Published in final edited form as:

Psychiatry Res. 2015 August 30; 228(3): 516–525. doi:10.1016/j.psychres.2015.06.005.

Adjunctive Psychosocial Intervention Following Hospital Discharge for Patients with Bipolar Disorder and Comorbid Substance Use: A Pilot Randomized Controlled Trial

Susan J. Wenze^{a,b}, Brandon A. Gaudiano^{b,c}, Lauren M. Weinstock^{b,c}, Katherine M. Tezanos^{b,c}, and Ivan W. Miller^{b,c}

^aDepartment of Psychology, Lafayette College, Easton, PA, USA

^bDepartment of Psychiatry & Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI, USA

^cPsychosocial Research, Butler Hospital, Providence, RI, USA

Abstract

Bipolar disorder and substance use disorders are highly debilitating conditions, and especially when co-occurring, are associated with a variety of negative outcomes. Surprisingly, there is a relative lack of research on feasible and effective psychosocial treatments for individuals with comorbid bipolar and substance use disorder (BD-SUD), and a dearth of literature examining interventions designed specifically to improve outcomes such as symptoms, functioning, and treatment engagement/adherence following psychiatric hospitalization in this population. In the current paper, we report results of a pilot randomized controlled trial ($n = 30$), comparing the recently developed Integrated Treatment Adherence Program, which includes individual and telephone sessions provided to patients and their significant others, versus Enhanced Assessment and Monitoring for those with BD-SUD. Participants who received the Integrated Treatment Adherence Program demonstrated significantly faster and greater improvements in depression, mania, functioning, and values-consistent living than participants randomized to Enhanced Assessment and Monitoring, and there was a trend for increased treatment adherence over time. Results are discussed in light of existing literature and study limitations, and suggestions for future research are proposed.

Keywords

depression; mania; values clarification; treatment adherence; psychiatric hospitalization

Corresponding Author Note: Susan J. Wenze, Department of Psychology, Lafayette College, 730 High Street, Easton, PA 18042, United States of America, +1 610-330-5739 (T), +1 610-330-5349 (F).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare that there are no conflicts of interest regarding the publication of this article.

1. Introduction

Bipolar disorder (BD) and substance use disorders (SUDs) are highly debilitating and often comorbid conditions (Murray and Lopez, 1996; Degenhardt et al., 2013). Epidemiological research suggests that rates of comorbid SUDs are higher in BD than in any other psychiatric disorder (Tohen et al., 1998; Goldberg, 2001), and individuals with BD have also been shown to have the highest rates of *multiple* substance use disorders (Kessler et al., 1997). The Epidemiologic Catchment Area study reported that over 60% of those with BD had a comorbid SUD, with 46% meeting criteria for alcohol abuse or dependence and 41% meeting criteria for drug abuse or dependence (Regier et al., 1990). Conversely, individuals with SUDs also have a significantly elevated risk of BD, with rates estimated at 5-8 times greater than in the general population (Regier et al., 1990; Kessler et al., 1997).

BD with comorbid SUD (hereafter abbreviated “BD-SUD”) is associated with many negative outcomes, including more frequent and severe mood episodes, greater persistence of clinically significant inter-episodic symptoms, longer time to recovery, shorter time to bipolar relapse, greater disability, higher mortality rates, poorer psychosocial outcomes, increased psychiatric hospitalizations, more suicide attempts, and poorer treatment adherence when compared to those with BD without a SUD (Aagaard et al., 1988; Brady et al., 1991; Brady and Sonne, 1995; Feinman and Dunner, 1996; Tondo et al., 1999; Potash et al., 2000; Salloum and Thase, 2000; Cassidy et al., 2001). Of note, research indicates that the period immediately following discharge from the hospital is associated with particularly poor outcomes in patients with BD (Miller et al., 2004; Gaudiano & Miller, 2006) and in those with SUDs (Merrall et al., 2013). Among individuals with BD-SUD, hospital discharge is similarly associated with a heightened risk of negative outcomes such as nonadherence, suicidality, mood and drug relapse, and rehospitalization (Keck et al., 1998; Strakowski et al., 1998a; Strakowski et al., 1998b; Gaudiano et al., 2008).

A number of psychosocial treatments have been developed as adjuncts to pharmacotherapy for BD. Cognitive-behavioral therapy, family therapy, interpersonal and social rhythm therapy, and psychoeducation have typically been shown to improve outcomes in at least some areas (Castle et al., 2009; Reinares et al., 2014). Reinares and colleagues (2014) note that one way to improve psychosocial treatment outcomes in BD is to tailor the treatment to the particular characteristics of the targeted population. However, most research to date on adjunctive treatments for BD has specifically excluded those with SUDs. In our earlier report of an open case series used to develop the current intervention (Gaudiano et al., 2011), we documented improvements in adherence, substance use, and mood symptoms in participants with BD and comorbid SUD. The 5 additional studies on BD-SUD also found positive effects on important clinical outcomes, such as reductions in substance use, increases functioning, and declines in mood symptoms (Weiss et al., 2000; Schmitz et al., 2002; Weiss et al., 2007; Weiss et al., 2009; Goldstein et al., 2014).

No previous clinical trials to our knowledge have focused on improving the often difficult transition from inpatient to outpatient treatment in acutely ill patients with BD-SUD. Furthermore, previous studies in BD-SUD samples have tested more traditional and intensive psychosocial interventions. There is an urgent need to develop and test adjunctive

psychosocial interventions that are more feasible to deliver and can work in concert with patients' other community treatments, which may include pharmacotherapy, case management, support groups, and other substance abuse treatment programs. Given the previously-discussed challenges often encountered in the post-hospitalization period (Keck et al., 1998; Strakowski et al., 1998a; Strakowski et al., 1998b), as well as especially high rates of psychiatric hospitalizations among those with BD-SUD (Brady et al., 1991), this constitutes an important gap in the literature.

With this background in mind, we sought to develop and test an adjunctive psychosocial intervention for BD-SUD that was designed to improve a range of clinical outcomes in the transition from acute to maintenance treatment. We were also interested in establishing the acceptability, feasibility, and credibility of such an intervention with this challenging and high-risk population. Details of the rationale for and initial development of the intervention are described in our report of the previous open trial (Gaudiano et al., 2011). In the current paper, we report results of a small, pilot, randomized controlled trial, comparing our intervention to an enhanced assessment and monitoring only condition to further assess its acceptability and potential efficacy in preparation for a future full-scale clinical trial.

2. Method

2.1. Participants

Participants ($n = 30$) were recruited at a private psychiatric hospital from inpatient units ($n = 27$, 90%), with supplemental recruitment of at-risk outpatients ($n = 3$, 10%)¹. Participants met the following criteria: 1) DSM-IV diagnosis of Bipolar I or II Disorder or Bipolar Disorder NOS (BD), as determined by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002); 2) DSM-IV drug and/or alcohol use disorder (abuse and/or dependence) also based on the SCID; 3) current prescription for at least one mood-stabilizing medication; 4) at least 18 years of age; 5) ability to speak and read English sufficiently well to complete study procedures; and 6) regular access to a telephone. Exclusion criteria were: 1) borderline or antisocial personality disorder with therapy-interfering behaviors (e.g., chronic suicidality and self-harm), based on the SCID-II (First et al., 1997); 2) nicotine dependence as the only substance use disorder; 3) a medical illness that contraindicated the use of mood-stabilizing medication; 4) pregnancy (due to the potential adverse effects of mood stabilizing medications for this population); 5) current homelessness; or 6) discharge to long-term residential substance abuse treatment. Whenever possible, participants identified a significant other (SO; spouse/partner, sibling, child, parent, or close friend), who also participated in the study ($n = 22$; see Procedure section). SOs were: 1) 18 years or older; 2) able to speak and read English; and 3) in weekly contact with the participant.

¹Outpatients were recruited based on clinical judgment regarding severity of mood symptoms, substance use, functional impairment, and/or treatment non-adherence. Two outpatients were in a manic/mixed episode and 1 was in a depressed episode. One had a diagnosis of Bipolar I Disorder, 1 had a diagnosis of Bipolar II Disorder, and 1 had a diagnosis of Bipolar Disorder NOS. All 3 had a lifetime diagnosis of alcohol dependence, and 2 also had a lifetime substance use disorder diagnosis. Outpatients did not differ from inpatients on any baseline clinical or demographic variables (all p 's > 0.05) except for lifetime suicide attempts; inpatients had a higher number of attempts ($t(26) = 4.73$, $p < 0.001$). We re-ran all analyses using baseline treatment status (inpatient versus outpatient) as a covariate at level 2. Results were similar (i.e., betas were comparable and significance levels did not change) for all but 2 analyses: the effect of treatment condition on suicidal ideation and on number of days using drugs was no longer marginally significant.

2.2. Procedure

The Butler Hospital Institutional Review Board approved all study procedures. Newly-admitted patients' hospital charts were screened based on inclusion and exclusion criteria using a Protected Health Information waiver. After obtaining permission from the treating psychiatrist, patients who appeared to meet study criteria were approached, given a brief verbal overview of the study, including the nature, purpose, risks, and benefits, and invited to participate. Informed consent was obtained from those who expressed interest. A Certificate of Confidentiality (issued by the National Institutes of Health), which permits refusal to comply with requests for identifying information from participants engaged in civil or criminal proceedings, was also obtained to further protect privacy.

Assessments were conducted at pre-treatment (baseline), mid-treatment (3 months), and post-treatment (6 months), and administered by trained interviewers (bachelor's or master's-level research assistants) who were blind to treatment condition. Training consisted of a formal didactic workshop followed by several weeks of: a) trainee review and practice scoring of gold standard assessment recordings, b) supervised role plays, c) trainee observation of assessments in real time, and d) supervisor observation of trainee-conducted assessments in real time. All raters were required to achieve acceptable inter-rater reliability (κ s > 0.80) with expert faculty ratings prior to conducting independent assessments with ongoing monitoring of assessment recordings to prevent rater "drift." Participants were compensated with gift cards for completing assessments.

Study participants were allocated to Enhanced Assessment and Monitoring or the Integrated Treatment Adherence Program using urn randomization procedures (Wei, 1978). Urn randomization is a stratified randomization technique, which randomly assigns patients of a given subgroup to treatment conditions, but systematically biases the randomization in favor of balance among the treatment conditions on the stratification variables (in this case, sex and polarity of mood episode at intake). During baseline assessments or early in treatment, participants identified an SO who was informed and consented in a similar fashion to participants. SOs participated in treatment (if the participant was randomized to the Integrated Treatment Adherence Program) as described below. Given the adjunctive nature of the intervention and its focus on increasing treatment engagement/adherence, treatment as usual was not restricted in this study. However, for ethical and safety reasons, participants in both conditions were required to have at least an outpatient medication provider. Referrals were provided to obtain other services (e.g., counseling) as needed.

2.2.1. Enhanced Assessment and Monitoring—Given that no previously-published studies have established effective interventions for the inpatient-to-outpatient transition in BD-SUD samples, we chose to compare our intervention to what was essentially an enhanced treatment-as-usual condition. Participants in the Enhanced Assessment and Monitoring condition were administered a battery of interviewer-rated and self-report assessments as part of study procedures. Based on the information collected, patients' medication and other outpatient providers (if applicable) were mailed brief feedback letters after each study assessment, thus making this condition one of *enhanced* monitoring. Releases of information were obtained for all such contacts. Letters included information on

the patient's overall status in the study, adherence, substance use, BD symptoms, and suicidality. This systematic assessment feedback was designed to improve treatment outcomes (Kashner, et al., 2003; Yeung, et al., 2012), minimize differences in expectancies for improvement between conditions, and ensure ethical care. If immediate safety concerns (e.g., bipolar/substance relapse, self or other harm) were identified during the assessments, participants were assessed further by a licensed clinician. Possible responses included referral for immediate evaluation for psychiatric rehospitalization or discussion with the person's outpatient provider or SO to ensure safety. We also provided study participants in the Enhanced Assessment and Monitoring condition with referrals to additional community treatment if requested or recommended based on the results of the assessments.

2.2.2. Integrated Treatment Adherence Program—The Integrated Treatment Adherence Program is explained in detail in the report of the previous open trial (Gaudiano et al., 2011). Briefly, the Integrated Treatment Adherence Program is a novel, cognitive-behavioral approach that seeks to promote successful transition from acute care to maintenance treatment by fostering treatment engagement, supporting post-discharge sobriety, and helping patients stay safe, monitor symptoms, and get support from family and providers. Treatment integrates individual and family/SO meetings, via both in-person and telephone-delivered sessions. The Integrated Treatment Adherence Program is based on the Family Intervention Telephone Tracking (FITT) program (Bishop et al., 1997) and Acceptance and Commitment Therapy, a “third wave” cognitive-behavioral therapy (ACT; Hayes et al., 1999). A key component of the intervention involves discussing and clarifying participants' personal values, and setting goals and choosing behaviors (e.g., treatment adherence, sobriety) that are in line with those values. Treatment also includes informal problem-solving and encourages increased communication between patients, SOs, and their non-study treatment providers. The focus on transition from acute to maintenance care, inclusion of family/SO meetings and telephone-delivered sessions, and the integration of elements of FITT and ACT (especially the focus on personal values) are unique to the Integrated Treatment Adherence Program; previous interventions for BD-SUD populations have not included these components.

In the current study, the Integrated Treatment Adherence Program spanned 6 months and was comprised of: 1) 3, hour-long, individual in-person sessions, 2) 1 hour-long in-person family session with the identified study SO, and 3) a target of 11 brief (15-30 minute-long) phone contacts, held separately with the participant and his/her SO. Telephone contact was provided weekly for the first month after the 4 in-person contacts, and then at a decreasing frequency for the remaining months. Individual in-person sessions focused on treatment and psychiatric history, psychoeducation about BD and treatment adherence, discussion of personal values and goals clarification, formulation of value-consistent treatment goals, and completion of a “Life Plan” document. The Life Plan sought to clarify important life goals in line with patients' core values, potential obstacles to achieving these goals and appropriate corrective action, early warning signs for relapse, and a safety plan. The in-person family meeting was used to provide the SO with psychoeducation about BD, substance use, and treatment adherence; to identify ways that the SO could appropriately support and assist in the participant's treatment; and to review the Life Plan document.

Subsequent telephone contacts with participants and SOs included a review of symptoms, substance use, and ongoing treatment, as well as identification of current challenges and use of relevant values and goals to guide problem-solving. Community treatment providers in the Integrated Treatment Adherence Program condition also were provided with regular feedback letters on participants' progress similar to those in the Enhanced Assessment and Monitoring condition (see description above).

The Integrated Treatment Adherence Program was provided by doctoral-level clinicians. Study therapists attended an initial didactic presentation on the Integrated Treatment Adherence Program, read relevant training materials, and participated in role plays and reviewed sample session recordings until the investigators judged that they were competent to deliver the Integrated Treatment Adherence Program. More intensive individual supervision was provided for study therapists by the investigators for their initial cases, and weekly group meetings were held for ongoing case review. Sessions were audio recorded and therapists' treatment integrity (i.e., therapists' adherence to the intervention) was determined using a rating instrument developed from the Integrated Treatment Adherence Program treatment manual (Gaudiano et al., 2011) that assessed their delivery of specific components of the protocol (e.g., values clarification; goal setting; informal problem solving; symptom substance abuse, and adherence monitoring; creation of the individualized "Life Plan" document) for the various in-person, telephone, and significant other sessions. During the earlier development of the treatment integrity scale, 20 sessions were rated by at least two raters. One rater was the "gold standard rater" (i.e., one of the intervention developers). There was 100% agreement between raters regarding the overall acceptability of the session, with kappas for individual items also very high (0.80-1.0). In the current study, approximately 10% of available session recordings ($n = 20$) were randomly selected and rated by the intervention developers. Overall study therapists' treatment integrity was high, with average adherence to the specific components of the protocol of 93.8% for the in-person sessions, 100% for the patient telephone sessions, and 100% for the significant other sessions. These results suggest that study therapists were able to reliably follow the treatment protocol.

2.3. Measures

At baseline, the mood and substance use modules of the *Structured Clinical Interview of DSM-IV* (SCID) (First et al., 2002) and the antisocial and borderline personality disorder sections of the SCID-II (First et al., 1997) were administered to determine diagnoses and study eligibility. The clinician-rated Quick Inventory of Depressive Symptoms-Clinician Rated (QIDS-C; Rush et al., 2003) is a reliable and validated 16-item, interview-based measure of severity of depressive symptoms. The *Clinician-Administered Rating Scale for Mania* (CARS-M; Altman et al., 1994) is a reliable and valid 15-item, interview-based measure of manic and psychotic symptoms. The *Timeline Follow-Back* (TLFB; Sobell and Sobell, 1996) assesses daily self-reported drug and alcohol use over a specified time period (in the current study, the 6 months prior to baseline and the 3 months prior to the 3 and 6-month assessments). "Heavy drinking days" were defined as 5 drinks/day for men and 4 drinks/day for women based on standard guidelines (SAMHSA, 2006). We administered an adapted form of the *Treatment History Interview* (THI; Linehan, 1987), which assesses

recent mental health care service utilization, including emergency room visits, inpatient admissions, and type of outpatient care. The *Valued Living Questionnaire* (VLQ; Wilson et al., 2010) is a reliable and valid self-report measure that assesses consistency between a person's individual values across 10 domains and his or her daily activities. The brief version of the World Health Organization Disability Assessment Schedule (WHODAS 2.0; Andrews et al., 1999) is a 12-item self-report measure that has evidence of reliability and validity for assessing various aspects of psychosocial and physical disability. Approximately one third of our sample was unemployed; therefore, we replaced the item assessing work impairment with the mean item score in these cases. The *Credibility and Expectancy Scale* (CES) is a reliable and valid self-report measure of patients' initial expectancies for improvement from treatment that has been used in numerous previous clinical trials (Deville and Borkovec, 2000). Of note, we used the scoring procedure described by Nock and colleagues (2007) for the CES.

We administered an adapted version of the *Medication Compliance Questionnaire* (MCQ), which has been used in previous bipolar treatment studies (Lam et al., 1996; Gaudiano et al., 2011). Patients were asked to report the number of missed doses or instances of over-use of their prescribed mood-stabilizing agent each month between assessment points. Only one participant in our sample reported over-use of medication at baseline. Thus, in our analyses, medication "nonadherence" was defined in terms of missed medication doses only. Specifically, and consistent with MCQ anchors, we looked at degree of nonadherence for participants' primary mood stabilizing medication (0 = never missed, 1 = missed once or twice, 2 = missed 3-7 times, 3 = missed > 7 times, 4 = stopped completely) as well as categories of adherence (missed 0-2 times versus missed 3 or more times or stopped the medication against medical advice). Based on the MCQ, we also created a companion *Treatment Adherence Form* (TAF; Gaudiano et al., 2011) that similarly assessed mental health treatment appointments missed each month between assessment points. From the TAF we calculated percent of scheduled appointments that the participant missed, as well as whether the participant stopped a treatment against medical advice.

At 3 and 6-month assessments, participants again completed the QIDS-C, CARS-M, TLFB, MCQ, TAF, THI, VLQ, and WHODAS 2.0. At 6 months, participants also completed the *Client Satisfaction Questionnaire-8* (CSQ-8), a reliable and valid 8-item self-report measure that evaluates satisfaction with services (Larsen et al., 1979). Finally, at baseline, 3-month, and 6-month assessments, study SOs estimated participants' medication adherence and appointment attendance using adapted versions of the MCQ and TAF.

2.4. Overview of Statistical Analyses

All analyses were conducted using SPSS 22.0 and HLM 6.01 software. HLM is preferable to other methods such as repeated measures analysis of variance in studies with small sample sizes and missing data, because it accounts for missing data at level 1 using listwise deletion. To circumvent the effects of non-random attrition, we conducted intent-to-treat analyses (instead of completers-only analyses) on all randomized participants. We used a multilevel modeling design (Bryk and Raudenbush, 1992) to predict treatment outcomes as a function of time (at level 1) and treatment condition (at level 2, controlling for baseline mood state).

For example, the level 1 regression equation modeling the relationship between time point and depression is:

$$QIDS - C_{ij} = \pi_{0i} + \pi_{1i} (TIMEPT_{ij}) + e_{ij}$$

where $QIDS - C_{ij}$ is participant i 's QIDS-C score at assessment j ; π_{0i} is the intercept (participant i 's QIDS-C score at time 0, i.e., baseline); π_{1i} is the slope (the change in participant i 's QIDS-C score for every one unit increase in time point, i.e., from one assessment to the next); and e_{ij} is the error term for person i . At level 2, we estimate how treatment condition affects QIDS-C scores over time. Level-1 parameters (intercept and slope) are modeled as a function of their own intercept components, slope components, and random error components:

$$\begin{aligned}\pi_{0i} &= b_{00} + b_{01} (TX) + b_{02} (MOODST) + r_{0i} \\ \pi_{1i} &= b_{10} + b_{11} (TX) + b_{12} (MOODST) + r_{1i}\end{aligned}$$

MOODST (but not TX) is grand mean centered. Thus, b_{00} represents QIDS-C score at baseline for the average participant in Enhanced Assessment and Monitoring, b_{01} is the change (i.e., from b_{00}) in baseline QIDS-C score for the average participant in the Integrated Treatment Adherence Program, and b_{02} is the change in baseline QIDS-C score for participants who were in a manic (vs. depressed) episode at baseline. Similarly, b_{10} represents the change in QIDS-C scores over time for the average participant in Enhanced Assessment and Monitoring, b_{11} is the change in this relationship between QIDS-C scores and time for the average participant in the Integrated Treatment Adherence Program (vs. Enhanced Assessment and Monitoring), and b_{12} is the change in the relationship between QIDS-C scores and time for participants who were in a manic (vs. depressed) episode at baseline.

3. Results

3.1. Sample Characteristics

Table 1 depicts sample characteristics. Equal numbers of men and women were included, with the average age of participants being in the mid-40s. Participants were largely white, non-Hispanic, unmarried, and had completed at least some college. On average, participants had made one suicide attempt and had been hospitalized for psychiatric reasons about 3 times. Baseline treatment adherence was relatively good. The majority of participants had a Bipolar I diagnosis and were recruited from inpatient units. Slightly more than half were in a depressed episode at baseline; among these participants, depressive symptoms fell in the severe to very severe range. Among participants who were in a (hypo)manic episode at baseline, manic symptoms fell in the moderate range. Clinically significant disability was the norm across the sample. All but one participant had a lifetime diagnosis of alcohol dependence, and most participants also had at least one lifetime drug use diagnosis, with the most commonly-abused drugs being cocaine, cannabis, and opioids. Drug and alcohol use were prevalent in the month prior to study enrollment.

3.2. Participant Flow

Figure 1 depicts participant flow. A total of 113 participants were initially consented and began baseline assessments to determine study eligibility. Forty-four patients did not meet inclusion criteria, the most common reason being presence of borderline or antisocial personality disorder with therapy-interfering behaviors ($N = 30$; 68%). Thirty-one did not complete baseline measures or were otherwise lost to follow-up prior to randomization, and 8 withdrew prior to randomization. This left 30 participants in our intent-to-treat (ITT) sample (Integrated Treatment Adherence Program = 14; Enhanced Assessment and Monitoring = 16). Of these, 22 (Integrated Treatment Adherence Program $n = 10$, Enhanced Assessment and Monitoring $n = 12$) completed study procedures ($\chi^2 = 0.05$, $df = 1$, $p = 0.83$): 2 (Integrated Treatment Adherence Program $n = 1$, Enhanced Assessment and Monitoring $n = 1$) withdrew, 5 (Integrated Treatment Adherence Program $n = 2$, Enhanced Assessment and Monitoring $n = 3$) were lost to follow-up, and 1 (Integrated Treatment Adherence Program) died of natural causes. The majority of participants ($n = 22$; Integrated Treatment Adherence Program = 11, Enhanced Assessment and Monitoring = 11) identified a study SO who also participated.

3.3. Treatment Received

Participants in the Integrated Treatment Adherence Program condition completed an average of 2.71 ($SD = 0.73$) in-person individual sessions, 0.36 ($SD = 0.50$) in-person family sessions, and 9.50 ($SD = 4.67$) individual phone sessions. SOs completed an average of 4.07 ($SD = 4.58$) phone sessions. In some cases (i.e., if participants' clinicians were available at the time), participants completed additional, brief, in-person "check-in" sessions at the time of their 3 and 6-month assessments; this occurred for 7 participants (50%) at the 3-month assessment and 5 participants (35.71%) at the 6-month assessment.

In terms of ongoing community treatment, participants reported being prescribed an average of nearly 3 psychotropic medications at baseline (see Table 1). Approximately 25% of the sample met the operational criteria for complex polypharmacy (4 psychotropic medications [Goldberg et al., 2009; Weinstock et al., 2014]). Community treatment consisted of medication management plus additional support for the majority of participants. Additional treatment modalities included individual therapy, group therapy, couples or family therapy, and self-help groups.

3.4. Baseline Differences

Participants randomized to Enhanced Assessment and Monitoring were significantly less medication adherent at baseline than participants randomized to the Integrated Treatment Adherence Program ($t(22) = 2.35$, $p = 0.03$). Therefore, we controlled for baseline degree of medication adherence at level 2 in relevant HLM analyses. Nonparametric tests did not indicate significant baseline differences between Enhanced Assessment and Monitoring and the Integrated Treatment Adherence Program on any other outcome variables or any demographic variables. We controlled for mood state at baseline (depressed vs. mixed/manic) at level 2 in all analyses. We also controlled for presence of a drug/alcohol abuse or dependence diagnosis (current, early partial remission, or early sustained remission) at level 2 in analyses examining relationships between treatment condition and drug or alcohol use.

Finally, since participants were engaged in a wide variety and frequency of treatments outside of study treatment procedures, we controlled for type of community treatment (medication only versus medication plus other treatment) at level 1 in analyses examining relationships between treatment condition and attendance at mental health appointments.

3.5. Treatment Outcomes

At baseline, the average CES total score was 34.13 ($SD = 8.85$) in Enhanced Assessment and Monitoring and 40.07 ($SD = 8.96$) in the Integrated Treatment Adherence Program, out of a possible total of 54 ($t(27) = -1.80, p = 0.08$). At post-assessment (6-month) follow-up, the average CSQ-8 total score was 25.17 ($SD = 4.61$) in Enhanced Assessment and Monitoring and 29.67 ($SD = 2.45$) in the Integrated Treatment Adherence Program, out of a possible total of 32 ($t(19) = -2.65, p = 0.02$). Thus, credibility/expectancy was marginally higher in the Integrated Treatment Adherence Program and overall treatment satisfaction/acceptability was significantly higher in the Integrated Treatment Adherence Program. However, credibility and satisfaction were relatively high in both groups.

Treatment outcomes are reported in Table 2. On average (i.e., across treatment conditions), mania scores, emergency room visits, re-hospitalizations, number of standard drinks, and number of drinking days decreased over time. Heavy drinking days marginally decreased over time. There was a significant effect of treatment condition on change over time in depression scores, mania scores, valued living, and functional impairment, such that participants randomized to the Integrated Treatment Adherence Program saw faster and greater improvements in these outcomes than participants randomized to Enhanced Assessment and Monitoring. Effect sizes were in the medium range for depression scores, the large range for mania scores, the medium-large range for valued living, and the small-medium range for functional impairment. There was a marginal effect of treatment condition on change over time in suicidal ideation, medication adherence (adherent vs. non-adherent), emergency room visits, and days using drugs, again with participants randomized to the Integrated Treatment Adherence Program showing trends toward greater improvement than those in Enhanced Assessment and Monitoring. Figures 2-5 depict changes in depression, mania, value-consistent living, and functional impairment, respectively, over time in Enhanced Assessment and Monitoring versus the Integrated Treatment Adherence Program.

3.6. Significant Other Adherence Ratings

In order to verify the validity of our self-report data, we compared SO estimates of participants' medication adherence (missed 0-2 times vs. missed 3 or more times or stopped a medication against medical advice) and appointment attendance (percent of appointments missed) with participants' own reports of these parameters when data were available. For 13 of 16 participants (81.3%), SO reports of medication adherence were either consistent with participants (i.e., in agreement at least 75% of the time) or involved over-estimation of adherence (i.e., the participant admitted non-adherence when the SO did not suspect it). In terms of appointment attendance, SO reports were consistent with participant self-report for 11 of 13 participants (84.6%). Overall, these patterns support our use of self-report data to measure treatment adherence in the present study.

4. Discussion

The present investigation represents the first RCT to our knowledge of a mid-intensity, primarily telephone-based intervention targeting clinical outcomes at a vulnerable point in care (i.e., the transition from hospital to outpatient treatment) in an acutely ill sample with BD-SUD. Given the high rate of comorbidity between BD and SUDs (Regier et al., 1990) and numerous associated negative outcomes (Salloum and Thase, 2000), this study fills an important gap in the literature. The observed high rates of adherence to the Integrated Treatment Adherence Program suggest that the intervention is implementable in an often challenging and non-adherent, acutely-ill clinical population. At the outset of treatment, credibility and expectancies for improvement were high, as was ultimate satisfaction with the intervention. Coupled with the results of our initial open trial (Gaudiano et al., 2011) and given the emerging interest in telephone-based interventions and potential for reimbursement in the healthcare system to assist patients transitioning from hospital settings (e.g., Richardson et al., 2014), these findings underscore the feasibility and acceptability of this intervention.

Participants in the Integrated Treatment Adherence Program saw significantly greater improvement over time in depression, mania, value-consistent living, and functioning than participants in Enhanced Assessment and Monitoring. The observed effects on mood symptoms and functioning are consistent with a growing body of literature on other adjunctive psychosocial interventions for BD that have integrated cognitive behavioral (e.g., Lam et al., 2003; Gonzalez et al., 2012), psychoeducational (e.g., Perry et al., 1999; Gonzalez et al., 2012) and/or family interventions (e.g., Clarkin et al., 1998; Miklowitz et al., 2003; D'Souza et al., 2010). In a recent review, Reinares and colleagues (2014) identified a number of potential mechanisms of action for such interventions, several of which were targeted in the Integrated Treatment Adherence Program, including enhancing medication adherence, identifying early signs of relapse, and improving family interactions. The Integrated Treatment Adherence Program's use of values clarification techniques and goal-setting in line with participants' identified values is largely unique in the published literature on psychosocial treatment for BD-SUD (although for an exception, see Bauer, 2004, which focuses on similar themes). As such, we were particularly encouraged to see that the Integrated Treatment Adherence Program resulted in significantly greater improvements in value-consistent living than Enhanced Assessment and Monitoring, which was a targeted mechanism of action of our intervention.

In contrast, there were no significant treatment effects on session attendance or alcohol consumption, and treatment effects on medication adherence and drug use were marginal. Participants who received the Integrated Treatment Adherence Program intervention were somewhat more likely than those in the Enhanced Assessment and Monitoring condition to become medication adherent and to use drugs on fewer days over the course of the study period. However, results did not meet conventional standards for statistical significance. There are a number of possible reasons for the subthreshold nature of these findings. Self-reported medication adherence and appointment attendance were relatively high throughout our study, suggesting that a larger sample size would be necessary for investigating treatment effects on these outcomes in the future. Further, previous work in populations with

BD without SUD suggests that adherence is most improved when interventions focus exclusively (Cochran, 1984; Peet & Harvey, 1991) or primarily (Colom et al., 2003) on medication adherence. However, the Integrated Treatment Adherence Program's focus was broader than adherence alone and addressed numerous other topics, including values clarification, problem-solving, safety, communication with family and providers, and substance use behaviors (Gaudiano et al., 2011). It is also possible that our comparison condition (*enhanced* treatment as usual) may have positively impacted both adherence and substance use in that regular assessments and feedback to providers could have indirectly improved participants' adherence with pharmacological regimens and decreased drug and alcohol consumption, thus reducing differences between treatment conditions. Lastly, diagnostic heterogeneity, differences in BD mood state at intake, and variability in community treatment in our sample could have obscured study treatment effects. Future, larger-scale studies examining differential treatment effects on subsets of participants (i.e., those with different substance use diagnoses or in different BD mood states, individuals engaged in different levels or types of outpatient treatment) should be examined.

There are a number of potential limitations to the present study. Our sample size was small given the pilot nature of our study and demographically homogeneous. The Enhanced Assessment and Monitoring condition did not control for time/clinician contact. Most participants reported that their outpatient care consisted of more than just medication management, which is not typical of individuals with BD (Vieta et al., 2013). The intervention was delivered by doctoral-level clinicians, who might not routinely provide care in many community mental health care settings; this might limit the generalizability of our findings. The current study's lack of inclusion of an objective measure of adherence constitutes another limitation. Although there is no "gold standard" method of assessing treatment adherence (Osterberg and Blaschke, 2005), and self-report measures of adherence in BD have in fact been shown to be highly reliable (e.g., Lam et al., 2003), most experts recommend a multi-modal assessment strategy when measuring adherence (Colom et al., 2000; Sajatovic et al., 2004). It is important to note that, when available, collateral information collected from patients' family members supported the validity of self-reported adherence in the current sample. However, future work should include additional methods, such as pill counts, electronic pill bottle caps, pharmacy records, or ecological momentary assessment of adherence-related behaviors (to reduce retrospective recall biases). Although beyond the scope of the current treatment development pilot trial, future work should also include an economic analysis of the intervention, as well as a 12-month follow-up timepoint to examine the longer-term effects of the Integrated Treatment Adherence Program. Finally, given the relatively high prevalence of screen failure in our sample due to presence of a personality disorder with therapy-interfering behaviors, future iterations of the Integrated Treatment Adherence Program should perhaps include such individuals, and may need to specifically address personality pathology.

Despite these limitations, the present study served to establish the feasibility, acceptability, and preliminary evidence of efficacy for one of the only published interventions to date designed specifically for acutely-ill, bipolar, substance-abusing populations. Our findings suggest that the Integrated Treatment Adherence Program is a useful approach for

improving outcomes during the often-challenging transition from inpatient to outpatient care in patients with BD and comorbid SUDs, by promoting value-consistent actions, enhancing functioning, and alleviating mood symptoms. By incorporating certain elements of ACT, the Integrated Treatment Adherence Program aligns well with the newer, “third wave” (Kahl et al., 2012) cognitive and behavioral therapeutic techniques. Such cutting-edge approaches have shown promise in early studies of those with BD and common comorbidities (e.g., Perich et al., 2014) and might constitute particularly useful ways to address transdiagnostic clinical concerns (e.g., values-driven living, behavioral and experiential avoidance). Future, larger-scale trials of this intervention may reveal mediators of the observed effects, as well as establish which patients are most likely to benefit from this type of treatment approach.

Acknowledgements

This work was supported by a Brain and Behavior Research Foundation (formerly NARSAD) 2007 Young Investigator Award, awarded to Dr. Gaudiano, and a National Institute of Drug Abuse Grant DA23072, awarded to Dr. Miller. Preparation of this manuscript was supported by National Institute of Mental Health Grant K23 MH093410, awarded to Dr. Wenze.

References

- Aagaard J, Vestergaard P, Maarbjer K. Adherence to lithium prophylaxis: II. Multivariate analysis of clinical, social, and psychosocial predictors of nonadherence. *Pharmacopsychiatry*. 1988; 21:166–170. [PubMed: 3205885]
- Altman EG, Hedeker DR, Janicak PG, Peterson JL. The clinician-administered rating scale for mania (CARS-M): Development, reliability, and validity. *Biological Psychiatry*. 1994; 36:124–134. [PubMed: 7948445]
- Andrews G, Kemp A, Sunderland M, Von Korff M, Ustun TB. Normative data for the 12 item WHO Disability Assessment Schedule 2.0. *PloS One*. 2009; 4:e8343. [PubMed: 20020047]
- Bauer, MS. Psychological treatment of bipolar disorder. In: Johnson, SL.; Leahy, RL., editors. *Supporting Collaborative Practice Management: The Life Goals Program*. The Guilford Press; New York: 2004. p. 203-225.
- Bishop, D.; Evans, R.; Miller, I.; Epstein, N.; Keitner, G.; Ryan, C.; Johnson, B. Family intervention: Telephone tracking: A treatment manual for acute stroke. Brown University Family Research Program; Rhode Island: 1997.
- Brady K, Casto S, Lydiard R, Malcolm R, Arana G. Substance abuse in an inpatient psychiatric sample. *The American Journal Of Drug And Alcohol Abuse*. 1991; 17(4):389–397. [PubMed: 1746501]
- Brady KT, Sonne SC. The relationship between substance abuse and bipolar disorder. *Journal of Clinical Psychiatry*. 1995; 56(Supplement 3):19–24. [PubMed: 7883738]
- Bryk, AS.; Raudenbush, SW. *Hierarchical linear models*. Sage publications; California: 1992.
- Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. *Bipolar Disorders*. 2001; 3:181–188. [PubMed: 11552957]
- Castle DJ, Berk L, Lauder S, Berk M, Murray G. Psychosocial interventions for bipolar disorder. *Acta Neuropsychiatrica*. 2009; 21(6):275–284.
- Clarkin JF, Carpenter D, Hull J, Wilner P, Glick I. Effects of psychoeducational intervention for married patients with bipolar disorder and their spouses. *Psychiatric Services*. 1998; 49:531–533. [PubMed: 9550248]
- Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *Journal of Consulting and Clinical Psychology*. 1984; 52:873–878. [PubMed: 6501672]
- Cohen, JE. *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Associates, Inc.; New Jersey: 1988.

- Colom F, Vieta E, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *Journal of Clinical Psychiatry*. 2000; 61:549–555. [PubMed: 10982196]
- Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea J, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corminas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of General Psychiatry*. 2003; 60:402–407. [PubMed: 12695318]
- Degenhardt L, Whiteford HA, Ferrari AJ, Baxter A, Charlson F, Hall W, Freedman G, Burstein R, Johns N, Engell R, Flaxman A, Murray C, Vos T. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013; 382(9904):1564–1574. [PubMed: 23993281]
- Devilley GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*. 2000; 31:73–86. [PubMed: 11132119]
- D'Souza R, Piskulic D, Sundram S. A brief dyadic group based psychoeducation program improves relapse rates in recently remitted bipolar disorder: a pilot randomized controlled trial. *Journal of Affective Disorders*. 2010; 120:272–276. [PubMed: 19428117]
- Feinman JA, Dunner DL. The effect of alcohol and substance abuse on the course of bipolar affective disorder. *Journal of Affective Disorders*. 1996; 37:43–49. [PubMed: 8682977]
- First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW.; Benjamin, LS. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II)*. American Psychiatric Press, Inc; Washington, D.C.: 1997.
- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. *Structured Clinical Interview for DSM-IVTR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. New York State Psychiatric Institute; New York: 2002.
- Gaudiano BA, Miller IW. Patients' expectancies, the alliance in pharmacotherapy, and treatment outcomes in Bipolar Disorder. *Journal of Consulting and Clinical Psychology*. 2006; 74(4):671–676. [PubMed: 16881774]
- Gaudiano BA, Weinstock LM, Miller IW. Improving treatment adherence in patients with bipolar disorder and substance abuse: Rationale and initial development of a novel psychosocial approach. *Journal of Psychiatric Practice*. 2011; 17:5–20. [PubMed: 21266890]
- Gaudiano BA, Uebelacker LA, Miller IW. The impact of remitted substance use disorders on the future course of illness in bipolar I disorder: Findings from a clinical trial. *Psychiatry Research*. 2008; 160:63–71. [PubMed: 18514326]
- Goldberg JF. Bipolar disorder with comorbid substance abuse: diagnosis, prognosis, and treatment. *Journal of Psychiatric Practice*. 2001; 7:109–122. [PubMed: 15990511]
- Goldberg JF, Brooks JO, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, Miklowitz DJ, Ketter TA, Sachs GS, Thase ME. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *Journal of Clinical Psychiatry*. 2009; 70:155–162. [PubMed: 19210946]
- Goldstein BI, Goldstein TR, Collinger KA, Axelson DA, Bukstein OG, Birmaher B, Miklowitz DJ. Treatment development and feasibility study of family-focused treatment for adolescents with bipolar disorder and comorbid substance use disorders. *Journal of Psychiatric Practice*. 2014; 20:237–248. [PubMed: 24847999]
- Gonzalez IA, Echeburua E, Liminana JM, Gonzalez-Pinto A. Psychoeducation and cognitive-behavioral therapy for patients with refractory bipolar disorder: a 5-year controlled clinical trial. *European Psychiatry*. 2012; 29:134–141. [PubMed: 23276524]
- Hayes, S.; Strosahl, K.; Wilson, K. *Acceptance and commitment therapy*. The Guilford Press; New York: 1999.
- Kahl KG, Lotta W, Schweiger U. The third wave of cognitive behavioural therapies: What is new and what is effective? *Current Opinion in Psychiatry*. 2012; 25(6):522–528. [PubMed: 22992547]
- Kashner TM, Rush AJ, Suris A, Biggs MM, Gajewski VL, Hooker DJ, Shoaf T, Altschuler KZ. Impact of structured clinical interviews on physicians' practices in community mental health settings. *Psychiatric Services*. 2003; 54:712–718. [PubMed: 12719503]

- Keck PE Jr, McElroy SL, Strakowski SM, West S, Sax K, Hawkins J, Bourne M, Haggard P. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *The American Journal Of Psychiatry*. 1998; 155(5):646–652. [PubMed: 9585716]
- Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry*. 1997; 54:313–321. [PubMed: 9107147]
- Lam D, Bright J, Jones S, Hayward P, Schuck N, Chisholm D, Sham P. Cognitive therapy for bipolar illness: A pilot study of relapse prevention. *Cognitive Therapy and Research*. 1996; 24:503–520.
- Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Archives of General Psychiatry*. 2003; 60:145–152. [PubMed: 12578431]
- Larsen D, Attkisson C, Hargreaves W, Nguyen T. Assessment of client/patient satisfaction: Development of a general scale. *Evaluation and Program Planning*. 1979; 2:197–207. [PubMed: 10245370]
- Linehan, MM. *Treatment History Interview (THI)*. University of Washington; Seattle: 1987.
- Merrall EL, Bird SM, Hutchinson SJ. A record-linkage study of drug-related death and suicide after hospital discharge among drug-treatment clients in Scotland, 1996-2006. *Addiction*. 2013; 108(2): 377–384. [PubMed: 22925008]
- Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the out patient management of bipolar disorder. *Archives of General Psychiatry*. 2003; 60:904–912. [PubMed: 12963672]
- Miller IW, Uebelacker LA, Keitner GI, Ryan CE, Solomon DA. Longitudinal course of bipolar I disorder. *Comprehensive Psychiatry*. 2004; 45:431–40. [PubMed: 15526253]
- Murray, C.; Lopez, A., editors. *The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020*. Harvard University Press; Massachusetts: 1996.
- Nock MK, Ferriter C, Holmberg E. Parent beliefs about treatment credibility and effectiveness: Assessment and relation to subsequent treatment participation. *Journal of Child and Family Studies*. 2007; 16:27–38.
- Osterberg L, Blaschke T. Adherence to medication. *New England Journal of Medicine*. 2005; 353:487–497. [PubMed: 16079372]
- Peet M, Harvey NS. Lithium maintenance: 1. A standard education programme for patients. *British Journal of Psychiatry*. 1991; 158:197–200. [PubMed: 1707323]
- Perich T, Manicavasagar V, Mitchell PB, Ball JR. Mindfulness-based approaches in the treatment of bipolar disorder: Potential mechanisms and effects. *Mindfulness*. 2014; 5(2):186–191.
- Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *British Medical Journal*. 1999; 318:149–153. [PubMed: 9888904]
- Potash JB, Kane HS, Chiu YF, Simpson SG, MacKinnon DF, McInnis MG, McMahon FJ, DePaulo JR Jr. Attempted suicide and alcoholism in bipolar disorder: clinical and familial relationships. *American Journal of Psychiatry*. 2000; 157:2048–2050. [PubMed: 11097977]
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *The Journal of the American Medical Association*. 1990; 264:2511–2518. [PubMed: 2232018]
- Reinares M, Sanchez-Moreno J, Fountoulakis KN. Psychosocial interventions in bipolar disorder: What, for whom, and when. *Journal of Affective Disorders*. 2014; 156:46–55. [PubMed: 24439829]
- Richardson JS, Mark TL, McKeon R. The Return on Investment of Postdischarge Follow-Up Calls for Suicidal Ideation or Deliberate Self-Harm. *Psychiatric Services*. 2014; 65(8):1012–1019. [PubMed: 24788454]
- Rush A, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A

- psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*. 2003; 54(5):573–583. [PubMed: 12946886]
- Sajatovic M, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disorder. *Psychiatric Services*. 2004; 55:264–269. [PubMed: 15001726]
- Salloum IM, Thase ME. Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar Disorders*. 2000; 2:269–280. [PubMed: 11249805]
- SAMHSA. Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings. Office of Applied Studies; Maryland: 2006.
- Schmitz JM, Averill P, Sayre S, McCleary P, Moeller GF, Swann A. Cognitive-behavioral treatment of bipolar disorder and substance abuse: a preliminary randomized study. *Addictive Disorders and Their Treatment*. 2002; 1:17–24.
- Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ. A practical guide to calculating Cohen's f^2 , a measure of local effect size, from PROC MIXED. *Frontiers in Psychology*. 2012; 3:1–6. [PubMed: 22279440]
- Sobell, LC.; Sobell, MB. Timeline followback user's guide: A calendar method for assessing alcohol and drug use. Addiction Research Foundation; Ontario, Canada: 1996.
- Strakowski SM, Keck PE Jr, McElroy SL, West SA, Sax KW, Hawkins JM, Kmetz GF, Upadhyaya VH, Tugrul KC, Bourne ML. Twelve-month outcomes after a first hospitalization for affective psychosis. *Archives of General Psychiatry*. 1998a; 55:49–55. [PubMed: 9435760]
- Strakowski SW, Sax KW, McElroy SL, Keck PE Jr, Hawkins JM, West SA. Psychiatric and substance abuse syndrome co-occurrence in bipolar disorder following a first psychiatric hospitalization. *Journal of Clinical Psychiatry*. 1998b; 59:465–471. [PubMed: 9771817]
- Tohen M, Greenfield SF, Weiss RD, Zarate CA Jr, Vagge LM. The effect of comorbid substance use disorders on the course of bipolar disorder: a review. *Harvard Review of Psychiatry*. 1998; 6:133–141. [PubMed: 10372281]
- Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, Masia M, Ghiani C, Mannu P. Suicide attempts in major affective disorder patients with comorbid substance use disorders. *Journal of Clinical Psychiatry*. 1999; 60(Supplement 2):63–69. and discussion 75–76, 113–116. [PubMed: 10073390]
- Vieta E, Langosch JM, Figueira ML, Souery D, Blasco-Colmenares E, Medina E, Moreno-Manzanaro M, Gonzalez MA, Bellivier F. Clinical management and burden of bipolar disorder: results from a multinational longitudinal study (WAVE-bd). *International Journal of Neuropsychopharmacology*. 2013; 16:1719–1732. [PubMed: 23663490]
- Wei L. An application of an urn model to the design of sequential controlled clinical trials. *Journal of the American Statistical Association*. 1978; 73:559–563.
- Weinstock LM, Gaudiano BA, Epstein-Lubow G, Tezanos K, Celis-Dehoyos CE, Miller IW. Medication burden in bipolar disorder: A chart review of patients at psychiatric hospital admission. *Psychiatry Research*. 2014; 216(1):24–30. [PubMed: 24534121]
- Weiss RD, Griffin ML, Greenfield SF, Najavits LM, Wyner D, Soto JA, Hennen JA. Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. *Journal of Clinical Psychiatry*. 2000; 61:361–367. [PubMed: 10847311]
- Weiss RD, Griffin ML, Kolodziej ME, Greenfield SF, Najavits LM, Daley DC, Doreau HR, Hennen JA. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *American Journal of Psychiatry*. 2007; 164:100–107. [PubMed: 17202550]
- Weiss RD, Griffin ML, Jaffee WB, Bender RE, Graff FS, Gallop RJ, Fitzmaurice GM. A “community-friendly” version of integrated group therapy for patients with bipolar disorder and substance dependence: A randomized controlled trial. *Drug and Alcohol Dependence*. 2009; 104:212–219. [PubMed: 19573999]
- Wilson KG, Sandoz EK, Kitchens J, Roberts ME. The Valued Living Questionnaire: Defining and measuring valued action within a behavioral framework. *Psychological Record*. 2010; 60:249–272.

Yeung AS, Jing Y, Brenneman SK, Chang TE, Baer L, Hebden T, Kalsekar I, McQuade RD, Kurlander J, Siebenaler J, Fava M. Clinical Outcomes in Measurement-based Treatment (Comet): a trial of depression monitoring and feedback to primary care physicians. *Depression and Anxiety*. 2012; 29:865–873. [PubMed: 22807244]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

We evaluated the Integrated Treatment Adherence Program in a pilot RCT.

The Integrated Treatment Adherence Program is an adjunctive psychosocial intervention for bipolar disorder and substance use.

The Integrated Treatment Adherence Program includes individual and telephone sessions for patients and significant others.

The Integrated Treatment Adherence Program improves depression, mania, functioning, and value-consistent living.

The Integrated Treatment Adherence Program is useful for improving outcomes during the post-hospitalization period.

Figure 1. Participant Flow

Figure 2. Changes in Depressive Symptoms^a

^aBased on predicted scores.

Figure 3. Changes in Manic Symptoms^a

^aBased on predicted scores.

Figure 4. Changes in Value-Consistent Living^a

^aBased on predicted scores.

Figure 5. Changes in Functional Impairment

^aBased on predicted scores.

Table 1

Baseline Demographic and Clinical Characteristics

Variable	Integrated Treatment Adherence Program n = 14 <i>M(SD)/N(%)</i>	Enhanced Assessment and Monitoring n = 16 <i>M(SD)/N(%)</i>
Age	47.29(10.83)	46.50(11.03)
Sex (female)	7(50%)	8(50%)
Ethnicity (Hispanic)	1(7.14%)	0(0%)
Race (Caucasian)	12(85.71%)	15(93.75%)
Education (years)	15.35(4.53)	14.06(3.23)
Marital Status (married)	1(7.14%)	5(31.25%)
Income (< \$30,000)	5(35.71%)	7(43.75%)
Lifetime Suicide Attempts	1.00(1.52)	1.13(0.99)
Lifetime Psychiatric Hospitalizations	3.29(1.94)	3.07(1.53)
Outpatient Treatment (medication only)	3(21.43%)	4(25%)
Recruitment Site (inpatient hospital)	13(92.86%)	14(87.50%)
Baseline Mood State (depressed)	6(42.86%)	12 (75%)
Functional Impairment (WHODAS 2.0)	19.18(9.46)	18.52(9.52)
Medications		
Number of Psychiatric Medications	2.84(1.34)	2.81(1.33)
Complex Polypharmacy ^a	3(21.43%)	5(31.25%)
Bipolar Diagnosis		
Bipolar I Disorder	12(85.71%)	11(68.75%)
Bipolar II Disorder	1(7.14%)	3(18.75%)
Bipolar Disorder NOS	1(7.14%)	2(12.50%)
Mood Symptoms		
Depression (QIDS-C ^b)	21.50(3.02)	18.58(4.64)
Mania (CARS-M ^c)	16.75(13.24)	16.75(3.59)
Lifetime Substance Use Diagnosis		
Alcohol Dependence ^d	14(100%)	15(93.75%)
Drug Dependence (with or without comorbid drug abuse)	8(57.14%)	11(68.75%)
Drug Abuse only (no dependence)	3(21.43%)	0(0%)
Categories of Drug Abuse/Dependence		
Amphetamines and stimulants	3(21.43%)	2(12.50%)
Cannabis	5(35.71%)	5(31.25%)
Cocaine	7(50%)	5(31.25%)
Hallucinogens	1(7.14%)	2(12.50%)
Opioid	2(14.29%)	4(25%)
Polysubstance	1(7.14%)	1(6.25%)
Sedative/anxiolytic/hypnotic	1(7.14%)	3(18.75%)
Substance Use, Past Month (TLFB)		

Variable	Integrated Treatment Adherence Program n = 14 M(SD)/N(%)	Enhanced Assessment and Monitoring n = 16 M(SD)/N(%)
Standard Drinks ^e	126.40(104.32)	175.32(164.36)
Days Drinking ^e	15.58(12.15)	19.14(10.17)
Heavy Drinking Days ^e	11.67(10.01)	14.43(12.13)
Days Using Drugs ^f	20.43(11.47)	12.00(14.70)
Primary Mood Stabilizer Adherence, Past Month (MCQ)		
Degree of Adherence ^{g, h}	0.57(0.85)	1.57(1.34)
Adherent ⁱ	11(78.57%)	7(43.75%)
Community Treatment Appointment Attendance, Past Month (TAF)		
Percent of Appointments Missed	0(0)	11.54(29.96)
Stopped Any Treatment Against Medical Advice	1(7.7%)	1(7.7%)

Notes. CARS-M = Clinician-Administered Rating Scale for Mania; MCQ = Medication Compliance Questionnaire; QIDS-C = Quick Inventory of Depressive Symptoms-Clinician-Rated; TAF = Treatment Adherence Form; TLFB = Time Line Follow Back; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0.

^a 4 psychotropic medications (Goldberg et al., 2009).

^b For participants who were in a depressive episode at baseline.

^c For participants who were in a manic/mixed episode at baseline.

^d No participants met criteria for Alcohol Abuse.

^e For participants with current Alcohol Dependence or Alcohol Dependence in early partial or early full remission. "Heavy drinking days" were defined as 5 drinks/day for men and 4 drinks/day for women (SAMHSA, 2006).

^f For participants with a current drug use disorder or a drug use disorder in early partial or early full remission.

^g 0 = never missed, 1 = missed once or twice, 2 = missed 3-7 times, 3 = missed > 7 times, 4 = stopped completely.

^h Significant between-group difference ($p < 0.05$).

ⁱ Never missed or missed once or twice.

Table 2

Multilevel regressions: Effects of treatment condition on change in outcomes over time

Outcome	Average within-person slope (b_{10})	Effect of treatment condition on this slope (b_{11})	f^2 ^a
Bipolar symptoms			
QIDS-C	-0.21 ($SE = 0.22$)	-0.92* ($SE = 0.39$)	0.24
CARS-M	-0.66* ($SE = 0.30$)	-1.19* ($SE = 0.45$)	0.37
SI	-0.05 ($SE = 0.07$)	-0.17 [†] ($SE = 0.09$)	---
Medication adherence (MCQ)			
Degree of adherence	0.07 ($SE = 0.07$)	-0.13 ($SE = 0.09$)	---
Adherent vs. non-adherent	0.02 ($SE = 0.03$)	-0.06 [†] ($SE = 0.04$)	---
Session attendance (TAF)			
Percent of appointments missed	0.25 ($SE = 0.90$)	-1.34 ($SE = 1.20$)	---
Stopped any treatment altogether	-0.00 ($SE = 0.01$)	-0.01 ($SE = 0.02$)	---
Value-consistent living (VLQ)	0.50 ($SE = 1.18$)	4.82* ($SE = 2.09$)	0.31
Service utilization (THI)			
Emergency room visits	-0.16* ($SE = 0.08$)	0.16 [†] ($SE = 0.08$)	---
Re-hospitalizations	-0.22* ($SE = 0.09$)	0.02 ($SE = 0.13$)	---
Substance use (TLFB)			
Number of standard drinks ^b	-14.55* ($SE = 5.92$)	7.19 ($SE = 8.11$)	---
Number of days drinking ^b	-1.53* ($SE = 0.72$)	0.64 ($SE = 0.94$)	---
Number of heavy drinking days ^b	-1.32 [†] ($SE = 0.70$)	0.81 ($SE = 1.04$)	---
Number of days using drugs ^c	-0.08 ($SE = 1.21$)	-1.67 [†] ($SE = 0.83$)	---
Functional Impairment (WHODAS 2.0)	-0.30 ($SE = 0.32$)	-1.84* ($SE = 0.86$)	0.12

[†] $p < 0.10$.* $p < 0.05$.

Notes. CARS-M = Clinician-Administered Rating Scale for Mania; MCQ = Medication Compliance Questionnaire; QIDS-C = Quick Inventory of Depressive Symptoms-Clinician-Rated; SI = suicidal ideation (QIDS-C item 12); TAF = Treatment Adherence Form; THI = Treatment History Inventory; TLFB = Time Line Follow Back; VLQ = Valued Living Questionnaire; WHODAS 2.0 = World Health Organization Disability Assessment Scale 2.0.

^a Cohen's f^2 is a measure of effect size that is appropriate for hierarchical data (Selya et al., 2012). By convention, $f^2 = 0.02$ signifies a small effect, $f^2 = 0.15$ signifies a medium effect, and $f^2 = 0.35$ signifies a large effect (Cohen, 1988).

^b For participants with a current alcohol use disorder or an alcohol use disorder in early partial or early full remission.

^c For participants with a current drug use disorder or a drug use disorder in early partial or early full remission.