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Improving Treatment Adherence in Bipolar Disorder: A Review of Current Psychosocial Treatment Efficacy and Recommendations for Future Treatment Development

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Abstract

Treatment adherence is a frequent problem in bipolar disorder, with research showing that upwards of 60% of bipolar patients are at least partially nonadherent to medications. Treatment nonadherence is consistently predictive of a number of negative outcomes in bipolar samples, and the discontinuation of mood stabilizers places these patients at high risk for relapse. Several types of adjunctive treatment (family, psychoeducational, cognitive-behavioral) have been investigated for improving symptoms and functioning in bipolar patients with some success. To date, less attention has been paid to developing treatments specifically to promote treatment adherence to and engagement with pharmacological as well as behavioral treatments in patients with bipolar disorder. First, we review the effects of adjunctive interventions specifically on treatment adherence outcomes in 14 published clinical trials. Based on this empirical knowledgebase, we present a preliminary description of the treatment strategies that appear most promising for improving adherence. We also provide research recommendations for developing more effective interventions for the purpose of improving bipolar treatment adherence. Special treatment considerations, including the potential impact of comorbid substance abuse and bipolar depression, are discussed.

Keywords

bipolar disorder; adherence; psychosocial treatments; mood stabilizers; clinical trials; bipolar depression; substance use disorders

Bipolar disorder is typically a chronic and severe mental illness present in 1–2% of the general population (Kessler et al., 1994; Regier et al., 1988). If diagnoses of bipolar II disorder are included in estimates, the prevalence increases to 3.9% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Bipolar disorder is reported to be the 6th leading cause of disability worldwide in those ages 15–44 (Murray & Lopez, 1996), and recent estimates suggest that medication and treatment costs for bipolar patients exceed \$17,000 per individual annually (Stender, Bryant-Comstock, & Phillips, 2002). The societal and personal burdens of bipolar disorder are due in part to its typically impairing course of illness. Over 70% of bipolar patients experience at least one recurrence within 4 years of the index episode (Gitlin, Swendsen, Heller, & Hammen, 1995). Judd et al. (2002) studied the symptomatic course in bipolar I patients for an average of 13 years, and reported that individuals spent 32% of the time with clinically significant depression symptoms, 9% with

manic symptoms, and 6% with mixed symptoms. Unfortunately, these high rates of relapse, symptomatic illness, and impairment are frequently reported even in bipolar samples receiving maintenance pharmacotherapy (Gitlin et al., 1995; Harrow, Goldberg, Grossman, & Meltzer, 1990; Miller, Uebelacker, Keitner, Ryan, & Solomon, 2004).

A World Health Organization (WHO, 2003) report defined treatment adherence broadly as: “The extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider” (p. 3). On average, treatment nonadherence rates of 25% have been reported across a variety of general medical conditions (DiMatteo, 2004). However, individuals being treated for psychiatric disorders tend to exhibit even higher rates (Cramer & Rosenheck, 1998). Although efficacious treatments are available for bipolar patients, research shows that upwards of 60% of these patients are at least partially treatment nonadherent to medication (Lingam & Scott, 2002), and that nonadherence predicts negative short- and long-term outcomes in those with the disorder (Keck et al., 1998). Therefore, there is an urgent need to identify cost-effective and efficacious adjunctive interventions that can improve treatment adherence in bipolar patients. In this paper, we examine the effects of current psychosocial interventions for improving treatment adherence in bipolar patients, and attempt to distill the strategies that appear most promising for further study. Based on this review, we provide recommendations for developing and testing novel interventions designed specifically to promote bipolar treatment adherence.

THE SCOPE OF THE BIPOLAR NONADHERENCE PROBLEM

Treatment nonadherence is predictive of a number of negative outcomes in bipolar patients (Keck et al., 1998; Scott & Pope, 2002b; Strakowski et al., 1998). In fact, some argue that nonadherence is responsible for the disorder’s “efficacy-effectiveness gap,” or the finding that 66% of bipolar patients respond to lithium in clinical trials, but only about 33% show similar improvements in clinical practice (Schou, 1997; Scott, 2002). A comprehensive review of the effects of nonadherence and factors predictive of this problem are beyond the scope of the current paper. Interested readers are referred to recent comprehensive reviews in this area (Colom, Vieta, Tacchi, Sanchez-Moreno, & Scott, 2005; Lingam & Scott, 2002). A brief overview is presented below.

Although estimates vary considerably across studies, recent reviews of the literature have reported that bipolar medication nonadherence rates typically range between 20% to 60%, with an average of 40% (Berk, Berk, & Castle, 2004; Colom, Vieta, Tacchi et al., 2005; Lingam & Scott, 2002). For example, using a definition of missing 30% or more of medication doses, Scott and Pope (2002a) reported that 32% of patients prescribed mood stabilizers reported being nonadherent within the past month, and that 50% were nonadherent during the previous 2 years. Several factors appear to predict nonadherence in bipolar patients, including a history of nonadherence, longer duration of treatment, increased complexity of medication regimen, decreased insight into illness, more negative beliefs about medications, poorer patient-doctor alliance, as well as the presence of psychotic features, personality disorders, and comorbid substance abuse (Berk et al., 2004; Colom, Vieta, Tacchi et al., 2005; Lingam & Scott, 2002; Miklowitz, 1992; Sajatovic, Bauer, Kilbourne, Vertrees, & Williford, 2006; Scott & Pope, 2002a).

Regardless of the specific method used to define nonadherence in past studies, findings consistently suggest that bipolar nonadherence is predictive of negative outcomes such as relapse, hospitalization, functional impairment, and suicidality (Gonzalez-Pinto et al., 2006; Keck et al., 1998; Strakowski et al., 1998). For example, Scott and Pope (2002b) prospectively followed 98 patients prescribed mood stabilizers and reported significantly

more patients with subtherapeutic (81%) compared to therapeutic (9%) blood levels of mood stabilizers required hospitalization. In recent years, there has been much effort devoted to developing efficacious pharmacological and, more recently, behavioral treatments for patients with bipolar disorder. However, the high rates of nonadherence commonly found in this population pose significant challenges to the implementation of currently available, state-of-the-art interventions.

DEFINING BIPOLAR TREATMENT ADHERENCE

Definitions of Adherence

Treatment adherence¹ can be difficult to study because the concept often is defined differently across populations, and even differently among studies within the same population. Similar to the wide range of nonadherence rates often reported among bipolar samples (20–60%), estimates have been equally variable among studies of patients with unipolar depression (10–60%) (Lingam & Scott, 2002) and schizophrenia (4–72%) (Lacro, Dunn, Dolder, Leckband, & Jeste, 2002). Factors affecting the frequently discrepant nonadherence rates reported in past research include the population or subpopulation under investigation, type of treatment, specific characteristics of the sample, length of the assessment period, method of measurement, and criteria for designating “nonadherence,” to name just a few. Therefore, estimates of nonadherence should be interpreted cautiously because rates tend to vary considerably as a function of the particular definition of nonadherence preferred by different researchers, as well as the measurement strategies employed to examine the problem in each study. These sometimes idiosyncratic definitions of adherence can lead to divergent conclusions about the impact of the problem and how it should be addressed in treatment.

In an attempt to improve the understanding of bipolar nonadherence, Colom, Vieta, Tacchi, et al. (2005) listed several different ways of categorizing nonadherence behaviors: 1) *full nonadherence*, or complete noncompliance with all provider instructions; 2) *selective nonadherence*, or compliance with some but not all instructions (e.g., taking only one of two prescribed medications); 3) *intermittent adherence*, or noncompliance, but only during certain periods (e.g., not taking medications when abusing alcohol or drugs); 4) *late adherence or nonadherence*, or initial noncompliance followed by later adherence (e.g., increased adherence over time due to improved insight into illness or specific intervention efforts), or vice versa; 5) *abuse*, or taking more medication than prescribed (e.g., attempts by patients to increase a medication’s effectiveness by taking more of it); and 7) *behavioral nonadherence*, or adherence to the nonmedication aspects of treatments. The last concept, behavioral nonadherence, includes a broader array of behaviors than simply taking medications as prescribed, and encompasses important treatment issues, such as attendance at scheduled appointments and the implementation of recommended lifestyle changes (e.g., diet/exercise plans or behavioral strategies designed to improve mood and regulate activity levels).

Behavioral nonadherence is particularly relevant to the current discussion as it has received surprisingly little attention in past research on bipolar disorder. This may be the case

¹Differing opinions exist regarding the preferred term to use when describing the degree to which patients follow treatment provider recommendations (Hearnshaw & Lindenmeyer, 2006). Although originally referred to as “compliance” in the literature, this term has fallen out of favor with researchers because it inaccurately implies a one-sided relationship in which the patient is expected to follow the physician’s treatment prescriptions without question. Terms such as “adherence” and “concordance” have become increasingly popular in the literature since the 1980s, and are thought to better reflect the two-way relationship between the provider and the patient that takes into account important factors such as the working alliance and patients’ treatment preferences (Gaudiano & Miller, 2006). For the sake of the current discussion, we generally prefer the term “adherence” as it is most commonly used in the literature today, and tends to focus on specific treatment-related behaviors that stem from the provider-patient relationship.

because behavioral nonadherence tends to be more complicated and difficult to measure compared with medication adherence, and also because psychosocial treatments for bipolar disorder have only recently begun to receive widespread clinical acceptance and serious attention from researchers. Although the evidence to date is limited, as few studies have examined behavioral nonadherence specifically in bipolar patients, the available evidence suggests that the problem is similar to that of medication nonadherence. For example, studies of severely mentally ill samples that have included bipolar patients have frequently reported high rates of community treatment attrition and failure to attend referral appointments (Nuttbrock, Ng-Mak, Rahav, & Rivera, 1997; Primm et al., 2000; Rosenheck, Frisman, & Gallup, 1995). Recently, Gaudiano and Miller (2006) identified predictors of treatment attendance in bipolar I patients enrolled in a larger clinical trial. Results showed that both patients' initial expectancies for improvement and the quality of the patient-doctor alliance significantly predicted time remaining in treatment up to 28 months following hospitalization. Moreover, a longer time remaining in active treatment was associated with less time spent symptomatically ill over follow-up.

Measures of Adherence

As the previous discussion illustrates, the process of defining treatment adherence begins at the conceptual level. However, equally important to defining adherence is the measurement strategy used for assessing the problem. Typically, measures of adherence are divided into two broad categories: objective and subjective (Hearnshaw & Lindenmeyer, 2006). Commonly used objective measures relevant to bipolar patients include serum levels of mood stabilizers, pharmacy records of prescription fills, pill counts, and missed appointments (Lingam & Scott, 2002; Sajatovic, Davies, & Hrouda, 2004). Subjective methods include patient self-report, and measures designed for this purpose have been developed for bipolar patients specifically, such as the Lithium Attitudes Questionnaire (Harvey, 1991). Corroborative reports from significant others and treatment providers are frequently used to help verify patient reports. Although some may find the use of self-report strategies for assessing bipolar treatment adherence to be questionable, researchers have reported high levels of agreement (91%) between self-report and more objective adherence data (e.g., serum drug levels) (Lam et al., 2003). Furthermore, objective data from blood lithium levels can be less accurate than patient self-report in some cases, especially when patient report can be corroborated by informants (Colom et al., 2000). Unfortunately, the measurement of specific behavioral adherence variables in bipolar patients has been largely ignored in the literature.

Based on a recent review of the literature on treatment adherence among bipolar patients, Sajatovic et al. (2004) recommend a multi-modal assessment of bipolar treatment adherence that includes a variety of different strategies. Some researchers have developed methods for combining methods in an attempt to improve and verify data on adherence. For example, Colom et al. (2000) assessed adherence based on patient interview, family member interview, and plasma drug levels. "Good compliance" was demonstrated when all three criteria suggested medication adherence. Other studies have used "blind," independent psychiatrists to categorize patients according to their level of adherence based on available adherence information (Miklowitz et al., 2000). Although these composite measures are likely to provide a more complete picture of adherence behaviors, they also are more likely to vary across different studies, making inter-study comparisons of adherence rates sometimes difficult to interpret.

REVIEW OF THE EFFECTS OF PSYCHOSOCIAL INTERVENTIONS ON BIPOLAR TREATMENT ADHERENCE

Selection of Studies for Review

Our aim was to review outcomes related to treatment adherence in published studies of psychosocial interventions for bipolar disorder. Therefore, we conducted a literature search of all published randomized controlled trials in this area. Relevant studies were identified from MEDLINE, PsychINFO, and the National Institutes of Health Computer Retrieval of Information on Scientific Projects (CRISP) databases, as well as the reference lists of review articles. Studies were included in the current review if they met the following criteria: a) random assignment to conditions, b) inclusion of a psychosocial treatment in at least one treatment arm, and c) report of at least one medication-related adherence outcome (e.g., blood levels of mood stabilizers). A total of 36 studies were identified and evaluated for possible review. Of this initial pool, 14 clinical trials met our review criteria and are summarized below. The most frequent reasons (non-mutually exclusive) for exclusion were: a) failure to use random assignment ($n = 7$), b) failure to report adherence outcomes ($n = 9$), and/or c) description of follow-up results from trials already included in our sample ($n = 6$). Each article was reviewed to collect information on study methodology (e.g., design, treatment conditions, sample characteristics), as well as outcomes related to treatment adherence. As recommended by Colom, Vieta, Tacchi, et al. (2005), we attempted to examine behavioral indices of adherence in addition to medication-related measures when available, including attrition and session attendance rates. However, study findings related to measures of symptoms and functioning are not described in detail here in the interests of space. Interested readers are referred to recent review articles that provide detailed descriptions of the primary findings from these trials (Bauer, 2001; Craighead & Miklowitz, 2000; Miklowitz, 2006; Otto, Reilly-Harrington, & Sachs, 2003; Rouget & Aubry, 2007; Vieta et al., 2005).

Although most psychosocial interventions tested in the selected studies contained strategies for improving bipolar treatment adherence, few of these trials were designed to assess treatment adherence programs specifically. Only two of the selected studies tested an intervention primarily designed to improve bipolar treatment adherence (Cochran, 1984; Peet & Harvey, 1991). In the remaining cases, treatment adherence was reported either as a secondary outcome or in order to determine if treatment differences on primary outcomes were, in fact, explained by nonadherence. Furthermore, methods used for assessing adherence in these studies were quite variable; although measures of adherence to mood stabilizers were consistently reported in the selected trials. Given the aforementioned caveats, findings from these trials can not provide definitive conclusions about the efficacy of psychosocial interventions for improving bipolar treatment adherence. However, we believe that reviewing the findings from these trials can be helpful for designing future psychosocial interventions to improve bipolar adherence specifically. For each category of intervention reviewed, we first summarize effects related to medication adherence, followed by a discussion of behavioral adherence outcomes.

Summary of Study Results Related to Adherence

Cognitive-Behavioral Interventions—See Table 1 for a summary of reviewed studies. Of the 14 trials identified for this review, 6 focused on the efficacy of adjunctive cognitive-behavioral therapies (CBT) for bipolar disorder (Ball et al., 2006; Cochran, 1984; Lam et al., 2000; Lam et al., 2003; Schmitz et al., 2002; Scott et al., 2006). Findings from 4 of these studies suggested that the addition of a cognitive-behavioral intervention might enhance treatment adherence (Cochran, 1984; Lam et al., 2000; Lam et al., 2003; Schmitz et al.,

2002); although only one trial specifically targeted adherence as a primary treatment outcome (Cochran, 1984).

Medication adherence: Cochran (1984) evaluated standard care alone versus standard care plus a 6 week CBT-based compliance intervention, and utilized a multi-modal assessment of adherence which included self, informant, and physician report, as well as serum lithium levels, chart review, and an independently rated 3-point “compliance index.” Across the 6-month post-treatment follow-up, patients in the experimental condition were significantly less likely to be rated as having “major noncompliance” problems on the compliance index, were significantly less likely to terminate the use of lithium against medical advice, and were significantly less likely to be hospitalized. Moreover, patients in the experimental condition were significantly more likely to be rated as “adherent” as per physician report and compliance index rating at post-treatment and at the 6-month follow-up. However, these effects were not evident at 3-month follow-up, and there were no differences between groups at any time point on self-reported adherence, informant ratings, or serum lithium levels. These mixed findings may have been related to limitations of the study, which included a small sample size and physician ratings that were not blind to experimental treatment condition. This limitation is particularly noteworthy, as physician ratings did not significantly correlate with self-report and informant ratings.

Through their treatment development work focused on cognitive therapy (CT) for relapse prevention in bipolar disorder, Lam and colleagues (2000; 2003) have also demonstrated some support for the notion that adjunctive cognitive-behavioral interventions may enhance treatment adherence. In an initial small-scale pilot trial evaluating CT versus treatment as usual (TAU), Lam et al. (2000) failed to find post-treatment differences in adherence as measured by the self-report Medication Compliance Questionnaire (MCQ), but reported significantly better adherence in the experimental condition at 6 months post-treatment. In a larger trial of this work (Lam, Hayward, Watkins, Wright, & Sham, 2005; Lam et al., 2003), in which 103 patients were randomized to receive 6 months of either “minimal psychiatric care” alone or with the addition of CT for relapse prevention, the patients in the experimental condition reported significantly greater compliance on the MCQ at immediate post-treatment. These results extended to 18 and 24 months post-treatment, although they were not replicated at the 12 month post-treatment assessment. As roughly half of the sample failed to comply with scheduled blood draws, serum mood stabilizer concentrations were only reported at immediate post-treatment, at which time there was a statistical trend such that patients enrolled in the experimental condition were more likely to have “adequate” serum levels than patients enrolled in the control condition.

In the only study reviewed targeting patients with bipolar disorder and comorbid substance use disorders, Schmitz et al. (2002) randomly assigned 46 individuals to either 12 weeks of low-intensity medication monitoring alone or in combination with CBT. The CBT condition showed somewhat better medication adherence on a composite measure derived from patient self-report and blood levels of mood stabilizers.

Despite the findings reported above, additional randomized trials have failed to demonstrate a link between cognitive-behavioral interventions and enhanced medication adherence. For example, in the largest trial of CBT for bipolar disorder to date (Scott et al., 2006), in which 253 patients with severe and recurrent bipolar disorder were randomized to either CBT or TAU, there was no group difference in adherence to any psychotropic medication. However, the authors did not report how medication adherence was assessed in this study. Similarly, although Ball et al. (2006) hypothesized that patients enrolled in a CT intervention for relapse prevention would demonstrate greater medication adherence when compared to patients enrolled in TAU, there was no group difference in self-reported adherence at post-

treatment or at 12 month follow-up. Given poor compliance with blood tests for serum mood stabilizer concentrations in this study sample, serum level data were not compared across groups.

Behavioral adherence: Results from CBT interventions were more inconsistent when behavioral indices of adherence were examined. In the Cochran (1984) study, mean number of CBT sessions attended was not reported, nor was the attrition rate for the control group. In addition, close to 30% of the patients enrolled in the trial did not designate an informant for participation. From a behavioral perspective, patients enrolled in the studies by Lam and colleagues (2000; 2003) were relatively adherent to the experimental intervention. That is, in both the pilot and larger-scale trials, patients were offered 12 to 20 sessions of CT and attended a mean of 16 and 14 sessions, respectively. Attrition rates did not differ between the experimental and control conditions. Although treatment retention was low in both groups, Schmitz et al. (2002) reported that more patients completed CBT (60%) than medication monitoring alone (33%). Also, the CBT group attended significantly more medication monitoring sessions. In the Scott et al. (2006) study, it is important to note that approximately 40% of patients enrolled in the CBT condition did not receive “all planned components of the package” (pp. 315–316). Further, although patients were offered up to 20 sessions of CT for relapse prevention in the Ball et al. (2006) study, the mean number of CT sessions attended was not reported.

Psychoeducation—Taken together, results from trials evaluating the efficacy of psychoeducational approaches for bipolar disorder have been similarly mixed. Of the 5 studies identified for this review, 3 studies provided some evidence that adjunctive psychoeducation (PE) might enhance treatment adherence (Clarkin, Carpenter, Hull, Wilner, & Glick, 1998; Colom et al., 2003; Harvey & Peet, 1991), and 2 did not show such benefits (Perry, Tarrier, Morriss, McCarthy, & Limb, 1999; van Gent & Zwart, 1991).

Medication adherence: Following a 6-week education program designed to enhance lithium knowledge and attitudes, patients were significantly less likely to report missed medication doses than patients enrolled in a waitlist control (Harvey & Peet, 1991; Peet & Harvey, 1991). However, there was no group difference in serum lithium levels at post-treatment. When data were combined for the two treatment groups, increased lithium knowledge was significantly associated with patient-reported tablet compliance and with serum lithium levels. In addition, Clarkin et al. (1998) evaluated differences in adherence among married patients randomized to receive either medication management alone or medication management plus a 25-session PE intervention with their spouses. Using a likert-type rating scale, self-reported medication adherence was found to be relatively good in both patient groups. Yet patients in the experimental intervention were significantly more medication adherent at post-treatment.

Colom and colleagues (2003; 2005) recently reported results of a group PE to prevent recurrence in remitted patients with bipolar disorder. In this trial, patients were randomized to receive either group PE or nonstructured group therapy. In comparison to controls, patients who had completed the PE group were significantly more likely to have adequate serum lithium levels at post-treatment, 18 months, and 24 months. Yet it is important to note that these findings may have been driven by differential attrition, as patients in the experimental condition were more than two times more likely to withdraw from treatment, and analyses were not conducted on an intent-to-treat basis. Thus, greater adherence to lithium among patients who completed the experimental condition may have been an artifact of their adherence to treatment, more generally. Also of note, there were no group differences in serum lithium levels at the 12-month assessment, nor were there group differences in serum concentrations of other mood stabilizing medications (e.g., valproate,

carbamazepine) at any time point. Although adherence was also assessed via interview with the patient and with a significant other, data from these interviews were not reported.

We identified 2 randomized trials of PE that failed to demonstrate a differential treatment effect on medication adherence. In particular, Perry, Tarrier, Morriss, McCarthy, & Limb (1999) randomized patients to receive 6 months of routine care or routine care plus PE aimed at relapse prevention, and found no group difference in serum concentrations of mood stabilizers at post-treatment or at one-year follow-up. van Gent and Zwart (1991) evaluated a 5-week PE for partners of patients with bipolar disorder in comparison to an assessment-only condition, and reported no group difference in adherence, measured categorically based on change in lithium serum levels between blood draws, at post-treatment or at 6-month follow-up.

Behavioral adherence: Although the outcomes reported in the Harvey and Peet (1991) study were generally positive with regard to PE and medication adherence, less is known about adherence to the interventions themselves. For example, the authors failed to report mean number of PE sessions attended; although there was no differential attrition between groups. In the Clarkin et al. (1998) study, the control condition had seven times as many drop outs as PE prior to completion. Session attendance was relatively high in both groups as reported by Colom et al. (2003), with patients attending an average of 19 PE and 18 control group sessions out of a total of 21. Overall, however, patients in the PE condition were twice as likely to withdraw from the study. As the attrition rate for the control condition was not reported in the Perry et al. (1999) study, differential treatment effects could not be assessed. However, it is noteworthy that slightly over 20% of patients in the experimental condition had withdrawn from treatment. Of those that remained, adherence to the intervention was relatively good, with patients in the experimental condition attending an average of 9 out of a maximum 12 sessions that were offered. Finally, van Gent & Zwart (1991) did not report data on behavioral adherence.

Family-Focused Therapy—Although fewer in number, trials of Family Focused Therapy (FFT, Miklowitz & Goldstein, 1997) have had a large impact on clinical recommendations regarding the treatment for bipolar disorder. Of these, we identified 2 randomized FFT trials for the purposes of this review. Although there are additional trials evaluating these treatments (Miklowitz et al., 2004; Miklowitz et al., 2007), including an integrated family and individual therapy (IFIT, Miklowitz, Richards et al., 2003) protocol that includes elements of FFT and Interpersonal and Social Rhythm Therapy (IPSRT, Frank, 2005), such studies did not systematically report medication adherence outcomes.

Medication adherence: In their outcome trial of 9 months of FFT versus crisis management (CM), Miklowitz and colleagues (2003; 2000) reported no difference between groups at post-treatment on a medication compliance index that incorporated patient report, physician report, and laboratory blood monitoring data. At one-year post-treatment, however, patients who had completed FFT were significantly more likely to be rated as adherent on the compliance index. In a separate trial evaluating 9 months of FFT versus individual therapy for bipolar disorder, Rea et al. (2003) reported no difference in psychiatrist-rated medication adherence at mid-treatment, post-treatment, or at one-year follow-up.

Behavioral adherence: Although the average patient was reasonably medication adherent in the study by Miklowitz et al. (2000), attrition was relatively high in both treatment groups, especially within the CM condition (39%). In addition, session attendance across the 9 months of treatment was not reported. However, there was no difference in the frequency of psychiatry visits at any time point. In Rea et al. (2003), the attrition rate for each group

was virtually identical, with approximately 20% of patients in each condition withdrawing from treatment. Mean number of FFT sessions attended was not reported.

Interpersonal and Social Rhythm Therapy—Similar to FFT, randomized controlled trials of IPSRT (Frank, 2005) have been fewer in number. To date, IPSRT has been evaluated in 2 large trials, although adherence outcomes were not reported in the more recent of the two (Miklowitz et al., 2007). In their investigation of IPSRT versus intensive clinical management (ICM), Frank et al. (2005) reported no difference in mood-stabilizer serum levels following acute phase treatment. However, in this study, length of acute phase treatment was dependent upon when patients met criteria for clinical stabilization, and some patients failed to achieve stabilization. Similar to findings by Rea et al. (2003), Frank et al. reported an attrition rate that was identical for the IPSRT and ICM conditions, with approximately 21% of patients in each group withdrawing from treatment.

POTENTIALLY PROMISING STRATEGIES FOR IMPROVING BIPOLAR ADHERENCE

Given the mixed evidence described above, it is important to note that any definitive conclusions regarding the utility of psychosocial interventions for increasing medication and behavioral adherence in bipolar disorder would be premature. Nevertheless, a review of the relevant literature suggests that there are a number of potentially promising strategies that would benefit from increased empirical and clinical attention. Indeed, 4 out of the 6 CBT trials and 3 out of the 5 PE trials reviewed above indicated some benefit of adjunctive psychotherapy. Although data from FFT and IPSRT trials were generally less favorable, it is important to note that the trials evaluating these treatments utilized active controls, whereas the majority of the remaining trials relied upon treatment as usual as the comparator.

Notably, there was substantial heterogeneity across studies in terms of how medication adherence was addressed within the respective treatments. Studies that fared particularly well benefited from directly targeting knowledge and attitudes about medication using either cognitive-behavioral (Cochran, 1984) or didactic (Peet & Harvey, 1991) approaches. Further supporting this approach, Peet and Harvey (1991) found that increased knowledge of and improved attitudes toward lithium were both significantly associated with adherence outcomes over time. Similarly, Scott and Tacchi (2002) conducted a small open trial ($n = 10$) using a tailored version of CBT that produced significant improvements in attitudes toward lithium, which predicted medication adherence. An integrated psychoeducational component emphasizing the role of medication adherence in preventing episode relapse and recurrence was also shown to be promising in some (Colom et al., 2003; Lam et al., 2000; Lam et al., 2003), but not all studies (Scott et al., 2006). In contrast, treatments that addressed medication adherence in a more nonspecific manner appeared to be less effective in generating positive adherence outcomes (Ball et al., 2006; Perry et al., 1999).

In addition to considering how investigators chose to target adherence within each intervention, it may also be useful to consider potential dose-response relationships within treatments. Indeed, although medication adherence was presumably addressed on an as-needed basis for the duration of treatment, interventions varied considerably in the proportion of time specifically dedicated to this topic. For example, treatments that fared particularly well focused exclusively on medication adherence (Cochran, 1984; Peet & Harvey, 1991) or otherwise devoted several sessions to a discussion of pharmacotherapy (Colom et al., 2003). One additional benefit of such targeted interventions is that they may be more cost-effective. For example, Cochran (1984) and Peet and Harvey (1991) reported positive adherence outcomes after only 6 weeks of treatment focused solely on medication adherence. Similarly, positive results for treatment adherence have been obtained in studies

using relatively low-intensity, yet targeted, interventions in other populations (e.g., the BRENDA model, see Starosta, Leeman, & Volpicelli, 2006). In contrast, longer duration interventions that only devoted a small fraction of time to medication adherence generated poorer adherence outcomes (Perry et al., 1999; Scott et al., 2006).

Although the evidence is mixed, the inclusion of a family member or significant other in psychotherapy for bipolar disorder deserves continued empirical attention in the adherence literature. Indeed, some (Clarkin et al., 1998; Miklowitz, George et al., 2003) but not all (Rea et al., 2003; van Gent & Zwart, 1991) studies suggest that family interventions may enhance medication adherence. Among the studies that have reported null effects, it is important to note that van Gent and Zwart (1991) did not include patients in their intervention, and lack of an immediate post-treatment effect for FFT may have been related to the use of an active treatment control in these trials (Miklowitz et al., 2000; Rea et al., 2003). For example, Miklowitz et al. (2000) reported relatively high rates of medication adherence in *both* FFT and crisis management (CM), each of which included active family member participation. Further, there is some preliminary evidence that the effects of FFT on medication adherence may be more enduring, as there was a significant, albeit small, effect of improved adherence in FFT versus CM at approximately 1 year post-treatment (Miklowitz, George et al., 2003).

Finally, there was little clear evidence that the interventions reviewed above improved behavioral adherence specifically. Only a few studies showed significantly different attrition rates, although the lack of significance in several studies may have been due to relatively small sample sizes. The study by Schmitz et al. (2002) indicated that bipolar patients with a comorbid substance use problem, for which treatment drop out is a particular concern, were retained in treatment at about twice the rate in the CBT condition compared to the medication monitoring alone condition. However, the study by Colom et al. (2003) reported significantly more drop out in the PE condition compared to the control condition, which may suggest problems with treatment acceptability. In the broader literature, there is reason to believe that the inclusion of a family member or significant other may be particularly useful in enhancing behavioral treatment adherence (e.g., by encouraging session attendance) (Fals-Stewart & O'Farrell, 2003; Uebelacker, Weishaar, & Miller, in press). In the Clarkin et al. (1998) study, patients receiving the marital intervention had better treatment retention. Nevertheless, studies of FFT failed to show differences in treatment retention (Miklowitz et al., 2000; Rea et al., 2003). It is clear from our review that much more work is needed developing strategies to retain bipolar patients in treatment, as well as ways of measuring importance behavioral adherence variables.

RESEARCH ISSUES RELATED TO DEVELOPING AND TESTING NOVEL BIPOLAR ADHERENCE PROGRAMS

There are a number of challenges faced when conducting randomized controlled trials of bipolar disorder in general, and these difficulties are amplified when the aim is to test the efficacy of a bipolar treatment adherence program. Below, we discuss methodological issues raised during our review of the extant literature and potential ways of addressing them.

Sample Characteristics

One of the difficulties with conducting bipolar treatment studies is dealing with patient heterogeneity. Review of the sample characteristics in the studies presented in Table 1 highlights the diverse characteristics of bipolar patients included in past trials. When developing a novel bipolar adherence program, important decisions need to be made regarding a variety of possible inclusion/exclusion criteria, including diagnostic subtypes

(bipolar I vs II), episode status at study entry (in episode vs in remission), type of mood episode (manic, depressed, or mixed), treatment setting (hospital vs outpatient), and potential comorbidities (psychiatric and general medical). Although it is generally considered preferable to reduce heterogeneity as much as possible when conducting efficacy trials, issues of internal and external validity need to be appropriately balanced in bipolar treatment studies, both to accurately represent the diverse characteristics of these patients and to ensure that any new treatment will be transportable to routine practice settings.

There are a number of potential differences between patients diagnosed with bipolar I versus II disorder, as well as differences in their respective treatment. Studies of bipolar I patients in particular are urgently needed, as these patients tend to have higher nonadherence rates. In addition, patients currently in episode receiving acute treatment in a hospital setting are at elevated risk for nonadherence and relapse after discharge, making them prime candidates for adherence interventions. However, bipolar outpatients in remission at study entry may actually prove more amenable to adherence interventions, and thus it may be easier to detect changes in their status over time. For example, studies by Colom et al. (2003; Colom, Vieta, Sanchez-Moreno et al., 2005) and Lam et al. (2005; 2003) found positive effects on adherence measures in samples of initially remitted patients; whereas Miklowitz et al. (2000; Miklowitz, George et al., 2003) found advantages for their intervention only over longer-term follow-up in a sample that was in a mood episode at study entry. Further, adherence interventions may need to contain distinctive elements for addressing mania versus depression, as the preferred treatments for different phases of bipolar illness vary. Therefore, the decision to recruit patients with a particular type of mood episode should largely be dictated by the content and aims of the particular intervention being tested. Finally, given the high comorbidity rates (e.g., anxiety disorders, Gaudiano & Miller, 2005) found in bipolar patients that make it the rule rather than the exception, the use of overly restrictive exclusion criteria would be unlikely to produce an adherence program that is generalizable to the majority of patients.

Choice of Comparison Conditions

Another key issue that emerged from our review of past studies was the diversity of comparison conditions used to assess psychosocial treatment efficacy in bipolar patients. Most psychosocial interventions for bipolar disorder have been adjunctive in nature and compared to some form of “treatment as usual,” which was usually pharmacotherapy alone. All patients in a bipolar adherence intervention trial, regardless of whether or not they are assigned to the experimental intervention, also would be receiving a primary treatment that most likely includes pharmacotherapy. Depending upon the aims of the proposed bipolar adherence program, patients also may be required to receive some form of behavioral treatment or therapy when appropriate, especially if they are experiencing depressive symptoms. Therefore, treatment as usual, as long as it is properly specified and defined, may also prove a useful backdrop for testing novel bipolar adherence programs. Alternatively, if the adherence intervention is specifically designed to target a particular type of treatment (e.g., lithium compliance or a particular behavioral therapy), then it may be necessary to provide the primary treatment as part of the study. Doing so would help to better isolate the effects of the adherence intervention on this specific aspect of a patient’s more comprehensive treatment regimen.

It is important to note that a study design containing only primary treatments would not provide sufficient evidence that any increases in adherence observed during the study could be attributed to the adjunctive adherence intervention itself. It is possible that increases in adherence merely would be an artifact of the additional professional contact received by patients in the adherence intervention, if the comparison group received no additional intervention. Therefore, patients assigned to the adherence intervention should preferably be

compared against a group of patients receiving some additional components that could help to compensate for the non-unique aspects of the adherence intervention. For example, providing increased assessment and periodic contact with a healthcare professional who refrains from discussing adherence to the control patients in a study may prove useful for substantiating the specific efficacy of a novel adherence program. It is important to note that of the two previous trials reviewed that specifically tested adherence programs (Cochran, 1984; Peet & Harvey, 1991), both were employed as adjuncts to pharmacotherapy, but did not control for the extra treatment provided. Thus, more sophisticated designs will need to be employed in future research on this topic.

Measurement Issues

As discussed, defining and measuring treatment adherence can be complicated, and this is especially the case with bipolar patients given the diversity of treatments they may be receiving. Our review of previous bipolar trials demonstrated that beneficial effects could be found using self-report, clinician-rated, and objective indices of adherence. In addition, newer technologies, such as “ecological momentary assessment” via personal digital assessment devices (Stone & Shiffman, 2002) or microelectronic devices for recording pill bottles (Choo et al., 1999), may help to increase the accuracy of assessment strategies and to provide more detailed information about potential contextual factors that may influence adherence behaviors. However, it is important to note that in almost every trial that we examined, the primary focus was on *medication* adherence specifically. For the purposes of our review, we also attempted to examine the potential effects on behavioral adherence by using proxy measures, such as attrition and treatment attendance rates. However, this information has been inconsistently reported in the literature. It will be necessary for future studies of bipolar adherence programs to include more specific measures of behavioral adherence, such as the newly-developed, clinician-rated measure called the Psychosocial Treatment Compliance Scale (Tsang, Fung, & Corrigan, 2006).

We were able to identify only one example of a bipolar psychosocial treatment study that specifically included the assessment of behavioral adherence. Bauer et al. (1998) reported findings from an open trial of the Life Goals Program, which is a group-based psychosocial intervention for bipolar patients focused on education and goal achievement. The study included behavioral adherence measures relevant to the psychosocial intervention: 1) session attendance rate; 2) overall duration of enrollment; 3) level of session participation; 4) completion of therapy assignments; and 5) achievement of functional goals. By measuring these variables, the researchers were able to demonstrate that their intervention was well tolerated by patients and produced good behavioral adherence to the treatment.

Finally, an issue that is particularly relevant to psychosocial trials for bipolar disorder is the complex relationship among adherence behaviors, symptomatic improvement, and other clinical variables. One would hypothesize that an adherence intervention should be able to demonstrate that earlier improvement in adherence behaviors is predictive of later symptomatic improvement, at least to a certain degree. However, the relationship between symptomatic improvement and adherence is likely interactional and reciprocal, such that improvement in symptoms affects adherence behaviors, and vice versa. Thus, more sophisticated statistical techniques may be necessary to examine the specific effects of an adherence intervention. An example of how some researchers have attempted to address this issue can be found in the seminal treatment trial of FFT. Miklowitz et al. (2000) conducted a series of analyses demonstrating that, when psychosocial treatment and medication adherence were evaluated together as predictors of symptom ratings over time, psychosocial treatment accounted for unique variance in depression symptom ratings whereas medication adherence did not, and adherence accounted for unique variance in mania symptomatology whereas psychosocial treatment did not.

SPECIAL CONSIDERATIONS FOR BIPOLAR ADHERENCE PROGRAMS

It has been observed that the efficacy of currently available treatments for bipolar patients tends to decrease considerably when these same treatments are delivered in the community (Schou, 1997; Scott, 2002). One reason for this problem may lie in the fact that some important aspects of bipolar illness are not being adequately addressed in the existing treatment literature. Below, we provide examples of two important aspects of bipolar illness that require careful consideration when developing and testing psychosocial interventions, which are especially relevant to the topic of adherence: comorbid substance use disorders and bipolar depression.

Comorbid Substance Use Disorders

Most of the studies that we reviewed specifically excluded patients with comorbid drug or alcohol use disorders. However, the co-occurrence of these disorders is substantial. Epidemiological research suggests that up to 60% of individuals diagnosed with bipolar disorder have a lifetime history of a substance use disorder (SUD) (Regier et al., 1990). Comorbid SUDs have been shown to be related to a variety of negative factors in bipolar patients, including earlier age of illness onset, higher frequency of mood episodes, greater symptom severity and impairment, shorter time to relapse, and higher rates of suicide attempts (for a review, see Salloum & Thase, 2000). Furthermore, the most important predictor of nonadherence in bipolar patients is the presence of a comorbid SUD (Lingam & Scott, 2002; Strakowski et al., 1998).

Although a frequent clinical concern in bipolar patients, we are aware of only three published studies of psychosocial treatments for bipolar substance abusers specifically. The pilot study of CBT for bipolar patients with SUDs by Schmitz et al. (2002) is reviewed above. In addition, Weiss et al. (2000) recruited 45 bipolar patients with SUDs in sequential blocks to receive group CBT (12–20 sessions) or outpatient pharmacotherapy and other community treatments. After 6 months, those receiving CBT showed significantly greater improvements in addiction severity, manic symptoms, and percentage of months abstinent. No group differences in self-reported medication compliance were found, although overall adherence in the sample was good. Most recently, Weiss et al. (2007) published findings from a larger randomized trial ($n = 62$) in which bipolar patients with comorbid SUDs received integrated group CBT or group drug counseling. The CBT group demonstrated better substance abuse outcomes during treatment and at follow-up. In addition, group attendance was significantly higher in the CBT condition (70% vs. 54%). Unfortunately, medication adherence rates were not reported in the study. Even though SUDs are highly comorbid with bipolar disorder and predictive a number of negative outcomes, especially nonadherence to treatments, it is important to note that none of the aforementioned studies tested interventions primarily designed to improve adherence. Thus, there is an urgent need to develop treatments specifically for bipolar patients dealing with drug and alcohol problems that targets nonadherence behaviors.

Furthermore, the issue of drug and alcohol use also appears relevant to primary clinical trials of bipolar disorder, even though most researchers exclude patients with a current SUD. Given the high lifetime prevalence of these disorders, many bipolar patients in these studies are likely to have a past SUD. Recently, we examined the potential effect of a past SUD diagnosis on the future course of bipolar disorder in patients taking part in a clinical trial of pharmacotherapy and family therapy (Gaudiano, Uebelacker, & Miller, in press). Patients were recruited during an acute episode and their mood symptoms and substance abuse were assessed longitudinally for up to 28 months. Somewhat surprisingly, 48% of the sample met criteria for a past SUD based on structured clinical interview. Those with a remitted (1 year) SUD showed a poorer acute treatment response, a longer time to remission of their

acute mood episode, and a greater percentage of time with subthreshold but clinically significant depression and manic symptoms over follow-up compared to those without a SUD history. Subsequent substance abuse assessed during follow-up could not fully account for the poorer course of illness. These findings demonstrate that it is important to screen for and assess substance abuse in patients participating in clinical trials, as lifetime history of a SUD may act as a moderator of treatment outcome. Furthermore, careful attention may need to be given to addressing drug and alcohol use in psychosocial interventions for bipolar patients, even if substance abuse is not the present clinical focus.

Bipolar Depression

Noticeably absent from the literature on psychosocial interventions and treatment adherence in bipolar disorder is a focus on the depressive phase of the illness. Indeed, within the trials reviewed above, depressed patients represented only a small proportion of the samples studied. Yet the issue of treatment adherence may be particularly relevant to bipolar depression, as it currently dominates the long-term clinical course of the disorder (Judd et al., 2002; Miller et al., 2004), is associated with significant functional impairment (Calabrese, Hirschfeld, Frye, & Reed, 2004), and confers substantial risk for suicide (Tondo, Isacson, & Baldessarini, 2003). Thus, if left untreated, bipolar depression is likely to be associated with significant morbidity and mortality.

Although this pernicious symptom course may be largely accounted for by the more limited armamentarium of effective treatments for bipolar depression (Thase, 2005), it is unclear to what extent it may also be accounted for by nonadherence to treatment. Indeed, there is reason to believe that certain depressotypic features adversely impact adherence behaviors, potentially contributing to the vicious cycle of depression that has emerged in bipolar disorder. For example, negative cognitions, especially those related to hopelessness about the future or helplessness about being able to reduce one's own symptoms, might interfere with adherence to both behavioral and pharmacological interventions (Basco, Merlock, & McDonald, 2004). Moreover, concentration difficulties may make it difficult for patients to manage their medications (Osterberg & Blaschke, 2005). Further impacting risk for treatment nonadherence, rates of alcohol dependence may be higher in bipolar depression in comparison to mania (Baethge et al., 2005). Finally, although there has been little empirical investigation of this notion, there has been a longstanding clinical belief that, when faced with the intense despair of depression, certain patients may abstain from treatment with a mood stabilizing agent with the hope that elevated or euphoric mood might return.

Emerging data suggest that adjunctive behavioral interventions may be particularly important for the treatment of bipolar depression (Miklowitz et al., 2007). Consequently, enhancement of adherence to behavioral treatments represents a critical target for bipolar depression. As discussed earlier, one promising strategy for promoting adherence to behavioral interventions is to actively encourage the participation of family members, who may provide support around session attendance or engage in the intervention themselves (Clarkin et al., 1998; Miklowitz et al., 2000; Rea et al., 2003). Not only is increased adherence to behavioral treatment likely to result in positive symptomatic outcomes for those who present with bipolar depression, but such interventions may be useful in targeting depression-related obstacles to medication adherence, as reviewed above. Although there is less evidence supporting a direct link between medication nonadherence and depressive symptomatology (Miklowitz et al., 2000), increased medication adherence is nevertheless critical during this period given that it promotes continued mania prophylaxis. Furthermore, to the extent that certain medications, such as lithium, have been demonstrated to significantly reduce suicide risk (Goodwin et al., 2003), a focus on both behavioral and pharmacological adherence continues to be warranted.

CONCLUSIONS

There exists an urgent need to develop and test novel treatment adherence programs for bipolar patients. Our review of the current psychosocial treatment literature suggests several promising approaches that have the potential for improving bipolar adherence, including cognitive-behavioral, psychoeducational, and family-based interventions. These strategies appear worthy of further clinical refinement and continued testing. However, the evidence for the efficacy of existing treatment adherence strategies is modest, and the study of behavioral (in contrast to medication) adherence in bipolar patients is only in its early stages. Thus, there is a particular need for future research efforts to focus on the development of novel, evidence-based programs that specifically target a variety of treatment-related adherence behaviors, and are based on interventions that currently show the most promise. Such programs may become the linchpins that will help bridge the current gap between the efficacy and effectiveness of the treatments for bipolar disorder.

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Table 1

Summary of Adherence Outcomes for Randomized Controlled Trials of Psychosocial Interventions for Bipolar Disorder

Study	Intervention	Duration	N	Participant Characteristics	Adherence Outcomes	Attrition	Attendance
Ball et al., 2006	CT vs. TAU	12 mos. 6 mos. + 6 mo. f/up	52 CT (n=25) TAU (n=27)	BPI, BPII; 0% in episode	No difference in adherence ratings at any time point. Serum levels also measured, but not reported due to poor compliance with blood draws.	16% vs. 41% (CT vs. TAU) <i>n.s.</i>	20 sessions of CT for relapse prevention. Mean number of CT sessions attended not reported.
Clarkin et al., 1998	Marital PE vs. "Medication Management"	11 mos.	42 PE (n=19) Control (n=23)	BP (type unspecified); % in episode not reported; inclusion limited to married/cohabiting patients	PE > Control on adherence scale ($p = .01$)	5% vs. 35% (PE vs Control) $p = .03$	25 marital PE sessions. Mean number of PE sessions attended not reported. All patients attended a mean of 32 ± 12.6 medication sessions.
Cochran, 1984	CBT vs. "Standard Clinic Care"	6 mos. 6 wks. + 4.5 mo. f/up	28 CBT (n=14) Control (n=14)	BPI, BPII, & cyclothymia; % in episode not reported; inclusion limited to patients prescribed Li	At post-Tx, CBT > Control on physician & objective ratings of adherence ($ps < .05$). No difference in serum Li levels or in self- and informant-reported adherence. At 3 mos, no group differences on any measure. At 6 mos., similar pattern to that reported for post-Tx. ($p < .05$)	14% vs. not reported (CBT vs. Control)	6 weekly sessions of CBT modified to target compliance. Mean number of CBT sessions attended not reported.
Colom et al., 2003; Colom, Vieta, Sanchez-Moreno, et al., 2005	Group PE vs. "Nonstructured Group"	24 mos. 21 weeks + 19 mo. f/up	120 PE (n=60) Control (n=60)	BPI, BPII; 0% in episode	At post-Tx, PE > Control for Li serum levels ($p = .04$). No difference for other medications. At 12 mos, no difference on any measure. PE > Control for Li serum levels at 18 ($p = .001$) & 24 mos ($p = .04$). No difference for other medications.	27% vs. 12% (PE vs. Control) $p < .05$	21 weekly sessions for each condition. Attended a mean of 19 PE groups, and 18 Control group sessions.
Frank et al., 2005	IPSRT vs. ICM	Varied Acute phase + 24 mo f/up	175 IPSRT/ IPSRT/ICM (n=39) ICM/ICM (n=43) ICM/IPSRT (n=45)	BPI, schizo-affective disorder, manic type; 100% in episode	No difference in mood-stabilizer serum levels following acute phase treatment.	21% vs. 21% (Acute IPSRT vs. ICM) <i>n.s.</i>	Acute phase of weekly Tx sessions until stabilization attained. Median time to stabilization was 19 weeks. 2 year preventive phase followed.
Harvey & Peet, 1991	"Education Programme" vs. WLC	6 mos. 6 wks. + 4.5 mo. f/up	60 Education (n=30) WLC (n=30)	BP (type unspecified); % in episode not reported; inclusion limited to patients prescribed Li	At post-Tx, Education > Control in reduction of missed Li doses ($p < .03$) No group difference in Li serum levels.	3% vs. 0% (Education vs. Control) <i>n.s.</i>	Videotaped lecture, handout, and home visit. Mean number of education sessions attended not reported.

Study	Intervention	Duration	N	Participant Characteristics	Adherence Outcomes	Attrition	Attendance
Lam et al., 2000	CT vs. TAU	12 mos. 6 mos. + 6 mo. f/up	25 CT (<i>n</i> = 13) TAU (<i>n</i> = 12)	BPI; 0% in episode	At post-Tx, no difference in adherence ratings. At f/up, CT > TAU for adherence ratings (<i>p</i> < .05)	8% vs. 8% (CT vs. TAU) <i>n.s.</i>	12 – 20 sessions of CT for relapse prevention. Attended a mean of 16 sessions.
Lam et al., 2003, 2005	CT vs. "Minimal Psychiatric Care"	30 mos. 6 mos. + 24 mo. f/up	103 CT (<i>n</i> = 51) Control (<i>n</i> = 52)	BPI; 0% in episode	At post-Tx, CT > Control for adherence rating (<i>p</i> = .02) CT > Control trend for serum levels (<i>p</i> = .06). At 18 mos., no group differences. CT > Control for adherence rating at 24 (<i>p</i> < .05) & 30 mos. (<i>p</i> < .05).	16% vs. 15% (CT vs. Control) <i>n.s.</i>	12 – 18 sessions of CT + 2 boosters for relapse prevention. Attended a mean of 14 sessions. No difference in frequency of psychiatric visits.
Miklowitz et al., 2000; Miklowitz, George, et al., 2003	FFT vs. CM	24 mos. 9 mos. + 15 mo. f/up	101 FFT (<i>n</i> = 31) Control (<i>n</i> = 70)	BPI; 100% in episode	At 12 mos., no difference in compliance index. At 24 mos., FFT > CM for compliance index (<i>p</i> = .04).	29% vs. 39% (FFT vs. CM) <i>n.s.</i>	21 sessions of FFT vs. 2 sessions CM. Mean number of sessions attended not reported. No difference in frequency of psychiatry visits at any time point.
Perry et al., 1999	PE vs. "Routine Care"	18 mos. 6 mos. + 12 mo. f/up	69 PE (<i>n</i> = 34) Control (<i>n</i> = 35)	BPI, BPII; % in episode not reported	No difference in serum blood levels at any time point.	21% vs. not reported (PE vs. Control)	7 – 12 sessions of PE. Completed a median of 9 PE sessions.
Rea et al., 2003	FFT vs. Individual Therapy	24 mos. 12 mos. + 12 mo. f/up	53 FFT (<i>n</i> = 28) Control (<i>n</i> = 25)	BPI; 100% in manic episode	No difference in compliance index at any time point.	21% vs. 20% (FFT vs. Control) <i>n.s.</i>	21 sessions of FFT or control + 3 additional mos. of med management. Mean number of sessions attended not reported.
Schmitz et al., 2002	CBT vs. MM	3 mos.	46 CBT (<i>n</i> = 25) MM (<i>n</i> = 21)	BP (type unspecified) + SUD; % in episode not reported	CBT > MM trend for composite measure of medication adherence at week 8 (<i>p</i> < .07)	60% vs. 33% (CBT vs. MM) <i>p</i> = .08	MM sessions at weeks 2, 4, 8, 12 and 16 CBT sessions CBT > MM for mean number of MM sessions attended (<i>p</i> = .02) Mean number of CBT sessions attended was 9.9
Scott et al., 2006	CBT vs. TAU	18.5 mos. 6.5 mos. + 12 mo. f/up	253 CBT (<i>n</i> = 127) TAU (<i>n</i> = 126)	BPI, BPII; 33% (CBT) & 32% (TAU) of patients in episode	No difference between groups at any time point on an unspecified measure of adherence.	17% vs. 12% (CBT vs. TAU) <i>n.s.</i>	20 + 2 booster sessions of CBT Mean number of sessions attended not reported. 40% of patients did not receive full CBT package

Study	Intervention	Duration	N	Participant Characteristics	Adherence Outcomes	Attrition	Attendance
van Gent & Zwart, 1991	Partner PE vs. "Assessment Only"	7.25 mos. 1.25 mos. + 6 mo. f/up	26 PE ($n=14$) Control ($n=12$)	BP (type unspecified); % in episode not reported	No difference in adherence ratings determined by change in Li serum levels between blood draws.	Not reported	5 sessions of partner PE. Mean number of sessions attended not reported.

Note. BPI = bipolar I disorder; BPPII = bipolar II disorder; CBT = cognitive-behavioral therapy; CM = crisis management; CT = cognitive therapy; FFT = family-focused therapy; ICM = intensive clinical management; IPSRT = Interpersonal and Social Rhythm Therapy; MM = medication monitoring; PE = psychoeducation; SUD = substance use disorder; TAU = treatment as usual; WLC = waitlist control