REVIEW

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# Patient, Treatment, and Systems-Level Factors in Bipolar Disorder Nonadherence: A Summary of the Literature

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## SUMMARY

This is a review of adherence determinants in bipolar disorder based on published prospective studies. Patient, treatment, and systems-level adherence determinants are summarized. The review concludes with recommendations on approaches that may minimize nonadherence. MEDLINE, PsychINFO, and the Cochrane Database were searched using key terms of adherence, compliance, or persistence, combined with terms of bipolar disorder, bipolar depression, or mania. Publications were filtered for randomized clinical trials (RCTs). Due to low yields of RCTs, we additionally included prospective nonrandomized clinical and epidemiologic studies, and prospective studies of severe mental illness that had a focus on adherence as an outcome and reported data separately for bipolar disorder. A targeted review of the broader bipolar literature provided background for concluding remarks. Twenty-two publications were identified describing RCTs with a specific population of bipolar disorder and a measure of adherence. Additional prospective nonrandomized studies were also identified. Studies identified three major categories of factors important to adherence: patient, treatment, and systems-associated factors. Patient factors include selected demographic features, symptom severity and phase of illness, presence of past suicide attempts, psychiatric comorbidity, illness and treatment duration, and relationship with providers. Treatment factors include type and intensity of pharmacotherapy and psychotherapy. Systems-level factors include differential levels of care access and costs. There is an overall lack of RCTs, and few prospective studies, on patient and systems-related determinants of adherence. Treatment-related determinants of adherence have the most evidence to date; however, would benefit from larger studies with diverse populations. Careful assessment of treatment adherence (including partial adherence) should be included in all prospective bipolar treatment studies, and studies should be conducted to prospectively evaluate interventions to minimize nonadherence.

## Introduction

Bipolar disorder is a severe and chronic mental illness characterized by recurrent cycles of manic or hypomanic episodes and depressive episodes, usually emerges in adolescence, and continues throughout the lifespan [1]. Bipolar spectrum disorder, which encompasses bipolar I and II disorders and subthreshold bipolar disorder, is reported by the National Comorbidity Study to have a combined lifetime prevalence of 4.4%, and a 12-month prevalence of 2.8%. Bipolar disorder is a leading cause of disability worldwide [2] as well as a leading cause of premature mortality due to suicide and comorbid health conditions [3,4].

Treatment nonadherence is a major problem in bipolar disorder—studies of the extent of nonadherence range from 20 to 60% [5–10]. Nonadherence is one of the major causes for the large gap between efficacy of treatments in research studies and effectiveness of the same treatments in clinical settings [11]. The clinical implications of these findings are sobering, including increases in time symptomatic, hospitalizations, suicide attempts, and completed suicides.

Treatment adherence has been defined as the extent to which the patient's behavior follows the recommendations given by the healthcare provider [12]. Adherence can be suboptimal for pharmacotherapy, psychotherapy, clinic attendance, and health maintenance. Treatment adherence has in the past been discussed as compliance or concordance, however the term adherence has become the preferred terminology both for healthcare providers [13] and researchers, across a wide range of medical specialties, as

it emphasizes active patient participation in a treatment formed through a therapeutic alliance [14], or shared decision making [15] in a patient-centered model of healthcare.

How adherence is measured or quantified, monitored, and reported has varied according to different studies, and our current understanding of what may constitute adherence continues to develop. Measurement of medication adherence ranges from simple patient report or observer report (subjective measures) to more intricate and sophisticated methods including pill counts, pharmacy records, electronic methods such as pill bottle caps that record openings of the pill bottle or cassette, and laboratory methods such as blood plasma levels (objective measures) [16].

Each of the adherence measurement methods has potential problems. Research on medical populations has found that self-report may overestimate adherence rates by 15%, albeit have a specificity of 90% [17]. However, self-report may be more reliable than clinician predictions, which have accuracies of 50–60% [18]. Devices that record the opening of pill bottles may overestimate the amount of medication taken, as the patient may be checking how much medication is left without actually ingesting a pill, or may underestimate the amount of medication taken if a patient takes out several pills at one time [16]. Pharmacy fill records have been endorsed as an alternative way to assess for adherence, however studies have concluded that medication possession ratio does not necessarily correlate to adherence, and may overestimate adherence if the patient does not take the medication as prescribed. Both pharmacy fill records and plasma levels give only one data point over several weeks to a month, and may not be sensitive enough to detect if the patient is taking too much medication near the time of the clinic visit (phenomenon of a loading dose) [19], and too little at other times. Larger studies have endorsed using at least two measures of adherence [20]. The Expert Consensus Guidelines report on treatment adherence found that most experts recommend using more objective measures such as pill counts, pharmacy records, and serum levels when appropriate, and consideration of a validated self-report scale to help improve accuracy [20].

Adherence to medication recommendations can be reported in a continuous (fraction or percentage of medication taken or not taken) or categorical fashion. The expert consensus guidelines on serious mental illness found that "medication not taken" is the preferred method of defining nonadherence in clinical samples, and that an appropriate cut off for adherence in bipolar disorder and schizophrenia, based on expert clinical opinion, is 20% or less of medication not taken [20]. In an effort to translate differences in adherence rates among individuals at a clinically relevant population level, some studies have combined the patient populations above and below a defined cut-off into "adherent" and "nonadherent" pools, respectively.

It remains to be determined exactly what level of adherence is necessary for positive clinical outcomes under different medication regimens and in different settings for bipolar disorder. It has been noted in recent literature that these discrepancies make it difficult if not impossible to compare studies, which may have chosen different levels of adherence. Furthermore, good adherence to drug therapy, in and of itself, is associated with positive health outcomes, namely lower mortality, in general medical populations, and it is postulated that adherence to drug therapy may serve as a marker for overall healthy behavior [21].

In spite of the challenges in measuring treatment adherence there has been a promising increase in the literature on treatment adherence in populations with psychiatric disorders over the last decade, including adherence literature focused on bipolar disorder. This is a focused review of evidence on adherence determinants in bipolar disorder based on prospective clinical trials including epidemiologic studies, drug studies, psychotherapy studies, and studies of treatment systems. The review concludes with recommendations on approaches and measures that may minimize nonadherence in bipolar populations.

## Methods

MEDLINE, PsychINFO, and the Cochrane Database were searched using key terms of adherence, compliance, or persistence, combined with terms of bipolar disorder, bipolar depression, or mania. Publications were filtered for randomized clinical trials (RCTs). Due to low yields of RCTs, we additionally included prospective nonrandomized clinical and epidemiologic studies, and prospective studies of severe mental illness that had a focus on adherence as an outcome and reported data separately for bipolar disorder for at least one treatment arm of the study. In order to provide a background to concluding recommendations, articles were gathered from a more extensive targeted review of the literature on adherence, compliance, or persistence, as well as a targeted review of the literature on bipolar disorder.

## Results and Discussion

We identified 22 publications that described RCTs, which had a specific population of individuals with bipolar disorder and a measure of adherence. We also identified a number of prospective but nonrandomized studies of bipolar patients that included adherence as an outcome. These studies identified three major categories of factors important to adherence: patient, treatment, and systems-associated factors. Table 1 summarizes the patient, treatment, and systems-level factors identified in this systematized review as important in treatment adherence among patients with bipolar disorder.

## Demographic Factors

Age, gender, and race have been found to be associated with adherence status in some studies [8,22] but did not differ statistically between categories of patients who were generally adherent versus nonadherent in other studies [23]. One study found marriage to be positively associated with adherence to medication [24]. Studies have also found adherence in veterans with bipolar disorder to be associated with a greater likelihood of being on disability status [18], which the authors felt might be related to common factors such as persistent help-seeking.

In a secondary analysis study of patients with rapid cycling bipolar disorder, educational level, ethnicity, and legal history were

**Table 1** Patient, treatment, and systems-level factors impacting treatment adherence in bipolar disorder

| Category | Factor | Finding correlated with poor adherence |
|---|---|---|
| Patient | Demographic features | |
| Factors | Age | Younger age |
| | Gender | Male gender |
| | Marital Status | Single |
| | Disability Status | Less likelihood of receiving disability |
| | Education level | Lower levels of education |
| | Legal history | Presence of legal history |
| | Bipolar disorder features | |
| | Illness presentation | BPI, psychosis, rapid cycling, elevated mood, low insight |
| | Neurocognitive function | Frontal executive impairment |
| | Illness duration | Longer duration |
| | Treatment duration | Longer duration |
| | Past suicide attempts | Presence of past suicide attempts |
| | Psychiatric comorbidity | Current substance abuse disorder |
| | Relationship with providers | Possibly, poor relationship and mistrust |
| | Treatment expectations | Low provider expectation |
| | Treatment history | Higher number of past irregular hospital discharges |
| Treatment | Medication factors | |
| Factors | Number of medications | Lower number of different prescriptions |
| | Intensity of pharmacotherapy | Suboptimal symptom response and |
| | Side effects | Lower doses of medications |
| | Psychotherapy factors | Presence or fear of side effects and |
| | Duration of therapy and aftercare | Negative attitudes toward mood stabilizer |
| | | Effects on adherence may diminish over time |
| Systems | Level of access to care | Lower access to care |
| Factors | Availability of resources | Fewer resources |

significant predictors of early study dropout, which was used as a measure for nonadherence [25]. Authors of this study suggested that understanding these factors would be helpful in order to identify individuals most at risk for treatment dropout.

## Symptom severity, Length of Illness, Duration of Treatment

Studies of patients with bipolar disorder have found symptom severity to be correlated with poor adherence status [22]. Patients with poor adherence were found to be significantly more likely to have the bipolar I subtype and have a prior history of psychotic symptoms [26]. Additionally, although even highly adherent, stabilized patients with bipolar disorder were shown to have cognitive impairments in attention, psychomotor speed, and semantic verbal fluency by neuropsychiatric testing, those patients with poor adherence to treatment were found to have more dysfunction on frontal executive tasks, a trend toward more perseverative errors, and worse performance in learning and recall measures.

Patients with bipolar mania may have greatly elevated mood, inflated self-esteem or grandiosity, thought disturbances, agitation, or distractibility, and may lack insight to be able to discern that pleasurable activities will have a high potential for painful consequences [27]. In the Expert Consensus Guidelines on treatment adherence, poor insight and lack of illness awareness has been endorsed by providers as one of the factors that is believed to lead to adherence problems in severe mental illness [20]. Furthermore, persistent grandiosity and manic symptoms in bipolar disorder were endorsed as the most important symptomatic contributors to adherence problems [20]. Connelly found that elevated mood is associated with overall nonadherence, both to treatment regimen and also to appointment keeping; furthermore, that perception of continuity of care, which may be related to insight or systems factors, was related to appointment-keeping [24]. Keck found that patient denial of need for their own treatment was the most often patient-cited reason for nonadherence [8]. Recently, Rosa found that nonadherence to lithium as measured by objective laboratory values, was linked to denial of illness severity and denial of therapeutic effectiveness, as well as general opposition to prophylaxis and fear of side effects [28].

In a prospective longitudinal study, adherence to medication was explored in patients with pure mania episodes versus mixed states [29]. Nonsignificant differences were found in rates of adherence to medication in the pure mania population and in the mixed state population; at baseline these figures were, respectively, 50% and 56% of patients reaching full adherence, and 16% versus 17% for partial adherence, and 7% and 3% for nonadherence. At 24-month follow-up, differences in adherence remained nonsignificant but improved to 92% and 84% for full adherence.

## Presence of Past Suicide Attempts

Several studies have found a relationship between nonadherence and suicide in bipolar populations [23,30,31]. In bipolar patients treated with lithium, good long-term adherence to lithium maintenance treatment was found to be associated with more than a 5-fold decrease in suicide attempts or suicide during close monitoring over the span of a decade.

## Psychiatric Comorbidity

Bipolar disorder may coexist with anxiety disorders, as well as alcohol or other substance-use disorders such as cocaine or amphetamine abuse disorders. While recent research on bipolar disorder has attempted to include patients with both psychiatric and medical comorbidities, there are limited data regarding the effects of comorbidity on adherence. Substance abuse has been shown to be significantly correlated with poor treatment adherence in a prospective study by Keck [8]. Current substance abuse, but not past substance abuse, nor the presence of anxiety, were shown to be associated with self-reported nonadherence in bipolar disorder in a cross-sectional study among a veteran population [32]. This study also found an association between self-reported adherence and the number of total medications reported.

Approximately 55% of patients with bipolar disorder also are found to have at least one concomitant anxiety disorder, which may include generalized anxiety, panic disorder, post traumatic stress disorder (PTSD), or social phobia among others [33]. The presence of anxiety is correlated with increased severity of bipolar disorder [34–37]. Although current or past anxiety symptoms as a composite variable were found to be significantly correlated with longer time to remission, anxious patients were not found to be less adherent with medications [38].

## Relationship with Providers

In a study based on self-report questionnaires completed by bipolar patients, Cochran and Gitlin found that adherence to treatment regimen is correlated with the patient-provider relationship, coupled with provider belief in treatment regimen [39].

A study of veterans with bipolar disorder recruited from inpatient stay did not find a difference between adherent and nonadherent groups on measures of patient-provider relationship, specifically working alliance per patient or clinician, patient satisfaction, or number of months in care with the provider [32], but did find nonadherence to be associated with a greater number of irregular discharges, essentially a measure of patients leaving against medical advice, or terminating care with inpatient providers.

## Attitudes and Beliefs Regarding Illness and Treatment

Some studies have found a correlation between negative attitudes toward mood stabilizing medication prophylaxis and nonadherence to lithium in mood disordered populations [9,40]. Patient adherence to lithium has been found to be correlated to illness concepts of trust in medication, trust in the treating physician, and absence of negative treatment expectations during maintenance therapy as measured by dropout rates [41], however the patient sample in this study included patients with schizoaffective bipolar disorder. This relationship has not been found in carbamazepine treatment in the sample studied. Although this may partly be a medication effect, particularly due to the very different severe side effects of the medications, it also may in part be affected by patient factors such as the relative importance of the side effects of lithium such as weight gain, nausea, acne, and sexual side effects, or patient feelings of decreased creativeness or slight depression on mood stabilizers.

## Treatment Factors

### *Pharmacotherapy Studies*

Pharmacotherapy is regarded as the cornerstone of treatment for bipolar disorder. Problems with adherence to prescribed medications are postulated to be a possible reason for the gap between efficacy and effectiveness of medications in clinical practice [42]. Various challenges in studying the literature in the area of adherence to medications include the relative newness of some of the medications as routine bipolar medications (notably the atypical antypsychotics), the need to study different phases of the illness for medications, and the relative lack of studies with adherence as an outcome measure [18]. Specifically, for each medication, adherence may differ at various times in treatment related to episode proximity, with resultant adherence rates differing in the acute and maintenance phases. Additionally, although there are case studies and retrospective studies of records and claims data that assess adherence in bipolar disorder, there is a paucity of RCTs and prospective trials, particularly ones powered to detect moderate and smaller effect sizes in treatment adherence. Lithium and valproate have been best studied with respect to prospective adherence determinants.

Lithium: Lithium has been most widely studied medication for treatment of bipolar disorder, and is considered the gold standard of treatment. Lithium has been shown to be more effective in controlling the manic phase than the depressive phase, which may complicate studies of adherence where these two phases are not separated, as well as in studies where all bipolar spectrum disorders are included without separation. In a long-term naturalistic study of patients in lithium treatment for bipolar disorders, poor lithium adherence was significantly more prevalent in partial or poor responders to lithium [43]. Another study of lithium maintenance treatment found poor adherence to be correlated with cognitive and coordination difficulties [44]. Thus lithium adherence may be reduced in circumstances where symptoms do not respond to treatment, or the medication may be causing burdensome or problematic side effects.

Valproate: In a study of bipolar I-disordered patients dually diagnosed with alcohol dependence, valproate was studied as adjunctive treatment to lithium [45]. Adherence to valproate, measured by self report and serum levels, was correlated with lower proportion of heavy drinking days. Additionally, higher levels of adherence to the valproate were associated with fewer drinks per

drinking day and heavy drinking day. In the same study, lithium levels and self reports were also recorded and analyzed, but the trend of lithium adherence predicting lower proportions of drinking days did not reach significance. As for mood symptoms, there was a trend for valproate serum concentrations to predict depression scores, however it did not reach significance in this study.

Additional mood stabilizers, atypical antipsychotics, and antidepressants: Prospective data on bipolar patient adherence determinants for other mood stabilizers, the newer atypical antipsychotics, and the antidepressants are generally lacking. Some of these medications have adherence rates studied from 3-week RCTs, however these rates are often not explained in the methods, and do not separate from placebo.

Intensity of Treatment: Nonadherence was found to be associated with lower intensity (fewer drugs at lower dosages) bipolar medication treatment in a veteran population with relatively severe bipolar disorder [23]. This may relate to the additional finding of nonadherent patients experiencing more barriers to care than the patients who reported adherence to treatment.

## *Psychotherapy Studies*

Psychotherapy for adjunctive treatment of bipolar disorder has been increasingly and more rigorously studied in the past decade [46,47] with assessment on a variety of clinical outcomes as well as medication adherence. Psychotherapy techniques that have been studied in this population have included supportive therapy, cognitive and cognitive-behavioral therapies (CBT), interpersonal and social rhythm therapy (IPSRT), psychoeducational methods, and combined methods such as family focused therapy (FFT). Individual, peer-group, and family settings have been studied. In addition to the effect of psychotherapy on adherence with treatment (such as medication, visits with provider), adherence with the psychotherapy regimen in itself may change the course of symptoms, episode recurrence, and overall disability and burden of bipolar disorder. Based on comparative data from several studies, adjunctive psychosocial interventions appear to decrease relapse risk in bipolar by 30–40% during intervals ranging from 1–2 years [48].

Study dropout rates, an extreme measure of nonadherence, have been found to be similar for psychotherapy and for medication therapy in bipolar disorder. Studies of specific psychotherapies have shown differences in rates of dropout, which in some studies are statistically significant, or approach statistical significance. Miklowitz and Scott have reviewed the issue of adherence to therapy, and find that the average rate of attendance for different psychosocial therapies for patients with bipolar disorder is 13 to 15 sessions [47]. In a multicenter study comparing treatments of cognitive behavioral therapy in patients with acute bipolar depression, FFT, interpersonal therapy, and a brief psychosocial treatment named collaborative care, study drop-out rates were found to be similar between the collaborative care group and the intensive psychotherapy group, with no statistical difference in dropout between the therapies (dropout ranged from 58.7% for CBT to 73% for FFT), and that patients attended merely half of the scheduled sessions (mean 14.1) [49]. While patients in intensive psychotherapies groups had equally higher year-end recovery rates, shorter times to recovery, and were more likely to be clinically well during the study compared to briefer intervention, there were no specific measures in this study of medication adherence. A study by Cakir et al. has examined the predictors of adherence to psychotherapy regimen, and find them similar to the patient factors listed above [50].

Psychoeducation and Adherence: A main goal of most psychoeducation treatments is to increase medication adherence and by extension the prevention of recurrence, although the effects of psychoeducation may extend beyond treatment adherence to improve many other measures of mental health and quality of life. In a study of highly medication-adherent stabilized patients with bipolar disorder, psychoeducation was found to significantly reduce the number of recurrent episodes of mania or depression, as well as decrease the number of hospitalizations [51]. In a related study, Colom et al. [52] found that, although adherence to psychoeducation did not separate between control and psychoeducation groups during the 6-month treatment phase, there were long-lasting effects in the treatment group in regards to recurrence and time ill or hospitalized, which were all decreased significantly in patients who had the manualized treatment versus those who had a control intervention, extending to 5-year postintervention. A subanalysis of patients from this treatment group showed that medication adherence as measured by serum lithium levels was significantly higher and more stable in the group of patient who had received psychoeducation [53]. Positive effects of psychoeducation on serum lithium levels had earlier been found in shorter term studies by Dogan [54]. Analysis of the long-term cost effectiveness of the therapy showed that patients who had received the group psychoeducation benefited from decreased costs of emergency and inpatient care making the treatment both economical and effective in the long term [55]. A study by Perry et al. [56] also found significant effects of psychotherapy on recurrence of episodes and psychosocial functioning, but no difference on medication adherence. In a study by Sajatovic et al. [57] no significant differences on measures of medication adherence attitudes were found at 12 months, between treatment groups given psychoeducation versus treatment as usual, although effects were seen earlier in treatment.

In summary, although beneficial primary outcomes for this psychosocial intervention are numerous, there are differing conclusions regarding the effect of psychoeducation on medication adherence; it remains unclear if psychoeducation has an effect on medication adherence or if the quantified effects are mediated by some other mechanism.

Cognitive Therapy and Adherence: RCT's of individual cognitive therapy as adjunctive therapy for bipolar disorder have shown effectiveness in decreasing both symptoms and episodes of and time in relapse during continuing treatment, as well as increased psychosocial functioning [46,56,58–65]. Studies including assessment of medication adherence (usually assessed by self report questionnaire) have shown that cognitive therapy modified for bipolar disorder is associated to a significant degree with better medication adherence at posttreatment versus treatment as usual [46], however these effects appear to diminish during the follow-up phase, indicating the

possible need for long-term continued treatment to maintain adherence gains [66].

Longer term follow-up after completion of cognitive therapy showed that patients continued to benefit from fewer days in episodes, fewer depressive and bipolar episodes, and many psychosocial gains; however, there were no significant differences found for manic or hypomanic episodes, nor for total percentage of patients suffering any relapse [46]. Psychosocial gains associated with cognitive therapy included decreases in dysfunctional attitudes, and decreased illness severity, and improved social adjustment and social performance, particularly immediately posttreatment although some gains remained significant for longer periods of time. Group psychotherapy has also been studied, and similarly shows psychosocial gains and high levels of adherence with the therapy at 80%, however this study did not examine medication adherence or have a control untreated group [67].

The effects of the addition of cognitive behavioral therapy to psychoeducation have been studied, and although the patients benefited from 50% fewer days with depressed mood over the course of 1 year and were able to avoid increases in antidepressant dose, there was no difference found in regards to medication adherence [68]. Cognitive behavioral group therapy for patients with bipolar disorder and substance use disorders has been developed, and results in better overall outcome (abstinence from substance and improved composite measures of substance use and mood) by secondary analysis, however there was no difference in medication adherence rates or therapy adherence rates (drop-out rates) between the two groups in this small study [69].

FFT and Adherence: FFT has been adapted for use in bipolar patients, and includes components of psychoeducation, therapy directed at enhancement of communication and problem solving for the patient with bipolar and their family, and family involvement in both care and monitoring of the patient. Studies to date show that patients involved with this type of therapy benefited from significantly longer relapse-free intervals than patients given a less intensive psychoeducational and case management intervention [48,70,71], as well as significant improvement in depression symptoms. The studies of this therapy show that effects were maintained for 1–2 years. Psychosocial treatment and time did not have an effect on medication adherence scores in the first year of study, however at 24 months, patients involved in FFT had higher mean drug adherence scores than patients with case management. Medication adherence scores were associated with greater improvement in manic symptom scores, and at 24 months it was found that adherence mediated the effects of the psychosocial intervention on mania symptoms.

### Systems Factors/Treatment Setting Factors

Few studies have looked at the association of treatment adherence with barriers to care. In a study of bipolar patients randomized to a systematic care program involving nurse care management, facilitated feedback of data to providers, collaborative treatment planning, structured monthly and as-needed telephone contact, and group psychoeducation, patients who disenrolled in the study were younger and had higher baseline mania scores [72]. Although medication adherence was not followed as an outcome, serum levels of medication were followed in the study and by providers through notifications, and therapy adherence was monitored. The intervention significantly reduced the mean level of mania symptoms and their duration over the 2 years of study in the subgroup of patients with clinically significant mood symptoms at baseline [72]. A related article shows this systemic approach yields significant increases in guideline concordant care, a combined measure of physician adherence to evidence-based guidelines of treatment, and patient adherence to treatment as measured by serum levels [73].

In a VA population, which is a centralized care system with inherently different levels of accessibility to both medical services and medications than the general system of US hospitals, gaps in healthcare use in those with serious mental illness were associated with increased distance from providers, while geographic accessibility to care and resource availability were associated with long-term continuity of care [74]. In studies of bipolar patients treated through the VA system, nonadherent patients are more likely to also have problems with telephone access [23].

Finally, while costs and insurance status are often believed to be a barrier to care, no data were identified specifically for bipolar-disordered patients regarding the relationship of adherence, either to medication or therapy, and costs associated with obtaining these therapies.

## Discussion and Conclusion

Much can be gained from appreciating the problem of treatment nonadherence from the standpoint of the patient, the treatments, and the systems of care that are currently available. Although progress has been made in the past 20 years regarding our understanding of adherence, more needs to be done in clearly identifying determinants or predictors of nonadherence across patient, treatment, and systems-level domains. This knowledge can then inform treatment approaches and methods that theoretically can optimize adherence.

Patient-related factors important in bipolar disorder treatment adherence include selected demographic features, symptom severity and phase of illness, presence of past suicide attempts, psychiatric comorbidity, illness and treatment duration, and relationship with providers. Adherence interventions that are implemented in "real-world," resource-limited settings might focus on bipolar patients who are particularly high-risk, for example, young male patients with severe manic or depressive symptoms, previous nonadherence, substance use comorbidity, and a history of suicide attempts. In some settings, such as community mental health clinics (CMHCs), this type of individual with more severe bipolar pathology might be assigned a case manager, and the case managers would ideally receive focused training in adherence assessment and enhancement.

A limitation to interpretation of the findings based upon available prospective studies is the relative heterogeneity in the bipolar samples. Recent research has begun to understand bipolar disorder as having distinct sub-groups, which are associated with differential treatment outcome, such as bipolar with substance abuse, bipolar disorder with psychotic symptoms versus a more "typical" bipolar presentation [75]. These bipolar subgroups or

variants might be expected to also have differential adherence outcomes. Unfortunately, there remains a relative lack of studies that have examined the role of treatment adherence in long-term or more global outcomes.

Treatment factors of importance to adherence in patients with bipolar disorder include type and intensity of pharmacotherapy and psychotherapy. Poor or suboptimal symptom response to treatment appears associated with reduced adherence, emphasizing the point that clinicians need to be extremely responsive to patient perceptions of the value of medication treatments and the risk-benefit ratio of pharmacotherapy. A patient who does not feel the medication is working is unlikely to continue to take it. Aggressive medication management with a goal of freedom from symptoms may optimize long-term adherence. Another valuable method of understanding treatment adherence in bipolar patients is with the use of qualitative techniques where individuals are encouraged to "tell their own story" regarding adherence and nonadherence. Such methods can reveal substantial gaps or inaccuracies in treatment expectations or understanding of bipolar illness [76] and may be helpful in designing interventions to improve adherence.

Additional research on long-term adherence rates in different medications will be essential in our understanding of medication effectiveness. It must be remembered that the goal of many treatment studies is determining efficacy, and there is a need for more studies on determining effectiveness that include the important issue of adherence. It is necessary to accumulate the type of long-range data for all drug therapies and types classes that are currently present for lithium and some of the psychotherapies.

Psychotherapy appears to be generally helpful in improving adherence although the mechanism of action for this is not known. The evidence appears to be stronger for the impact of psychotherapy on bipolar disorder outcomes such as time in episodes, and frequency of episodes. It is encouraging that there has been much research done in this area over the past two decades, as it will be important to continue this work to determine the optimal use, and mechanisms of action, of these therapies.

Systems-level factors that appear important to adherence include differential levels of care access and availability of resources. Unfortunately, in situations where health insurance and healthcare is often tied to employment status (such as in the United States) individuals with the most severe illness might be least likely to have access to care and this could potentially affect treatment adherence.

In contrast to some previous summaries of treatment adherence in populations with bipolar disorder [22] this review did not include reports gathered from retrospective drug claims data. Although studies of adherence to medication using drug claims data can add valuable insights into how prescribing practices, costs, and various patient and treatment factors appear to affect adherence, and the patient sample can be large, there are limitations to using retrospective claims methods. Limitations include imprecision in diagnosis, sample bias, and these studies generally do not have a way of ascertaining if a patient actually took the medication [77,78]. However, these studies may be essential in guiding future prospective studies on adherence, and also may be the vehicle to identify relationships with smaller effect sizes.

In conclusion, there are patient, treatment, and systems-level factors that appear important in relation to treatment adherence among patients with bipolar disorder. Effective interventions for treatment nonadherence will only be forthcoming from careful consideration and methodological study of factors that can be modified, and understanding of those that must be clinically followed.

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## Conflict of Interest

The authors have no conflict of interest in relation to this paper.

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