, group assignment was significantly associated with time to recovery (log-rank $\chi^2=4.1, P<.05$) after adjusting for bipolar age at onset ($\chi^2=4.3, P<.04$) and 2 covariates that met the inclusion criteria into the model: index mixed state ($\chi^2=4.8, P<.03$) and sex ($\chi^2=4.6, P<.04$). Although symptomatic recurrences of affective episodes were common among all groups, the survival curves did not differ significantly (Figure 2; log-rank $\chi^2=3.0, P>.2$), nor were there significant group differences in time to recurrence in the Cox regression model ($\chi^2=0.02, P>.8$). Rapid cycling during follow-up was not significantly associated with recovery or recurrence in these models.

Table 3 lists the percentages of follow-up weeks spent in mood episodes as well as with subsyndromal mood symptoms. Group comparisons were made adjusting for differences in bipolar age at onset; age; education; sex; and index rates of psychosis, mixed states, and cannabis-use disorders. The 3 groups did not significantly differ in total weeks of follow-up ($F_{9,134}=1.4, P=.24$), percentages of weeks with total treatment adherence ($F_{9,134}=1.42, P=.25$), percentages of weeks in recovery ($F_{9,134}=1.2, P=.3$), or weeks with subsyndromal affective symptoms ($F_{9,134}=1.7, P<.2$), after adjusting for covariates. However, the Bipolar First group spent a significantly greater percentage of follow-up with a full affective episode than the other groups. This difference resulted from nonsignificantly more time in manic ($F_{9,134}=2.3, P=1$) and significantly more time in mixed episodes, particularly compared with the Alcohol First group. Finally, the Bipolar First group demonstrated significantly more rapid cycling during follow-up.

**Course of Alcohol-Use Disorders**

Figure 3 illustrates survival curves for recovery from alcohol-use disorders for the 2 comorbid groups; additionally, the Bipolar First group is divided between those who were abusing alcohol prior to hospital admission and those whose alcohol-use disorder developed during follow-up. This latter curve starts at the time the alcohol-use disorder began whereas the other 2 curves begin at hospital discharge. The 2 comorbid groups exhibited significant differences in recovery curves (log-rank $\chi^2=10.0, P=.002$) and time to recovery from the Cox regression model ($\chi^2=5.4, P=.02$), adjusted for age at onset of alcohol-use disorders ($\chi^2=0.2, P=7$). These differences were primarily due to the patients in the Bipolar First group who developed an alcohol-use disorder after hospital discharge (n=16); this subgroup demonstrated slower recovery than the remaining patients in the Bipolar First group (log-rank $\chi^2=6.6, P=.01$) and the Alcohol First group (log-rank $\chi^2=16.6, P<.001$) whereas the latter 2 survival curves did not significantly differ (log-rank $\chi^2=1.6, P>.2$). In other words, patients in whom an alcohol-use disorder began prior to hospital admission, no matter whether the bipolar or alcohol-use disorders were antecedent, were more likely to recover than patients in whom alcohol use began during follow-up. Much of this effect may have been related to hospitalization because nearly 75% of the patients who were using alcohol prior to hospitalization did not resume alcohol use for at least 8 weeks following hospital discharge.

Symptomatic recurrences of alcohol-use disorders were common, occurring in all of the Bipolar First and most (78%) of the Alcohol First groups; this difference in survival curves between groups was not significant, controlling for age at onset of alcohol-use disorders (log-rank $\chi^2=2.7, P=.1$; figure not shown). The groups significantly differed in the percentages of weeks with symptoms of an alcohol-use disorder (Table 3); the Bipolar First group spent a greater percentage of follow-up with these symptoms than the Alcohol First group, even after controlling for age at onset of alcohol use, age, sex, education, history of a cannabis-use disorder, psychosis, and mixed state ($F_{8,32}=14.8, P<.001$). To extend this work, we compared alcohol-use ratings when patients were prescribed anticonvulsants (mean±SD alcohol-use score, 1.5±1.0), antipsychotics (mean±SD score, 1.4±0.8), and lithium (mean±SD score, 1.4±0.6) and found no significant differences ($t<0.8, P>.5$).

Sixteen patients developed a new diagnosis of an alcohol-use disorder during follow-up. Compared with the No Alcohol group, these patients were similarly aged (mean±SD age, 19±5 years, t=1.0, P=.33), nonsignificantly more likely to be male (n=10, 63%; 2-tailed Fisher exact test, P>.1), and significantly more likely to have psychosis at index (n=9, 60%; Fisher exact test, P<.02); indeed, psychosis was significantly associated with developing a new alcohol-use disorder (Wald $\chi^2=8.2, P=.004$). They had YMRS scores (35±9) and Hamilton Depression Rating Scale scores (14±5) that were similar to those for the larger group. Ten of these subjects developed the new alcohol-use disorder within the first year after the index hospitalization (mean±SE, 78±18 weeks).

In addition to alcohol use, the 3 groups exhibited significant differences in the percentages of follow-up with symptoms of cannabis-use disorders ($F_{6,138}=5.7, P<.005$). Specifically, the No Alcohol group spent 8%±19% of weeks in follow-up with symptoms of cannabis-use disorders compared with 21%±28% in the other groups.

**Interactions Between Courses of Bipolar and Alcohol-Use Disorders**

To extend these primary analyses, we performed correlations between the percentage of weeks with alcohol-use disorder and affective symptoms, while adjusting for percentage of weeks with cannabis abuse. In the combined comorbid group (n=61), the percentage of weeks during follow-up in a full affective episode was significantly associated with the percentage of weeks of alcohol-use disorder symptoms (adjusted $r=0.28, P<.04$). This association arose from the Bipolar First (adjusted $r=0.33$) rather than Alcohol First group (adjusted $r=0.03$). Within the Bipolar First group, the percentage of weeks with alcohol-use disorder symptoms was significantly associated with the percentage of time in mixed episodes (adjusted $r=0.43, P<.02$) but not manic episodes (adjusted $r=0.28, P>.1$) nor depressed episodes (adjusted $r=0.28,$
was less severe in the Alcohol First group, qualitatively
toms. Therefore, although the course of bipolar illness
affective relapses virtually identical to those of the other
drawal. Third, these patients exhibited a pattern of
sisted beyond the period of acute intoxication and with-
ond, inclusion criteria required manic symptoms to per-
ister were observed between the comorbid groups. The Bi-
spend less time in affective epi-
ers were observed between the comorbid groups. The Bi-
period immediately following hospitalization, suggesting
rates of recovery from the alcohol-use disorder in the pe-
alcohol-use disorder did not begin until after the index
peared to be secondary to the subgroup of patients whose
ly prior to a manic hospitalization for a first manic episode.

tory relapse. Additionally, most of the patients who devel-
window of opportunity to decrease rates of alcohol abuse
many patients with these co-occurring con-
jorbid groups. The Bipolar First group exhibited more time with symp-
after the index hospitalization. In fact, both groups exhibited very high
rates of recovery from the alcohol-use disorder in the pe-
period immediately following hospitalization, suggesting
that hospitalization for acute mania initiates a period of sobriety in many patients with these co-occurring conditions. However, both patient groups exhibited relatively rapid and common recurrences, suggesting that aggressive intervention in this period might provide a window of opportunity to decrease rates of alcohol abuse relapse. Additionally, most of the patients who developed a new alcohol-use disorder did so in the first year following the index hospitalization for mania, further suggesting a therapeutic window in which preventative treatment might be introduced to decrease the risk of new alcohol-use disorders in young bipolar patients.

As noted in the introduction, alcohol abuse in bipolar disorder has been associated with mixed affective

**COMMENT**

These results support the hypothesis that differences in relative ages at onset of alcohol-use and bipolar disorders in patients with both conditions differentially affect the early course of illness. Bipolar patients with antecedent alcohol-use disorders exhibited a number of characteristics consistent with a less severe form of affective illness compared with other bipolar patients. Specifically, they had a later age at bipolar onset, symptomatically recovered more rapidly, and spent less time in affective episodes. These findings are consistent with the suggestion by Winokur et al that patients with a history of an alcohol-use disorder prior to a later age at bipolar onset “may have needed the added insult of alcoholism to make it [bipolar disorder] manifest.” Moreover, these patients exhibited a relatively rapid rate of recovery during the initial posthospitalization period, when most patients maintained sobriety from alcohol.

One criticism of this finding could be that the Alcohol First group did not suffer from “true” bipolar disorder, but rather from an alcohol-induced affective syndrome. Several factors mitigate against this interpretation. First, patients were recruited during a manic episode, which is an atypical presentation of alcoholism. Second, inclusion criteria required manic symptoms to persist beyond the period of acute intoxication and withdrawal. Third, these patients exhibited a pattern of affective relapses virtually identical to those of the other 2 bipolar groups, in the absence of a meaningful correlation between alcohol-use disorder and affective symptoms. Therefore, although the course of bipolar illness was less severe in the Alcohol First group, qualitatively it was otherwise quite similar to the course of illness in the other groups. Nonetheless, the relatively delayed onset of bipolar symptoms in this patient group suggests that aggressive management of alcohol abuse in people at risk for bipolar disorder warrants further investigation.

Both comorbid groups exhibited relatively low percentages of follow-up with symptoms of an alcohol-use disorder, consistent with Winokur et al, who found that the course of alcohol abuse in bipolar patients was much less severe than in primary alcoholics or in patients with unipolar depression and co-occurring alcoholism. However, differences in the course of the alcohol-use disorder were observed between the comorbid groups. The Bipolar First group exhibited more time with symptoms of alcohol abuse during follow-up and were more likely to exhibit symptomatic recurrences of an alcohol-use disorder after recovery than the Alcohol First group. Many of the differences observed between these 2 groups appeared to be secondary to the subgroup of patients whose alcohol-use disorder did not begin until after the index hospitalization. In fact, both groups exhibited very high rates of recovery from the alcohol-use disorder in the period immediately following hospitalization, suggesting that hospitalization for acute mania initiates a period of sobriety in many patients with these co-occurring conditions. However, both patient groups exhibited relatively rapid and common recurrences, suggesting that aggressive intervention in this period might provide a window of opportunity to decrease rates of alcohol abuse relapse. Additionally, most of the patients who developed a new alcohol-use disorder did so in the first year following the index hospitalization for mania, further suggesting a therapeutic window in which preventative treatment might be introduced to decrease the risk of new alcohol-use disorders in young bipolar patients.

As noted in the introduction, alcohol abuse in bipolar disorder has been associated with mixed affective

---

**Table 3. Course-of-Illness Characteristics of Patients Hospitalized for a First Manic Episode According to Whether They Have No Alcohol-Use Disorder or Whether the Onset of the Alcohol-Use Disorder Occurred Before or After the Onset of the Bipolar Disorder**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Alcohol (n = 83)</th>
<th>Bipolar First (n = 34)</th>
<th>Alcohol First (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, mean ± SD, wk</td>
<td>120 ± 84</td>
<td>159 ± 81</td>
<td>147 ± 108</td>
</tr>
<tr>
<td>Time recovered, mean ± SD, % of wk</td>
<td>25 ± 32</td>
<td>30 ± 32</td>
<td>53 ± 34</td>
</tr>
<tr>
<td>Time in any affective episode, mean ± SD, % of wk</td>
<td>21 ± 25</td>
<td>35 ± 26</td>
<td>15 ± 21</td>
</tr>
<tr>
<td>Depressed</td>
<td>10 ± 18</td>
<td>16 ± 17</td>
<td>5 ± 8</td>
</tr>
<tr>
<td>Mixed                           ‡</td>
<td>6 ± 14</td>
<td>10 ± 15</td>
<td>9 ± 20</td>
</tr>
<tr>
<td>Time with subsyndromal affective symptoms, mean ± SD, % of wk†</td>
<td>4 ± 13</td>
<td>9 ± 18</td>
<td>1 ± 3</td>
</tr>
<tr>
<td>Time with symptoms an alcohol-use disorder, mean ± SD, % of wk§</td>
<td>54 ± 34</td>
<td>35 ± 23</td>
<td>33 ± 33</td>
</tr>
<tr>
<td>Time with full compliance with at least 1 mood stabilizer, mean ± SD, % of wk</td>
<td>2 ± 10</td>
<td>19 ± 19</td>
<td>11 ± 18</td>
</tr>
<tr>
<td>Rapid-cycling criteria met during follow-up, No. (%)</td>
<td>70 ± 56</td>
<td>47 ± 41</td>
<td>52 ± 58</td>
</tr>
<tr>
<td></td>
<td>4 (5)</td>
<td>9 (26)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Comparisons adjusted for age; age at bipolar onset; sex; education; and rates of psychosis, mixed states, and cannabis-use disorders at index.
†Significant group difference: F9,134 = 4.6, P < .01. The Bipolar First group had more time than both other groups.
‡Significant group difference: F9,134 = 3.0, P = .05. The Alcohol First group had less time than both other groups.
§Significant group difference: F9,134 = 12.1, P < .001. The Bipolar First group had more time than the Alcohol First group, which had more time than the No Alcohol group. Significant difference between Bipolar First and Alcohol First groups: F9,134 = 14.8, P < .001.
||Significant group difference: x2 = 5.8, P = .02. |
states.\textsuperscript{11} This association is clinically relevant because mixed states tend to be more difficult to treat than pure manic or depressive episodes and may represent a more severe type of mood episode.\textsuperscript{22} Our study suggests a potentially more refined view of the association between mixed states and alcohol abuse in that mixed states were significantly correlated with alcohol abuse only in the Bipolar First group and not the Alcohol First group. The former group also exhibited the most time spent in mixed states and more rapid cycling during follow-up. These data suggest that the association of mixed states and alcohol abuse may be related to specific temporal characteristics of the onset of these disorders. The relative lack of mixed states in the Alcohol First group may also indicate another marker that this patient group is, overall, less ill than the Bipolar First group.

This study had limitations to consider when interpreting findings. Although the total sample size was relatively large, particularly for a first-episode study, some subgroup analyses were based on relatively small numbers. This limitation was particularly true of contrasts of variables late in follow-up due to subject attrition. The patients were recruited from a single inpatient site and, as a consequence, may not generalize to other populations. Symptom ratings were primarily based on patient self-reports; therefore, the possibility of reporting bias or symptom minimization exists. Similarly, assessments of medication compliance were based on self-reports, rather than routine medication levels, introducing similar potential biases. The Timeline Follow-Back methodology has been primarily validated in monthly follow-ups; therefore, its validity at 4-month intervals is less certain. How-ever, these results are similar to previous studies, and there is no a priori reason to expect the patient subgroups to differentially bias self-reporting, suggesting the relative differences among groups are likely to be valid. Finally, this report is restricted to analyses of alcohol use with relatively minimal attention to the complex interactions with abuse of other substances.

Despite limitations, this study directly extends previous work exploring the associations between alcohol-use and bipolar disorders. Additionally, it reinforces prior findings that there is a subgroup of bipolar patients who may require several years of alcohol abuse before their mood disorders are manifest. Finally, it informs future clinical studies that might provide direct interventions to diminish the negative effects of the co-occurrence of these conditions, encouraging additional detailed investigation of this important and common clinical problem.

Submitted for Publication: October 8, 2004; final revision received January 13, 2005; accepted January 14, 2005.

Correspondence: Stephen M. Strakowski, MD, Division of Bipolar Disorders Research, 231 Albert Sabin Way (ML0559), PO Box 670559, Cincinnati, OH 45267-0559 (Stephen.Strakowski@uc.edu).

REFERENCES


©2005 American Medical Association. All rights reserved.