Depression Precipitated by Alcohol Use in Patients With Co-Occurring Bipolar and Substance Use Disorders

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Objective: Bipolar disorder and substance use disorder frequently co-occur. However, little is known about the near-term effects of substance use on bipolar disorder. Thus, the present study tests whether alcohol use precipitates depression among patients with co-occurring bipolar disorder and substance use disorder.

Method: This study uses data collected as part of 2 clinical trials (the first study was conducted from March 1999 through March 2004 and the second study was conducted from August 2003 through May 2007) of a manualized group therapy for patients with co-occurring bipolar disorder and substance dependence. One hundred fifteen participants were assessed at baseline and each month through month 8. Baseline diagnoses were made using the Structured Clinical Interview for DSM-IV, and monthly substance use and mood data were collected using the Longitudinal Interval Follow-Up Evaluation and the Addiction Severity Index. Generalized estimating equation methodology was used to analyze these longitudinal data.

Results: Our primary hypotheses were supported: days of alcohol use and an increase in days of alcohol use each significantly predicted the presence of a depressive episode in the subsequent month when controlling for current depression and current drug use.

Conclusion: These data suggest that alcohol use in patients with bipolar disorder and substance dependence increases the risk of a depressive episode in the near term.

Trial Registration: This study draws on data generated during 2 clinical trials. One was exempt from trial registration; clinicaltrials.gov Identifier for other trial: NCT00227838

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Bipolar disorder and substance use disorders frequently co-occur,[1–3] and people with both disorders experience worse outcomes than those having either disorder alone.[4–6] Despite the frequent co-occurrence of these disorders, little is known about the near-term impact of substance use itself on bipolar disorder episodes. Prior research in this area has either used correlational methodology or has examined the association between substance use disorder symptoms and bipolar disorder. To our knowledge, no prior research has longitudinally examined the near-term effects of substance use itself on bipolar disorder episodes. The present study tests whether alcohol use precipitates a depressive episode among patients with co-occurring bipolar disorder and substance use disorder in the month subsequent to alcohol consumption.

A number of correlational studies have examined the relation between alcohol use and/or alcohol use disorders and the course, treatment, and outcome of bipolar disorder and other mood disorders. In a retrospective chart review of outpatients with bipolar disorder, excessive alcohol use (defined as alcohol consumption causing impaired physical, social, or economic functioning) predicted hospitalization for manic symptoms during the period reviewed.[7] Furthermore, nearly twice as many patients hospitalized for manic symptoms versus depressive symptoms drank excessively. Similarly, a cross-sectional study of bipolar disorder patients with alcohol use disorders found that moderate alcohol use (< 4 drinks/week for men and < 2 drinks/week for women), when compared to less or no

use, was associated with significantly worse outcomes in men but not in women.[8] For men, higher than moderate levels of alcohol consumption were associated with a greater number of lifetime manic episodes and emergency room visits. For women, however, higher than moderate levels of alcohol consumption were associated with a shorter duration of bipolar illness and fewer depressive symptoms. Finally, a case register study demonstrated that current alcohol use increased the risk of hospitalization during the first 3 episodes of mood disorder, but not during subsequent episodes.[9] In sum, these correlational studies suggest that even moderate quantities of alcohol use may be associated with a more difficult course of bipolar disorder, particularly early in the course of the disorder.

Other substance use disorders also appear to be related to a more problematic course of bipolar disorder. For example, a study that examined the effects of substance use disorders (including alcohol use disorders) in first-episode bipolar I disorder did not find significant differences in the number of weeks ill during the 2-year follow-up period between patients with a single substance use disorder and patients without any substance use disorder.[10] However, patients with more than 1 substance use disorder had nearly twice as many weeks ill with bipolar disorder as either of these other groups. Finally, in a study of patients hospitalized for a current manic episode, a history of alcohol use disorders or marijuana use disorders predicted significantly lower rates of remission during hospitalization than was seen among patients without such a history.[11]

To date, 2 studies have prospectively examined the temporal association between substance use disorder symptoms (i.e., DSM-IV symptoms and/or Addiction Severity Index [ASI][12] scores)—but not necessarily substance use itself—and bipolar disorder course. In a study of 50 patients experiencing a first hospitalization for bipolar disorder, longer duration of alcohol use disorder symptoms (i.e., DSM-IV symptoms and/or ASI[12] scores) was associated with longer duration of mood episode, particularly depression, after the researchers controlled for cannabis use disorder symptoms during the study follow-up period of up to 24 months.[13] Furthermore, during follow-up, the amount of time participants experienced cannabis use disorder symptoms (i.e., DSM-IV symptoms and/or ASI scores) was significantly associated with the amount of time they experienced mania. In a subsample of these participants who experienced changes in both alcohol use disorder symptoms and a mood episode, there was no statistically significant pattern of temporal association between any substance use disorder symptoms and mood episode. In a later study of 71 participants recruited during their first manic episode, there was no statistically significant evidence of a temporal association between alcohol use disorder symptoms (i.e., DSM-IV symptoms and/or ASI scores) and bipolar disorder symptoms.[14]

In sum, all of the preceding studies show a robust relationship between alcohol use, substance use disorders, or substance use disorder symptoms and different aspects of the onset, course, and outcome of bipolar disorder. However, none of these studies have examined the near-term effects of active substance use on bipolar disorder episodes.

The present research seeks to build upon this prior work by examining the effects of alcohol use on the course of bipolar disorder during the month subsequent to alcohol consumption. To do so, this study used a longitudinal, repeated-measures design that assessed alcohol use and bipolar disorder episodes prospectively among patients with co-occurring bipolar disorder and substance use disorder. On the basis of research summarized above, we hypothesized that alcohol use during the current month will predict an increased likelihood of a depressive episode during the subsequent month, with alcohol use measured in 2 ways: (1) days of alcohol use and (2) increased days of alcohol use from the prior month. Additionally, we hypothesized that these relationships would remain significant when controlling for current depression and other drug use. We also conducted a total of 4 post hoc analyses that examined (1) days of heavy alcohol use (≥ 3 drinks/day), (2) increased days of heavy alcohol use (≥ 3 drinks/day), (3) days of non–heavy alcohol use (< 3 drinks/day), and (4) increased days of non–heavy alcohol use (< 3 drinks/day).

METHOD

Participants and Procedures

This study used data collected as part of 2 clinical trials (the first study was conducted from March 1999 through March 2004 and the second study was conducted from August 2003 through May 2007) of a manualized group therapy for patients with co-occurring bipolar disorder and substance use disorder.[15] Both research protocols were approved by the McLean Hospital Institutional Review Board (Belmont, Mass.). Participants were recruited from McLean Hospital programs, advertisements, fliers, and clinician referrals. Inclusion criteria were (1) current diagnoses of bipolar disorder and substance dependence other than nicotine, based on the Structured Clinical Interview for DSM-IV (SCID),[16] (2) substance use within 60 days of intake, (3) a mood stabilizer regimen for ≥ 2 weeks, and (4) ≥ 18 years of age. Exclusion criteria were (1) current psychosis, (2) current danger to self or others, (3) concurrent group treatment, and (4) residential treatment restricting substance use. After completely describing the study to the subjects, we obtained their written informed consent.

At the time we performed these analyses, 115 participants had completed 1 of the 2 clinical trials. Of 227 potential participants who met initial screening criteria of clinical diagnoses of bipolar disorder and substance

dependence, 51 did not meet full study criteria and 61 were eligible but decided not to participate.

Participants in both study cohorts were assessed at baseline and monthly during active treatment (5 months for the initial cohort and 3 months for the second cohort). Following active treatment, monthly follow-up data were collected during assessments through month 8.

After a baseline assessment, participants were randomly assigned to 1 of 2 active treatment conditions: integrated group therapy for bipolar disorder and co-occurring substance use disorder[15] or standard group drug counseling.[17] Participants in both group treatments met weekly for 1 hour for 20 weeks in the first study and for 12 weeks in the second study.

Measures

Psychiatric diagnoses. Psychiatric diagnoses were based on the SCID.[16] The SCID is a semistructured interview that uses a decision tree approach for lifetime and current diagnoses of many DSM-IV Axis I psychiatric disorders. Module A (mood episodes), module B (psychotic symptoms), module C (differential diagnosis of psychotic disorders), module D (mood differential), and module F (anxiety disorders) were administered by a trained Ph.D. or Masters-level clinician.

Substance use disorder diagnoses. Baseline substance use disorder diagnoses were determined by a trained, supervised research assistant using the SCID module E (substance use disorders).

Mood episodes. Mood episodes were assessed by using the Longitudinal Interval Follow-Up Evaluation (LIFE).[18] The LIFE is a combination of the Hamilton Rating Scale for Depression (HAM-D),[19] the Young Mania Rating Scale (YMRS),[20] and a SCID-based interview. It employs the timeline follow-back technique,[21] which uses a calendar to assist recall and to track mood weekly. The HAM-D and YMRS were administered monthly, and the SCID-based interview was completed at baseline and every 3 months until study completion. Our primary focus in this study was weeks ill, i.e., the number of weeks in which criteria were met for a depressive, manic, hypomanic, or mixed-mood episode.

Substance use. Substance use data were obtained by trained, supervised research assistants with the ASI.[12] The ASI is a well-validated and widely used instrument designed to measure functioning in different areas during the past 30 days. The timeline follow-back technique supplemented the drug and alcohol sections of the ASI. In the present study, we focused on both of 2 ways in which the ASI assesses alcohol use: (1) days of any alcohol use in the most recent 30 days and (2) days of heavy alcohol use (≥ 3 drinks/day) in the most recent 30 days.

Sociodemographic data. Age, gender, education, marital and work status, and household income were obtained via a self-report questionnaire.

Data Analysis

To examine our primary hypotheses, we considered 2 measures of alcohol use: (1) number of days of alcohol use and (2) the change in number of days of alcohol use from the prior month to the current month for those who increased their use. To determine whether the quantity of alcohol consumed had an effect on outcome, we also performed post hoc analyses using 4 additional variables: (1) the number of days of heavy alcohol use (≥ 3 drinks/day), (2) the change in number of days of heavy alcohol use from the prior month to the current month for those who increased their use, (3) the number of days of non–heavy alcohol use (< 3 drinks/day) and, (4) the change in number of days of non–heavy alcohol use from the prior month to the current month for those who increased their use.

Since a depressive episode in the subsequent month can be directly linked to a current depressive episode, a current episode was entered as a covariate in all analyses. Additionally, we examined whether results would differ when including several other covariates individually in the analyses, including other drug use, treatment group, and type of bipolar disorder. Finally, to address the possibility that the relationship between substance use and mood episode differed depending on mood state, an interaction model was tested.

Generalized estimating equation (GEE) methodology[22] was used to analyze these longitudinal data, since it offers flexibility to accommodate both continuous and discrete data. In addition, GEE methodology also accounted for the correlation of the repeated measures for each patient over time, which was modeled through an exchangeable correlation matrix. Parameter estimates were produced with empirical standard errors, and z statistics were computed to assess statistical significance. Finally, odds ratios for the alcohol use variable were generated. The odds ratio is calculated as exp(B), where B is the regression coefficient for the alcohol use variable. To facilitate comparison between models, we calculated a percentage figure by subtracting the odds ratio from 1 and multiplying by 100%. A positive percentage indicated an increase in the odds of being depressed per unit increase in the use measure. A negative percentage indicated a decrease in the odds of being depressed per unit increase in the alcohol use measures. For a more clinically relevant odds measure, we include the odds ratio for each 10-day increase in the alcohol use measures. GEE was implemented in the GENMOD procedure of SAS version 9.1 (SAS Institute Inc., Cary, NC).

Our analyses used the standard α level of .05. In confirmatory analyses, for any aspect of multiplicity, adjustments should always be considered, but, since this investigation is exploratory, we refrained from making any correction methods to the alpha level.[23] Furthermore, some investigators note that no adjustments are needed

Table 1. Generalized Estimating Equation Results for Primary Hypotheses of Study: Predicting Depression in the Subsequent Month From 4 Measures of Alcohol Use

Predictor	Odds Ratio	95% CI Lower Boundary	95% CI Upper Boundary	Z	Probability > Z
Days of alcohol use				2.71	0.007
Per day	1.036	1.010	1.062		
Per 10 days	1.4205	1.1015	1.8319		
Increase in days of alcohol use				3.17	0.002
Per day	1.088	1.033	1.146		
Per 10 days	2.3257	1.3796	3.9206		
Days heavy alcohol use				2.53	0.011
Per day	1.043	1.010	1.078		
Per 10 days	1.5267	1.10001	2.11871		
Increase in days of heavy alcohol use				2.04	0.041
Per day	1.073	1.003	1.148		
Per 10 days	2.0215	1.0279	3.9753		

for multiple comparisons in exploration of large bodies of data.[24] Since there is the potential for multiplicity, the reader must observe the significance levels with some caution.

RESULTS

Participant Characteristics

The sample of 115 patients was 46.1% female (N = 53) and 92.2% white (N = 106). Mean age was 39.9 (SD = 10.9) years. Approximately half of the sample had completed college (N = 63, 55.8%) and half were currently employed (N = 60, 52.6%). Most participants were not married (N = 77, 67.0%). The treatment groups were similar in these characteristics.

Most patients (N = 91, 79.8%) were diagnosed with bipolar I disorder, 17 (14.9%) had bipolar II disorder, and 6 (5.3%) had bipolar disorder not otherwise specified. Most patients (N = 66, 57.4%) had both drug and alcohol dependence, 37 (32.2%) had alcohol dependence only, and 12 (10.4%) had drug dependence only. Among those with drug use disorders (N = 80), the most common primary drugs of abuse were marijuana (N = 35, 44.3%) and cocaine (N = 32, 40.5%), followed by opioids (N = 5, 6.3%), sedative/hypnotics (N = 4, 5.1%), amphetamines (N = 2, 2.5%), hallucinogens (N = 1, 1.3%), and benzodiazepines (N = 1, 1.3%).

During the intake month, patients reported a mean of 10.6 (SD = 9.7) days of substance use, excluding time spent in a controlled environment: 5.5 (SD = 9.3) days of drug use and 7.6 (SD = 8.6) days of alcohol use. During the study period, heavy drinking days occurred 2.75 times more often than did non–heavy drinking days. The mean number of days each month that patients engaged in heavy drinking was 3.96 and was 1.44 for those engaged in non–heavy drinking.

During the intake month, 84 participants (73.0%) had engaged in at least 1 individual psychotherapy session, and 55 (47.8%) had attended at least 1 Alcoholics Anonymous, Narcotics Anonymous, or some other type of self-help meeting. Also, as noted previously, all participants were taking a mood stabilizer as a criterion of study eligibility.

Primary Hypothesis #1: Days of Alcohol Use During the Current Month Will Increase the Likelihood of a Depressive Episode During the Subsequent Month

Applying the GEE method described earlier, we found that each day of alcohol use during the current month significantly increased the odds of experiencing a depressive episode during the subsequent month by an average of 3.6% when controlling for depressive episode during the current month (Table 1). Ten days of use within the current month increased this odds ratio to 42.1%. When we included other drug use, treatment group, and type of bipolar disorder individually as covariates in the predictive model, days of alcohol use remained statistically significant. There was not a significant interaction between days of alcohol use and depressive episode in predicting depression during the subsequent month.

Primary Hypothesis #2: An Increase in Days of Alcohol Use From Prior Month Will Increase the Likelihood of a Depressive Episode During the Subsequent Month

Similar to the results for days of alcohol use, we found that each day of increase in the number of days of alcohol use from the prior to the current month significantly increased the odds of experiencing a depressive episode during the subsequent month by an average of 8.8% when controlling for the presence of a depressive episode during the current month (Table 1). An increase of 10 days of use within the current month increased this odds ratio to 132.6%. When we included other drug use, treatment group, and type of bipolar disorder individually as covariates in the predictive model, an increase in days of alcohol use remained statistically significant. As in the previous analysis, there was not a significant interaction between increase in days of alcohol use and depressive episode in predicting depression during the subsequent month.

Post Hoc Analysis #1: Does Days of Heavy Alcohol Use (≥ 3 drinks/day) During the Current Month Increase the Likelihood of a Depressive Episode During the Subsequent Month?

Applying the same analyses using days of heavy alcohol use as a predictor, we found that each day of heavy alcohol use (≥ 3 drinks/day) during the current month increased the odds of experiencing a depressive episode during the subsequent month by an average of 4.3% when controlling for depressive episode during the current month (Table 1). Ten days of heavy use within the current month increased this odds ratio to 52.7%. When we included other drug use, treatment group, and type of bipolar disorder individually as covariates in the predictive model, days of heavy alcohol use remained statistically significant. There was not a significant interaction between days of alcohol use and current depressive episode in predicting depression during the subsequent month.

Post Hoc Analysis #2: Does an Increase in Days of Heavy Alcohol Use (≥ 3 drinks/day) From Prior Month Increase the Likelihood of a Depressive Episode During the Subsequent Month?

Each day of increase in days of heavy alcohol use from the prior to the current month significantly increased the odds of experiencing a depressive episode during the subsequent month by an average of 7.3% when we controlled for depressive episode during the current month. An increase of 10 days of heavy use within the current month increased this odds ratio to 102.2%. When we included other drug use, treatment group, and type of bipolar disorder individually as covariates in the predictive model, increase in days of alcohol use remained statistically significant. As in the previous analyses, there was not a significant interaction between increase in days of alcohol use and depressive episode in predicting depression in the subsequent month.

Post Hoc Analyses #3 and #4: Do Non–Heavy Drinking (< 3 drinks/day) and an Increase in Non–Heavy Drinking Increase the Likelihood of a Depressive Episode During the Subsequent Month?

Neither days of non–heavy alcohol use nor an increase in days of non–heavy alcohol use significantly predicted the presence of a depressive episode in the subsequent month when we controlled for depression and other substance use in the current month.

DISCUSSION

This study examined the effects of active alcohol use on the likelihood of experiencing a subsequent depressive episode in a sample of participants with co-occurring diagnoses of bipolar disorder and substance use disorder. To our knowledge, this is the first study to examine the effects of alcohol use itself, rather than symptoms of use (i.e., DSM-IV symptoms and/or ASI scores), on subsequent depressive episodes in this population. Our primary hypotheses were supported: the number of days of any alcohol use predicted depression in the subsequent month, and an increase in the number of days of alcohol use from the prior month to the current month predicted an increased likelihood of a depressive episode in the subsequent month. Our post hoc analyses suggested that heavy alcohol use in the current month as well as an increase in heavy alcohol use from the prior month to the current month predicted an increased likelihood of a depressive episode in the subsequent month. However, our post hoc analyses did not indicate that non–heavy drinking or an increase in non–heavy drinking would predict depression in a subsequent month. Overall, then, it appears that our main findings were attributable primarily to heavy drinking (≥ 3 drinks/day).

The fact that we did not find a relationship between non–heavy drinking and subsequent depression may be attributed to 2 factors that limited the statistical power of these analyses. First, power was reduced by the necessity of splitting the sample (and thus reducing sample size) to examine days of non–heavy drinking. Power was further reduced by the fact that days of non–heavy drinking were fewer in number than were days of heavy drinking. We do not have sufficient data to determine whether more frequent non–heavy drinking would predict depression.

Our findings suggest that in this population, alcohol use itself may adversely affect the course of bipolar disorder. On average, 10 days of daily alcohol use in the current month would increase the likelihood of experiencing a depressive episode by 42.1% in the subsequent month, and 10 days of heavy use would increase the likelihood of experiencing a depressive episode by 52.7%. For alcohol users, a 10-day increase in alcohol use in the current month or, for heavy users, a 10-day increase in heavy use in the current month would more than double the likelihood of experiencing a depressive episode in the subsequent month. These findings are consistent with prior research indicating that duration of alcohol abuse symptoms is associated with longer duration of a depressive episode.[13]

Primary strengths of this study are the frequency with which assessments occurred, as well as the use of clinical interview rather than self-report data collection methods. Additionally, the use of monthly assessments of both mood episode (not simply mood symptoms) and substance use allowed us to address temporal prediction. Limitations include the use of a primarily white treatment-seeking clinical sample with a history of both bipolar disorder and substance use disorder. It thus does not address the issue of alcohol use and its impact (if any) on mood in bipolar disorder patients without a substance use disorder. We also do not know the extent to which these findings would generalize to other sociodemographic populations.

Since this study involved a secondary analysis of existing data, we were limited by the ASI in measuring alcohol use in terms of days of any use in the past 30 days and days of heavy use (i.e., ≥ 3 drinks/day) in the past 30 days. A more precise measure of alcohol use, such as one that assessed the number of standard drinks consumed each day, could have increased the power of the study. This in turn could have improved our ability to answer questions about the effects of different levels of alcohol use on depression. Similarly, although our sample size was sufficient for the overall analyses performed, it was insufficient to fully address questions regarding the effects of all levels of use (i.e., non–heavy drinking) on mood. A larger sample size would also permit a closer look at other variables involved in these outcomes—such as onset, duration, and severity of illnesses; the effects of specific drugs of abuse; and other variables such as age, gender, and treatment history.

Additional research that employs a larger sample as well as more precise measures of drinking will be useful in answering several questions noted earlier. For example, it would be useful to determine whether the use of specific substances in addition to alcohol predict specific types of mood episode in this population. It is also important to determine whether such predictions differ as a function of the onset, temporal primacy, and course of bipolar disorder, as well as other variables, such as age, gender, and the amount of substance used. A more precise identification of these as well as other variables that contribute to mood episodes may improve treatment by providing clinicians with clear, empirically-supported rationale for abstaining from or reducing substance use.

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