Psychiatry Research 190 (2011) 253–258

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Medication adherence and attitudes in patients with bipolar disorder and current versus past substance use disorder

Christian J. Teter [a,b,*], Anthony E. Falone [a,c], Amanda M. Bakaian [a], Chunhao Tu [b], Dost Öngür [d], Roger D. Weiss [a,e]

[a] Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA, USA
[b] College of Pharmacy, University of New England, Portland, ME, USA
[c] Behavioral Neuroscience, Northeastern University, Boston, MA, USA
[d] Schizophrenia and Bipolar Disorders Program, McLean Hospital, Belmont, MA, USA
[e] Department of Psychiatry, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 26 May 2010
Received in revised form 24 May 2011
Accepted 25 May 2011

Keywords:
Mood disorder
Addiction
Pharmacotherapy
Compliance
Comorbidity
Attitude

ABSTRACT

We examined the impact of substance use disorder (SUD) history among patients with bipolar I disorder (BD) in regards to medication-taking behaviors and attitudes. Interviews were conducted with inpatients hospitalized for BD, which included diagnostic instruments and measures of attitudes concerning psychiatric medications. We compared patients with BD and no history of SUD (BD-NH), BD and past history of SUD (BD-PH), and BD and current SUD (BD-C). The primary outcome variable was a standardized medication adherence ratio (SMAR) of [medication taken]/[medication prescribed]. Fifty-four patients with a BD diagnosis participated, which included BD-NH ($n=26$), BD-PH ($n=19$), and BD-C ($n=9$). The SMAR was significantly different among the three groups; post-hoc analyses revealed the SMAR was significantly lower among BD-C ($M=0.70$) compared to BD-NH ($M=0.90$) and BD-PH ($M=0.97$) patients. This finding remained significant after controlling for numerous patient characteristics. Attitudes regarding medications, measured by the Drug Attitude Inventory (DAI), were positive among a significantly higher percentage of BD-PH (89.47%) and BD-NH (65.38%) compared to BD-C (44.44%) patients. In conclusion, patients with BD-C demonstrated poor medication adherence and attitudes concerning medication management. Helping patients with BD achieve remission from SUD may lead to a more successful course of BD pharmacotherapy.

1. Introduction

High rates of medication nonadherence are found among patients with bipolar disorder (BD) (Keck et al., 1997; Scott and Pope, 2002); patients with BD and co-occurring substance use disorders (SUDs) appear to be particularly at risk for medication nonadherence (Keck et al., 1997; Goldberg et al., 1999; Weiss, 2004; Sajatovic et al., 2006; Manwani et al., 2007; Baldessarini et al., 2008; Sajatovic et al., 2009; Perlis et al., 2010). Further complicating matters, high rates of co-occurrence and very strong associations between SUDs and BD have been consistently documented over the years (Regier et al., 1990; Kessler et al., 1997; Goldberg et al., 1999; Weiss, 2004; Grant et al., 2005).

Numerous explanations have been put forth to explain why patients with co-occurring BD and SUD are at high risk for medication nonadherence. These have included disorganized lifestyle (Weiss, 2004), impulsivity (Sajatovic et al., 2006), and neurocognitive impairment (Levy et al., 2008). However, despite these proposed etiologic explanations, causal factors for medication nonadherence among this difficult-to-treat population remain unclear. Researchers have begun to consider patients with BD and a *past* history of SUD separately from those with *current* SUD, to fully examine the impact of active substance use on the course of BD. A study using data from the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) demonstrated that a past history of SUD was associated with significantly better role functioning compared to a current SUD. Furthermore, patients in SUD recovery demonstrated similar role functioning to patients with no SUD history after controlling for other variables in multivariate analyses (Weiss et al., 2005). Sajatovic et al. (2006) demonstrated that veterans with a current SUD displayed higher rates of medication nonadherence, while a past SUD history was not associated with treatment nonadherence. Gaudiano et al. (2008) conducted a post-hoc analysis of clinical trial data to explore the impact of remitted SUD on the course of BD. This study demonstrated that patients with BD and past SUD history appeared to have poorer clinical outcomes than did patients without an SUD history. However, this study did not include patients with a current SUD, so comparisons between current and past SUD were not available (Gaudiano et al., 2008). Taken

* Corresponding author at: Psychopharmacology, College of Pharmacy, University of New England, Room #223, 716 Stevens Avenue, Portland, ME, USA, 04103. Tel.: +1 207 221 4076; fax: +1 207 523 1927.
E-mail address: cteter@une.edu (C.J. Teter).

0165-1781/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2011.05.042

together, these studies lend support to the idea that patients with BD and varying SUD histories (i.e., no SUD history, current SUD, or past SUD history) each possess unique characteristics that must be considered separately in both research and treatment settings.

To extend these observations, we conducted an observational inpatient study to determine whether there are similar patterns of medication-taking behaviors, attitudes, and beliefs regarding psychiatric medications among patients with BD and one of three mutually exclusive SUD histories: (1) *no history* of an SUD (BD-NH), (2) *past history* of an SUD (BD-PH), and (3) *current* SUD (BD-C). Our primary hypothesis was that BD-C patients would demonstrate lower medication adherence as compared to BD-PH patients, despite the well-controlled inpatient environment in which other theorized risk factors (e.g., disorganized lifestyle) were eliminated. Our secondary hypothesis was that attitudes concerning BD medication would follow a similar pattern and be more negative among the BD-C patients. Lastly, based upon the work by Weiss et al. (2005) described above, we anticipated finding similar patterns of medication adherence and attitudes regarding medication in BD-PH and BD-NH patients.

2. Methods

2.1. Study overview

Face-to-face interviews were conducted with patients admitted for acute hospitalization to the Schizophrenia and Bipolar Disorder Program at McLean Hospital, Belmont, MA. To be eligible for inclusion, patients needed to receive a diagnosis of Bipolar I Disorder (BD), according to the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995). Patients were further classified according to their acute mood episode (i.e., manic, mixed, or depressed) at the time of the study interviews. In addition to BD, SUD history was established using the SCID. BD-PH was defined as lifetime abuse or dependence on any substance not occurring during the last year. In contrast, BD-C was defined as abuse or dependence on any substance within the past year. BD-NH meant not meeting SCID criteria for either a past or current SUD. Nicotine dependence and data on other co-occurring Axis I or Axis II psychiatric disorders was not collected for the purposes of this study. Approval was obtained from the Institutional Review Board of the McLean Hospital Human Research Protection Program, and all patients provided written informed consent after the study had been thoroughly explained to them. Patients were compensated $40.00 at the conclusion of the final interview for their time and effort.

2.2. Rating scales and outcome measures

Psychiatric symptom rating scales were administered to each patient to assess their illness severity. Instruments to measure manic, depressive, and psychotic symptoms included the Young Mania Rating Scale (Young et al., 1978), the Montgomery–Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979), and the Positive and Negative Syndrome Scale (Kay et al., 1987), respectively.

Medication-taking behaviors were directly observed and recorded daily for information on the proportion of psychotropic medication taken by each patient in relation to the amount prescribed. More precisely, we calculated a standardized medication adherence ratio (SMAR) for each patient as follows: [dose medication taken]/[dose medication prescribed]. This ratio was applied to every regularly scheduled psychotropic medication being used to treat symptoms of BD. The ratios for individual medications were averaged into one total SMAR for each patient. Data for this variable were collected daily from psychiatric nursing medication administration records. Medication refusals were identified as circles in which the letters "REF" were documented and initialed by the treating psychiatric nurse. To be conservative and not over-estimate treatment refusals, a missed dose was confirmed only when the patient never received a prescribed dose at any point during the day. In other words, if a patient refused medication at one time-point, but ultimately took the prescribed dose at a later time-point within the same day, it was not considered a missed dose. It is important to note that patients have the right to refuse medication while hospitalized. This results in varying levels of medication adherence, even in the closely monitored environment of an inpatient setting. Also, the treatment structure surrounding medication administration to patients in this study ensured that other variables (e.g., forgetfulness, disorganization, or other cognitive difficulties) did not contribute to our medication adherence findings. Medications included in this study were psychotropic medications prescribed for the treatment of BD. Medications prescribed to treat extrapyramidal or other side effects were not included in our analyses. Although additional data were collected for 'as-needed' (i.e., p.r.n.) medications as well as non-psychotropic medications, the current report focuses on standing psychotropic medications prescribed for the management of BD. Medication-taking behaviors were recorded for the first seven days of hospitalization to capture as much proximal information as possible following admission, while providing a standardized timeframe for data collection and outcome analyses.

Attitudes and beliefs regarding psychiatric medications being used to treat BD were assessed using the 10-item version of the Drug Attitude Inventory (DAI) (Hogan and Awad, 2000). The DAI is intended to assess subjective feelings (i.e., medication-related dysphoria as compared to physical side effects), as well as attitudes and beliefs concerning psychiatric medications. For the purposes of this study, the scope of the DAI was narrowed by informing patients during the research interview that the DAI pertained to medications specifically being used to treat their BD. Patients respond to each item by answering true or false. The scoring of the DAI requires some interpretation since a "true" response indicates positive views for some items, but negative views for others. For example, a "true" response to "I take medication only when I am sick" represents a negative attitude toward medication (score $= -1$), whereas a "true" response to "For me, the good things about medication outweigh the bad" represents a positive attitude (score $= +1$). Further information on the specific content of each DAI-10 item will be discussed in the Results section. The scoring of the 10-item version equals the total sum of the items, ranging from -10 to $+10$. Patients in our study were categorized as having a positive (total score ≥ 0) or negative (total score <0) view toward psychiatric medications, consistent with the original scoring method used among patients with schizophrenia (Hogan and Awad, 2000). When used in psychiatric populations, the reliability and validity of the DAI has been shown to be similar to or greater than other commonly used brief medication adherence screening instruments (Pomykacz et al., 2007).

The open-ended questionnaire that was used to collect reasons for medication nonadherence was taken from earlier work by our research group (Weiss et al., 1998). It contains an extensive list of reasons for medication nonadherence organized by category (e.g., side effects, substance-use related, mood-related) and includes probing reminders for the interviewer. During the semi-structured interview each category of potential reasons for not adhering to BD medications was discussed with the patient, and examples were provided from within each category to serve as cues for the patient.

Psychiatrists and research staff members involved in the study were trained in assessments. To maximize consistency and reliability, monthly diagnostic reliability exercises were conducted in which a study subject was interviewed in the presence of the research team. Each rater independently assessed each subject. Reliability was demonstrated by rate of agreement, as determined by the fraction of raters who showed perfect agreement on a specific measure. Rates of agreement were perfect (1.0) for SCID diagnoses and near-perfect for current mood episodes (major depression, 1.0; mania, 0.93) (Öngür et al., 2008). The DAI-10 and the reasons for medication nonadherence were administered once to each patient by a single investigator (CJT) throughout the study, and the SMAR is an objective measure directly observed and recorded from the medical records. Therefore, reliability analyses were not performed for these medication-specific measures.

2.3. Data analysis

Patient subgroups (i.e., BD-NH, BD-PH, and BD-C) were compared using Fisher's Exact Test for categorical variables and Kruskal–Wallis for continuous variables. Post-hoc analyses among subgroups were completed when significance was initially detected: Mann–Whitney Test with Bonferroni correction for continuous variables and Simultaneous Agresti-Caffo 95% Confidence Intervals (CI) for Comparing Proportions (Agresti et al., 2008) for categorical variables. The ordinary least squares method was used to control for potentially confounding variables in order to estimate parameters (i.e., slopes) that represent differences in SMAR between patient subgroups (i.e., BD-NH, BD-PH, and BD-C). The potential confounding variables were chosen based on the following: (1) visual inspection of bivariate results for statistical significance (i.e., YMRS), (2) pronounced numerical differences (i.e., age, marital status), or (3) high theoretical likelihood of contributing to medication nonadherence (i.e., acute psychiatric severity as measured by the YMRS, MADRS and PANSS). Lastly, effect sizes (Cohen's d) were calculated for differences in mean SMAR between groups including bias-corrected and accelerated 95% CIs (Efron and Tibshirani, 1993). All statistical analyses were performed using R 2.12.0 software (R Development Core Team, 2010).

3. Results

3.1. Patient characteristics

Fifty-four patients completed the face-to-face interviews and received a formal diagnosis of BD according to the SCID. As shown in Table 1, baseline characteristics were similar among the three subgroups of patients, with the exception of YMRS scores; patients with BD-C reported greater mania symptom severity according to the YMRS ($M = 36.78 \pm 8.44$) as compared to patients with BD-NH ($M = 24.85 \pm 13.21$; $P<0.05$) and BD-PH ($M = 24.84 \pm 11.70$; $P<0.05$). A majority of each group was acutely manic, although depressive and mixed profiles were also present. Regarding specific substance use disorders, 55.6% of the BD-C patients had an alcohol-only disorder, while the remaining 44.4% had a drug-only disorder.

Table 1
Characteristics and outcomes of patients with bipolar I disorder and no, past, or current SUD ($n=54$) [†,‡].

	BD-NH ($n=26$)	BD-PH ($n=19$)	BD-C ($n=9$)	Statistical analyses
Age (years)	38.19 ± 13.95	40.63 ± 13.47	30.00 ± 9.35	NS
Gender				
Male	10 (38.46%)	10 (52.63%)	7 (77.78%)	NS
Female	16 (61.54%)	9 (47.37%)	2 (22.22%)	
Race/ethnicity				
White	20 (76.92%)	16 (84.21%)	9 (100.00%)	NS
Non-White	6 (23.08%)	3 (15.79%)	0 (0.0%)	
Marital status (non-married includes single, divorced, and widowed)				
Married	6 (23.08%)	4 (21.05)	0 (0.0%)	NS
Non-married	20 (76.92%)	15 (78.95%)	9 (100.00%)	
Bipolar disorder current episode				
Manic	18 (69.23%)	13 (68.42%)	8 (88.89%)	NS
Depressive	5 (19.23%)	2 (10.53%)	0 (0.0%)	
Mixed	3 (11.54%)	4 (21.05%)	1 (11.11%)	
Psychiatric symptom rating scales				
YMRS	24.85 ± 13.21[A]	24.84 ± 11.70 [A]	36.78 ± 8.44[B]	K-W $X^2=7.28$, d.f. = 2, $P<0.05$
MADRS	17.2 ± 12.4	18.1 ± 9.7	11.8 ± 4.1	
PANSS	64.7 ± 18.7	64.9 ± 11.9	67.9 ± 11.9	
Medication adherence measurement				
SMAR	0.90 ± 0.19[A]	0.97 ± 0.06[A]	0.70 ± 0.17[B]	K-W $X^2=18.57$, d.f. = 2, $P<0.0001$

[†] To explore differences among the three groups, categorical and continuous variables were statistically compared using Fisher's Exact Test and the Kruskal–Wallis test, respectively.
[‡] Superscripts (A, B) associated with group means which differ from each other indicate statistically significant differences ($P<0.05$) in post-hoc pairwise comparisons according to the Mann–Whitney test with Bonferroni correction. The significant differences in SMAR remained after controlling for age, marital status, YMRS, MADRS, and PANSS using the ordinary least squares method ($P<0.05$).
Abbreviations: K-W = Kruskal–Wallis, MADRS = Montgomery Asberg Depression Rating Scale, NS = not statistically significant, PANSS = Positive and Negative Syndrome Scale, SMAR = Standardized Medication Adherence Ratio, YMRS = Young Mania Rating Scale.

Among the BD-PH patients, specific SUDs were alcohol-only (36.8%), drug-only (21.1%), and both alcohol and drug disorders (42.1%). The broader alcohol and drug use profile among the BD-PH group may reflect the longer time-frame and more opportunities for alcohol and drug use as compared to the BD-C group defined by past-year criteria.

3.2. Medication adherence

The primary dependent outcome variable (i.e., the SMAR) was significantly lower among patients with BD-C as compared to BD-NH and BD-PH. Post-hoc analysis revealed that patients with BD-C demonstrated significantly lower rates of medication adherence ($M=0.70\pm0.17$) compared to BD-PH ($M=0.97\pm0.06$; $P<0.01$) and BD-NH ($M=0.90\pm0.19$; $P<0.01$). Significantly lower rates of medication adherence remained among BD-C patients after controlling for numerous independent variables using the ordinary least squares method ($P<0.05$). Please see Table 1 for a listing of these independent variables. Lastly, to examine the clinical significance of the magnitude of these medication adherence differences, the standardized mean difference between the three patient groups was calculated, which resulted in a large Cohen's *d* effect size equal to 2.4 [95% CI: 1.4, 3.4].

Medication-level data were explored for the presence of noticeable patterns among the patient groups. However, the large number of polytherapy combinations identified in this sample made it impossible to disentangle the impact of individual medications on adherence rates. Therefore, the results presented here are purely descriptive in nature, and in most cases involve non-mutually exclusive medication prescribing patterns. Lithium was the medication most often prescribed ($n=31$), followed by risperidone ($n=19$), olanzapine ($n=18$), valproate formulations ($n=18$), and lorazepam ($n=12$). Of the most-commonly prescribed medications, lithium was associated with the highest average medication adherence rate (95.2%), followed by olanzapine (94.3%), valproate formulations (86.5%), lorazepam (84.8%), and risperidone (80.1%). Furthermore, lithium was prescribed in the most patient cases ($n=18$) in which no doses of prescribed medication were missed during the 7-day evaluation period. In other words, 58.1% of treatment regimens that included lithium were always taken 'as prescribed' compared to 43.5% of regimens without lithium. The corresponding mean adherence rates for lithium versus non-lithium regimens were $M=0.92$ and $M=0.85$, respectively (non-significant difference).

Pharmacological class comparisons were conducted since many medications appeared infrequently (e.g., carbamazepine, haloperidol, perphenazine, topiramate). Therefore, medications were collapsed into their respective pharmacologic classes for comparison (with lithium remaining its own drug entity). In this broader comparison, lithium maintained the highest mean adherence (95.2%), followed by mood stabilizers (89.9%), antipsychotics (89.0%), and benzodiazepines (84.8%).

The three patients groups were very similar in terms of BD medication usage. For example, the mean number of BD medications was nearly identical for BD-NH ($M=2.9$), BD-PH ($M=2.8$), and BD-C ($M=2.6$). Furthermore, regardless of SUD history, most patients (85.2%) were receiving lithium and/or a mood stabilizer in combination with an atypical antipsychotic. There were few deviations from this general pattern, and only two cases of monotherapy were located in the entire sample. Lastly, there appeared to be a minor shift towards valproate formulations ($n=5$) as compared to lithium ($n=2$) in the BD-C group. However, these numbers are too small to draw any firm conclusions, which also made a useful medication-level adherence comparison between groups impossible.

3.3. Psychotropic medication attitudes and beliefs

The sample-level median DAI score was +2.75 (range −10 to +10), indicating these patients tended to report more favorable views towards their psychiatric medications. Regardless of SUD category, medication adherent patients demonstrated a statistically significantly higher mean DAI score ($+5.3\pm4.4$) as compared to medication nonadherent patients (-0.25 ± 6.4; $P<0.001$). It appears the DAI-10 was able to discriminate medication adherence from nonadherence among patients with BD. Exploratory analyses assessing commonly accepted 'adherence

Table 2
Drug Attitude Inventory (DAI) responses consistent with positive attitudes towards bipolar disorder medications.

	BD-NH ($n=26$)	BD-PH ($n=19$)	BD-C ($n=9$)
DAI total scores[†‡]	$n=17$ (65.38%)[A]	$n=17$ (89.47%)[A]	$n=4$ (44.44%)[B]
1. For me, the good things about medication outweigh the bad.	$n=21$ (81%)	$n=17$ (90.0%)	$n=6$ (66.7%)
2. I feel weird, like a "zombie", on medication.[†]	$n=12$ (46%)	$n=3$ (16%)	$n=5$ (56%)
3. I take medications of my own free choice.	$n=17$ (65%)	$n=9$ (47.4%)	$n=6$ (66.7%)
4. Medications make me feel more relaxed.	$n=18$ (69.2%)	$n=15$ (79.0%)	$n=5$ (56%)
5. Medication makes me feel tired and sluggish.[†]	$n=16$ (61.5%)	$n=10$ (52.6%)	$n=9$ (100.00%)
6. I take medication only when I am sick.	$n=8$ (30.8%)	$n=5$ (26.3%)	$n=6$ (66.7%)
7. I feel more normal on medication.[†]	$n=16$ (61.5%)	$n=16$ (84%)	$n=3$ (33.3%)
8. It is unnatural for my mind and body to be controlled by medications.	$n=12$ (46%)	$n=7$ (36.8%)	$n=3$ (33.3%)
9. My thoughts are clearer on medication.	$n=17$ (65%)	$n=16$ (84%)	$n=4$ (44.4%)
10. By staying on medications, I can prevent getting sick.	$n=19$ (73%)	$n=17$ (90.0%)	$n=6$ (66.7%)

[†] To explore differences among the three groups, DAI response proportions were statistically compared using Fisher's Exact Test. Statistically significant differences ($P<0.05$) were identified for DAI total scores and three individual items (#2, #5, and #7).
[‡] Superscripts (A, B) associated with group proportions which differ from each other indicate statistically significant differences ($P<0.05$) in post-hoc comparisons according to the Simultaneous Agresti-Caffo 95% Confidence Intervals for Comparing Proportions.

thresholds' (e.g., 80% medication adherence) did not alter the pattern of our findings.

Differences in SUD category-level DAI scores were found: a significantly higher proportion of patients with BD-C reported negative DAI scores compared to BD-NH and BD-PH. In other words, patients with BD-C self-reported more negative attitudes and beliefs regarding medications used to treat their BD. Please see Table 2 for a full DAI-10 analysis, including the individual items it contains. Notably, three individual items were significantly different among the three groups. For example, all nine of the BD-C patients reported "medication makes me feel tired and sluggish," as compared to BD-NH (61.5%) and BD-PH (52.6%) patients.

3.4. Reasons for medication nonadherence

The most commonly reported reasons for lifetime medication nonadherence among these patients (regardless of SUD subgroup) were from the medication side effects category; 64.8% of the patients reported at least one physical side effect provided in the category as a direct cause for medication nonadherence over their lifetime. Notably, the individual reason endorsed most frequently for medication nonadherence was the belief they "did not need" medications for BD (50.0%). This remarkably high percentage was similar among the three groups. In fact, there were few notable patterns among the three groups regarding reasons for medication nonadherence, with two minor exceptions. First, the BD-C patients endorsed an average of 10 individual reasons to explain their medication nonadherence, as compared with an average of five individual reasons for both BD-NH and BD-PH. Second, eight of nine BD-C patients (88.9%) endorsed at least one physical side effect as a cause for medication nonadherence, followed by BD-PH ($n=14$, 73.7%) and BD-NH ($n=13$, 50.0%). Lastly, contrary to what we expected, few patients endorsed substance use-related reasons (e.g., intoxication, not wanting to mix medication with substances) for lifetime medication nonadherence ($n=3$ in each SUD group).

4. Discussion

4.1. Conclusions

Supporting our primary hypothesis, results of the present study indicate that hospitalized patients with BD and a past history of SUD (i.e., patients in remission) are more likely to adhere to their medication regimen as compared to patients with a current SUD. Furthermore, patients in recovery from an SUD appear to have a more positive attitude concerning their psychiatric medications as compared to patients with a current SUD. The fact that patients in remission from SUDs are taking their medications at higher rates than current substance users appears to relate more to substance use history than to age, marital status, and current manic, depressive, or psychotic symptoms; ordinary least squares revealed that SUD history remained significant after controlling for these patient characteristics. As expected, BD-NH patients demonstrated similar patterns to the BD-PH group. Our findings are consistent with previous work that demonstrated improved functional outcomes among patients with BD who were in recovery from an SUD (Weiss et al., 2005). However, other studies describe potentially conflicting findings. For example, Gaudiano et al. (2008) described the course of BD in patients with remitted SUD. These patients showed poorer acute BD treatment response and a longer time for mood episode remission as compared to patients without SUD comorbidity. In the Weiss et al. (2005) study, patients with current or past SUD demonstrated similar rates of being "recovering/recovered" from BD. However, this same study revealed improved functioning for the past-SUD and no-SUD groups as compared to the current SUD group; this pattern of improved functional outcomes among the past SUD group is parallel to our medication adherence findings. Perhaps clinical course and functional outcomes for patients with BD will follow different trajectories secondary to substance use; a theory that is supported in recent literature (Lagerberg et al., 2010).

Taken together, the above findings suggest that helping patients with BD achieve remission from substance use may lead to improved medication-taking behaviors and attitudes, as well as help with functioning in other areas of life (Weiss et al., 2005). However, further research is needed to fully explore which specific aspects of SUD remission are helping patients to better function in various areas of their lives, and to clarify differences in the response of clinical and functional outcomes in relation to substance use. Furthermore, the impact of co-occurring disorders (i.e., beyond SUDs) could help provide a larger view regarding patient adherence and attitudes towards medications.

The question as to why current substance users experience poorer outcomes such as medication nonadherence (despite our well-controlled inpatient environment in which disorganized lifestyle, acute intoxication, and other confounding variables have been removed) remains unanswered. The finding that current substance users reported poorer attitudes in regards to psychiatric medications may partially explain this phenomenon. Despite a sample median DAI score in the "positive" range (+2.75), the BD-C group reported significantly higher rates of negative scores on the DAI. This highlights the finding that most of the negative DAI scores in the total sample were from the smaller patient BD-C subgroup. Perhaps more attention needs to be given to these patients' views towards medication management, which would allow for the early identification of those at risk for nonadherence to their treatment plan.

Lithium in combination with other medications (usually atypical antipsychotics) was the single medication most often prescribed across our study sample, and was associated with the highest levels of medication adherence. A recent, large database study revealed congruent

findings in that antipsychotic-lithium treatment combinations were associated with higher rates of medication adherence as compared to antipsychotic-anticonvulsant regimens (Gianfrancesco et al., 2009). Although the populations and methods differ, these two studies agree that lithium showed benefit in terms of medication adherence. It seems plausible that patients are willing to adhere to lithium regimens despite the required therapeutic monitoring and potential for adverse effects and toxicity. A signal for less lithium use and more valproate formulation use among the BD-C group is intriguing. However, the size of the BD-C group does not allow for meaningful comparison of the impact of this prescribing shift or of potential adherence differences. If this pattern was replicated in larger inpatient BD samples with co-occurring SUDs, it could have important implications on medication adherence rates in this patient population, given our findings that lithium was associated with the highest adherence rates.

Similar to earlier research (Keck et al., 1996; Weiss et al., 1998), many patients in our study reported they did not need medication for BD, irrespective of SUD history. This remains a serious challenge for clinicians and researchers to overcome. Keck et al. (1996) demonstrated that "denial of illness" was the most commonly reported reason for total or partial nonadherence among patients with manic symptoms. In a study of patients with co-occurring BD and SUD, Weiss et al. (1998) found that 20% of the patients that were noncompliant with lithium saw "no need" for the medication. More recent work by Clatworthy et al. (2009) suggests that medication nonadherence continues to be associated with doubts about the need for treatment. Interestingly, the authors advocate these concerns can be placed into the context of the Necessity-Concerns Framework model, which may help improve the current nonadherence situation. Taken together, these findings suggest that a sizeable group of patients with BD (with and without a co-occurring SUD) perceive medication as unnecessary. More work is clearly needed to improve acceptance towards medication management for this chronic and debilitating illness.

4.2. Limitations

Our small sample size may have limited our power to detect statistically significant differences in patient characteristics between all three patient comparison groups. Another issue to consider regarding the small sample size is the generalizability of our findings. Given there were only nine patients with a current SUD, it is difficult to extrapolate these findings to all patients with co-occurring BD and SUDs in various settings. Despite limitations associated with sample size, the large standardized mean difference in medication adherence rates suggests that we were able to identify clinically relevant differences in our primary outcome variable.

The 10-item DAI used in the current study has not undergone formal psychometric analyses in patients with BD or SUD. However, the patterns in DAI scores and medication adherence rates mirrored each other closely, which may signal an expected relationship between the two variables that can be used to predict adherence. Our sample was predominantly white, decreasing our ability to generalize our data to other ethnicities with BD. We collected information regarding medication nonadherence, but did not ask patients why they *would* take their medication as prescribed (i.e., reasons for being medication adherent). Collecting this information in the future will provide a more balanced clinical picture. Lastly, the "lifetime" timeframe of measures such as reasons for medication nonadherence may not provide the information necessary to discriminate between patients with differing SUD histories since the three patient groups appeared very similar according to this variable.

4.3. Research and clinical implications

More attention is needed to correctly classify patients with a lifetime SUD into *past* or *current* subgroups. The results of the present study, in addition to previous research, suggest that there are meaningful differences between these subgroups of patients. Failing to separate these patients into subgroups could have a negative impact on trial results as important findings may be obscured.

The findings suggest that the DAI can be used as a brief assessment to help identify patients less likely to take their psychiatric medications as prescribed. Perhaps these patients can be educated further about the importance of BD pharmacotherapy and can be encouraged to attend medication-focused groups during their inpatient hospital stay. A targeted approach for providing education to patients with BD on the benefits of pharmacotherapy in specific patient subgroups (e.g., current substance users, patients with negative attitudes concerning medications) could be a helpful component of treatment. Lastly, there appears to be something unique about patients with BD who have remitted from substance use that is associated with improved medication-taking behaviors and better attitudes. This suggests that paying attention to co-occurring SUD remains a priority in this population.

Acknowledgments

1. This project was made possible by a Bouvé College of Health Sciences Research & Development Faculty Award (CJT) and a Provost Undergraduate Research Award (AEF).
2. This manuscript was presented in part as a poster presentation at a national meeting and as online continuing education materials for Physicians Postgraduate Press, Inc.:
   - Teter C, Falone AE, Lower A, Weiss RD. Does recovery from substance use disorders among patients with bipolar disorder predict improved medication taking behaviors and drug attitudes? Poster presented at: 49th Annual Meeting of the New Clinical Drug Evaluation Unit (NCDEU); June 29–July 2, 2009; Hollywood, FL.
   - NCDEU Online Poster Session 2009. Web site: http://www.cmeinstitute.com/postersession/2009Session5/ABSTeter.asp.
3. The research was supported in part by Grant K24 DA022288 (RDW) from the National Institute on Drug Abuse.

References

Agresti, A., Bini, M., Bertaccini, B., Ryu, E., 2008. Simultaneous confidence intervals for comparing binomial parameters. Biometrics 64, 1270–1275.
Baldessarini, R.J., Perry, R., Pike, J., 2008. Factors associated with treatment nonadherence among US bipolar disorder patients. Human Psychopharmacology 23, 95–105.
Clatworthy, J., Bowskill, R., Parham, R., Rank, T., Scott, J., Horne, R., 2009. Understanding medication non-adherence in bipolar disorders using a Necessity-Concerns Framework. Journal of Affective Disorders 116, 51–55.
Efron, B., Tibshirani, R.J., 1993. An Introduction to the Bootstrap. Chapman & Hall/CRC Press, Boca Raton, Fl.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J., 1995. Structured Clinical Interview for DSM-IV (SCID-I) (User's Guide and Interview) Research Version. Biometrics Research Department, New York State Psychiatric Institute, New York.
Gaudiano, B.A., Uebelacker, L.A., Miller, I.W., 2008. Impact of remitted substance use disorders on the future course of bipolar I disorder: findings from a clinical trial. Psychiatry Research 160, 63–71.
Gianfrancesco, F.D., Sajatovic, M., Tafesse, E., Wang, R.H., 2009. Association between antipsychotic combination therapy and treatment adherence among individuals with bipolar disorder. Annals of Clinical Psychiatry 21, 3–16.
Goldberg, J.F., Garno, J.L., Leon, A.C., Kocsis, J.H., Portera, L., 1999. A history of substance abuse complicates remission from acute mania in bipolar disorder. Journal of Clinical Psychiatry 60, 733–740.
Grant, B.F., Stinson, F.S., Hasin, D.S., Dawson, D.A., Chou, S.P., Ruan, W.J., Huang, B., 2005. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Journal of Clinical Psychiatry 66, 1205–1215.
Hogan, T.P., Awad, A.G., 2000. Drug Attitude Inventory. In: Rush, A.J. (Ed.), Handbook of psychiatric measures. American Psychiatric Association Publishing, Arlington, VA.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13, 261–276.
Keck Jr., P.E., McElroy, S.L., Strakowski, S.M., Stanton, S.P., Kizer, D.L., Balistreri, T.M., Bennett, J.A., Tugrul, K.C., West, S.A., 1996. Factors associated with pharmacologic noncompliance in patients with mania. Journal of Clinical Psychiatry 7, 292–297.

Keck Jr., P.E., McElroy, S.L., Strakowski, S.M., Bourne, M.L., West, S.A., 1997. Compliance with maintenance treatment in bipolar disorder. Psychopharmacology Bulletin 33, 87–91.

Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., Anthony, J.C., 1997. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Archives of General Psychiatry 54, 313–321.

Lagerberg, T.V., Andreassen, O.A., Ringen, P.A., Berg, A.O., Larsson, S., Agartz, I., Sundet, K., Melle, I., 2010. Excessive substance use in bipolar disorder is associated with impaired functioning rather than clinical characteristics, a descriptive study. BMC Psychiatry 10 (9), 1–9.

Levy, B., Monzani, B.A., Stephansky, M.R., Weiss, R.D., 2008. Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. Psychiatry Research 161, 28–35.

Manwani, S.G., Szilagyi, K.A., Zablotsky, B., Hennen, J., Griffin, M.L., Weiss, R.D., 2007. Adherence to pharmacotherapy in bipolar disorder patients with and without co-occurring substance use disorders. Journal of Clinical Psychiatry 68, 1172–1176.

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. British Journal of Psychiatry 134, 382–389.

Öngür, D., Lin, L., Cohen, B.M., 2008. Clinical characteristics influencing age at onset in psychotic disorders. Comprehensive Psychiatry 50, 13–19.

Perlis, R.H., Ostacher, M.J., Miklowitz, D.J., Hay, A., Nierenberg, A.A., Thase, M.E., Sachs, G.S., 2010. Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. Journal of Clinical Psychiatry 71, 296–303.

Pomykacz, B., Mao, M., Weiss, R.D., Teter, C.J., 2007. A review of brief medication-adherence instruments used in patients with schizophrenia and bipolar disorder. Harvard Review of Psychiatry 15, 259–263.

R Development Core Team, 2010. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Available at: http://www.R-project.org (accessed 12-6-2010).

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264, 2511–2518.

Sajatovic, M., Bauer, M.S., Kilbourne, A.M., Vertrees, J.E., Williford, W., 2006. Self-reported medication treatment adherence among veterans with bipolar disorder. Psychiatric Services 57, 56–62.

Sajatovic, M., Ignacio, R.V., West, J.A., Cassidy, K.A., Safavi, R., Kilbourne, A.M., Blow, F.C., 2009. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Comprehensive Psychiatry 50, 100–107.

Scott, J., Pope, M., 2002. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. American Journal of Psychiatry 159, 1927–1929.

Weiss, R.D., 2004. Adherence to pharmacotherapy in patients with alcohol and opioid dependence. Addiction 99, 1382–1392.

Weiss, R.D., Greenfield, S.F., Najavits, L.M., 1998. Medication compliance among patients with bipolar disorder and substance use disorder. Journal of Clinical Psychiatry 59, 172–174.

Weiss, R.D., Ostacher, M.J., Otto, M.W., Calabrese, J.R., Fossey, M., Wisniewski, S.R., Bowden, C.L., Nierenberg, A.A., Pollack, M.H., Salloum, I.M., Simon, N.M., Thase, M.E., Sachs, G.S., for STEP-BD Investigators, 2005. Does recovery from substance use disorder matter in patients with bipolar disorder? Journal of Clinical Psychiatry 66, 730–735.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. British Journal of Psychiatry 133, 429–435.