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Comorbid anxiety disorders and baseline medication regimens predict clinical outcomes in individuals with co-occurring bipolar disorder and alcohol dependence: Results of a randomized controlled trial

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ABSTRACT

Despite the high prevalence and detrimental impact of alcoholism on bipolar patients, the diagnostic and treatment factors associated with better or worse clinical outcomes in alcohol-dependent patients with bipolar disorder are not well understood. The present study investigated the prospective impact of baseline psychiatric comorbidities and treatment regimens on clinical outcomes in bipolar alcoholics. Data were drawn from an 8-week randomized controlled clinical trial of acamprosate for individuals ($n = 30$) with co-occurring bipolar disorder and alcohol dependence. Depressive and manic symptoms, and alcohol craving and consumption were monitored longitudinally using standardized instruments. Path analysis was used to estimate the prospective associations between patient characteristics and outcomes. More than 50% of patients were diagnosed with at least one anxiety (76.7%) or drug dependence disorder (60.0%). Comorbid anxiety disorders were prospectively associated with increased depressive symptoms and alcohol use. Participants were prescribed an average of 2.6 psychotropic medications at baseline. Antipsychotics and anticonvulsants were prospectively associated with increased alcohol use; anticonvulsants and benzodiazepines were associated with increased alcohol craving. Antidepressants were associated with increased depressive symptoms. Conversely, lithium was associated with decreased alcohol craving and depressive symptoms. The findings from the present study suggest areas for future research in this population.

1. Introduction

Epidemiological data have suggested that more than half of individuals with bipolar I disorder develop a substance use disorder at some point in their lives (Reiger et al., 1990; Merikangas et al., 2007). Among these comorbid individuals, alcohol is the most commonly abused substance. In fact, almost half of individuals diagnosed with bipolar I and bipolar II disorders meet lifetime criteria for either alcohol abuse (46.2%) or dependence (39.2%) diagnoses (Reiger et al., 1990). Bipolar patients with co-occurring alcohol use disorders often have substantially poorer outcomes than individuals with bipolar disorder alone, including a worse course of illness and increased mortality and disability (Feinman and Dunner, 1996; Tohen et al., 1998; Weiss et al., 2005). Despite the exceedingly high prevalence and impact of alcoholism in bipolar patients, little is known about the clinical characteristics or treatment regimens associated with better or worse outcomes in this important clinical population.

Almost 30% of individuals diagnosed with a psychiatric disorder are diagnosed with three or more such disorders (Kessler et al., 2005). It is not surprising, then, that bipolar patients, with or without co-occurring alcohol use disorders, have very high rates of additional psychiatric problems (McElroy et al., 2001). Work on this topic has increasingly focused on the particular combination of bipolar, substance use, and anxiety disorders (Simon et al., 2004a; Kolodziej et al., 2005; Levander et al., 2007; Goldstein and Levitt, 2008; Gao et al., 2010). Simon et al. (2004a, 2004b) demonstrated that 40% of bipolar patients with alcohol dependence from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) were diagnosed with at least one current anxiety disorder. A secondary analysis of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) data demonstrated that individuals with bipolar, substance use, and anxiety disorders had higher levels of health service utilization, psychiatric hospitalization, and depressive and manic symptoms than those with bipolar and substance use

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disorders but no anxiety disorder (Goldstein and Levitt, 2008). This research is revealing, but it is part of a limited literature that would benefit from further replication and extension.

Equally scarce is literature regarding optimal medications for individuals with comorbid bipolar and alcohol use disorders. Randomized, placebo-controlled trials of medications for patients with comorbid bipolar and alcohol use disorders have been few and have focused primarily on medications used for mood stabilization such as lithium and divalproex (Geller et al., 1998; Salloum et al., 2005; Kemp et al., 2009) or the atypical antipsychotic quetiapine (Brown et al., 2008; Stedman et al., 2010). These studies have suggested that divalproex may reduce heavy drinking (Salloum et al., 2005) and that quetiapine may improve depressive symptoms (Brown et al., 2008) in individuals with co-occurring alcoholism and bipolar disorder. Though some evidence suggests that lithium may be beneficial, at least in substance abusing bipolar adolescents (Geller et al., 1998), other investigators have reported that comorbid substance use disorders predict poor response to lithium in bipolar patients (Himmelhoch and Garfinkel, 1986; Goldberg et al., 1999). Thus more research is needed to establish the efficacy of currently approved mood stabilizing medications in dually diagnosed patients and to better understand how the full range of medications typically prescribed to dually diagnosed patients influence clinical outcomes (e.g., alcohol consumption). The present study investigated the relationship of comorbid psychiatric diagnoses (i.e., anxiety disorders, drug dependence, and antisocial personality disorder) and concomitant medications with mood and drinking outcomes over the course of an 8-week clinical trial in individuals with co-occurring bipolar disorder and alcohol dependence.

2. Methods

2.1. Participants and procedures

Participants in the present study were enrolled in an 8-week, randomized, double-blind clinical trial of acamprosate for individuals with co-occurring bipolar and alcohol use disorders (Tolliver et al., submitted). Briefly, participants were 30 treatment-seeking individuals, aged 18–65, with primary DSM-IV diagnoses of bipolar I or II disorder and alcohol dependence with active alcohol use in the past 90 days. Participants were required to be receiving psychiatric management outside of the study setting for bipolar disorder and to be taking stable doses of mood stabilizing medications as prescribed by an outside treating psychiatrist for at least one month prior to randomization. As a required condition for study participation, each subject provided written consent for the study psychiatrist to exchange clinical status information with the outside treating psychiatrist at any time from study entry to study completion. However, the choice and dosing of mood stabilizing medications for each participant was solely the responsibility of the outside treating psychiatrist. The duration of treatment with each medication being taken at study entry was recorded, but past medication histories for all subjects were not systematically assessed. Participants were permitted but not required to be undergoing outpatient addiction treatment, but the use of FDA-approved medications for alcohol dependence (disulfiram, naltrexone, or acamprosate) was not permitted during study participation to prevent confounding of the results.

Primary exclusion criteria were severe mania (i.e., Young Mania Rating Scale [YMRS; Young et al., 1978]>25), severe depression (i.e., Montgomery Asberg Depression Rating Scale [MADRS; Montgomery and Asberg, 1979]>35), imminent risk of suicide or homicide as determined by the study psychiatrist, or any Axis I diagnoses considered to be primary other than bipolar disorder and alcohol dependence. Other exclusions included significant cognitive impairment that would interfere with capacity to give informed consent, or other significant medical/neurological conditions such as epilepsy, human immunodeficiency virus, renal failure, hepatic failure, unstable angina, or chronic obstructive pulmonary disease. Females of childbearing age who were pregnant, breastfeeding, or who refused adequate forms of contraception were also excluded. Participants were required to remain abstinent from alcohol for the three days immediately preceding their baseline study visit.

Following baseline assessment, participants were randomized to receive either two 333 mg tablets of acamprosate, taken three times daily, or matched placebo. Participants returned weekly for eight visits to assess alcohol use and bipolar symptoms. All study procedures were approved by the Medical University of South Carolina Institutional Review Board, and written informed consent was obtained from participants prior to all study procedures at the initial study appointment.

2.2. Measures

Substance use disorders were assessed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Affective disorders, anxiety disorders and antisocial personality disorder were assessed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Information regarding concomitant psychotropic medications at baseline was gathered via clinical interview. Alcohol use was assessed at baseline and weekly for 8 weeks using the Timeline Followback method (TLFB; Sobell and Sobell, 1996); at baseline, participants were asked to recount the number of standard alcoholic beverages they consumed each day for the past 60 days. Subsequent TLFB data were assessed for the past week at each visit. These data were divided into two-week summary variables (i.e., percent days alcohol consumed, average daily number of drinks) for subsequent analysis. The average daily number of drinks variable was log transformed to correct for non-normality. Depressive symptoms and alcohol craving were evaluated at baseline, weeks 2, 4, 6, and 8 using the MADRS and the Obsessive–Compulsive Drinking Scale (OCDS; Anton et al., 2006), respectively. Consistent with subject inclusion on the basis of relative euthymia, YMRS scores were low throughout the trial, exhibited little variability across participants (e.g., baseline $M = 6.50$, S.D. = 4.55), and were thus not considered further in statistical analyses.

2.3. Data analysis

Associations between baseline concomitant medications and psychiatric diagnoses, and alcohol use and depressive symptoms over the course of the 8-week clinical trial were evaluated using univariate Markov simplex models with time-invariant covariates in a path analysis framework. In order to model co-occurrence within diagnostic and medication categories, and to reduce model complexity, drug dependence, anxiety disorder and medication variables were represented as within-category counts (e.g., # of anxiety disorders). Separate path models were estimated for 1) concomitant medications and 2) co-occurring psychiatric diagnoses predicting a) MADRS, b) OCDS, c) TLFB quantity, and d) TLFB frequency. In each path model, the recurring (i.e., observed weeks 2, 4, 6, 8) dependent variable (DV) was represented by a univariate Markov chain with time-invariant covariates (e.g., concomitant medications and psychiatric diagnoses). In other words, for a given DV, each measurement occasion was modeled as an additive function of the preceding measurement occasion, time-invariant covariates (including the baseline measure of the DV), and residual (i.e., error) variance. In addition to baseline functioning, time-invariant covariates included acamprosate group status (i.e., "0" = placebo group, "1" = acamprosate group) and a set of either *DSM* diagnostic (i.e., drug dependence, anxiety disorders, antisocial personality disorder), or concomitant medication (i.e., atypical antipsychotic, anticonvulsant, lithium, antidepressant, benzodiazepine) count variables. In the case of co-occurring psychiatric diagnoses, if a count predictor (e.g., # of anxiety disorders) was significantly associated with a given outcome, the path model involving that outcome was re-estimated with the constituent members of the significant predictor (i.e., generalized anxiety disorder, social phobia, obsessive–compulsive disorder, panic disorder, and posttraumatic stress disorder) represented as individual binary (present vs. absent) predictors, and with other nonsignificant predictors (e.g., # of drug dependence diagnoses) removed from the model.

A number of parameter constraints were imposed to improve our ability to estimate the models, and to improve the models' parsimony; the following sets of parameters were constrained to be equal to one another: a) autoregressive parameters, b) regression coefficients from the baseline measure of a DV to all other measurement occasions of that DV (with the exception of the association between the baseline and week 2 DV measurements), c) regression coefficients from the acamprosate group status variable to each post-baseline measurement of the DV, and d) within-category regression coefficients from each diagnostic or medication category to each post-baseline measurement of the DV.

Models were estimated using maximum likelihood, which uses all available observed data and yields unbiased parameters given that missing data are missing at random. Swain's (1975) correction of the chi-square statistic was employed to obtain model fit indices that were less biased by small sample size (Herzog and Boomsma, 2009). Although we report select fit indices (i.e., χ^2/d.f., Comparative Fit Index [CFI], Root Mean Square Error of Approximation [RMSEA]) for each model, fit was deemphasized in the present investigation because we were primarily interested in the value and statistical significance of the path coefficients from concomitant psychiatric diagnoses and medications to mood, craving, and alcohol use. Path models were estimated in MPlus version 5.21 (Muthén and Muthén, 2009).

3. Results

3.1. Participant characteristics

Baseline participant characteristics are presented in Table 1. Participants were primarily Caucasian (90.0%), male (63.3%), unemployed (70.0%) and had a mean age of 42.33 (S.D. = 9.41). Almost half (43.3%) were current cigarette smokers. The majority of participants had at least one anxiety disorder (76.7%) or drug dependence (60.0%)

Table 1
Baseline participant characteristics ($n=30$).

Demographics		
Age (*M*, S.D.)	42.33	(9.41)
Female, %	36.67	
Caucasian, %	90.00	
≤High school graduate, %	40.00	
Employed, %	30.00	
Current smoker, %	43.33	
Past smoker, %	40.00	
Psychiatric diagnoses		
Comorbid anxiety disorders		
Generalized anxiety disorder, %	50.00	
Obsessive–compulsive disorder, %	10.00	
Panic disorder, %	13.04	
Posttraumatic stress disorder, %	6.67	
Social phobia, %	30.00	
# of comorbid anxiety disorders		
0, %	23.33	
1, %	53.33	
2, %	13.33	
3, %	10.00	
Comorbid drug dependence disorders		
Cannabis dependence, %	43.33	
Amphetamine dependence, %	13.33	
Cocaine dependence, %	43.33	
Opioid dependence, %	23.33	
# of comorbid drug dependence diagnoses		
0, %	40.00	
1, %	16.67	
2, %	26.67	
3, %	13.33	
4, %	0.00	
5, %	3.33	
Antisocial personality disorder, %	70.00	
Psychotropic medications		
# of atypical antipsychotics		
0, %	50.00	
1, %	43.33	
2, %	6.67	
# of anticonvulsants		
0, %	30.00	
1, %	56.67	
2, %	13.33	
Lithium, %	23.33	
# of antidepressants		
0, %	46.67	
1, %	40.00	
2, %	10.00	
3, %	3.33	
# of benzodiazepines		
0, %	90.00	
1, %	6.67	
2, %	3.33	
Baseline assessments		
Montgomery Asberg Depression Rating Scale	11.80	(5.97)
Young Mania Rating Scale	6.50	(4.55)
# of drinks consumed in past month	97.88	(103.66)
% days alcohol consumed in past month	31.67	(27.72)

diagnosis. Specifically, participants were diagnosed with between 0 and 3 (median = 1) anxiety disorders, and between 0 and 5 (median = 1) drug dependence diagnoses (see Table 1). Among anxiety disorders, generalized anxiety disorder (50.0%) and social phobia (30.0%) were most prevalent, and among drug dependence diagnoses, cannabis (43.33%) and cocaine dependence (43.33%) were most prevalent.

In terms of concomitant medications, participants were taking an average of 2.6 psychotropic medications at study entry. Specifically, participants were prescribed up to two antipsychotics (median = 0.50), anticonvulsants (median = 1) or benzodiazepines (median = 0); and up to three antidepressants (median = 1). With one exception, all antipsychotics were 2nd generation ("atypical"); among this class of medication, quetiapine was most frequently prescribed (i.e., $n=6$ or 20% of the total sample). Most individuals who were prescribed anticonvulsants were taking either valproic acid ($n=10$) or lamotrigine ($n=9$). Study retention was high; 76.7% of participants who returned for at least one post-randomization visit completed all study appointments. Acamprosate group status was included as a covariate in all statistical models because it was a manipulated variable in present study, however, it did not significantly predict outcomes in any of the estimated path models (see Tables 2–4).

3.2. Associations between co-occurring diagnoses and outcomes

Fit indices for models featuring co-occurring diagnoses as predictors included: quantity of alcohol use, χ^2/d.f. = 1.82, CFI = 0.87, RMSEA = 0.17; frequency of alcohol use, χ^2/d.f. = 1.31, CFI = 0.96, RMSEA = 0.10; alcohol craving (OCDS), χ^2/d.f. = 1.06, CFI = 0.99, RMSEA = 0.05; depressive symptoms (MADRS), χ^2/d.f. = 1.14, CFI = 0.95, RMSEA = 0.07. Results regarding associations between co-occurring diagnoses and outcomes are presented in Table 2. Diagnoses of drug dependence and antisocial personality disorder were not uniquely associated with any outcomes. Alternatively, number of anxiety disorders was significantly associated with elevated levels of quantity of alcohol use ($\beta=0.12$, $p=0.04$) and depressive symptoms ($\beta=1.79$, $p=0.02$), as well as marginally elevated levels of frequency of alcohol use ($\beta=3.12$, $p<0.10$), controlling for baseline levels of these outcomes (along with acamprosate group status and other psychiatric diagnoses). Given that only anxiety disorders were uniquely related to outcomes in the present analyses, a follow-up path model was estimated to determine which particular anxiety disorder diagnoses were driving these effects. Fit indices for models featuring individual anxiety disorders as predictors included: quantity of alcohol use, χ^2/d.f. = 2.17, CFI = 0.78, RMSEA = 0.20; frequency of alcohol use, χ^2/d.f. = 1.82, CFI = 0.88, RMSEA = 0.17; alcohol craving (OCDS), χ^2/d.f. = 1.30, CFI = 0.95, RMSEA = 0.11; depressive symptoms (MADRS), χ^2/d.f. = 1.47, CFI = 0.79, RMSEA = 0.13. Results from these models are presented in Table 3. From the evaluated anxiety disorder diagnoses, only generalized anxiety disorder was uniquely associated with alcohol use (both quantity, $\beta=0.26$, $p=0.01$ and frequency, $\beta=8.97$, $p<0.01$). Additionally, social phobia was associated with marginally elevated levels of depressive symptoms ($\beta=2.17$, $p=0.09$).

Table 2
Results from path models with concomitant medications predicting outcomes.

Predictor	Outcome			
	$TLFB_t$ quantity	$TLFB_t$ frequency	$OCDS_t$	$MADRS_t$
$Antipsychotics_B$	0.23**	5.58*	2.31**	0.11
$Anticonvulsants_B$	0.10	7.61**	−1.04	−1.34
$Lithium_B$	<0.01	3.65	−2.80**	−2.72*
$Antidepressants_B$	0.02	1.48	0.28	1.24*
$Benzodiazepines_B$	0.13	6.34	4.80**	−0.41
$Outcome_B$	0.41**	0.42**	0.13*	0.60**
$Outcome_{t-1}$	0.41**	0.52**	0.78**	0.21
$Acamprosate_B$	0.02	0.42	0.68	−0.85

Note. The "TLFB quantity" variable was log transformed prior to statistical modeling to correct for non-normality.
Subscript "t" = reference time point; "t − 1" = immediately preceding; "B" = baseline. In the "Predictor" column, $Outcome_B$ and $Outcome_{t-1}$ refer to the baseline and immediately preceding measurement occasion, respectively, of the corresponding variable listed in the "Outcome" column. MADRS = Montgomery Asberg Depression Rating Scale; TLFB = Timeline Followback; OCDS = Obsessive–Compulsive Drinking Scale; $Acamprosate_B$ = acamprosate group status ("0" = placebo, "1" = acamprosate).
* $p<0.05$.
** $p<0.01$.

Table 3
Results from path models with co-occurring diagnoses predicting outcomes.

Predictor	Outcome			
	$TLFB_t$ quantity	$TLFB_t$ frequency	$OCDS_t$	$MADRS_t$
Drug dependence$_B$	0.04	1.46	0.11	0.02
Anxiety disorders$_B$	0.12*	3.12†	0.56	1.79**
Antisocial PD$_B$	0.12	5.04	1.38**	−1.49*
Outcome$_B$	0.39**	0.44**	0.07	0.49**
Outcome$_{t-1}$	0.42**	0.51**	0.82**	0.23†
Acamprosate$_B$	−0.04	−1.79	−0.38	−0.54

Note. The "TLFB quantity" variable was log transformed prior to statistical modeling to correct for non-normality.
Subscript "t" = reference time point; "t − 1" = immediately preceding; "B" = baseline. In the "Predictor" column, Outcome$_B$ and Outcome$_{t-1}$ refer to the baseline and immediately preceding measurement occasion, respectively, of the corresponding variable listed in the "Outcome" column. MADRS = Montgomery Asberg Depression Rating Scale; TLFB = Timeline Followback; OCDS = Obsessive–Compulsive Drinking Scale; PD = personality disorder. Acamprosate$_B$ = acamprosate group status ("0" = placebo, "1" = acamprosate).
† $p<0.10$.
* $p<0.05$.
** $p<0.01$.

3.3. Associations between concomitant medications and outcomes

Fit indices for models featuring concomitant medications as predictors included: quantity of alcohol use, χ^2/d.f. = 1.61, CFI = 0.86, RMSEA = 0.14; frequency of alcohol use, χ^2/d.f. = 1.24, CFI = 0.96, RMSEA = 0.09; alcohol craving (OCDS), χ^2/d.f. = 1.98, CFI = 0.87, RMSEA = 0.18; depressive symptoms (MADRS), χ^2/d.f. = 1.36, CFI = 0.83, RMSEA = 0.11. Results regarding associations between concomitant medications and outcomes are presented in Table 4. Patients who were taking atypical antipsychotics at baseline had significantly greater levels of alcohol use (both quantity, $\beta = 0.23$, $p<0.01$; and frequency, $\beta = 5.58$, $p = 0.03$) and craving ($\beta = 2.31$, $p<0.01$) over the course of the 8-week study period, controlling for baseline levels of these outcomes (as well as for acamprosate group status and prescription of other psychotropic medications). Patients taking anticonvulsants similarly exhibited more frequent alcohol use ($\beta = 7.61$, $p<0.01$) than those taking other medications. Those prescribed benzodiazepines exhibited relatively higher levels of alcohol craving ($\beta = 4.80$, $p<0.01$), and patients taking antidepressants had higher levels of depressive symptoms ($\beta = 1.24$, $p<0.05$). Conversely, lithium use at baseline was associated with less alcohol craving ($\beta = -2.80$, $p<0.01$) and depressive symptoms ($\beta = -2.72$, $p<0.05$) over the study period.

Table 4
Results from path models with specific co-occurring anxiety disorders predicting outcomes.

Predictor	Outcome			
	$TLFB_t$ quantity	$TLFB_t$ frequency	$OCDS_t$	$MADRS_t$
GAD$_B$	0.26**	8.97**	0.97	1.46
Social phobia$_B$	0.04	4.00	−0.07	2.17†
Panic disorder$_B$	0.22	−2.18	1.50	0.39
OCD$_B$	0.05	6.31	2.48	2.95
PTSD$_B$	0.24	6.65	1.09	−1.03
Outcome$_B$	0.38**	0.47**	0.05	0.41**
Outcome$_{t-1}$	0.50**	0.56**	0.87**	0.25†
Acamprosate$_B$	<0.01	−1.12	−0.49	−1.27

Note. The "TLFB quantity" variable was log transformed prior to statistical modeling to correct for non-normality.
Subscript "t" = reference time point; "t − 1" = immediately preceding; "B" = baseline. In the "Predictor" column, Outcome$_B$ and Outcome$_{t-1}$ refer to the baseline and immediately preceding measurement occasion, respectively, of the corresponding variable listed in the "Outcome" column. MADRS = Montgomery Asberg Depression Rating Scale; TLFB = Timeline Followback; OCDS = Obsessive–Compulsive Drinking Scale; GAD = generalized anxiety disorder; OCD = obsessive–compulsive disorder; PTSD = posttraumatic stress disorder. Acamprosate$_B$ = acamprosate group status ("0" = placebo, "1" = acamprosate).
† $p<0.10$.
* $p<0.05$.
** $p<0.01$.

4. Discussion

The present study extends previous research indicating that multimorbidity is common in patients with co-occurring bipolar disorder and alcohol dependence, and suggests that comorbid anxiety disorders, as well as maintenance medication regimen, may influence or serve as markers of near-term clinical outcomes. Most subjects were diagnosed with at least one anxiety or drug dependence disorder, and, on average, participants were prescribed between two and three psychiatric medications at study entry. The number of anxiety disorder diagnoses participants' carried was associated with quantity and frequency of alcohol use as well as with the severity of depressive symptoms. Of individual anxiety disorders assessed, GAD was significantly associated with alcohol use (quantity and frequency) whereas social phobia was marginally associated with depressive symptoms. Furthermore, multiple classes of concomitant psychiatric medications were associated with poorer outcomes over the course of the trial: antipsychotics and anticonvulsants were associated with increased alcohol use, anticonvulsants and benzodiazepines were associated with increased alcohol craving, and antidepressants were prospectively associated with increased depressive symptoms. In contrast, lithium was prospectively associated with decreased alcohol craving and (generally subsyndromal) depressive symptoms.

Results from the present study are partially consistent with past research. For example, as reported by Geller et al. (1998), we found that lithium was associated with improved near-term clinical outcomes in individuals with bipolar and substance use disorders. This finding appears to contradict accumulated evidence that comorbid substance use disorders predict poor response to lithium in adult bipolar patients (Himmelhoch and Garfinkel, 1986; Goldberg et al., 1999; Passmore et al., 2003). However, the short duration of the assessment period, selection for euthymia at study entry, and lack of systematic assessment of mixed episode histories in the current study prevent generalization of our results to the population of bipolar alcoholics at large. Similarly, we found that baseline use of concomitant atypical antipsychotics and anticonvulsants was associated with poorer outcomes in these patients, a finding that diverges from the results of controlled clinical trials of agents such as divalproex (Salloum et al., 2005) and quetiapine (Brown et al., 2008). However, it is important to note that positive clinical trials involving dually diagnosed patients have been scarce, and attempts to replicate such positive findings have not been uniformly successful. For example, though Brown et al. (2008) found that quetiapine reduced depressive symptoms in bipolar alcoholics, these findings were not replicated in a subsequent multi-site clinical trial (Stedman et al., 2010). In contrast, our results regarding the impact of anxiety disorders on clinical outcomes are largely consistent with previous investigations. For example, as with Goldstein and Levitt's (2008) analysis of the NESARC data, we found that individuals with anxiety disorders had significantly higher levels of symptomatology over the course of our study.

Given the correlational nature of our study, our findings are most relevant to understanding the naturalistic relationship between medications, comorbid diagnoses, and clinical outcomes. Understanding these relationships may be especially important for clinicians who encounter new bipolar alcoholic patients, as improved prognostic information could help guide clinical decision-making in the months following intake. For example, our results would suggest that a dually diagnosed patient who also meets criteria for GAD and is maintained

on an antipsychotic medication may benefit from focused clinical attention on alcohol use, whereas patients meeting criteria for social phobia who are maintained on antidepressants may need careful monitoring of depressive symptoms even if abstinence has been established. Similarly, it may be advisable to monitor alcohol craving in bipolar alcoholics who are treated with benzodiazepines given the risk for adverse events of concomitant benzodiazepine use with active alcohol use. Of course, such recommendations are advanced only to suggest avenues for future research, and should be viewed as tentative until our findings are replicated in larger samples.

Our data do not lend themselves to causal explanations. For example, though we found that antipsychotic and anticonvulsant medications were associated with increased alcohol use over time, it cannot be concluded that taking these medications caused our participants to drink more alcohol. Instead, antipsychotic and anticonvulsant medications may have been more likely to be prescribed to individuals in our sample with more severe alcohol dependence, more severe bipolar disorder, or both. Furthermore, associations between anxiety disorders and clinical outcomes in the present study considered only the presence of subject-reported anxiety symptoms sufficient to meet criteria for a given disorder; anxiety symptom severity and its impact on mood and drinking outcomes were not addressed. With these caveats in mind, it is important to mention that we did statistically control for the influence of some potentially confounding variables such as medication load and baseline severity of clinical outcomes, making it unlikely that our observed associations (e.g., between antipsychotics and alcohol use) were simply a reflection of the number of psychiatric medications participants were taking or of their initial levels of severity of alcohol use or depression.

As noted above, the primary limitations of the present study included small sample size and correlational design. As such, it is premature to generalize these results to treatment-seeking alcohol-dependent patients with bipolar disorder at large. Indeed, though consistent regarding mood stabilizer use, our sample had somewhat greater percentages of patients taking antidepressants and antipsychotic medications, and a lower proportion taking benzodiazepines, than reported for the first 1000 subjects enrolled in the much larger STEP-BD trial (Simon et al., 2004b). Thus until replicated by future research investigating co-occurring bipolar and substance use disorders, our findings should be interpreted as provisional. Nonetheless, the findings from the present investigation provide descriptive and predictive information regarding individuals with co-occurring bipolar and alcohol use disorders and suggest areas for future research in this population. Further controlled studies regarding the impact of anxiety disorders or their treatment with benzodiazepines on clinical outcomes, and the potential efficacy of lithium for patients with co-occurring bipolar and alcohol use disorders seem particularly warranted given our findings.

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