Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy

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INTRODUCTION

Adherence to pharmacotherapy is often poor in chronic medical illnesses, including bipolar disorder [1-3]. Poor adherence is usually addressed during maintenance-phase treatment when patients are euthymic and stable.

This topic reviews management of poor adherence to medications in bipolar disorder. Selecting a treatment regimen for maintenance treatment of bipolar disorder and the adjunctive psychotherapies that are used for maintenance treatment are discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment" and "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies".)

DEFINITIONS

Bipolar disorder — Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [4]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience hypomanic and major depressive episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults:

Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

Medication adherence — Adherence to pharmacotherapy encompasses taking medication as prescribed with regard to dose, frequency, and timing [5]. Adherence can be quantified on a continuum as a percentage of doses taken as prescribed during a specific interval, or expressed categorically as good, partial, and poor adherence [6]. It is not known what level of adherence is required for good outcomes such as avoiding relapse. Common but arbitrary cutoffs for good adherence are taking at least 70 or 80 percent of prescribed doses [7].

Adherence within patients can change over time and vary between different drugs [8]. As an example, a prospective observational study of patients with bipolar disorder (n = 88) found that adherence was worse with psychotropic medications than medications prescribed for general medical illnesses [9].

EPIDEMIOLOGY OF NONADHERENCE

Prevalence — Many studies have found that poor adherence with pharmacotherapy occurs in roughly 50 percent of bipolar patients [8,10-21]. As an example:

- A retrospective registry study (n >44,000 bipolar patients prescribed lithium or anticonvulsants) found that poor adherence occurred in about 46 percent, and that the median duration of adherence was 270 days [22].
- A prospective observational study of patients (n = 275) in maintenance treatment who were followed for up to three years found that nonadherence occurred in 50 percent [23].

However, a wide range of values for poor adherence in bipolar disorder have been reported; prevalence rates vary from 7 to 65 percent [7,24,25].

Studies of adherence in bipolar disorder include retrospective analyses of relatively large registries and administrative claims databases, as well as prospective or retrospective studies of clinical samples that are generally smaller. Different objective and subjective methods have been used to quantify adherence, such as counting pills; measuring serum drug concentrations; pharmacy refill records; electronic monitoring of pill bottle caps that record the opening of the bottle; electronic monitoring of blister pill packs; and reports from patients, clinicians, and family members [6,7,26]. Studies also differ in their definition of adherence, the clinical status (euthymic, depressed, or manic/hypomanic) of patients when they were assessed for

adherence, and length of follow-up, as well as the patients' course of illness (eg, lifetime number of mood episodes) at the time of assessment.

Long-acting injectable antipsychotics — Although long-acting injectable antipsychotics (eg, risperidone) are considered an option for nonadherent patients [7,27], these drugs do not necessarily improve adherence. In a retrospective study of bipolar patients (n = 221) who received long-acting injectable second generation antipsychotics, nonadherence occurred in 47 percent; in patients (n = 413) treated with long-acting injectable first-generation antipsychotics, nonadherence occurred in 48 percent [11].

Risk factors — There are many potential risk factors for poor medication adherence that may act individually or in concert [7,28]. In addition, the reasons for poor adherence may change over time. Factors that are associated with nonadherence across multiple studies include:

- **Comorbid substance use disorders** – This factor appears to be associated with poor adherence more than any other factor [7,10,18,20,29-36].
- **Side effects** – Poor adherence is associated with adverse effects (eg, cognitive dysfunction, extrapyramidal symptoms, sedation, sexual dysfunction, and weight gain) as well as fear of side effects (eg, the medications are addictive) [7,12,14,20,23,26,30].
- **Patient insight and beliefs** – Adherence is worse among bipolar patients who [7,12,13,17,23,36-39]:
  - Deny that they are ill
  - Believe the illness is not severe
  - Have negative attitudes toward medications (eg, "Drugs are useless," "I'm tired of taking medications," or "They remind me that I'm sick")

Poor adherence is also associated with polypharmacy [7,20,40]; difficulty with medication routines [39,41]; cognitive impairment [7,42]; comorbid personality disorders [7,14,43]; impulsivity [44]; more severe symptoms of bipolar disorder [7,36]; younger age (eg, <40 years) [7,10,22,31,36]; nonwhite race [7,31]; never married, separated, or divorced marital status [7,31,32]; and homelessness [36].

Consequences — Based upon multiple retrospective analyses of administrative claims databases with thousands of bipolar patients, nonadherence is associated with [11,45-47]:

- Emergency department visits (both all cause and for psychiatric diagnoses)
- Hospitalizations (both all cause and for psychiatric diagnoses)

Studies of clinical samples also suggest that nonadherence may lead to recurrent mood episodes [7,32,36,48] as well as more suicide attempts [7,36] and hospitalizations [7,14,19,31,36].

Beyond the direct costs of hospitalizations [31], nonadherence is associated with increased indirect costs due to absenteeism, disability, and worker's compensation [24]. In addition, noncompliance that is not recognized by clinicians can leave them with the false impression that patients are treatment-resistant, which may lead to unnecessary dose increases, medication switches, or adjunctive medications [26].

In general medical patients, good adherence to drug therapy, compared with poor adherence, is associated with lower mortality [49].

MANAGEMENT

General approach — Nonadherence takes many forms, and it is important to distinguish patients who decline pharmacotherapy from patients who are willing to take their medications but do not do so for reasons such as forgetting, misunderstanding instructions, or misinformation about pharmacotherapy (eg, "I don't want to get addicted") [26]. The reasons for nonadherence influence the interventions that are selected to improve adherence.

It is worthwhile determining how patients understand their illness (eg, asking "What do you think causes bipolar disorder?", "How does it affect you?", and "Can it be controlled?"), and exploring patients' attitudes and expectations of treatment [50]. Irrational or erroneous beliefs about medications, negative attitudes towards pharmacotherapy, and the desire to manage the illness without medication can all interfere with adherence. In addition, it is helpful to know whether patients think they are at risk for recurrences and if so, what are the consequences. Patients who understand the personal consequences of recurrences may better absorb general information about the risk of recurrence.

Three prerequisites for patient adherence to pharmacotherapy are that the regimen should be [50]:

- Acceptable – Patients are more likely to accept pharmacotherapy if they can acknowledge their illness.
- Understandable – Does the patient understand the rationale for the drug regimen? As an example, euthymic patients may not realize the need for maintenance therapy.
- Manageable – Practical issues often affect adherence.

Patients who are prescribed maintenance pharmacotherapy are likely to be nonadherent at some point. Clinicians should adopt a long-term perspective and try to use episodes of nonadherence as a learning tool for patients [26].

To promote adherence to treatment at the onset of therapy, patients starting pharmacotherapy should be told the following [7,50-56]:

- Take the medication as prescribed rather than on an as-needed basis.
- There may be a lag of at least one week before a discernible response is apparent.
- Side effects frequently occur during the first few days, but typically resolve within a week of starting the medication.
- If a dose is missed, the next scheduled dose should not be doubled.
- If medication is effective, it is important to continue treatment for several (eg, six) months, even if symptoms remit sooner, to prevent relapse. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Maintenance of medications'.)
- Call to discuss side effects or other concerns or questions.
- Talk with the prescribing clinician before stopping medications.

Techniques that can improve medication adherence include the following [7,50-56]:

- Help patients accept the diagnosis
- Ask about prior use of pharmacotherapy
- Discuss with patients their expectations of benefits and adverse effects
  - Elicit and emphasize benefits that are important to the patient
  - Negative expectations about the effects of medications can diminish therapeutic efficacy and amplify unwanted side effects (see 'Negative expectations' below)
- Discuss plans for dose titrations and how the clinician will monitor the use and benefit of medications
- Provide simple and clear written instructions for taking prescribed medications
- Suggest pill boxes to organize daily doses

- Suggest the use of cues (eg, smartphone alarms, a written record, or pairing pill taking with another regular activity such as eating breakfast) as a reminder to take medications
- Ask about the patient's ability to follow the regimen and address barriers to adherence
- Discuss the need to maintain pharmacotherapy despite feeling better
- Praise desirable behavior and results

Knowledge about bipolar disorder may also aid adherence. As an example, patients who become depressed after starting a medication may incorrectly attribute the depressive syndrome to the drug, rather than the course of illness. In addition, pharmacotherapy may preserve or increase cortical gray matter, white matter integrity, and hippocampal volume. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Mechanism of action'.)

Therapeutic alliance — It may be possible to enhance adherence by developing a therapeutic alliance (relationship) with patients and encouraging them to actively participate in treatment as partners [7,36,57]. A prospective study of bipolar patients (n >3000) followed for up to one year found that positive perceptions of collaboration with and empathy from psychiatrists was associated with better medication adherence [58]. In addition, a study of depressed patients reported a high rate of medication adherence (85 percent) that was attributed to alliance building, which involved providing information about the illness and treatment, and approaching treatment as an experiment in which clinicians, patients, and family members were co-investigators [54].

One model of the therapeutic alliance hypothesizes that the quality of the therapeutic relationship is better when clinicians and patients [59]:

- Agree on the goals of treatment – Few patients pursue treatment with the goal of obtaining medications [50]. Rather, they want relief (eg, to sleep better or return to work).
- Agree on the tasks to be completed to achieve the goals – It is helpful for patients to understand that adherence is not about control and obedience [26]. Rather, adherence is a means for patients to reach their goals.
- Develop a bond (like and trust one another).

Suggested questions to ask patients include, "Do you think I understand your concerns?" and "Is there anything I can do to help you become more willing to take your medicines?"

Some situations demand that clinicians act without patient approval (eg, involuntary admission and court-ordered treatment) [50]. Nevertheless, by listening to patients and attempting to address their concerns, patients may feel that their point of view matters.

Monitoring — Multiple methods are available to monitor adherence and using more than one may provide more accurate estimates. Adherence is typically monitored through patient interviews, and less often by interviewing family members and reviewing medical records [26]. Clinicians should ask patients about adherence behavior and attitudes in a nonjudgmental manner. One approach is to begin by stating, "It can be difficult to always take your medication," and then asking, "Have you had any problems with that?" or "Do you think you might have problems?" Asking about problems with adherence is thought to be more useful than simply asking whether patients are taking their medications. Additional useful questions include:

- What time of day do you take your medications?
- Where do you store your medications?
- How do you remember to take your medications? Does someone help or remind you?
- How do feel about taking your medications?
- Are the medicines helpful?
- What do you dislike about taking the medicines?
- Do the medicines cause side effects?
- Do you plan to continue taking your medications?
- Have you ever skipped taking your medications on purpose?

For patients who acknowledge poor adherence, follow-up questions should explore the reasons (eg, "What gets in the way of taking your medications?" or "Did you feel better when you stopped the medicines?"). Clinicians often ascribe noncompliance to incorrect reasons [39].

Monitoring serum concentrations, which is required for some medications (eg, lithium, valproate, and carbamazepine) to achieve therapeutic levels and avoid toxicity, can also indicate the level of adherence. Serum concentrations of other drugs that do not have established therapeutic levels can nevertheless be assayed to check whether patients are taking any of their drugs.

The frequency of monitoring adherence depends upon the patient's clinical status and presumed level of adherence [26]. A lack of response to treatment, noticeable change in symptoms, or missed appointments should prompt an assessment. In addition, well-known patients who are thought to be fully compliant are generally assessed every one to three months. Relatively new patients who regularly adhere to treatment are monitored monthly. Patients whose adherence is problematic or who are not responding to treatment are monitored weekly.

Other methods to monitor adherence include validated self-administered scales (eg, the Medication Adherence Rating Scale, which is in the public domain) and clinician administered scales (eg, the Brief Adherence Rating Scale, which is in the public domain), counting pills in the bottle, checking pharmacy records for missed refills, and electronically monitoring pill bottle caps to detect each time the bottle is opened [26,60,61]. However, these methods are not standard clinical practice and are generally limited to research settings.

All methods used to monitor adherence are potentially inaccurate [6]. Patient self-report and clinician rating are the most common means of assessing adherence and both tend to underestimate noncompliance [6,26,62]. Even electronic monitoring, which is regarded as the gold standard, can be compromised by patients removing more than one dose at a time, failing to replace the cap before the next dose, or opening the bottle solely to check how much medication is left.

Customized pharmacotherapy — We suggest clinicians take a flexible approach and accommodate patient preferences to the extent that they are feasible [7]. One option when selecting a medication is to provide a list of possibilities and allow patients to make the final choice [50]. In addition, patients are more likely to adhere to treatment if they choose the drug formulation (eg, extended release pills, sublingual tablets, transdermal patches, and liquid), frequency of doses, and timing of administration. In addition, some patients with bipolar disorder want to try a drug regimen that differs from their current regimen [63]. Many patients prefer simpler regimens with fewer drugs that are prescribed less often per day [7]. Studies in bipolar disorder as well as multiple reviews of different illnesses indicate that adherence is superior with medications administered once per day compared with more frequent doses [53,64,65].

Some patients avoid medications because they are not "natural." It may be possible to accommodate this belief by suggesting lithium, which is found in nature as a salt [66]. In addition, lithium can be administered once daily. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Lithium dose and serum concentrations'.)

One option for maintenance treatment of bipolar disorder is a long-acting injectable antipsychotic (eg, risperidone), but this option is used infrequently because many patients dislike injections [27]. In addition, long-acting injectable antipsychotics do not necessarily improve adherence. (See 'Prevalence' above.)

Access to clinicians — Bipolar patients who perceive that their clinicians are available report better medication adherence [7]. Thus, clinicians are encouraged to optimize their availability (eg, open the clinic during evening hours) [53]. We suggest informing patients to consult the clinician if problems arise and before discontinuing medications. In addition, ask patients [26]:

- Is it difficult to get an appointment when you feel you need to see me?
- When you call the office with a question about your illness or medications, do you get an answer? Do you have to wait long?

Negative expectations — Negative expectations about the effects of medications can diminish therapeutic efficacy and amplify unwanted side effects; adverse outcomes that are induced by psychological factors are referred to as nocebo effects [67]. As an example, a study found that negative expectations regarding treatment were related to bipolar patients discontinuing lithium [68].

Clinicians can manage negative expectations about medications by [67]:

- Explaining the desired therapeutic effects (eg, "Lithium reduces the risk of relapse by almost 50 percent") when discussing potential side effects. It may be helpful to elicit benefits that are meaningful and specific to the patient; doing so communicates understanding and acceptance. Explain that it may take several weeks for the benefits to manifest.
- Ensuring that patients understand that many side effects are transient and benign. In addition, side effects can be reframed as an indication that the medication is working.
- Discussing techniques for coping with side effects other than stopping the drug.

Specific interventions — Specific interventions for maintaining or improving adherence to pharmacotherapy for bipolar disorder typically consist of psychosocial interventions that include an element that addresses adherence [1,2]. In nearly all psychosocial interventions that support adherence, psychoeducation constitutes either a major component of the intervention or the entire intervention [7,60]. However, many interventions are complex and require substantial resources [60], and adherence-enhancement interventions are more likely to be adopted if they are readily available, affordable, and practical [7].

Evidence supporting the use of interventions for medication adherence in bipolar disorder includes a meta-analysis of 18 randomized trials (n >1300 patients) that compared specific interventions with control conditions [60]. Active treatment included psychoeducation, cognitive-behavioral therapy, or family therapy; control conditions included usual care. The median number of treatment sessions was 17 and the median length of follow-up after the last treatment session was six months. Adherence was two times more likely with specific interventions than control conditions (odds ratio 2.3, 95% CI 1.5-3.6). However, heterogeneity across studies was moderate.

Separate topics discuss the adjunctive psychotherapies that are used for maintenance treatment of bipolar disorder, as well as choosing a specific psychotherapy for maintenance treatment. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies" and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Choosing adjunctive psychotherapy'.)

Group psychoeducation — Psychoeducation is often considered the treatment of choice for improving adherence [69]. Multiple randomized trials indicate that group psychoeducation can enhance medication adherence in bipolar disorder [70]:

- A 21-week randomized trial compared group psychoeducation with a nonspecific support group as add-on treatment in 120 euthymic patients who were receiving pharmacotherapy; both groups met weekly for 90 minutes, and patients were followed for up to two years after treatment [71]. Lithium serum concentrations were greater in the subgroup of patients who received psychoeducation (n = 49) than the subgroup that received nonspecific support (n = 44) (0.8 versus 0.7 mEq/L [0.8 versus 0.7 mmol/L]) [72]. This benefit was consistent with the finding in the total sample that prevention of relapse was superior with psychoeducation.

- A six-week randomized trial compared group psychoeducation (weekly sessions, each lasting 90 to 120 minutes) with a control condition (weekly group sessions, each lasting 5 to 10 minutes) as add-on treatment in 71 euthymic patients who were receiving pharmacotherapy [73]. Approximately 40 percent of patients in each group were adherent at study enrollment. At the end of treatment, the number of patients who were adherent was greater in the group who received psychoeducation, compared with the control group (80 versus 31 percent of patients).

- A six-week randomized trial compared group psychoeducation (a 12-minute videotaped lecture and written information about the use of lithium) plus a home visit with a waiting-

list control group in 60 patients receiving lithium [74]. Improvement of adherence (reduced number of missed doses) was greater in patients who received active treatment.

In addition, a 12-week randomized trial compared group psychoeducation (weekly sessions lasting 90 minutes) plus pharmacotherapy with pharmacotherapy alone in 53 remitted patients; each patient assigned to group psychoeducation attended the sessions with a companion (eg, spouse) [75]. Adherence during follow-up lasting 48 weeks was superior with active treatment.

Another randomized trial compared group psychoeducation plus pharmacotherapy with individual CBT plus pharmacotherapy in 204 remitted bipolar patients [76]. Medication adherence was excellent in both treatment arms. However, group psychoeducation was more efficient. Psychoeducation was administered in six sessions in a group format (minimum of four patients per group), with each session lasting 90 minutes. By contrast, CBT was administered individually (one therapist and one patient) over 20 sessions, with each session lasting 50 minutes. Also, administering group psychoeducation requires less training and skill than is needed for CBT [77].

Patients who complete psychoeducation may perhaps benefit from a serious game, which involves a computer application that provides a fun means of learning and accomplishing a goal. In a small, open-label, one-month randomized trial in 41 euthymic patients with bipolar disorder, medication adherence at baseline was less in patients who received a serious game rather than usual care [78]. Subsequently, at the one- and four-month assessments, adherence in the two groups was comparable.

The administration, content, and efficacy of adjunctive group psychoeducation for the maintenance treatment of bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Group psychoeducation'.)

Cognitive-behavioral therapy — CBT can help bipolar patients adhere with pharmacotherapy. A meta-analysis of randomized trials (number of trials and study patients was not reported) compared CBT with a control condition and found a significant, clinically moderate effect favoring CBT [79]. Additional information about the use of CBT for the maintenance treatment of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Cognitive-behavioral therapy'.)

Family therapy — Enlisting family members and significant others to support the use of pharmacotherapy can enhance adherence. Family members can promote optimism about treatment, assist with adherence, and provide information about barriers to adherence [55,56]. Family psychoeducation is indicated if family members are advising patients to not take their

medications [33]. Evidence for the efficacy of adjunctive family therapy includes randomized trials:

- A nine-month randomized trial (n = 101 remitted bipolar patients) compared family therapy (21 one-hour sessions) plus pharmacotherapy with pharmacotherapy augmented by two psychoeducation sessions, each lasting one hour [80]. Family therapy and psychoeducation sessions were conducted in patients' homes, and patients were followed for up to two years. Medication adherence was better in patients who received family therapy.

- An 11-month randomized trial that compared marital therapy focused upon psychoeducation plus pharmacotherapy with pharmacotherapy alone in 33 bipolar patients who completed the study [81]. Each couple met with their therapist for up to 25 sessions. Adherence was greater in the group that received adjunctive marital therapy.

Additional information about the use of family therapy for the maintenance treatment of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Family therapy'.)

Integrative therapy — This adjunctive treatment integrates psychoeducation, family therapy, cognitive remediation, mindfulness training, and physical health care for patients with bipolar disorder [82,83]. Treatment typically occurs in a group format but can be implemented individually. A 12-week randomized trial compared usual care alone with usual care plus integrative therapy (weekly group sessions lasting 90 minutes) in 94 patients who were either euthymic or had subthreshold bipolar symptoms [83]. Improvement of psychosocial functioning and subsyndromal depression was greater with add-on integrative therapy; however, attrition was substantial.

Other options — Other interventions that may possibly reinforce adherence include:

- **Motivational interviewing** – Motivational interviewing is used to enhance adherence in many illnesses, including bipolar disorder [7]. A three-week prospective observational study of motivational interviewing (one individual meeting and two follow-up telephone sessions) in 14 bipolar patients found that the therapy improved medication adherence [84].

  The basic aim of motivational interviewing is to help patients acknowledge that adherence with pharmacotherapy is problematic, make a commitment to change their behavior, and take action to change. The general approach is to initially ask questions and to give advice

later. Other elements include expressing empathy (eg, "I know this is hard"), focusing upon collaboration, and avoiding arguments.

Treatment sessions explore the:

- Physical, psychological, and psychosocial effects of bipolar disorder and nonadherence upon the patient's life
- Pros and cons of nonadherence
- Value and meaning of nonadherence in the patient's life
- Patient's goals in life
- Motivations for changing medication behavior (potential benefits)
- Ambivalence about and barriers to changing medication behaviors
- Discrepancy between the patient's current state of functioning and desired future state

- **Customized adherence enhancement** – Customized adherence enhancement initially identifies bipolar patients who poorly adhere to medications and the reasons for noncompliance, and then administers up to four intervention modules based upon those reasons [85,86]. The modules are psychoeducation about bipolar disorder, motivational interviewing for substance abuse, communicating with clinicians about treatment planning, and medication routines. Treatment is administered over four weekly, individual, 60-minute sessions with two follow-up telephone sessions. A six-month prospective observational study in 43 patients with poor adherence found that customized adherence enhancement was associated with improved adherence, symptoms, and functioning [87].

- **Telephone- and internet-based interventions** – Telephone- and internet-based interventions may improve treatment adherence in bipolar disorder [88]. As an example, a six-month randomized trial compared pharmacotherapy plus semimonthly telephone calls with pharmacotherapy alone in patients discharged from the hospital (n = 120, 20 percent with bipolar disorder) [89]. After adjusting for potential confounding factors (eg, age, diagnosis, and number of medications), the analyses found that medication adherence was greater in patients who received adjunctive telephone calls (odds ratio 7, 95% CI 2-23). In addition, pooled data from two randomized trials found that smartphone-based monitoring of adherence to medication is valid compared with a validated paper-based adherence questionnaire [90].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

SUMMARY

- Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [4]. (See 'Bipolar disorder' above and "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

- Adherence to pharmacotherapy encompasses taking medication as prescribed with regard to dose, frequency, and timing. Common but arbitrary cutoffs for good adherence are taking at least 70 or 80 percent of prescribed doses. (See 'Medication adherence' above.)

- Many studies have found that poor adherence with pharmacotherapy occurs in roughly 50 percent of bipolar patients. Long-acting injectable antipsychotics do not necessarily improve adherence. Factors that are associated with nonadherence include comorbid substance use disorder, side effects, and patient beliefs. (See 'Epidemiology of nonadherence' above.)

- Techniques that can improve medication adherence include the following: help patients accept the diagnosis; discuss with patients their expectations of benefits and adverse effects, how the clinician will monitor the use and benefit of medications, the clinician's availability for questions about treatment, and plans for dose titrations; elicit benefits that are important to the patient; provide written instructions for taking prescribed medications; suggest using pill boxes and cues as a reminder to take medications; ask about the patient's ability to follow the regimen and address barriers to adherence; discuss the need to maintain pharmacotherapy despite feeling better; identify poor adherence; and reinforce desirable behavior. (See 'General approach' above.)

- Aspects of treatment relevant to medication adherence include developing a therapeutic alliance, monitoring adherence, customizing pharmacotherapy, providing access to the clinician, and managing negative expectations. (See 'Therapeutic alliance' above and 'Monitoring' above and 'Customized pharmacotherapy' above and 'Access to clinicians' above and 'Negative expectations' above.)

- Randomized trials indicate that adherence to pharmacotherapy for bipolar disorder can be enhanced with group psychoeducation, cognitive-behavioral therapy, family therapy, and online mental health resources. (See 'Specific interventions' above.)

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