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Impact of Remitted Substance Use Disorders on the Future Course of Bipolar I Disorder: Findings from a Clinical Trial

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Abstract

Given the high lifetime prevalence rates of bipolar disorder and comorbid substance use disorders (SUDs), the aim of the study was to examine the effect of a *remitted* SUD on the future course of bipolar I disorder in patients taking part in a clinical trial. Patients with bipolar I disorder were enrolled in a larger study examining the effects of pharmacotherapy plus family interventions. These patients were recruited during an acute mood episode and their mood symptoms and substance abuse were assessed longitudinally for up to 28 months. Patients with a remitted SUD showed a poorer acute treatment response, a longer time to remission of their acute mood episode, and a greater percentage of time with subthreshold but clinically significant depression and manic symptoms over follow-up compared to those without this comorbidity pattern. Subsequent substance abuse during follow-up could not fully account for the poorer course of illness. As remitted SUDs appear to negatively predict treatment outcome, current findings have implications for both clinical trials of bipolar patients as well as clinical practice.

1. INTRODUCTION

Bipolar disorder is one of the top ten leading causes of disability worldwide in those ages 15–44 (Murray and Lopez, 1996). The direct treatment cost of bipolar disorder was \$7.6 billion annually in the U.S. in 1990, and 8% of this figure was accounted for by substance abuse treatment (Wyatt and Henten, 1995). The substantial resources devoted to the treatment of drug and alcohol problems in bipolar patients are not surprising given the high co-occurrence between these disorders. Epidemiological research suggests that the lifetime prevalence of substance use disorders (SUDs) is higher in bipolar disorder than in any other psychiatric disorder, including unipolar depression (Goldberg, 2001). The National Comorbidity Survey found an 8 to 10 fold greater risk of substance or alcohol dependence in bipolar patients (Kessler et al., 1997). Brown et al. (2001) reported rates of SUDs in bipolar patients ranging from 14 to 65% in inpatient and outpatient treatment settings. Conversely, epidemiological studies indicate that individuals with SUDs have a 5 to 8 times greater risk of bipolar disorder (Kessler et al., 1997; Regier et al., 1990). Rates of bipolar disorder in samples from drug and alcohol clinics have ranged from 2 to 31% (Salloum and Thase, 2000).

In their review, Salloum and Thase (2000) reported that bipolar disorder and a comorbid SUD are associated with an earlier age of bipolar illness onset, higher frequency of mood episodes,

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greater persistence of significant symptoms between mood episodes, delayed time to recovery and shortened time to bipolar relapse, greater depression and manic severity, more mixed and rapid cycling episodes, greater disability, and higher mortality rates. Research also has shown that “bipolar substance abuse” (Weiss, 2004) is associated with increases in violence (Salloum et al., 2002) and psychiatric rehospitalizations (Cassidy et al., 2001), as well as poorer psychosocial outcomes (Tondo et al., 1999) when compared to patients with bipolar disorder and no SUD. Even more disturbing, patients with bipolar substance abuse are twice as likely to attempt suicide (Dalton et al., 2003). Comorbid SUDs also have been shown to predict lower medication compliance in numerous studies (Lingam and Scott, 2002). For example, Keck et al. (Keck et al., 1998) prospectively followed 134 bipolar patients following hospitalization and found that patients without comorbid SUDs were almost twice as likely to be adherent to medications (58% versus 32%).

Most previous studies on bipolar patients with comorbid SUDs have focused either on samples that included individuals with a current SUD diagnosis or that combined patients with current and past SUDs. Given the high lifetime prevalence of SUDs in bipolar patients and the known negative impact of substance abuse, a post hoc analysis of a larger clinical trial was conducted to examine the potential impact of a past SUD history on the longitudinal course of illness of bipolar I disorder when individuals were currently SUD asymptomatic (i.e., in remission for ≥ 1 year prior to study entry). Although many clinical trials of bipolar patients exclude those with current SUD diagnoses, a substantial proportion of these patients are likely to have a past SUD history. In addition, if a past SUD history can be shown to negatively impact the future course of illness, there are important clinical implications for the routine screening and treatment of bipolar patients. Given the known negative effects of comorbid SUDs on the course of bipolar illness and the results from previous studies of bipolar patients with current or past SUDs, we hypothesized that bipolar I patients with a remitted SUD would show a poorer acute treatment response, have a longer time to remission from their acute mood episode, and spend a greater percentage of time symptomatic over a 28 month follow-up period compared to patients without a SUD history.

2. METHOD

2.1. Participants

Ninety-two patients were enrolled in the larger clinical trial assessing pharmacotherapy versus pharmacotherapy plus family therapy for bipolar disorder (study recruitment period: 1992–1997). Please refer to the original study for a detailed description of the trial (Miller, Solomon et al., 2004). Patients were enrolled during an acute mood episode, and the vast majority of the original sample was recruited during an index hospitalization (96%). Inclusion criteria for the “parent” clinical trial were: 1) diagnosis of bipolar I disorder (current episode manic, depressed, or mixed) according to the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1990); 2) age 18 to 75; 3) fluency in English; and 4) regular contact with a significant other. Exclusion criteria were: 1) diagnosis of alcohol or drug *dependence* during the past year; 2) a mood disorder due to a medical condition or substance; 3) a medical illness severe enough to contraindicate the use of mood stabilizing medication; 4) or pregnancy or inadequate contraception use. Current or past substance *abuse* was permitted in the clinical trial if determined at the time of enrollment to be secondary to bipolar disorder, but these patients were excluded from current analyses ($n = 7$). Past substance *dependence* was diagnosed according to the SCID and must have been in full remission for at least 1 year prior to study entry.

2.2. Assessments

The SCID (Patient Edition) for DSM-III-R (Spitzer et al., 1990) was used to determine current and lifetime diagnoses. The Bech-Rafaelsen Mania Scale (BRMS) (Bech et al., 1979) is an 11-item interviewer-rated scale used to assess the severity of manic symptoms. The Modified Hamilton Rating Scale for Depression (MHRSD) (Miller et al., 1985) is a 25-item interviewer-rated instrument that was used to assess depression severity. The MHRSD is an adapted form of the original scale that includes standardized question prompts to increase reliability. The commonly used 17-item total was used in analyses. The Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) is a clinical interview that was used to determine if patients met criteria for a SUD during the follow-up period. All interviewers were trained to proficiency on assessment devices and blind to treatment conditions. LIFE interviewers were certified by the developers of the instrument. Raters were trained to initial interrater reliability ($>.85$) with periodic checks to ensure continued reliability.

2.3. Treatments

Following hospitalization, patients were randomized to the following treatment conditions: pharmacotherapy alone ($n = 29$) or in combination with adjunctive family therapy ($n = 33$) or family psychoeducational groups ($n = 30$). The “acute” treatment period was defined as the first 4 months post-hospitalization. Pharmacotherapy was administered by board-certified psychiatrists using a protocol of standardized procedures adapted from the Clinical Management-Imipramine/Placebo Administration Manual (Fawcett et al., 1987). Participants met with their psychiatrist once per week for the first month, and then less frequently based on patient improvement ($M = 13$ sessions). Each medication management session included a review of symptoms, assessment of side effects, and provision of support, encouragement, and advice as appropriate. All patients were prescribed a mood stabilizer. Additional medications, including antidepressants (54%) and neuroleptics (84%) also were prescribed as appropriate based on the type and severity of patients’ symptoms. A total of 95% of patients were judged by independent chart review to have received adequate medication treatment during the “acute” treatment phase of the trial. For patients randomized to the combined treatment conditions, family therapy ($M = 12$ sessions) (Ryan et al., 2005) or a family educational group intervention ($M = 4$ sessions) (Keitner et al., 2002) was also provided during the acute treatment phase. After 4 months, all patients were continued on pharmacotherapy for a total period of up to 28 months. Sixty-six percent of the sample completed at least 6 months of active study treatment. However, to ensure the generalizability of findings, assessments were continued when possible even if patients relapsed or dropped out of study treatments.

2.4. Procedure

Following a complete description of the study, patients and their family members provided written informed consent (Institutional Review Board-approved). After baseline assessment, patients were randomly assigned to conditions. Follow-up assessments were completed monthly for up to 28 months. In-person assessments were conducted at baseline, discharge from the hospital, and 2, 4, 10, 16, 22, and 28 month follow-ups. The LIFE was administered during the in-person assessments and retrospectively assessed the time between assessment points. Raters assigned participants a Psychiatric Status Rating that ranged from 1 (asymptomatic) to 3 (definite criteria) for SUDs. BRMS and MHRSD assessments occurring during each intervening month were conducted via telephone. Previous research has documented the validity of phone assessments (Simon et al., 1993), and scores between face-to-face and phone interviews were highly correlated in the sample (Miller, Uebelacker et al., 2004). The more intensive, acute treatment phase of the study started immediately after hospital discharge and continued for the first 4 months outpatient.

2.5. Calculation of Percent Time Symptomatic Variables

Scores on clinician-rated measures were used to classify patients as asymptomatic, partially symptomatic, or fully symptomatic. Based on established criteria (Bech et al., 1986; Frank et al., 1991), scores of ≤ 7 (MHRSD) and ≤ 5 (BRMS) were considered asymptomatic, 8–14 (MHRSD) and 6–14 (BRMS) were considered partially symptomatic, and ≥ 15 (MHRSD and BRMS) were considered fully symptomatic. Based on this classification system, percent time variables were calculated by dividing the number of months spent in the respective symptom categories by the total number of months for which data were collected in the study (Miller, Uebelacker et al., 2004). Percent time variables were only computed for patients with at least 5 months of data available to ensure a reasonable period of assessment (77% of original sample).

2.6. Statistical Analyses

Tests were two-tailed and alpha was set at $p < .05$. Repeated-measures analyses of covariance (ANCOVAs) were computed to investigate acute phase treatment response (hospital discharge to 4 months) on bipolar symptom measures, covarying baseline scores (Behar and Borkovec, 2003). Analyses were based on the intent-to-treat principle, and the expectation maximization (EM) algorithm was used for imputing missing data (Hill, 1997). EM imputes missing values based on maximum likelihood estimates using known participant variables in an iterative process that preserves variability (Demster et al., 1977; Graham and Donaldson, 1993). In addition, time to remission of the acute bipolar episode was defined as two consecutive months of BRMS scores < 6 and MHRSD scores < 7 (Miller, Solomon et al., 2004). Time to remission was analyzed by means of survival analysis (Kaplan and Meier, 1958). The duration of illness for the index mood episode began at baseline and ended with remission, study completion, or drop out. Finally, long-term course of illness was investigated by computing the percentage of time patients spent symptomatic or asymptomatic for depression and/or mania.

3. RESULTS

3.1. Rates of Past Substance Use Disorders in the Sample

As mentioned, a current diagnosis of substance dependence was an exclusionary criterion for the study, but substance abuse was permitted. Therefore, current analyses were only conducted on those patients enrolled in the study who were not diagnosed with current substance abuse. Of the sample of patients without a current substance abuse diagnosis ($n = 85$), 48% had a past history of a SUD diagnosis. A diagnosis of past alcohol dependence (33%) was the most frequent disorder in the subsample with a SUD history. The percentages of other past SUDs were: alcohol abuse = 7%; sedative abuse = 8%; cannabis abuse = 7%; cannabis dependence = 13%; stimulant abuse = 1%; stimulant dependence = 4%; opioid dependence = 4%; cocaine dependence = 9%; hallucinogen abuse = 1%; hallucinogen dependence = 3%; polysubstance-related dependence = 2%; other substance dependence = 3%.

3.2. Group Comparisons for Baseline Variables

First, BP (bipolar disorder only) and BP-SUD (bipolar disorder with a SUD history) groups were compared on demographic variables, including age, gender, race/ethnicity, marital status, and education level. Chi square analysis showed that the BP-SUD group was comprised of significantly more males than the BP group, $\chi^2(1) = 6.13$, $p < .05$. No other significant differences were identified. We also compared the groups on history of illness variables, including age of first mood episode, the number of past mood episodes, and lifetime non-SUD comorbid disorders (primarily anxiety). No significant group differences were found. Finally, we examined baseline severity, including scores on the MHRSD, BRMS, and Global Assessment of Functioning (GAF), as well as the polarity of the index episode (manic/mixed

versus depressed) and the presence or absence of psychotic features. Again, no significant differences were found on any of these variables. See Table 1 for descriptive statistics of all baseline variables.

3.3. Acute Phase Treatment Response

First, we assessed for group differences in the number of follow-up assessments available for analysis, group drop out rates, and representation across randomized conditions. However, no significant differences were found. The acute treatment phase of the trial began after hospital discharge and continued for 4 months during outpatient treatment. A 2 (BP versus BP-SUD) $\times$ 3 (hospital discharge, 2, and 4 months) repeated-measures ANCOVA (covarying baseline scores) on the MHRSD demonstrated significant main effects for time and group, but no significant interaction (see Figure 1). After hospital discharge, the sample showed a slight increase in depression severity over the 4-month period, $F(2, 164) = 11.29, p < .001, \eta^2 = .12$. Note that most patients (78%) were in a manic episode at the time of hospitalization. However, the BP-SUD group had significantly higher depression severity than the BP group during the acute treatment phase (controlling for baseline scores), $F(1, 82) = 11.32, p < .001, \eta^2 = .31$. A similar ANCOVA conducted on the BRMS revealed no significant main or interaction effects.

3.4. Time to Remission of Index Mood Episode

Time to remission was assessed by means of a Kaplan-Meier survival analysis (see Figure 2). Results revealed that bipolar patients with a SUD history had a longer time to remission of their index mood episode compared to those without a SUD history, log-rank $\chi^2 = 3.76, p = .05$. Furthermore, results indicated that the longer time to remission in the BP-SUD group was particularly pronounced at the beginning of the follow-up period, Breslow $\chi^2 = 6.89, p < .01$. The median time to remission for the BP group was 5 months ($SE = 1, 95\% CI = 3-7$), whereas the median time in the BP-SUD group was 11 months ($SE = 3, 95\% CI = 5-17$). By study completion, a total of 70% in the BP group recovered from their index mood episode, compared to 56% of the BP-SUD group, $\chi^2(1) = 1.88, p = ns$.

3.5. Percentage of Time Spent Symptomatic During 28 Month Follow-Up

Table 2 depicts descriptive and inferential statistics for percent time symptomatic variables. The BP and BP-SUD groups were compared on the percentage of time depressed and/or manic according to the following symptom categories: fully symptomatic, partially symptomatic, and asymptomatic. The BP-SUD group spent significantly less time asymptomatic over the 28 month follow-up period ($p < .01$). The BP-SUD group also spent significantly more time partially symptomatic for depression ($p < .05$). Furthermore, the BP-SUD group spent significantly more time with either partial depression or hypomania ($p < .001$). Finally, the BP-SUD group spent significantly more in mixed partial depression and hypomania ($p < .01$). No other significant differences were found. Effect size differences for significant group comparisons were in the medium to large range ($ds = .56-.81$) according to Cohen's criteria (Cohen, 1988).

3.6. Effects of Substance Abuse during Follow-Up

Of the 61 patients with sufficient LIFE data available, 4 met diagnostic criteria for a current SUD during the follow-up period. Three had a past SUD diagnosis at baseline, but one of these patients did not. Therefore, analyses for outcome variables were rerun using SUD diagnosis (yes or no) at follow-up as a covariate. A Cox regression analysis for SUD history on time to recovery including follow-up SUD diagnosis as a covariate was no longer significant, $Wald \chi^2(1) = 2.44, p = .11, HR = 1.59, 95\% CI = 0.9-2.8$. All other analyses using ANCOVAs remained significant at $p < .05$. These findings suggest that substance use during the follow-up period did not fully account for the poorer course of illness.

3.7. Effects of Treatment and Gender

The treatment conditions were combined in current analyses to increase statistical power. Results from the “parent” trial showed no significant main effects for treatment condition (Miller, Solomon et al., 2004), although baseline level of family function acted as a moderator of treatment outcome for time spent depressed during follow-up (Miller et al., under review). Therefore, we examined the possibility of differential outcomes for SUD groups based on treatment condition, as well as gender due to baseline differences on this variable. Interaction terms constructed between SUD History X Treatment (medication alone versus medication plus family intervention) and SUD History X Gender were tested for all study outcomes. However, these interaction terms were not significant in any of the analyses of acute treatment response on the MHRSD/BRMS (two-way repeated-measures ANCOVA), time to episode remission (Cox regression analysis), or percent time symptomatic variables (two-way ANOVA). These results suggest that patients with a SUD history had poorer outcomes regardless of gender or treatment received. Finally, rates of past SUDs were not significantly different across the three treatment conditions, $\chi^2(2) = 3.12, p = ns$.

4. DISCUSSION

Results demonstrated that a SUD history was predictive of a poorer future course of bipolar I disorder, even when the SUD was in remission at the start of treatment. During the acute treatment phase of the study, bipolar patients with a SUD history showed greater depression severity. Hamilton depression scores for patients with a SUD history fell within the partially symptomatic range (average 11 points) at months 2 and 4. In contrast, those without a SUD history had mean depression severity scores falling within the minimally symptomatic or asymptomatic range (average 7 points) during the same period.

Furthermore, bipolar patients with a SUD history showed a longer time to remission of their acute episode when compared to those without this history. Past SUD patients also spent a smaller percentage of time asymptomatic following hospital discharge, and a greater percentage of time with subthreshold but clinically significant depression and manic symptoms over long-term follow-up. These group differences appeared to be primarily due to the presence of more severe depression symptoms in those with a SUD history. Patients with or without a SUD history did not show differences in time spent in a full mood episode over the follow-up period. However, the experience of subthreshold symptoms in bipolar disorder, especially depression, predicts future relapse and is associated with significant functional impairment and other negative outcomes (Altshuler et al., 2002).

At study entry, all bipolar patients in the current sample were asymptomatic regarding their SUD for a period of at least 1 year. Consistent with previous research (Salloum and Thase, 2000), patients in the study with a SUD history were more likely to be male. However, there were no clear differences found between patients with or without a SUD history on any other demographic or clinical variables. During the follow-up period, 7% of the sample met diagnostic criteria for a current SUD. However, the presence of a SUD during follow-up did not fully account for the poorer course of illness found in the sample. More specifically, only the finding of a longer time to remission of the index mood episode was no longer significant when subsequent substance abuse was taken into account. All other findings remained significant. Therefore, our results suggest that the presence of a remitted SUD is predictive of a poorer initial response to treatment and long-term course of illness, even in the absence of significant subsequent substance abuse. One possible explanation is that patients with a history of bipolar substance abuse simply have a more severe form of illness compared to those without this comorbidity pattern. Alternately, the effects of comorbid substance abuse could be accounted for by a third variable that was not assessed in the study, such as antisocial personality or risk-seeking/impulsive personality traits. Another possibility is that previous

central nervous system exposure to high levels of alcohol and illicit drugs produces a “kindling” effect that increases the future risk of treatment refractory mood states (Post and Weiss, 1989).

We are aware of only one other published study that attempted to investigate the impact of recovery from SUDs on the course of bipolar disorder. Weiss et al. (2005) compared and contrasted the course of illness in bipolar patients with no comorbid SUD, a current comorbid SUD, or a past but not a current comorbid SUD in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. Patients with a current or past SUD did not differ in terms of their “recovered” or “recovering” clinical status. However, patients with a current SUD exhibited poorer role functioning than patients with a past SUD, who in turn demonstrated poorer functioning compared to those with no SUD history. Patients with a current or past SUD also showed lower quality of life compared to bipolar patients with no SUD history. Results of the current study were consistent with these previous findings, and provide additional details about the effects of remitted SUDs on the short- and longer-term course of bipolar illness.

Weiss et al. (2005) point out that SUDs tend to “wax and wane” over time in bipolar patients, and therefore should be a focus of clinical attention even if not currently problematic. For example, Strakowski et al. (2007) recently reported that most bipolar patients with co-occurring cannabis use disorders had a remission following hospitalization. Nevertheless, a high rate of recurrence was observed over a 5-year follow-up period. Findings from the current study and past research hold important implications for clinical trial research involving bipolar patients. In general, researchers frequently have been hampered in their development and testing of novel treatments of bipolar disorder because of the inherent methodological challenges involved in studying the illness. There is emerging empirical support for the efficacy of adjunctive family therapy, cognitive-behavioral therapy, or psychoeducation interventions for bipolar patients (Craighead and Miklowitz, 2000). However, it is not uncommon for clinical trials of psychosocial interventions to report null or inconsistent findings in this area (Bauer, 2001; Miller, Solomon et al., 2004). Results of the current study suggest that it is important for clinical researchers to thoroughly assess current and past SUDs at study entry and to measure subsequent substance use over the course of the study, as a past history may act as a moderator of outcome. In addition, it may be useful to employ stratified randomization to ensure that patients with SUD histories do not become randomized differentially to treatment conditions. Finally, some researchers may decide to exclude patients from their trials based on a current *or* past SUD diagnosis, although this will limit generalizability.

Current findings also have important implications for clinical practice. At least a subgroup of patients with bipolar substance abuse frequently report “self-medicating” to alleviate or avoid their mood symptoms (Weiss et al., 2004). In addition, comorbid substance use is often associated with treatment nonadherence, which in turn can lead to continued mood symptoms, relapse, and rehospitalization (Lingam and Scott, 2002). Research suggests that fear of the consequences of combining alcohol/illicit substances with mood stabilizers may lead some bipolar patients to be nonadherent to pharmacotherapy (Weiss, 2004). Our research indicated that bipolar patients’ expectancies about medication treatment predicted the subsequent quality of the therapeutic alliance with their psychiatrist, which in turn predicted treatment attrition (Gaudiano and Miller, 2006). However, data on medication adherence was not collected in the “parent” clinical trial, and therefore this issue needs to be investigated in future studies. The high co-occurrence between bipolar disorder and SUDs highlights the need for clinicians to monitor the use of alcohol and other substances based on past history and to examine patients’ beliefs about medication treatment.

Potential study limitations could affect the interpretation of results. Our sample size was relatively modest, particularly for calculations of percent time symptomatic variables, and loss to attrition is a common problem in longitudinal bipolar samples. Sample size was too small to explore the impact of type of substance abuse. Attempts should be made to replicate current findings in larger datasets of bipolar patients. In addition, some patients in the sample received family therapy after hospital discharge, although secondary analyses did not suggest that treatment received affected the current results. Furthermore, inclusion criteria for the clinical trial required patients to have a significant other also willing to participate. Results based on the current sample may be limited in terms their generalizability to bipolar patients with low levels of community support. It should be noted, however, that course of illness in our sample was similar to results found in other studies in which family involvement was not a requirement (Judd et al., 2002). Finally, it is possible that some patients were symptomatic for their SUDs at study entry or during the follow-up period, but this was not accurately detected by our assessments. Urine drug screens and collateral reports of substance abuse were not collected to ensure the reliability of SUD assessments in the current study.

Findings highlight the need to develop tailored treatments specifically to address common comorbid conditions in bipolar patients (Gaudiano and Miller, 2005). Weiss et al. (2000) reported promising results of a pilot study comparing an adjunctive group intervention for bipolar substance abusers to treatment as usual. At 6 months, patients receiving the cognitive-behavioral treatment targeting substance use and promoting coping skills for mood symptoms showed superior medication compliance, increased abstinence rates, and decreased manic symptoms relative to the comparison condition. In a recently published, larger, follow-up study of the same intervention, bipolar patients with comorbid substance dependence demonstrated significantly decreased substance use and higher retention rates in the cognitive-behavioral group compared with regular group drug counseling (Weiss et al., 2007). Even though studies of psychosocial treatments for bipolar disorder often exclude patients with current SUDs, it still may be necessary to ensure that treatment addresses the possibility of subsequent substance abuse given the fact that many patients will likely have a SUD history.

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FIGURE 1. Acute Phase Treatment Response for Depression Severity Based on Substance Use Disorder (SUD) History

^a Baseline scores covaried and subsequent time points adjusted accordingly.

^b Points represent means and vertical lines represent error bars.

FIGURE 2.
Kaplan-Meier Estimates of Survival Probabilities for Time to Remission Based on Substance Use Disorder (SUD) History

TABLE 1
Sample Demographics, History of Illness Variables, and Baseline Severity Measures

	SUD History (<i>n</i> = 41)	No SUD History (<i>n</i> = 44)	Test Statistic ^d
	M (<i>SD</i>)/Proportion (n)	Mean (<i>SD</i>)/Proportion (n)	
Demographic Variables			
Age	39.2 (10.2)	40.6 (12.9)	<i>t</i> = 0.56
Education (years)	13.3 (2.2)	13.4 (2.7)	<i>t</i> = 0.13
Gender (% male)	59 (24)	32 (14)	$\chi^2 = 6.13^*$
Race/ethnicity (% white)	88 (36)	91 (40)	$\chi^2 = 0.22$
Marital status (% spouse/partner)	34 (14)	30 (13)	$\chi^2 = 0.21$
History of Illness			
Age of first depressive episode	19.7 (9.3)	23.8 (9.9)	<i>t</i> = 1.67
Age of first manic episode	28.0 (8.9)	29.7 (12.1)	<i>t</i> = 0.70
# of past depressive episodes	6.0 (10.2)	4.1 (6.9)	<i>t</i> = 0.89
# of past manic episodes	5.4 (5.4)	4.2 (4.0)	<i>t</i> = 1.00
Non-SUD Comorbid Disorders (% yes)	22 (9)	18 (8)	$\chi^2 = 0.19$
Baseline Severity			
BRMS	20.0 (11.7)	20.8 (9.9)	<i>t</i> = 0.34
MHRSD (17-item)	10.2 (9.6)	7.7 (9.1)	<i>t</i> = 1.26
GAF	26.7 (6.6)	28.3 (6.9)	<i>t</i> = 1.08
Episode polarity (% manic/mixed)	73 (30)	84 (37)	$\chi^2 = 1.52$
Psychosis (% positive)	71 (29)	66 (29)	$\chi^2 = 0.06$

*
p < .05.

SUD = Substance Use Disorder, BRMS = Beck-Rafaelson Mania Scale, MHRSD = Modified Hamilton Rating Scale for Depression (17-item), GAF = Global Assessment of Functioning Scale.

^a *t*-test *dfs* = 83, chi-square test *dfs* = 1.

Percentage of Time Spent at Each Symptom Level During the 28-Month Follow-Up Period

	SUD History(<i>n</i> = 30)		No SUD History(<i>n</i> = 36)		<i>t</i> (<i>df</i> = 64)	Cohen's <i>d</i>
	Mean (SD)	Mean (SD)				
Percent Time Mood Asymptomatic	39 (29)	61 (32)	2.86**	-0.72		
Percent Time Partially Mood Symptomatic	24 (15)	15 (17)	2.11*	0.56		
Subsyndromal depression only	6 (6)	5 (6)	0.98	0.17		
Hypomania only	7 (11)	2 (3)	3.00**	0.62		
Subsyndromal depression and hypomania	37 (17)	22 (20)	3.41**	0.81		
Percent Time Fully Mood Symptomatic	13 (14)	8 (13)	1.80	0.37		
Full depression only	22 (6)	24 (7)	1.00	-0.31		
Full mania only	16 (4)	14 (4)	0.24	0.50		
Mixed episode	23 (21)	17 (27)	0.98	0.25		
Any episode						

* *p* < .05,
** *p* < .01.

SUD = Substance Use Disorder.

Depression ratings based on Modified Hamilton Rating Scale for Depression (17-item); mania ratings based on Bech-Rafaelson Mania Scale.