

Promoting treatment adherence in patients with bipolar disorder

Consider your patients' perspectives and goals when choosing interventions

Treatment nonadherence among patients with chronic illness is high, and bipolar disorder (BD) is no exception. Approximately 21% to 50% of patients with BD do not adhere to their recommended treatment regimen,¹ which adds to the burden of illness and worsens prognosis.

Although treatment nonadherence is a concern with any psychiatric disorder, we focus on BD because of the high prevalence of the disorder, the lifelong nature of the illness, and its resulting disability. BD is challenging to treat even with motivated patients, and psychiatrists cannot count on individuals to follow their prescribed regimen just because they were told to do so. Choosing the best treatment for each patient is complicated, and as physicians, we need to learn how to connect with our patients, increase our insight into their concerns, and work collaboratively to find a treatment they can follow.

This article describes methods of assessing adherence, factors that affect adherence, and pharmacologic and psychosocial interventions to enhance adherence and improve outcomes.

What is adherence?

As the doctor-patient relationship and medical treatment evolved to become more patient-centered, so have the terms used to describe individuals' treatment-related behavior. *Compliance*, a physician-centered term that mandates following instructions to achieve treatment goals, evolved to *adherence*, the extent to which a person fulfills their part of an agreed-upon treatment plan, followed



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Although convenient to administer in the office, adherence behavior scales tend to overestimate patients' adherence



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Table 1

Tools for measuring adherence to medications

Components/characteristics	Advantages	Disadvantages
Rating of Medication Influences³		
19 items. Subscales: Reasons for adherence (prevention, influence of others, medication affinity), reasons for nonadherence (denial, dysphoria, logistical problems, label rejection, family influence, negative therapeutic alliance)	Valid, reliable. Correlates with other scales (DAI)	Developed on a population including only patients with schizophrenia treated with antipsychotics. Requires a trained rater
Drug Attitude Inventory⁴		
30 items. Reflects patients' attitudes about medication	Self-rated. High internal consistency. Accurately discriminates between adherent and nonadherent patients	Developed on a population including only patients with schizophrenia
Lithium Attitudes Questionnaire⁵		
19 items. Areas of assessment: opposition to continue lithium, therapeutic effectiveness of lithium not accepted, difficulty with pill-taking routine, denial of illness severity, subcultural attitudes opposed to drug treatment, dissatisfaction with factual knowledge of lithium	Self-rated. Developed on patients with BD attending a lithium clinic. Good test/retest reliability for most items	The questionnaire is fairly long; shorter versions were adapted from original version
Medication Adherence Rating Scale⁶		
10 items that assess medication adherence behavior, attitudes toward taking medication, negative side effects, attitudes toward psychotropic medication, measures adherence in past week	Self-rated. Validated on patients with various diagnoses, including BD. Correlates well with DAI, MAQ, and mood stabilizer drug levels (lithium and carbamazepine)	Validation methods may be limited by the other measures (for example, medication levels can be influenced by metabolism)
Brief Adherence Rating Scale⁷		
3 items. Number of pills prescribed daily, days with no medication taken, and days with medication taken less than prescribed. Nonadherence defined as <70% of doses taken. Measures adherence in past month	Clinician-rated. Short. Good correlation with electronic medication monitoring. High internal reliability. Good test/retest reliability. Greater adherence on BARS correlates with lower psychotic symptom scores. Sensitive and specific in identifying nonadherence	Validation study only on patients with schizophrenia and schizoaffective disorder taking antipsychotics
BARS: Brief Adherence Rating Scale; BD: bipolar disorder; DAI: Drug Attitude Inventory; MAQ: Medication Adherence Questionnaire		

by *concordance*, which describes a decision-making alliance between patient and provider that strongly considers patients' input.

Adherence is considered adequate when it occurs at the minimum level necessary for the patient to respond to treatment and avoid relapse.² Research on adherence in BD can be difficult to interpret because results may be influenced by:

- selection bias (patients who are adherent and insightful are more likely to consent to research)

- complications caused by polypharmacy and comorbidity
- investigators' ability to choose the proper measure to delineate medication adherence attitudes and behaviors
- patients' compliance with the adherence-enhancing interventions.²

Assessment methods. Several tools can be used to measure adherence to mental illness treatment. Attitudinal scales capture a person's subjective feelings (such as

being on a medication, insight, perceived strength of the therapeutic alliance, and level of stigma faced) and can reflect attitude change that may result from adherence-enhancing interventions. Adherence behavior scales may be convenient to administer in the office but tend to overestimate patients' adherence (*Table 1*).³⁻⁷

Pill counts are inexpensive but patients can manipulate unused medication. Prescription refill counts are easy to obtain but do not confirm that the patient took the medication. Electronic medication monitors capture the time of specific doses and can calculate the adherence rate, but they are expensive and do not ensure that the medication was ingested. Measuring the drug in urine or blood is an objective measure of adherence and can serve as clinical guide to pharmacotherapy, but offers limited correlation with the amount of medication taken and is expensive. A combination of measures to estimate adherence may be best.²

BD adherence studies

Treatment adherence in BD is challenged by the chronic remission-relapse pattern of the disorder. Manic episodes carry the highest risk of nonadherence.² Scott and Pope⁸ evaluated self-reported adherence to mood stabilizers (lithium, carbamazepine, or valproate) among 98 patients with major depressive disorder and 78 with BD. They found that 32% of patients were partially adherent (defined as having missed >30% of doses in the past month) and >60% of these patients had subtherapeutic plasma levels of mood stabilizers.

In a study of 106 BD outpatients treated with lithium who completed scales regarding their attitudes toward and knowledge of lithium and the Medication Adherence Rating Scale (MARS), 86% of patients had a therapeutic serum lithium level (.6 to 1.2 mEq/L), and knowledge of lithium was correlated with adherence.⁹ Jónsdóttir et al¹⁰ looked at medication adherence among 280 patients with schizophrenia and BD by comparing patient self-reports to pro-

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A patient's age, sex, culture, symptom severity, worldview, and socioeconomic status can influence adherence

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Patients' concerns about side effects may contribute more to nonadherence than actually experiencing side effects

vider reports and measuring serum drug concentrations; adherence was defined as having a serum concentration within the reference level for the specific medication. BD patients had an adherence rate of 66%, and self-reported adherence as measured by MARS and provider reports correlated with serum concentrations.

In a study of 71 adolescents with BD followed for 1 year after their first hospitalization for a manic or mixed episode, DeBello et al¹¹ defined nonadherence as taking medication <25% of the time and partial adherence as taking medication 25% to 75% of the time. They found that 42% of patients were partially adherent and 23% were nonadherent.

Strakowski¹² followed 46 adults from Taiwan and 96 from the United States for 1 year after their first manic or mixed episode and found that 79% of the Taiwanese patients and 50% of U.S. patients were adherent. Using the medication possession ratio (MPR)—which is calculated based the number of days between expected and

actual prescription refills—to determine adherence, Sajatovic¹³ found that 54% of 44,637 veterans being treated for BD with lithium or anticonvulsants were fully adherent (MPR >.80), 25% were partially adherent (MPR >.50 to .80), and 21% were nonadherent (MPR ≤.50). In a survey of 131 randomly selected psychiatrists and 429 of their adult BD patients, Baldessarini¹⁴ found that 34% of patients reported missing ≥1 medication dose in past 10 days, but psychiatrists recognized only 18% of patients as nonadherent.

What affects adherence?

Although all BD patients share the same diagnosis, the factors that ultimately result in their medication adherence are as variable as the individuals themselves. Patients' age, sex, culture, symptom severity, worldview, socioeconomic status, opinion of mental illness, and self-image influence their individual decisions on adhering to a prescribed medication regimen.^{1,15}

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Table 2

FDA-approved medications for adult bipolar disorder

Bipolar disorder indication	Medications
Acute treatment of mania/ mixed episodes	Aripiprazole, ^{a,b} asenapine, ^a carbamazepine extended release, ^a divalproex sodium, ^a lithium, ^a quetiapine, ^a risperidone, ^{a,c} ziprasidone ^{a,b}
Depressive episodes	Olanzapine/fluoxetine, ^a quetiapine ^a
Maintenance treatment	Aripiprazole (as monotherapy and as adjunct to lithium or divalproex sodium), ^{a,b} asenapine, ^d lamotrigine, ^a lithium, ^a olanzapine, ^{a,c} quetiapine (as adjunct to lithium or divalproex sodium), ^a risperidone, ^e ziprasidone (as adjunct to lithium or divalproex sodium) ^a

^apill form
^bintramuscular for acute agitation
^cdisintegrating tablet
^dsublingual tablet
^elong-acting injectable

Perception of medication efficacy. Not surprisingly, if a medication does not seem to decrease debilitating symptoms, a patient is unlikely to continue taking it. Patients with BD feel more affected by depressive symptoms than by manic symptoms, and have indicated that they are more likely to adhere to and view as successful treatments that reduce depressive symptoms.^{16,17}

Tolerability. In an Internet-based survey, 469 patients with BD indicated that medication-related weight gain and cognitive impairment were the most important factors that affected adherence.¹⁶ Individuals' concerns about possible side effects may contribute more to nonadherence than actually experiencing side effects.¹⁷ Concerns about long-term metabolic side effects from atypical antipsychotics also may limit adherence.¹⁷

Neurocognitive impairment. Whether caused by BD, aging, or a combination of these factors, deficits in memory, attention, and executive functioning can lead to unintentional nonadherence. In a study that assessed medication management ability among middle-aged and older adults, patients with BD were found to make 2.8 times more errors than healthy controls.¹⁸

Therapeutic alliance and psychoeducation. Patients' expectations for pharmacotherapy vary from specific symptom relief to hopes for a complete cure, and their fears may be influenced by media and advertisements.¹⁷ Nonetheless a positive therapeutic

alliance with the treating provider improves illness outcomes.¹⁹

A clinician's ability to help patients build insight is invaluable for their current and future treatment. In a survey of 435 veterans with BD, nonadherence was greater among patients with limited insight about the role of medication in their illness.²⁰ A study of 65 BD patients that evaluated insight into medication adherence at initial interview and 1 year later found that difficulty with adherence at the initial interview predicted future nonadherence and was correlated with lack of insight.²¹ Rosa et al⁹ found that BD patients in denial of their illness and those who had little psychoeducation were more frequently non-adherent with lithium treatment.

Other factors that may contribute to medication nonadherence in BD patients include comorbid substance abuse or personality disorders, both of which are associated with more frequent relapse.¹⁵ Marriage has a beneficial affect on adherence.¹⁵ A good support system may contribute to treatment adherence; in a study of 107 children and adolescents with BD, nonadherent patients were more likely to experience family dysfunction and have a parental history of psychiatric hospitalization.²²

Adherence and BD course

Treatment adherence decreases the suicide rate among BD patients. Angst et al²³ evaluated the rate of suicide among 406 patients

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Once-daily formulations may improve adherence by providing consistent serum levels and fewer adverse effects



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Long-acting injectable formulations of antipsychotics may be used for maintenance treatment to improve adherence

Box

Brain changes and the progression of bipolar disorder

As emerging studies document morphologic brain changes associated with bipolar disorder (BD), researchers have been relating these changes to the duration and progression of illness. A longer duration of illness is associated with a smaller total gray matter volume on brain MRI of BD patients compared with unipolar patients and normal controls.^a Brain MRI analysis of grey and white matter in elderly patients with longstanding BD who underwent neuropsychological testing to rule out dementia

showed a decreased concentration of grey matter in the anterior limbic areas as well as reduced fiber tract coherence in the corpus callosum when compared with normal controls.^b

Additionally, microstructural brain changes have been associated with acute mood states, in particular bipolar depression.^c Lithium, valproate, olanzapine, and clozapine are neuroprotective in cultures of human-derived neuroblastoma cells, by enhancing the cells' proliferation and survival.^d

Source: For reference citations, see this article at CurrentPsychiatry.com

with BD and unipolar depression who were followed for 40 years. They found that 11% committed suicide; untreated patients had significantly higher standardized mortality rates than of those who were treated with lithium, antipsychotics, or antidepressants. Other studies confirm this finding.¹⁵

Repeated relapse may predict poorer cognitive performance. Lopez-Jaramillo et al²⁴ showed that patients with BD who had more manic episodes performed poorer on cognitive tests assessing attention, memory, and executive functioning compared with patients with less episodes and with normal subjects.

Medication adherence in BD is a priority because of potential neurodegeneration in BD and the neuroprotective effects of mood stabilizers and some atypical antipsychotics (**Box**).

Increasing adherence

Pharmacologic strategies. Adherence in BD often is difficult when patients require a complex medication regimen to control their illness. Patients and clinicians may prefer to use once-daily dosing drug formulations, which can provide consistent serum levels and fewer adverse effects. Divalproex extended-release (ER) allows once-daily dosing and improved tolerability by reducing fluctuations in valproic acid serum concentrations compared with the delayed-release formulation. In a retrospective chart review,²⁵ most patients (62%) who switched to divalproex ER from divalproex delayed-release preferred the ER formulation; 52% showed

clinical improvement, 81% did not experience side effects, and 8% demonstrated higher adherence after switching.²⁵ Similarly, an extended-release formulation of carbamazepine is approved for treating acute mania.

Many atypical antipsychotics are FDA-approved for acute mania, acute bipolar depression, and/or maintenance (**Table 2, page 49**). Long-acting injectable formulations (LAIs) may be used as maintenance treatment if nonadherence is an issue. LAI risperidone, which is FDA-approved for maintenance treatment of bipolar I disorder (BDI), was found to be safe and effective in stable BD patients who were switched from an oral antipsychotic.²⁶ Asenapine is provided in a rapidly absorbed, sublingual form and is FDA-approved for treating acute mania or mixed episodes associated with BDI.²⁷ Overall, however, only slightly more than one-half of BD patients are adherent to atypical antipsychotics.¹⁵

Although antidepressant use in BD is controversial, Sajatovic¹⁷ found 44% of depressed BDI patients were treated with antidepressants. Novel extended-release antidepressant formulations—including controlled-release fluvoxamine, paroxetine, extended-release bupropion and venlafaxine, once-weekly fluoxetine, rapidly dissolving mirtazapine, and transdermal selegiline—can optimize drug delivery, minimize side effects, and delay onset of action.¹

Psychosocial strategies used in BD include psychoeducation, cognitive-behavioral therapy (CBT), family-focused interventions, and interpersonal and social rhythm therapy

Table 3

Psychosocial interventions for bipolar disorder

Intervention	Description	Results in bipolar disorder	Optimal stage of illness for intervention
Individual and family psychoeducation ^{28,29}	Strategies to educate the patient about the illness, medications, side effects, and relapse prevention	Decreases relapse, (particularly manic episodes) and hospitalizations. Increases adherence	Manic episodes
Cognitive-behavioral therapy ²⁸⁻³⁰	Focuses on understanding patient's perceptions of illness and treatment. Equates resistance with exploring, rather than challenging resistance to take medication. Identifies and modifies negative automatic thoughts about medication. Motivation techniques useful in comorbid substance use	Decreases clinical symptoms. Increases adherence, quality of life, and social functioning	Depressive episodes
IPSRT ^{28,29}	Uses motivational interviewing and CBT techniques to stabilize daily routines and resolve interpersonal problems	Prevents relapse	Depressive episodes
Family-focused therapy ^{28,29}	A combination of psychoeducation, communication, and problem-solving skills training	Reduces mood symptoms, number of depressive relapses, and time depressed. Increases adherence	Depressive episodes

IPSRT: interpersonal and social rhythm therapy

(IPSRT) (Table 3).²⁸⁻³⁰ Psychoeducation alone or combined with other interventions can decrease the risk of relapse and hospitalization and improve adherence.²⁸ In a 2-year study of 50 euthymic BD patients treated with lithium who participated in a brief hospital-based psychoeducation program, Even et al³¹ found patients' knowledge about lithium but not their attitudes changed significantly after the program. The changes persisted 2 years after the intervention, with a trend toward a decreased hospitalization rate.

Miklowitz³² reported on 293 BD patients randomized to receive collaborative care (3 psychoeducational sessions delivered over 6 weeks) or 1 of 3 types of intensive psychotherapy: CBT, IPSRT, or family-focused therapy. Attrition was similar for both groups. Compared with those receiving collaborative care, significantly more patients receiving intensive psychotherapy recovered after 1 year, and did so in shorter time.

In a 3-year, multi-site Veterans Administration (VA) study, 306 BD patients received psychoeducation and support from nurse care coordinators who were responsible for access, continuity of

care, and information flow to psychiatrists or usual care according to VA guidelines.³³ Compared with the usual care group, patients who received psychoeducation and support from nurse care coordinators had shorter duration of manic episodes and improved function and quality of life. A meta-analysis³⁰ of 12 randomized controlled trials of CBT in BD showed a medium effect size of CBT on adherence at 6 months post-treatment.

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Psychoeducation alone or combined with other interventions can reduce relapse risk and improve adherence



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A meta-analysis found CBT had a medium effect size on adherence in bipolar disorder

Related Resource

- Deegan PE. The importance of personal medicine: a qualitative study of resilience in people with psychiatric disabilities. *Scand J Public Health Suppl.* 2005;66:29-35.

Drug Brand Names

Aripiprazole • Abilify	Olanzapine • Zyprexa
Asenapine • Saphris	Olanzapine/fluoxetine • Symbyax
Bupropion • Wellbutrin	Paroxetine • Paxil
Carbamazepine • Carbatrol, Tegretol	Quetiapine • Seroquel, Seroquel XR
Carbamazepine extended-release • Equetro	Risperidone • Risperdal
Clozapine • Clozaril	Risperidone long-acting injectable • Risperdal Consta
Divalproex • Depakote, Depakote ER	Selegiline • Eldepryl, Emsam
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Lithium • Eskalith, Lithobid	
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Bottom Line

Including patients' perspectives and goals in treatment planning is key to maximizing treatment adherence. This may include personalizing pharmacotherapy by using a formulation and combination the patient tolerates best and augmenting medication with psychoeducation and cognitive-behavioral, interpersonal, or family-focused therapy.

Box

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