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Predictors of Clinical Trial Dropout in Individuals with Co-occurring Bipolar Disorder and Alcohol Dependence

James J. Prisciandaro, Julie Rembold, Delisa G. Brown, Kathleen T. Brady, and Bryan K. Tolliver

Medical University of South Carolina; Department of Psychiatry and Behavioral Sciences; Clinical Neuroscience Division; 67 President Street, MSC861; Charleston, SC 29425

Abstract

Background—Individuals with co-occurring bipolar disorder and alcohol dependence have particularly low rates of retention in clinical trials. Past research has identified a variety of factors associated with dropout in this population, but few have been replicated. The present study investigated the ability of several baseline variables, to predict clinical trial dropout in a sample of individuals with co-morbid bipolar and alcohol use disorders.

Methods—Demographics, psychiatric diagnoses, recent alcohol use, mood pathology, and risk taking behavior (measured with the Balloon Analogue Risk Task) were evaluated as predictors of dropout from a randomized clinical trial of acamprosate for individuals with co-morbid bipolar and alcohol use disorders ($n = 30$) using stepwise logistic regression.

Results—Risk taking behavior was the only significant predictor of dropout in the present study ($OR = 1.44, p = 0.03$), opiate dependence marginally predicted dropout as well ($OR = 13.46, p = 0.08$). A model consisting of these predictors, as well as acamprosate group status ($p = 0.13$), provided excellent prediction of dropout (i.e., area under the ROC curve = 0.94; $R^2 = 0.53$).

Conclusions—Given the robust relationship between risk taking and dropout in the present study, the Balloon Analogue Risk Task may represent a valuable tool for researchers to predict who will drop out of clinical trials for comorbid bipolar and substance use disorders.

Keywords

Bipolar; alcohol; dropout; attrition; risk taking; balloon analogue risk task; retention

1. Introduction

More than half of all individuals with bipolar disorder develop a co-occurring substance use disorder (SUD) at some point in their lifetime (Regier et al., 1990; Grant et al., 2005). Bipolar patients with co-occurring SUD are significantly less likely to adhere to treatment than bipolar patients without a history of substance abuse (Manwani et al., 2007). Poor treatment adherence and dropout predicts poor prognosis in bipolar disorder (Scott and

Pope, 2002), and may contribute to a host of negative outcomes in bipolar patients with SUD (Salloum and Thase, 2000).

Nonadherence and treatment dropout are major obstacles to progress in treatment research for this population. Of the few clinical trials conducted in substance-dependent bipolar patients, most have involved high attrition rates (Frye and Salloum, 2006, Singh and Zarate, 2006). For example, in the five published double-blind, placebo-controlled medication trials conducted in alcohol-dependent bipolar disorder patients, dropout rates have ranged from 40% to 74% (Salloum et al., 2005, Brown et al., 2008, Kemp et al., 2009, Brown et al., 2009, Stedman et al., 2010). The impact of missing data on treatment research depends on whether the missingness is random or systematic. Specifically, when the missingness does not depend on either observed or unobserved outcomes ("missing completely at random"), the consequence of missing data is a reduction in statistical power to detect treatment effects. However, when the missingness depends on observed outcomes ("missing at random") or unobserved outcomes ("missing not at random"), the consequences of missing data are reduced statistical power and biased parameter estimates (Little and Rubin, 2002). Determinants of attrition in individuals with comorbid bipolar and substance use disorders are not well understood, but recent analyses have found that factors such as cigarette smoking, low education, recent mood episodes (Graff et al., 2008), comorbid panic disorder (Nomamiukor and Brown, 2009), and impulsivity (Akingbala et al., 2006) have predicted dropout from group therapy and medication trials.

Impulsivity is a core clinical feature of bipolar disorder that is increased in patients with co-occurring SUD (Swann et al., 2004, Najt et al., 2007). Risk taking behavior is one dimension of impulsivity that has been studied with the Balloon Analogue Risk Task (BART) in persons with addiction and other externalizing disorders (Lejuez et al., 2002). A recent study found that individuals with bipolar disorder and a history of alcohol use disorder exhibit impaired performance on the BART relative to bipolar subjects without an alcohol use disorder history (Holmes et al., 2009). The present study examined the relationship between risk taking/impulsivity and other variables and study retention using data collected as part of a double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent subjects with bipolar disorder.

2. Method

2.1. Participants and procedures

Data were collected as part of an 8-week, randomized, double-blind placebo-controlled clinical trial of acamprosate (1998 mg/day) in individuals with bipolar disorder and alcohol dependence (Tolliver et al., submitted). Participants were treatment-seeking men and women aged 18–65 with a primary DSM-IV diagnosis of bipolar I or II disorder and alcohol dependence with alcohol use in the past 90 days. The Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1996) was used for diagnosis of SUD; all other disorders were evaluated using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Alcohol use was assessed using the Time-line Follow-back method (TLFB; Sobell and Sobell, 1996) and manic and depressive symptoms were evaluated using the Young Mania Rating Scale (YMRS; Young et al., 1978) and Montgomery Asberg Depression

Rating Scale (MADRS; Montgomery and Asberg, 1979), respectively. Participants were required to be taking stable doses of mood stabilizing medications for one month prior to randomization, and to remain abstinent from alcohol for three consecutive days preceding the baseline visit. Exclusion criteria included severe depression (MADRS score > 35) or mania (YMRS score > 25), imminent risk of harm to self or others, primary Axis I diagnoses other than bipolar disorder and alcohol dependence, cognitive impairment sufficient to prevent informed consent, or serious medical conditions that would jeopardize the subject or confound interpretation of study results. Randomized participants were asked to return weekly for 8 visits to assess alcohol use and depressive and manic symptoms. Participants were given a 10-day supply of study medication at each weekly visit. Written informed consent was obtained from all participants at the initial study appointment. All study procedures were approved by the Medical University of South Carolina Institutional Review Board.

As part of the baseline assessment, propensity for risk taking was assessed with the BART, a computer task in which a high level of risk taking is associated with low performance (Lejuez et al., 2002). Participants were asked to inflate a series of 30 balloons on a computer screen by pressing a button; for each button-press (“pump”) they earned 2 cents. If participants inflated the balloon past its individual explosion point (variably preset, 64 pumps on average), the money earned for that balloon was lost; if instead they pressed a button labeled “Collect \$\$\$” prior to the balloon’s explosion point, the money earned for that balloon was banked and added to the total amount earned. Subjects were notified before beginning the task that they would be compensated in cash for the total amount earned. The number of balloon explosions and average adjusted number of pumps (i.e., average number of pumps excluding balloons that exploded) were used as the primary BART outcomes (Lejuez et al., 2002).

2.2. Data analysis

Following the method used previously in a similar sample (Graff et al. 2008), dropout was defined as missing at least the last 4 weekly study visits. Group differences on baseline characteristics were evaluated using chi-square and independent sample t-tests. Stepwise logistic regression models were constructed to identify predictors of clinical trial dropout (Hosmer and Lemeshow, 2000). Six groups of predictors were evaluated in sequential models. Distal predictors (demographics, psychiatric diagnoses) were entered into the model prior to proximal predictors (alcohol use and mood symptoms); order of entry was: 1) demographics, 2) anxiety disorders, 3) drug use disorders, 4) recent alcohol use (TLFB), 5) mania (YMRS) and depression (MADRS), and 6) risk taking behavior (BART). Predictors with $p < .10$ were retained for subsequent models. Because acamprosate status was a manipulated variable, it served as a covariate in all regression models. Area under the receiver operating characteristic curve was calculated for the final model. All analyses were conducted in SPSS 17.

3. Results

3.1 Participant characteristics

Participants were 19 men and 11 women, with a mean age of 42.33 (SD = 9.41). Most participants were Caucasian (90%), unemployed (70%), and had completed some post-high school education (59%). Just under half (43%) were current cigarette smokers. Seven participants (23%) missed at least the last 4 weekly study visits and were thus classified as study dropouts; three participants did not return following their 1st weekly visit, two participants did not return following their 2nd weekly visit, and two participants did not return following their 3rd weekly visit. There were no other missing data points for any participants. Although reasons for study dropout remain unknown for most participants, two dropouts discontinued acamprosate following hospitalization. The full range of available participant characteristics organized by dropout status is presented in Table 1. Significantly more participants who dropped out of the study (57%) were diagnosed with opioid dependence than those who remained in the study (13%).

3.2. Logistic regression models

Logistic regression results are presented in Table 2. Most variables did not significantly predict dropout. However, risk taking behavior (as measured by the BART) significantly predicted dropout, and opioid dependence marginally predicted dropout. A final model with acamprosate group status (OR = 0.08, $p = 0.13$), opioid dependence (OR = 13.46, $p = 0.08$), and explosions on the BART (OR = 1.44, $p = 0.03$) provided good fit to the data ($\chi^2 = 11.97$, $p < .01$; $R^2 = 0.53$). This final model also provided excellent prediction of dropout, with an area under the receiver operating curve (AUC) of 0.94.

BART explosions and average adjusted number of pumps were not simultaneously evaluated because they were highly correlated ($r = 0.87$). A separate model with average adjusted number of pumps yielded very similar results to the model containing explosions (i.e., overall model: $\chi^2 = 11.86$, $p < .01$, $R^2 = 0.53$; acamprosate status: OR = .08, $p = 0.13$; opioid dependence: OR = 13.87, $p = 0.07$; BART pumps OR = 1.14, $p = 0.03$; AUC = 0.92).

4. Discussion

The present study evaluated the ability of demographics, psychiatric diagnoses, recent alcohol use and mood symptoms, and risk taking behavior to predict dropout from a clinical trial of acamprosate in individuals with comorbid bipolar disorder and alcohol dependence. Of these variables, only risk taking behavior significantly predicted dropout, though lifetime DSM-IV diagnoses of opioid dependence were also marginally associated with attrition. An aggregate model containing only these variables, along with acamprosate group status, afforded remarkably precise prediction of study dropout.

Risk taking behavior is of particular relevance to patients with co-occurring bipolar disorder and SUD. Affording simultaneous opportunity for reward and potential for harm, high risk behavior is commonplace in addictive disorders (Leigh, 1999) and is central to the phenomenology of mania (APA, 2000). Accordingly, elevated risk taking behavior has been observed in individuals with comorbid bipolar and alcohol use disorders relative to those

with bipolar disorder alone (Holmes et al., 2009). To our knowledge, the relationship between risk taking behavior and clinical trial dropout has not been evaluated previously. In contrast, impulsivity, a multidimensional trait that overlaps with risk taking (Lejuez et al., 2002), has been demonstrated to predict dropout in a clinical trial involving individuals with comorbid bipolar disorder and stimulant dependence (Akingbala et al., 2006). Akingbala and colleagues (2006) found that non-planning impulsivity, characterized by a present orientation and a lack of future thinking or planning, was negatively correlated with participants' length of retention. Future research simultaneously investigating impulsivity and risk taking is needed to determine if each construct uniquely predicts dropout, or if impulsivity and risk taking are redundant predictors of dropout.

In addition to risk taking behavior, the present study found that a diagnoses of opioid dependence also marginally predicted dropout. Consistent with this finding, Paraherakis and colleagues' study of individuals diagnosed with substance dependence found that individuals with opioid dependence had substantially elevated rates of treatment dropout relative to those with alcohol, cocaine, and sedative dependence (Paraherakis et al., 2000). Nonetheless, given that the finding for opioid dependence was marginally significant (i.e., $p = 0.08$) in the present study, and given that previous research has not evaluated the impact of opioid dependence on dropout in individuals with comorbid bipolar disorder and SUD, this finding should be considered provisional until replicated.

If the present findings are replicated in future research, risk taking behavior and opioid dependence may be useful as stratification variables for group randomization, or as screening variables for participation in clinical trials involving individuals with comorbid bipolar and substance use disorders to reduce the harmful effects of dropout on research. On a clinical level, the present findings imply that risk taking may also be associated with treatment dropout. Cognitive strategies designed to decrease impulsivity and risk-taking may be particularly important in optimizing treatment outcomes for this important population.

This discussion should be tempered by the present study's limitations. First, the small size of our sample provided limited statistical power for detecting significant predictors of dropout. Second, given the small sample size, relatively short trial duration, and higher than usual treatment retention in our sample, generalization to patients seen in clinical settings with bipolar disorder and co-occurring SUD may be premature. However, despite the small sample size, our final model afforded strong and reliable prediction of clinical trial dropout. Furthermore, as noted by Graff and colleagues (2008), those who did drop out of the study may represent an especially difficult to retain population. Our preliminary results suggest that it may be possible to identify patients at high risk of clinical trial dropout who could benefit from new and/or intensified retention strategies.

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Table 1Participant characteristics by dropout status ($n = 30$)

	Retained (n = 23)	Lost (n = 7)	<i>p</i>
Demographic			
Age (M, SD)	42.13 (8.53)	43.00 (12.68)	0.87
Female, %	43.48	14.29	0.16
Caucasian	86.96	100.00	0.31
High school graduate, %	30.43	71.43	0.15
Employed, %	30.43	28.57	0.93
Current smoker, %	39.13	57.14	0.40
Past smoker, %	43.48	28.57	0.48
Comorbid Anxiety Disorders			
Generalized Anxiety Disorder, %	47.83	57.14	0.67
Obsessive-Compulsive Disorder, %	8.70	14.29	0.67
Panic Disorder, %	13.04	14.29	0.93
Posttraumatic Stress Disorder, %	8.70	0.00	0.42
Social Phobia, %	30.43	28.57	0.93
Comorbid Drug Dependence			
Cannabis Dependence, %	43.48	42.86	0.98
Amphetamine Dependence, %	13.04	14.29	0.93
Cocaine Dependence, %	39.13	57.14	0.40
Opioid Dependence, %	13.04	57.14	0.02*
Baseline Assessments (M, SD)			
MADRS	11.22 (6.09)	13.71 (5.53)	0.34
Young Mania Rating Scale	6.26 (4.77)	7.29 (3.99)	0.61
# of drinks consumed in past month	79.61 (100.30)	133.79 (104.63)	0.23
% days alcohol consumed in past month	26.38 (27.38)	35.71 (29.42)	0.44

Note. MADRS = Montgomery Asberg Depression Rating Scale.

* $p < 0.05$.

Table 2Stepwise logistic regression models predicting study dropout ($n = 29$)

Baseline measures	1: Demographic ($p = 0.35$)	1 + Anxiety Disorders ($p = 0.89$)	2 + Drug Depend ($p = 0.34$)	3 + Alcohol Use ($p = 0.23$)	4 + Mood ($p = 0.33$)	5 + Risk Taking ($p = 0.01$)
Acamprosate	0.24	0.28	0.52	0.46	0.33	0.08
Demographic						
Age	1.02					
Female	0.14					
High school grad	10.55					
Employed	1.05					
Current Smoker	0.33					
Past Smoker	0.05					
Anxiety Disorders						
GAD		1.06				
OCD		4.98				
Panic Disorder		1.03				
Social Phobia		1.05				
Drug Dependence						
Cannabis Dep.			0.68			
Amphetamine Dep.			0.23			
Cocaine Dep.			2.46			
Opioid Dep.			13.75 [†]	10.37 [†]	7.03 [†]	13.46 [†]
Past Month Alcohol Use						
# of drinks consumed				1.01		
% days consumed				0.98		
Mood						
MADRS					1.04	
YMRS					1.04	
Risk Taking						
BART Explosions						1.44 [*]
Nagelkerke R²	0.54	0.09	0.28	0.27	0.23	0.53

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Note. Coefficients are odds ratios. GAD = Generalized anxiety disorder; OCD = Obsessive-compulsive disorder; MADRS = Montgomery Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; BART = Balloon Analogue Risk Task.

[†] $p < 0.10$;
* $p < 0.05$.