FEATURE: IAN WARD, MMS, PA-C

Pharmacologic options for bipolar disorder

Lithium has been the mainstay of treatment for decades, but several other classes of medication have recently been used with varying degrees of success.

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Patients with bipolar disorder have high relapse rates.

Bipolar disorder is a mood disorder that affects 2% of the population worldwide and is associated with high rates of relapse and suicide.[1] Statistics on relapse rates show the difficulty of treating bipolar disorders; patients with stable bipolar disorder relapse into either mania or depression at a rate of 37% after 1 year and 60% after 2 years.[1] Patients who have bipolar disorder can present with manic or depressive episodes, and the initial treatment depends on the presentation.

For several decades, lithium or other "mood stabilizer" medications have been the mainstay of treatment for bipolar disorder. Patients taking lithium require regular monitoring to keep a safe and effective level of the drug in the bloodstream; excess lithium causes toxicity. Over the last decade, several other medications in different drug classes have been evaluated in clinical trials and approved by the Food and Drug Administration (FDA). In addition, psychiatrists prescribe many medications "off label" to treat bipolar disorder.[2]

Angst et al[3] provide compelling numbers on the importance of treating bipolar disorder and other mental health disorders over the long term. Over the course of 22 to 38 years, their study followed 406 patients with bipolar disorder. The rate of deaths from suicide was significantly lower in those treated with maintenance therapy than in those who did not receive treatment (6 vs 27 deaths).

The purpose of this article is to review the current best practices and recommendations

for the treatment of bipolar disorder, including mania and depression, and for long-term therapy.

Characteristics and diagnostic criteria

Bipolar disorder is categorized as bipolar I or bipolar II. Characteristics of bipolar I disorder include manic episodes (*Table 1*). Patients with bipolar I disorder may also experience hypomania, as described in *Table 2*, and periods of major depression, as described in *Table 3*. The diagnostic criteria for bipolar I disorder are presented in *Table 4*. Bipolar II disorder differs in that patients experience no mania but have at least one episode of hypomania and major depression.[4] The diagnostic criteria for bipolar II disorder are presented in *Table 5*.

Methods

This article researches the most recent meta-analyses and recommendations to arrive at conclusions for the best treatment options for patients with bipolar disorder. The author used PubMed, Google Scholar, UpToDate, and the American Psychiatric Association website to search for published articles. Search terms included *bipolar disorder treatment, mania treatment, bipolar disorder management,* and *bipolar meta-analysis.* Articles based on research directly sponsored by the manufacturer of a medication were eliminated, as were those with a perceived bias or marketing intention. Priority was given to articles completed in the last 5 years. Particular attention was given to articles that focused on medication efficacy and tolerability, and on direct comparisons of treatment regimens.

Treatment of mania

Haloperidol, risperidone, and olanzapine are the best options for treating patients presenting with acute manic episodes, according to a meta-analysis by Cipriani et al.[5] The meta-analysis included 68 studies of the treatment of acute mania, comparing the acceptability and efficacy of various antimanic medications. All trials included patients with a diagnosis of bipolar I disorder, and the trials were double-blinded.

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TABLE 1. Diagnostic criteria for a manic episode[15]

1. A minimum of one week (or any duration if hospitalized) where, for the most part of most days, an abnormal mood is observed. The mood is continually elevated, expansive, or irritable, and there is a persistently increased level of energy and activity towards specific goals.
2. During this period, three or more of the following symptoms are observed (four when the mood is described as irritable). These symptoms are a marked change from usual behavior and are present significantly during the period of mood elevation.
   a. Increased self-esteem or appearing grandiose
   b. Need for lower amounts of sleep (typically 2–3 hours per day).
   c. Increased talkativeness or a subjective feeling of the need to keep talking
   d. An experience of racing thoughts or flight of ideas
   e. Attention is easily distracted
   f. Increased levels of activity towards specific goals (for example, at work or school, socially, or sexually) or an increased level of activity without purpose, leading to psychomotor agitation
   g. Excessive risk-taking activities with potentially bad outcomes (eg, promiscuity or misguided financial decisions)
3. The severity of mood disturbance causes impaired social functioning, impaired functioning at work, requires hospitalization, or involves psychotic episodes.
4. The mood change is not due to a medical condition or the effects of a substance.

Notes: One manic episode in a lifetime is required to diagnose bipolar I disorder. A manic episode is defined by criteria 1–4 above, or by an episode that occurs during antidepressant treatment and persists beyond the effect of that treatment.

TABLE 2. Diagnostic criteria for a hypomanic episode[15]

1. A minimum of four days where, for the most part of most days, an abnormal mood is observed. The mood is continually elevated, expansive, or irritable, and there is a persistently increased level of energy and activity.
2. During this period, three or more of the following symptoms are observed (four when the mood is described as irritable). These symptoms are a marked change from usual behavior and are present significantly during the period of mood elevation.
   a. Increased self-esteem or appearing grandiose
   b. Need for lower amounts of sleep (typically 2–3 hours per day).
   c. Increased talkativeness or a subjective feeling of the need to keep talking
   d. An experience of racing thoughts or flight of ideas.
   e. Attention is easily distracted
   f. Increased levels of activity towards specific goals (eg, at work or school, socially, or sexually) or an increased level of activity without purpose, leading to psychomotor agitation
   g. Excessive risk-taking activities with potentially bad outcomes (eg, promiscuity or misguided financial decisions)
3. There is a definite change in the level of functioning of the individual compared to functioning when asymptomatic.
4. The change in mood and level of functioning is noticeable to others.
5. The severity of mood disturbance does not cause markedly impaired social functioning, markedly impaired functioning at work, require hospitalization, or involve psychotic episodes.
6. The mood change is not due to a medical condition or the effects of a substance.

TABLE 3. Diagnostic criteria for a major depressive episode[15]

1. Over a continual two-week period, five or more of the symptoms below are present. These symptoms are not due to a medical condition and are different from the individual's previous level of functioning. One of the five symptoms must be either (a) depressed mood or (b) anhedonia.
   a. Depressed mood for the most part of most days; the mood can be self-reported or observed by others; for those aged less than 18 years, the mood can be irritable.
   b. Anhedonia (eg, almost or complete loss of pleasure or interest in daily activities)
   c. Reduced or increased appetite, or marked unintended weight loss or gain
   d. Increased or reduced level of sleep most days
   e. Restlessness or slowing down, which can be noticed by others on most days
   f. Feeling fatigued or lacking energy most days
   g. Feeling worthless or guilty; these feelings may be delusional or excessive.
   h. Reduced concentration levels or ability to think, or being indecisive most days
   i. Recurring suicidal ideation; this may occur with or without a specific plan or attempted suicide
2. The individual has significant distress or functional impairment in important areas of the daily life.
3. The mood change is not due to a medical condition or the effects of a substance.

TABLE 4. Diagnostic criteria for bipolar I disorder[15]

A. At least one episode meets the criteria for a manic episode (criteria 1–4 under "Diagnostic criteria for a manic episode" in *Table 1*).

B. The manic episode(s) and any major depressive episode(s) are not better diagnosed as a different psychotic disorder.

TABLE 5. Diagnostic criteria for bipolar II disorder[15]

A. At least one episode meets the criteria for a hypomanic episode (criteria 1–6 under "Diagnostic criteria for a hypomanic episode" in *Table 2*), and there has been at least one major depressive episode (criteria 1–3 under "Diagnostic criteria for a major depressive episode" in *Table 3*).

B. There is no history of any manic episodes.

C. The hypomanic episode(s) and any major depressive episode(s) are not better diagnosed as a different psychotic disorder.

D. The individual has significant distress or functional impairment in important areas of daily life, due to depressive symptoms or unpredictable fluctuations between periods of hypomania and depressive episodes.

Researchers used patients' rating of symptoms to define efficacy and patients' discontinuation of treatment within 3 weeks after initiation of the treatment to determine acceptability. For the treatment of acute mania, haloperidol, risperidone, and olanzapine showed the best efficacy results, which were superior to those of 5 other drugs studied: valproate, gabapentin, topiramate, lamotrigine, and ziprasidone. For acceptability, olanzapine, quetiapine, risperidone, and haloperidol scored highest. Other drugs compared and found to have inferior acceptability were lithium, placebo, topiramate, gabapentin, and lamotrigine.

A second meta-analysis of antimanic treatments, conducted by Yildiz et al,[6] focused on direct comparisons of individual medications and on effects of classes of medication. Second-generation antipsychotic medications in general and haloperidol (a first-generation antipsychotic) proved more effective than mood stabilizers (lithium, valproate, and carbamazepine) for the treatment of acute mania. The differences in efficacy among the antipsychotics were inconclusive for recommending specific medications.

Persons with acute mania can present in either inpatient and outpatient settings. Patients with a previous diagnosis of bipolar disorder may present with severe manic episodes, defined by suicidal ideation, homicidal ideation, psychosis, or aggression. For these patients, continuance of their mood stabilizer (typically lithium or valproate) plus the addition of an antipsychotic leads to a 20% higher rate of response.[7] For patients whose symptoms are resistant to treatment, different combinations of medications are recommended. For example, a patient can switch from lithium to valproate (or vice versa) and/or can change from one antipsychotic medication to another among the choice of haloperidol, olanzapine, quetiapine, and risperidone.[7] Electroconvulsive therapy (ECT) can be reserved as a treatment of last resort for patients with refractory symptoms who have failed a minimum of 4 to 6 combinations of medications.[7]

Treatment of depression in patients with bipolar disorder

Patients who have bipolar disorder and present with major depressive symptoms face a difficult situation because treatment with regular antidepressants can precipitate a swing into a state of mania or rapid cycling between manic and depressive symptoms. Bobo and Shelton[8] present clinical trial evidence against the use of antidepressants as monotherapy in patients with bipolar disorder. However, these authors also present evidence for the limited use of antidepressants in conjunction with a mood stabilizer or antipsychotic. The

TABLE 6. Main polarity benefit of maintenance treatments for bipolar disorder[10]

Medication	Mania	Depression
Lithium	Yes	Some
Aripiprazole	Yes	No
Olanzapine	Yes	No
Adjunctive quetiapine	Yes	Yes
Risperidone long-acting injectable	Yes	No
Adjunctive ziprasidone	Yes	No
Lamotrigine	No	Yes

best-studied therapy with effective results for the treatment of depression in patients with bipolar disorder is fluoxetine plus olanzapine, now available as a combination drug.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE)[9] made recommendations for the treatment of bipolar disorder after consulting with experts and agreed with the recommendation of the fluoxetine and olanzapine combination. NICE also recommends quetiapine as a good adjunct to the antidepressant prescribed.

Transitioning from acute to maintenance treatment

Transitioning patients from the acute treatment of bipolar disorder to long-term maintenance therapy requires careful management. The rates of relapse and suicide are higher among patients with bipolar disorder than among those with many other diseases and disorders. Manning[10] provides a methodology to monitor adverse effects, symptom reduction, and signs of relapse. The author proposes the use of common rating scales to judge patient outcomes. These include the Patient Health Questionnaire 9 (PHQ-9) for symptoms of depression and the National Institute of Mental Health Life-Chart Method (NIMH-LCM) to track the long-term efficacy of bipolar disorder maintenance therapy. Manning[10] proposes continuation of the medication(s) used for acute remission, with thorough monitoring of response levels.

Maintenance treatment of bipolar disorder

The FDA has approved 7 medications for the maintenance treatment of bipolar disorder: lithium, lamotrigine, aripiprazole, olanzapine, quetiapine (as an adjunct), ziprasidone (as an adjunct), and long-acting injectable (LAI) risperidone.[11] Most patients with bipolar disorder demonstrate polarity, relapsing more frequently into either mania or depression. Patient polarity influences the choice of maintenance treatment (*Table 6*). Lamotrigine or quetiapine reduces depressive relapses in patients who have a depressive polarity. For patients with a mania polarity, the recommended therapies are lithium, aripiprazole, olanzapine, LAI risperidone, and either ziprasidone or quetiapine with mood stabilizers.[10]

Miura et al[2] conducted research into the longer-term efficacy and tolerability of the medications used for the maintenance treatment of bipolar disorder. The authors analyzed 33 randomized, controlled trials to determine recommendations. The trials did not distinguish between subtypes of bipolar disorder. The authors concluded that lithium remains a good first-line option for maintenance treatment, but that olanzapine should be considered for

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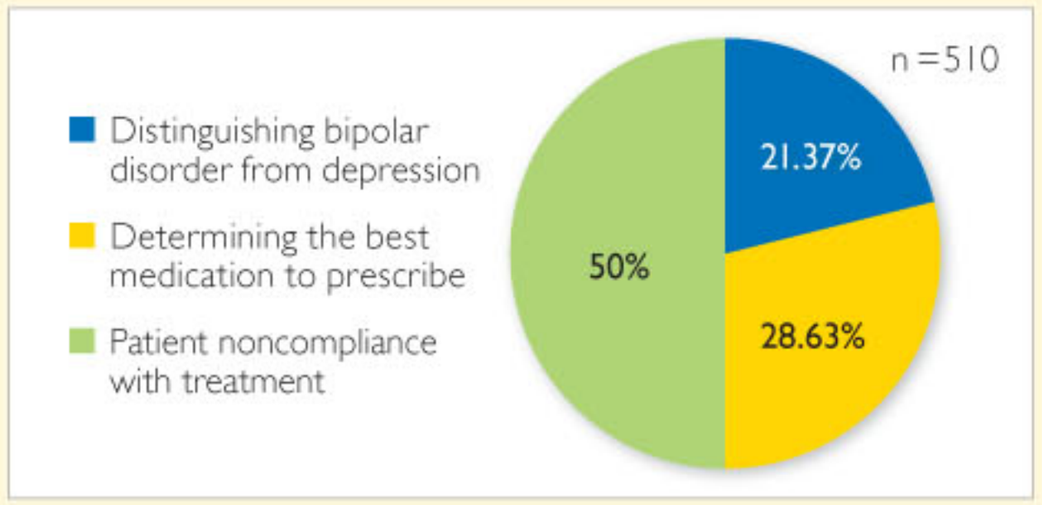
TABLE 7. Long-acting injectable antipsychotic medications[13]

Generic	Brand name	Indication	Dose, mg	Time between injections, d	Overlap with oral medication, wk	Loading dose
Risperidone	**Risperdal Consta**	Bipolar disorder, schizophrenia	12.5–50	14	3	None
Aripiprazole	**Abilify Maintena**	Schizophrenia	160–400	30	2	None
Paliperidone palmitate	**Invega Sustenna**	Schizophrenia, schizoaffective disorder	39–234	28	Variable	Required
Haloperidol decanoate	**Haldol Decanoate**	Psychosis	20–450	28	4	May be required
Olanzapine	**Zyprexa Relprevv**	Schizophrenia	150–405	14–28	Variable	Required
Fluphenazine decanoate	**Prolixin Decanoate**	Psychosis	12.5–100	7–21	1	May be required

POLL POSITION

Which of the following issues is the most difficult that you encounter in patients with bipolar disorder?



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patients with mania-dominant polarity and quetiapine for patients with depression-dominant polarity.

Hayes et al[12] conducted one of the most recent large studies to compare lithium with newer second-generation antipsychotics as maintenance monotherapy for bipolar disorder. The authors concluded that for monotherapy, lithium remains the best option. The time to failure (defined as the need to add a second drug to treat symptoms or the need to stop treatment) was approximately twice as long with lithium. This study adds to evidence for the use of lithium as a first-line drug, with antipsychotics as second-line or adjunct therapies.

Post[4] reviewed the recommendations in recent clinical trials for first-, second-, and third-line options in treating bipolar disorder. The recommended first-choice therapy is continuation of the medication(s) used to treat the acute episode. For second-line options, data show that lithium once again is the superior initial monotherapy. Data also support valproate, quetiapine, and lamotrigine as second-line options for monotherapy, especially for patients who fail or have contraindications to lithium therapy. Third-line options include drug combinations of lithium or valproate with an antipsychotic.

Long-acting injectable medications

A major problem in the treatment of bipolar disorder is patient noncompliance with treatment. Patients may be given short-term intramuscular antipsychotic treatment for acute mania, but the use of LAI antipsychotics in psychiatry has been increasing during the last decade. Presently, several LAI antipsychotics are available (*Table* 7). Although several LAI antipsychotics are used for psychosis and schizophrenia, their use for bipolar disorder is off label. Presently, only Risperdal® Consta®, the LAI form of risperidone, has an FDA-approved indication for the treatment of bipolar disorder.[13]

Future research considerations

In their review, Severus et al[14] do not make additional treatment recommendations but argue for the necessity of further clinical trials. The authors state that trials should enroll broader populations of patients with bipolar disorder (including patients distinguished by subtype and polarity). Ideally, these patients would be naïve to the treatments used in comparisons. The trials should also more frequently involve direct comparisons between medications. The high relapse rates among patients with bipolar disorder suggest that all current medications are less than ideal. Conducting further clinical trials of current medications, as described, would be beneficial, as well as continuing the development of newer treatments.

Conclusions

The treatment of patients with bipolar disorder requires careful monitoring, conducted best with continuation of care by a primary provider skilled in treatment or by referral to a specialist. For the treatment of acute mania, haloperidol, risperidone, and olanzapine show the best efficacy. If the manic patient has a previous diagnosis of bipolar disorder, his or her prior medication should be continued or restarted if needed. For patients who have bipolar disorder presenting with a depressive episode, antidepressant monotherapy should be avoided. Mixed therapy with fluoxetine and olanzapine or another selective serotonin reuptake inhibitor with quetiapine is recommended. For the maintenance treatment of bipolar disorder, the first-line treatment should be continuation of the medications used during the manic or depressive episode. In case of treatment failure, lithium is the best first-line monotherapy, with valproate, quetiapine (for patients with depression-dominant polarity), and olanzapine (for patients with mania-dominant polarity) as viable alternatives. Second-line dual therapy for patients with resistant symptoms should consist of either lithium or valproate with a second-generation antipsychotic. LAI risperidone is available as an option for noncompliant patients. Patients with bipolar disorder continue to have high relapse rates, indicating that further clinical trials are needed to identify the best options for specific subtypes of patients, and that research into new treatment solutions should be continued. ■

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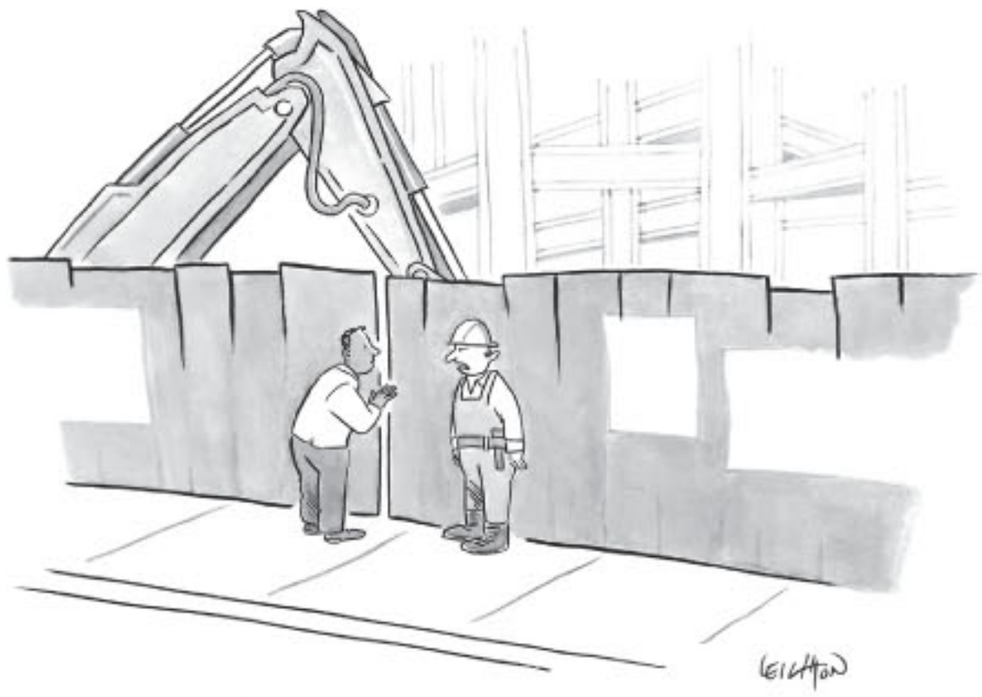
"Where do you see yourself when the hot weather hits?"



"You'll see it when it's done."

"Remember, Joey, life is a good preparation for stocks—lots of ups and downs."