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Improving Treatment Adherence in Patients with Bipolar Disorder and Substance Abuse: Rationale and Initial Development of a Novel Psychosocial Approach

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Abstract

Patients with comorbid bipolar and substance use disorders are at particularly high risk for treatment nonadherence and a host of negative consequences. However, no previous interventions have been designed specifically to address this problem. In the current study, we describe the rationale for and initial development of an adjunctive, psychosocial intervention that targets adherence in patients with bipolar disorder who are substance abusers. The intervention involves brief in-person sessions and follow-up phone contacts with the patient and a significant other/family member. We describe the effects of this novel intervention on adherence and other psychiatric outcomes in a series of cases treated as part of our initial development work. Results suggest that the intervention is feasible and acceptable to patients and could be helpful in enhancing the effects of existing treatments. Given these promising results, we plan to test the intervention further in a randomized clinical trial.

Keywords

bipolar disorder; substance use disorders; treatment adherence; treatment development

Introduction

Comorbid substance use disorders (SUDs) are more prevalent in patients with bipolar disorder than in any other psychiatric group.[1-3] The Epidemiologic Catchment Area study reported that over 60% of individuals with bipolar disorder have a lifetime history of co-occurring SUDs.[4] Brown et al. reported rates of SUDs in patients with bipolar disorder ranging from 14%-65% in treatment settings.[5] Comorbid substance abuse is associated with an earlier age of onset of the bipolar illness, higher frequency of mood episodes, greater persistence of symptoms between mood episodes, longer time to recovery, shortened time to relapse, greater severity of both depression and mania, more mixed and rapid cycling episodes, greater disability, and higher mortality rates.[6,7] Furthermore, substance abuse in patients with bipolar disorder is associated with increases in violence[8] and psychiatric rehospitalizations,[9-11] as well as poorer psychosocial outcomes[12,13] compared with bipolar disorder without SUDs. In addition, patients with bipolar disorder and comorbid SUDs are

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more likely to attempt suicide than patients with bipolar disorder who do not have comorbid SUDs.[10,12,14] Gaudiano et al. found that even a history of an SUD, in the absence of a current SUD, was associated with poorer acute treatment response, a longer time to remission of an acute mood episode, and a greater percentage of time with clinically significant mood symptoms.[15]

Treatment adherence is defined as "The extent to which a person's behavior… corresponds with agreed recommendations from a healthcare provider."[16] Between 20% and 60% of patients with bipolar disorder are nonadherent to medication.[17,18] For example, Scott and Pope found that 32% of patients with bipolar disorder who were prescribed mood stabilizing medication had been nonadherent within the past month and that 50% had been nonadherent during the previous 2 years.[19] Medication nonadherence is associated with a number of negative outcomes in bipolar disorder.[20] Scott and Pope prospectively followed 98 patients with bipolar disorder over 18 months and found that significantly more patients with subtherapeutic (81%) compared to therapeutic (9%) blood levels of mood stabilizers were hospitalized.[21] In addition, adherence can be defined more broadly to include behavioral adherence, such as keeping treatment appointments and following prescribed lifestyle changes that are recommended as part of treatment.[17] Studies of patients with severe mental illness show high rates of treatment drop out and failure to attend referral appointments.[22-24]

Research has suggested that several factors may have an important relationship with nonadherence in bipolar disorder. These include past history of nonadherence, longer duration of treatment, poor insight into illness, fear of medication side effects, negative beliefs about treatment, poor patient-doctor alliance, certain cultural beliefs, and the presence of psychotic features, mania, and cluster B personality traits.[17-19,25,26] The recent Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study of 3,640 patients also demonstrated that substance abuse predicted poorer adherence and subsequent lower functioning.[27] This findings are consistent with previous research, leading Lingam and Scott to conclude that the most important predictor of nonadherence in bipolar disorder is comorbid alcohol and/or drug abuse.[18] The exact relationship among drug use, treatment nonadherence, and bipolar outcomes is likely complex, reciprocal, and variable. However, substance use appears to predict poor adherence in bipolar disorder, which in turn can lead to a variety of negative outcomes (e.g., bipolar relapse).

Weiss et al. assessed 44 patients with comorbid SUDs and bipolar disorder, using a clinical interview to examine factors related to their medication nonadherence.[28] Side effects were the most frequently cited reason for medication nonadherence. Intriguingly, results also showed that over half of the sample reported nonadherence that involved taking *more* medication than prescribed, either in order to enhance the rapidity of the medication's effects or because of substance intoxication. It also appears that at least a subsample of bipolar patients may "self-medicate" with substances to treat their mood symptoms.[29] For example, Sonne et al. found that 96% of patients with bipolar disorder and substance abuse in their sample reported using drugs and alcohol to improve symptoms.[30] Additional research has also shown that about 25% of bipolar patients increase their alcohol use during mania.[29]

Several different psychosocial treatments, such as family therapy, psychoeducation, and cognitive-behavioral therapy (CBT), have been developed and tested as adjuncts to pharmacotherapy for bipolar patients. Although there are exceptions,[31] studies generally have supported the benefits of adjunctive therapies for improving adherence in at least some areas.[32-34] For example, Cochran conducted a small randomized trial comparing CBT to treatment as usual in a sample of 28 newly admitted outpatients at a lithium clinic.[35] Following 6 weekly group sessions, patients receiving CBT showed superior improvements on several indices of medication adherence at post-treatment and 6-month follow-up.

Clarkin et al. randomized 33 patients with bipolar disorder and their spouses to a psychoeducational intervention or treatment as usual and found greater improvements in the psychoeducational condition in the areas of functioning and medication adherence at 1 year.[36] More recently, Lam et al. randomized 103 patients with bipolar disorder who had experienced frequent relapses to CBT or treatment as usual.[37] Results showed that the patients in the group who received CBT had significantly fewer episodes and improved medication adherence over 12 month follow-up. In addition, Colom et al. reported that 102 bipolar patients randomized to a psychoeducational group showed significantly higher mean serum lithium levels over 24 month follow-up.[38] Miklowitz et al. reported no differences between patients with bipolar disorder who received family-focused therapy compared with crisis management, as measured on a medication compliance index at post-treatment; however, patients in the family condition showed better adherence 1 year post-treatment.[39,40]

Some psychosocial treatments are beginning to be designed specifically for patients with bipolar disorder who are substance abusers. However, these interventions have not been designed primarily to target treatment adherence. Weiss et al. recruited 45 bipolar patients with SUDs in sequential blocks to receive group CBT (up to 20 sessions) or no additional treatment.[41] All patients were receiving outpatient pharmacotherapy and additional community treatments were unrestricted. After 6 months, those receiving CBT showed significantly greater improvements in addiction severity, manic symptoms, and percentage of months abstinent. No group differences in medication adherence were found; although overall adherence in the sample was good. Weiss et al. later conducted a follow-up study of a briefer version of the intervention.[42] They randomly assigned 61 patients to either 12 sessions of integrated group therapy or group drug counseling. Results showed trends favoring the integrated group in terms of improvements in substance abuse and mood episodes. Again, no differences in treatment adherence were found between the groups. In another study, Schmitz et al. randomly assigned 46 patients with bipolar disorder and SUDs to either 12 weeks of low-intensity medication monitoring alone or in combination with CBT.[43] Although treatment retention was low in both groups, significantly more patients completed CBT (60%) than medication monitoring alone (33%). No differences in drug or alcohol use were found between groups. Although the group receiving CBT showed somewhat better medication adherence, group differences were not significant.

In summary, the rate of co-occurrence of SUDs and bipolar disorder is extremely high, and patients with such comorbidity often exhibit poorer treatment adherence and a worse course of illness compared to patients with bipolar disorder who do not have SUDs. Adjunctive psychosocial interventions have been shown to be helpful for improving treatment adherence and outcomes in both bipolar and SUDs samples. However, little research has been done on feasible and effective psychosocial treatments for patients with bipolar disorder who abuse substances. Further, no intervention to date has been designed specifically to improve treatment adherence in the population of patients with comorbid bipolar disorder and SUDS, even though nonadherence is associated with a variety of negative outcomes. This article describes the development of a novel psychosocial approach targeting treatment adherence that is tailored for patients with bipolar disorder who are substance abusers. We call our approach the Improving Treatment Adherence Program (ITAP). In this article, we present outcome data from an initial series of cases to illustrate the potential utility of this intervention. We also describe the lessons learned from this preliminary work and our plans to test the treatment further in a randomized controlled trial.

Developing the ITAP Intervention

Target Population

Although treatment nonadherence occurs across a wide range of medical and psychiatric populations, we chose to develop an intervention specifically for initially hospitalized patients with bipolar disorder who are substance abusers. First, both SUDs and bipolar disorder are associated with high nonadherence rates, and the combination of these two conditions creates even greater risk for nonadherence. Second, although research has demonstrated the efficacy of psychosocial interventions for improving outcomes in high-risk populations of individuals with affective disorders, very little research has investigated treatments for patients with bipolar disorder who are substance abusers, even though these patients have a worse course of illness than patients with bipolar disorder who do not have SUDs. Third, hospital discharge is associated with a particularly heightened risk for nonadherence and other negative outcomes for patients with bipolar disorder who are substance abusers (e.g., suicidality, mood and drug relapse, rehospitalization).[20,44]

Treatment Parameters

The first decision was whether the treatment should be “primary” or “adjunctive.” Given our focus on improving treatment adherence, we were concerned that a “primary” intervention would: a) dilute the specific focus on treatment adherence, b) require the development of an intensive and therefore more costly intervention, and c) limit generalizability and applicability of the intervention to a wide range of patients. Thus, ITAP was designed to be used as an adjunctive intervention; other treatment is not restricted and is encouraged based on the patient's specific needs. Referrals for additional treatment are provided by the ITAP therapist as needed.

Another decision concerned the intensity of the intervention. From one perspective, a more intensive intervention may increase the probability of identifying treatment effects and may be useful due to the severity of the illness in this population. Alternatively, an intensive intervention is likely to have limitations in generalizability and transportability to “real-world” clinical settings. Also, given our decision to develop an adjunctive intervention, we did not want our treatment to conflict or interfere with patients' other ongoing treatments. Finally, some studies have obtained positive results for treatment adherence using relatively low-intensity interventions.[45,46] Weighing these factors and given the severity of illness in this patient population and the adjunctive nature of the proposed intervention, we decided to pursue the “middle ground” and develop a treatment that was more extensive than some low-intensity interventions (e.g., 1-2 sessions), but that was less intensive than “full-scale” psychotherapy (e.g., 12-20 in-person sessions).

Attrition is a concern with this population. We expected that telephone contacts with patients, as well as inclusion of a significant other in the treatment, would help maximize adherence to ITAP as well as to community treatment. ITAP telephone contacts have greater flexibility than typical in-person treatment contacts. Contacts can, if necessary, be made in the evenings or on weekends, and the therapist can make multiple outreach attempts via phone if a patient misses a scheduled call. Such contacts are also useful for reminding and urging patients to attend their in-person sessions with outpatient clinicians. Our experience has shown that inclusion of a significant other in these contacts helps improve adherence and provides important collateral information to help inform the clinical decisions of the ITAP therapist. Telephone interventions are also relatively cost-effective, have been found effective in a number of disorders, including mood disorders and SUDs,[47-53] and have been used by our research team in previous trials.[54,55]

Finally, we chose to focus our treatment on the 6 months following discharge from the hospital. Studies that have followed the longitudinal course of illness in initially hospitalized patients with bipolar disorder have found a high risk of nonadherence and relapse immediately following discharge.[20,44,56,57] Evidence also suggests that the first 6 months following hospital discharge is a time when patients are at particularly high risk for negative outcomes such as suicide.[58]

Treatment Targets

Available research suggests that treatment adherence is a multi-determined phenomenon. Therefore, we used a "risk reduction" theory of treatment similar to that used in prevention and treatment efforts for coronary artery disease[59-61] and diabetes.[62-64] These risk-reduction models are based on two primary assumptions. First, modifying identified risk factors will decrease the incidence of the unwanted outcome (e.g., a heart attack). Second, the more risk factors that are modified, the lower the risk of the unwanted outcome. Several large-scale studies have demonstrated the utility of this approach.[65-68] Our intervention for improving adherence in patients with bipolar disorder and comorbid SUDs is based on similar theoretical assumptions. Therefore, we hypothesized that an intervention that addresses multiple risk factors for nonadherence would increase adherence behaviors. We then expected that an increase in treatment adherence would contribute to improved symptomatic and functioning outcomes for these patients.

Some of the known predictors of nonadherence are relatively static and difficult or impossible to change (e.g. historical and demographic variables). Thus, we selected malleable intervention targets related to adherence. In the following section, we describe and provide a rationale for each of the proposed treatment targets: 1) substance use behaviors, 2) communication with family and providers, 3) effective problem solving, and 4) safety issues (e.g., suicidality).

Substance use behaviors—As discussed in the introduction to this paper, numerous studies have shown that substance abuse is a strong predictor of treatment nonadherence and poor outcomes in patients with bipolar disorder. Patients being treated for both bipolar disorder and an SUD appear to have unique clinical issues requiring a tailored intervention.[69] For example, while a patient with bipolar disorder and substance abuse may believe that medications are effective, he or she may fear the negative consequences that could result from combining medications with illicit drugs and discontinue medications while abusing substances. In addition, some patients with bipolar disorder may be using illicit drugs to "self-medicate." Drug and alcohol abuse can, of course, exacerbate the symptoms of bipolar disorder. Furthermore, some patients may abuse prescribed medications, such as benzodiazepines. Finally, interactions between psychotropic medications and illicit drugs can increase the likelihood of serious side effects and medical complications. Thus, decreasing substance use is likely to lead to better treatment adherence and health outcomes.

Communication with family and providers—Family members and significant others can provide important "cues to action" for supporting and encouraging treatment adherence in patients with both bipolar disorder and SUDs. Unfortunately, fractured family relations, such as those commonly found in substance abusing populations,[70] can have a negative impact on patients' social support and motivation for change. Families of patients with bipolar disorder also often experience significant family problems.[71] Relationships with healthcare providers are also critical for promoting adherence to treatment in patients with bipolar disorder. Research has demonstrated that the quality of patients' working alliance with treatment providers is predictive of adherence and other clinical outcomes in bipolar

disorder[25,57] and SUDs.[72] We therefore hypothesized that fostering increased support and communication between the patient, his or her significant others, and treatment providers would help improve adherence behaviors.

Effective problem solving—Scott et al. found that patients with bipolar disorder had significant deficits in their ability to generate solutions to social problem-solving tasks.[73] Psychosocial treatments for bipolar disorder typically teach patients to identify problematic symptoms and behaviors so that action can be taken to prevent relapse.[74] Research suggests that such interventions can improve patients' knowledge and awareness of their illness.[75-77] Research has also shown that stressful life events can affect the course and severity of bipolar illness.[78] Thus, it is important that patients learn effective strategies for problem solving to deal with psychosocial stressors and other treatment obstacles in order to reduce potential barriers to adherence.

Safety issues—Patients with bipolar disorder and comorbid substance abuse are almost twice as likely to have a lifetime history of a suicide attempt as patients with bipolar disorder without substance abuse.[12] They are also at higher risk for developing HIV/AIDS and being nonadherent to antiretroviral treatment.[79-81] Concurrent substance abuse in patients with bipolar disorder may also increase the likelihood of engaging in other risky and impulsive behaviors that can increase life stress (e.g., financial debt) or even result in lethal outcomes (e.g., violence). Therefore, it is important that a treatment designed for patients with bipolar disorder and substance abuse include a risk reduction plan for dealing with unsafe/risky patient behaviors that can have an impact on treatment adherence.

Program Description

Given our overall “risk reduction” approach and our choice of risk factors to be addressed, the question arose whether ITAP should focus on a single psychotherapeutic approach or should integrate multiple approaches. Although use of a single psychotherapy approach has the advantages of conceptual clarity, ease of integration of different components, and simplicity, we did not think a single approach could optimally address each of the relatively distinct risk factors that had been identified. Increasing evidence from our own[82,83] and other studies[84-94] also indicates that treatment programs that include significant others/ family members can increase treatment efficacy. We therefore decided to integrate a novel cognitive-behavioral approach adapted from Acceptance and Commitment Therapy[95] and the significant other/family intervention described in the Family Intervention Telephone Tracking (FITT) program.[96] The ITAP intervention thus involves a hybrid of traditional psychotherapy and case management services, delivered in three formats: 1) individual sessions, 2) a meeting with a significant other and/or a family member, and 3) a series of telephone follow-up contacts with the patient and his or her significant other. ITAP targets multiple factors related to treatment nonadherence and other poor outcomes in patients with bipolar disorder who are substance abusers. A detailed outline of ITAP is presented in Table 1.

Clarification of Values and Goals

Acceptance and Commitment Therapy, which was developed as a “next generation” cognitive-behavioral treatment, has been shown to be efficacious in a wide range of psychiatric populations,[95] including in patients with depressive, psychotic, and substance use disorders.[98] One component of Acceptance and Commitment Therapy focuses on values clarification. The relationship between values and behavior is particularly relevant when dealing with patients who are questioning if life is worth living, and who have difficulty adhering to difficult treatment plans. Acceptance and Commitment Therapy proposes that a

discussion and clarification of patient values can facilitate motivation and compliance in behavior therapies.[99] Values are defined as broad, personally defined verbal constructs that provide the context for more specific behaviorally consistent goals. Goals represent narrowly defined desired consequences that can be impeded by various internal and external factors. In contrast, broadly defined life values help to guide and direct behavior in the face of obstacles to goal attainment, thereby fostering greater flexibility in dealing with life challenges. Values also provide a personal rationale that can help motivate individuals to remain committed to desired actions, even if they are associated with other undesirable consequences (e.g., the intentional production of hyperarousal symptoms in the treatment of panic). Procedures have been developed to clarity values and goals in order to assess and decrease discrepancies between patient values and daily actions.

Values work serves several purposes in ITAP. First, the distinction between long-term values and short-term goals, and between living in accordance with values versus meeting detached goals, helps to reduce hopelessness and provide a framework for treatment planning and adherence. Second, it provides a collaborative framework between patient and therapist, since the focus is on the patient defining his or her own values. Third, values clarification is likely to help provide patients with a more personally compelling rationale for broadening desirable behavioral repertoires in the face of both perceived and real obstacles that often accompany such pursuits. As part of values clarification work, adherence is conceptualized as a set of behaviors that can facilitate other important life goals and can help the person better succeed with them. Perceived problems that arise with the patient's medication regimen and treatment plan are addressed using the problem-solving strategies described below. For a more detailed discussion of values work in Acceptance and Commitment Therapy, see Wilson and Murrell.[99] In the ITAP intervention, the culmination of the in-person sessions is the development of an individualized “Life Plan” document, which integrates the patient's values with his or her behavioral goals in a structured way and provides a framework for the upcoming phone calls that comprise the remainder of the treatment.

Family Intervention Telephone Tracking

Family Intervention Telephone Tracking (FITT)[54,55] was developed based on the McMaster Model of Family Functioning[100,101] and is designed to improve problem solving among patients with chronic illness and their significant others. FITT consists of a single “in-person” family meeting followed by a series of telephone contacts between a therapist and the identified patient and his or her significant other. Telephone contacts are structured a) to identify, monitor, and address problems in key areas relevant to the patient's disorder and b) to provide additional support, and c) to facilitate informal problem solving. The FITT intervention has been found effective in improving family functioning and overall health status in stroke patients and their caregivers,[55] as well as in reducing burden in dementia caregivers.[54]

The structure of the FITT telephone contacts and the overall therapeutic stance of FITT fit well with the objectives of ITAP in several ways. First, the telephone contacts with both patient and significant other (separately) and the focus on increasing communication between patient and significant other increase levels of social/family support. Second, the regular phone calls allow routine monitoring of the patient's levels of substance use and other important factors. Third, the problem-solving stance of FITT increases patient and significant other problem solving. Finally, the focus on providing support and problem solving regarding obtaining community treatment increases treatment adherence. The problem-solving strategies central to FITT target patients' perceived barriers to treatment adherence. FITT strategies designed to improve communication among patient, significant other, and treatment provider also improve external cues to action. Internal cues to action are

addressed though FITT's ongoing assessment and monitoring procedures, which help patients identify signs of relapse and take preventive steps. In ITAP, brief phone contacts (15-30 minutes each), held separately with patient and significant other, follow the four in-person sessions and are provided weekly for the first month and then at a decreasing frequency for the remaining months, for a target of up to 13 total phone contacts.

Feedback Letters

As part of ITAP, brief 1-page feedback letters are mailed to the patient's other treatment providers on a monthly basis to foster communication and aid in treatment planning. The letters include information on the patient's overall status in the study (e.g., number of sessions attended/missed), as well as information on the intervention targets regularly assessed as a part of the treatment plan (e.g., adherence, substance use, suicidality). This clinical information is obtained from relevant assessments and treatment sessions.

Pilot Study Design

Participants

Subjects for this study were recruited from a psychiatric hospital and met the following criteria: 1) DSM-IV diagnoses of bipolar disorder and substance use disorder (other than nicotine dependence) as determined by Structured Clinical Interview for DSM-IV,[102] 2) 18 years of age or older, and 3) ability to speak and read English sufficiently well to complete the study procedures. Exclusion criteria include: 1) a medical illness severe enough to contraindicate the use of mood stabilizing medication, or 2) pregnancy. Significant others were over 18 years of age and could speak and read English.

Measures

Diagnoses—The *Structured Clinical Interview for DSM-IV Patient Version* (SCID) [102] was administered to determine psychiatric diagnoses.

Treatment adherence—The *Medication Compliance Questionnaire* (MCQ) is a self-report scale designed to assess medication compliance in bipolar patients.[103] Respondents rate their medication adherence according to the following schedule over the past month: never missed, missed once or twice, missed between 3 and 7 times, missed more than 7 times, stopped taking altogether. Research on the reliability of self-reported adherence in bipolar patients indicates generally strong agreement with objective measures of assessment.[19,104]

The *Treatment Assessment Form* (TAF) was created for this study based on the MCQ. Respondents reported the number of treatment appointments (e.g., medication management, psychotherapy) missed and attended per month.

Psychiatric symptoms—The *Clinician-Administered Rating Scale for Mania* (CARS-M)[105] is a 15-item interviewer-rated scale that assesses mania and psychosis. The CARS-M was designed to assess DSM criteria for a manic episode, and has been shown to possess excellent interrater reliability, validity, and sensitivity to change in clinical trials.[105,106] The severity ranges for the CARS-M are: 0-7 = none/questionable, 8-15 = mild, 16-25 = moderate, > 25 = severe. The *Quick Inventory of Depressive Symptomatology-Clinician Version* (QIDS-C) is a 16-item clinical rating scale that assesses depression severity.[107] It has evidence of good reliability and validity.[108] The severity ranges for the QIDS-C are: 0-5 = none, 6-10 = mild, 11-15 = moderate, 16-20 = severe, and 21-27 = very severe.

Substance use—The *Time-Line-Follow-Back* (TLFB)[109] interview was used to assess drug and alcohol use at baseline (in the previous 3 months) and during the 3 and 6 month follow-up intervals. The TLFB interview is a calendar-assisted structured interview that provides a way to cue memory so that accurate recall is enhanced. A structured interview of patients' substance use behavior has been found to be the most reliable and valid method of assessing prior alcohol use.[110]

Collateral information—A close family member or friend was interviewed about the subject's substance use and treatment adherence for each interview period, using a structured *Significant Other Interview* developed for the study.

Treatment acceptability—Finally, the *Client Satisfaction Questionnaire-8* (CSQ-8)[111] is an 8-item scale that yields a total score that reflects a patient's satisfaction with services. Respondents rate their degree of agreement with each item on a 4-point Likert scale. A sample item is: “In an overall, general sense, how satisfied are you with the service you have received?” The CSQ-8 has been used in mental health services research and has evidence of adequate reliability and validity.[112]

Procedure

Charts of newly admitted patients were screened based on study criteria. Approval was obtained from the patient's treating physician to approach the patient. If the patient was interested in the study, the nature, purpose, risks, and benefits of the study were fully explained and informed consent was obtained as approved by the Butler Hospital Institutional Review Board. Once the patient was enrolled, in early sessions with the therapist he or she discussed the involvement of a significant other in the study and informed consent was obtained from that person in a similar fashion. Assessments were conducted at baseline and after 3 and 6 months. Clinical interviewers were trained to achieve initial reliability on the study measures, with periodic checks to ensure continued reliability. Given the adjunctive nature of ITAP and the goal of increasing treatment adherence, treatment as usual was not restricted in the study. The patient was required to have at least an outpatient medication provider. Other psychosocial treatments (e.g., support groups, psychotherapy, substance abuse counseling) were encouraged, and the ITAP therapist helped the patient obtain these services if interested.

Results of Pilot Study

Participant Characteristics

The background characteristics of the four initial patients in this pilot study of ITAP are shown in Table 2. Three patients were male and three were middle-aged. All patients had completed at least a high school degree. Two of the patients had never been married and two were either married or cohabitating. All of the patients were white/non-Hispanic. All of the patients were either receiving disability compensation or were unemployed. Two patients initially received inpatient hospitalization only, while the other two also completed a partial hospital program following their inpatient stay. All patients were diagnosed with bipolar I disorder, three with a most recent manic episode and one with a most recent depressive episode. Three of the patients were diagnosed with alcohol dependence. All patients were diagnosed with drug dependence disorders, which included cocaine, sedatives, and cannabis. Three patients had a romantic partner and one had a friend/roommate serving as the significant other in the program.

Treatment Adherence

Treatment outcomes are presented in Table 3. All patients completed the four initial in-person sessions (which included a family meeting) and 10-12 brief follow-up phone contacts over 6 months. As has been done in other studies,[27] we grouped treatment adherence data into the following categories based on the MCQ: full adherence (100%), partial adherence (< 75% or ≥ 75%), or complete nonadherence (0%). Missing more that a quarter of medication doses per month is typically considered problematic nonadherence in bipolar patients.[19] During the 3 months prior to hospitalization, none of the patients reported full medication adherence. Three patients reported partial adherence and one patient was not taking any psychiatric medications as this person did not have previous treatment providers before entering the hospital. One patient reported no treatment appointments during the baseline period; one patient reported partial adherence and one patient reported full adherence with treatment appointments; and baseline data for appointments were missing for one of the patients. At 3 months, three patients reported full medication adherence and one reported an improvement in adherence; although still not 100%. All patients reported full adherence with treatment appointments at mid-treatment. At 6 months, two patients reported partial medication adherence and two reported full adherence. All patients reported full appointment adherence at 6 months. No patients were rehospitalized during the treatment period. Information from the significant other interviews was consistent with patient reports.

Mood Symptoms and Substance Abuse

The week before hospitalization, one patient fell in the very severe range, one patient fell in the severe range, one patient fell in the moderate range, and one patient fell in the mild range on the QIDS-C.[108] At 3 months, two patients fell in the none/minimal range, one fell in the mild range, and one patient remained in the very severe range on the QIDS-C. At 6 months, three patients fell in the none/minimal range and one patient fell in the mild range.

In terms of the CARSM-M,[105] at baseline, three patients fell in the severe range and one patient fell in the moderate range. At 3 months, two patients fell in the none/questionable range and two patients fell in the mild range. At 6 months, one patient was in the moderate range and three patients were in the none/questionable range.

In terms of substance use as assessed by the TLFB, three patients reported excessive alcohol consumption (in terms of number of standard drinks) and all patients reported drug abuse during the baseline period. At 3 months, two patients denied any alcohol or drug use. One patient denied alcohol use but admitted to one day of drug use. Another patient reported consuming a somewhat lower frequency of standard drinks compared to the baseline period but alcohol use remained significant. Drug use (i.e., marijuana) also remained the same for this patient. At 6 months, three patients denied alcohol and drug use. One patient reported a further decrease in alcohol intake but his drug use remained the same. Information from the significant other interviews was consistent with patient reports.

Treatment Acceptability

At post-treatment, all patients reported high satisfaction with the intervention according to the CSQ. Scores ranged from 28 to 32, with the highest score possible on the scale being 32. Patients were also interviewed and asked to provide their thoughts about participation in the program. Comments included the following:

> “When I first started I was not in good shape. It was good to see progress and learn about symptoms of bipolar disorder.”

> “I became aware of preliminary precautions for the onset of bipolar disorder.”

"My support network was activated quickly."

"Phone calls helped out a lot."

"I learned not to use sleep aids to escape."

"The program helped me change behavior that wasn't good."

"I wouldn't shorten the program, but keep it either the same or another 3 months; 6 months is good though."

"Phone sessions were not as helpful as in person, but still helpful."

"I thought the program was pretty good; talking with the doctor about treatment was helpful."

Discussion

In this article, we described the rationale and initial development of ITAP, an adjunctive psychosocial approach for improving treatment adherence in patients with bipolar disorder who are substance abusers. We chose this psychiatric population because they are at the highest risk for nonadherence in terms of stopping medication and treatment contact and subsequent negative symptomatic and functional outcomes. ITAP is a hybrid approach that combines brief in-person patient and family sessions with longer term follow-up phone contacts with the patient and a significant other over a 6-month period. As an initial step in treatment development, we piloted this newly designed intervention in four patients to refine the intervention and assessment procedures so that they could be used in a subsequent randomized clinical trial. Review of measures assessing treatment adherence, symptoms, and substance use over the course of treatment suggested that ITAP was well tolerated and appeared to improve patients' targeted outcomes. The patients also reported that they were satisfied with the program and found it acceptable and useful as part of their treatment. Patients who achieved better treatment adherence appeared to have better symptom outcomes. One patient showed only partial adherence by post-treatment and had moderately severe manic symptoms at the end of 6 months.

In developing ITAP, we followed a model of treatment development described by Rounsaville et al.,[113] which is broken down into stages with differing goals. The initial stage involves developing a treatment manual and therapist training procedures and then piloting the study recruitment procedures and assessment protocol for measuring outcomes. At this initial stage, the focus is not on assessing the efficacy of the intervention per se but on developing the intervention and procedures for use in a subsequent controlled study and establishing that the intervention is feasible and potentially acceptable to patients. This initial work is typically completed in a small number of patients so that the investigators can gain valuable experience with the population and work through issues that arise in conducting the outcome research. This article described the first stage of research on ITAP. A pilot randomized controlled trial is currently underway to further assess the potential effects of the intervention and develop an appropriate comparison condition. After that study is completed, a full scale randomized controlled trial can be planned to formally test the efficacy of the intervention with full statistical power.

Our initial treatment development efforts taught us a number of important lessons that we believe will be useful when conducting further research on ITAP. First, the heterogeneity of bipolar substance abuse can pose problems for both research and treatment efforts. Bipolar disorder is best conceptualized as a spectrum of psychopathology, with differences in severity and polarity within and across patients over time. These differences are further compounded by abuse of substances, which could take the form of alcohol, drugs, or various

combinations of the two. Given the nature of these problems, treatment may include hospitalization, outpatient pharmacotherapy, individual counseling, case management, and attendance at support groups. Thus, it is important that ITAP be inherently flexible and applicable to various presentations of bipolar substance abuse and the differing treatment needs of these patients.

Second, the patient's significant other often played a key role in treatment. Significant others provided useful collateral information and could help the patient directly as needed during the phone contact phase of ITAP when the patient and therapist did not have face-to-face contact. Nevertheless, given the number of bipolar and substance abusing patients who may lack an appropriate significant other to participate, in future research we plan to examine ways in which ITAP could be adapted for patients for whom no significant other is available to participate.

Third, given the adjunctive nature of ITAP, the role of community treatment providers was essential. Coordinating care and maintaining communication between the treatment provider and the ITAP therapist were crucial for the success of the intervention. We believe that the monthly summary letters sent to nonstudy treatment providers played an important role in fostering communication between providers. Provider buy-in to the program was considered important. All providers were contacted at the start of the study to obtain their consent to receive the monthly letters. The goals of the study program were explained to the providers at this time. The providers of all patients in the current study agreed to receive these letters. Also, the study therapist attempted to contact the treatment provider by phone at least once to answer any questions and to coordinate care as needed. The letters contained brief information on the patients' current symptoms and functioning, as well as their reported degree of treatment adherence and substance use. Sometimes the study therapist would provide treatment recommendations, but the ITAP therapist always sought to remain respectful of the community provider's treatment plan and to support and foster that process as appropriate without interference.

Finally, given the often long-standing and chronic nature of the patients' problems and the adjunctive nature of the intervention, we found it important to keep the ITAP goals modest. The ITAP therapists had limited time to work with patients and thus focused their efforts on goals they could be most helpful in addressing, such as improving patients' use of their existing treatments. The focus was also on relative improvement in areas such as treatment adherence. Improving adherence over time, even if the patient does not achieve 100% adherence, was considered a worthy goal that was likely to benefit the patient and his or her long-term functioning.

This study had a number of limitations. First, there was no control group and it was not possible to draw firm conclusions about the efficacy of ITAP, so a future randomized controlled trial is needed. In addition, patients who agreed to participate in our study may not be representative of all patients with bipolar disorder and substance use. For example, not all patients we approached agreed to participate in the study (consent rate was 44%). We might not expect the same outcomes in patients who are less accepting of help for their problems, perhaps due to lack of insight or motivation. The patients we treated also had support from a significant other; adherence may be poorer in those with less social support. In addition, all patients were recruited during a current hospitalization and may have been more motivated to improve their adherence following discharge. Thus, further testing of ITAP is required in more diverse outpatient settings. In addition, although collateral information was collected from the significant other on treatment adherence and substance use to confirm patient self-report, it would be helpful to include additional objective indices

(e.g., medication blood levels, pharmacy records, pill counts, saliva drug screens) in future studies.

Schou suggested that nonadherence is responsible for the "efficacy-effectiveness gap" in bipolar disorder—the finding that 66% of bipolar patients respond to lithium in clinical trials, but only about 33% show similar improvements in clinical practice.[114] Although the literature has focused almost exclusively on the importance of *medication* adherence alone, it is useful to expand the concept to include important behavioral forms of adherence (e.g., keeping scheduled treatment appointments), which are also likely to lead to improved outcomes. Given the initial promising findings presented here, we plan to further test ITAP in a randomized controlled trial to examine outcomes in a larger group of patients and develop an appropriate comparison condition. Comparing ITAP to a treatment-as-usual group will allow us to better determine the effects of adding this intervention to patients' existing outpatient treatment regimens. Problems with treatment adherence in patients with bipolar disorder can frequently lead to a multitude of negative outcomes. Further study will provide useful information on the potential of ITAP and similar interventions to reduce the efficacy-effectiveness gap in bipolar disorder.

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Table 1
Outline for the Improving Treatment Adherence Program (ITAP)

I. Session 1 (in-person meeting)

- **a.** Introduction and description of program
- **b.** Psychoeducation about treatment adherence and bipolar disorder
- **c.** Review of recent psychiatric history emphasizing links between nonadherence, substance abuse, and bipolar symptoms
- **d.** Quick assessment of mood symptoms, suicidality, substance use, treatment adherence, social support
- **e.** Introduce values/goals clarification
  - **i.** Review the patient's Valued Living Questionnaire (VLQ)[97]
  - **ii.** Highlight discrepancies between the patient's important life values and behavioral consistency with those values as reflected in daily activities
  - **iii.** Pick one relevant value from the VLQ and create a more detailed value narrative
  - **iv.** Emphasize that the program will focus on helping the person be more consistent with important life values
- **f.** Review current outpatient treatment plan and provide additional referrals if needed

II. Session 2 (in-person meeting)

- **a.** Quick assessment of mood symptoms, suicidality, substance use, treatment adherence, social support
- **b.** Complete values/goals clarification discussion from previous session as needed
- **c.** Formulation of valued treatment goals
  - **i.** Discuss differences between values (i.e., general life directions that the person finds important and meaningful) versus goals (i.e., specific plans of action for working toward the values)
  - **ii.** Formulate list of short-term goals over the next few months
  - **iii.** Discuss role of adherence, sobriety, and symptom management in achieving goals
  - **iv.** Discuss adherence as something that can help the person better work toward his or her valued life goals

III. Session 3 (in-person meeting)

- **a.** Quick assessment of mood symptoms, suicidality, substance use, treatment adherence, social support
- **b.** Complete the “Life Plan” document which includes the following questions:
  - **i.** What are my most important life goals?
  - **ii.** What obstacles or hurdles may get in the way of my goals?
  - **iii.** What plan will I put into action if I get off track with my life goals?
  - **iv.** What are the first signs of trouble in the way I think, feel, and behave, so that I can spot problems earlier and take action?
  - **v.** What is my plan of action for keeping safe?
- **c.** Discuss objectives for significant other (SO) meeting

IV. Session 4 (in-person family meeting)

- **a.** Orientation
  - **i.** Therapist introduction
  - **ii.** Set agenda and elicit expectations for session
- **b.** Psychoeducation
  - **i.** Review information on treatment adherence and bipolar disorder
  - **ii.** Review risk factors for negative health outcomes: mood symptoms, suicidality, substance abuse, tre9atment nonadherence, lack of communication with family and providers
- **c.** Significant other's (SO's) role in treatment
  - **i.** Elicit SO's perspective on patient's psychiatric history and current functioning

ii. Review Life Plan

1. Provide copies of plan to patient and SO to review
2. Identify ways that the SO can be included in the Life Plan (e.g., helping patient monitor symptoms)

iii. Identify conflicts between SO and patient and provide referrals for further treatment if needed

d. Explanation of phone sessions

V. Telephone phase (13 phone contacts with patient and SO; 15-30 minutes each)

a. Patient contact

i. Quick assessment (change since last contact?): mood symptoms, suicidality, treatment adherence, substance use, social support

ii. Discuss in-depth problem areas identified during assessment

iii. Review relevant values/goals to guide problem solving

iv. Informal problem solving

1. Encourage patient to communicate issues with SO or treatment provider
2. Help patient brainstorm alternatives and formulate action plan
3. Assess outcome of patient's previous problem-solving attempts

v. Other possible interventions

1. Review Life Plan document
2. Therapist contacts treatment provider(s) directly (with patient's permission)
3. Therapist increases frequency of phone contacts during crisis

vi. Schedule next phone session

b. Significant other contact

i. Quick assessment (change in patient since last contact?): mood symptoms, suicidality, treatment adherence, substance use, social support

ii. Discuss in-depth problem areas identified during assessment

iii. Informal problem solving

1. Encourage SO to communicate issues to patient or treatment provider
2. Help SO brainstorm alternatives and formulate action plan
3. Assess outcome of SO's previous problem-solving attempts

iv. Schedule next phone session

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Table 2

Participant characteristics

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Sex	Male	Female	Male	Male
Age (years)	46	56	46	25
Race	White	White	White	White
Education (years)	16	18	18	12
Marital status	Cohabitating	Married	Never married	Never married
Employment	Disability	Disability	Unemployed	Employed
Medications	lamotrigine, olanzapine, citalopram	lamotrigine, venlafaxine	lamotrigine	quetiapine
Hospital status	Inpatient only	Inpatient, partial	Inpatient only	Inpatient, partial
Bipolar type	I, manic	I, depressed	I, manic	I, manic
Substance use	Alcohol + cocaine dependence	Sedative dependence	Alcohol + cocaine dependence	Alcohol + cannabis dependence
Sessions attended	15	16	16	14
Significant other	Partner	Spouse	Friend	Significant other

Table 3

Case series outcome data

	Medication adherence	Appointment adherence	Standard drinks	Days of drug use	QIDS-C	CARS-M	CSQ
Patient 1							
Baseline	≥ 75%	100%	128	7	20	27	—
3 Month	100%	100%	0	0	10	10	—
6 Month	≥ 75%	100%	0	0	4	5	30
Patient 2							
Baseline	< 75%	≥ 75%	0	44	24	23	—
3 Month	≥ 75%	100%	0	1	22	11	—
6 Month	≥ 75%	100%	0	0	8	22	32
Patient 3							
Baseline	≥ 75%	N/A	44	4	6	29	—
3 Month	100%	100%	0	0	2	1	—
6 Month	100%	100%	0	0	5	0	32
Patient 4*							
Baseline	None	None	32	90	14	31	—
3 Month	100%	100%	24	90	2	4	—
6 Month	100%	100%	18	90	4	0	28

N/A = not available; QIDS = Quick Inventory of Depressive Symptoms-Clinician Version; CARS-M = Clinician-Administered Rating Scale for Mania; CSQ = Client Satisfaction Questionnaire.

*Patient 4 reported using marijuana at the same frequency and amount throughout the study