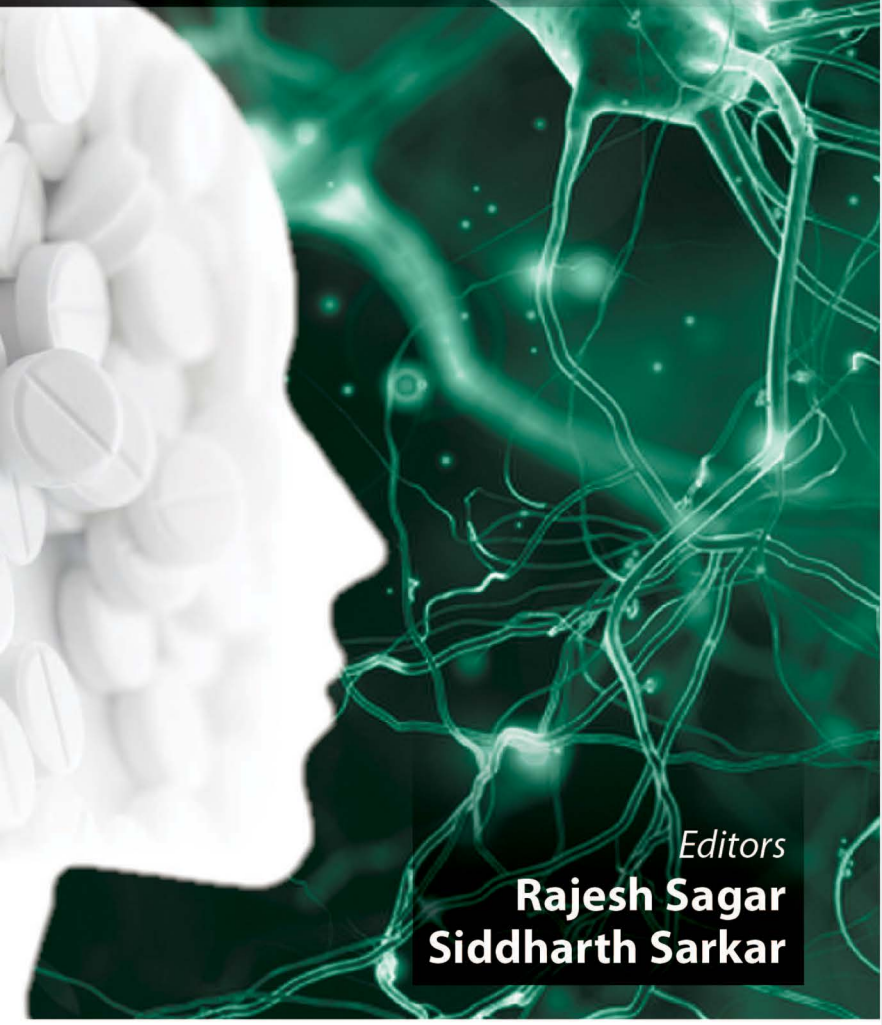
Drug Therapy for Psychiatric Disorders



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CHAPTER 3

Pharmacological Treatment of Bipolar Disorder

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INTRODUCTION

The pharmacological management of bipolar disorder is complex and involves the management of acute episodes of not only depression and hypomania or mania, but also mixed episodes. Treatment of acute episodes also needs to take into account the long-term course of the illness with a high risk of future relapses. The situation in clinical practice is also complicated by the paucity of evidence to support treatment strategies and the complex clinical picture that can be present for many patients including, for example, high rates of comorbid substance misuse, anxiety and other psychiatric illnesses and personality disorders. Unfortunately, there is very limited evidence regarding the management of bipolar disorder in the context of comorbidity. This chapter will review both acute and prophylactic pharmacological treatments for bipolar disorder. It will draw on recent guidelines published by the British Association for Psychopharmacology (BAP).[1] Before the management of different episodes is highlighted, the reader is referred to Table 1 which summarizes the various treatment options for the treatment of bipolar disorder, based on BAP guidance.

TABLE 1: Treatment options for bipolar disorder.

Acute management	
Manic phase	• Antipsychotics such as olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, chlorpromazine • Mood stabilizers lithium, valproate
Depressive phase	• Mood stabilizers: lithium, lamotrigine • Antipsychotics: quetiapine, lurasidone, olanzapine, cariprazine • Olanzapine-fluoxetine combination
Mixed episode	• Olanzapine, aripiprazole, asenapine, quetiapine, lurasidone, cariprazine
Long-term prophylaxis	• Lithium • Other mood stabilizers (valproate, carbamazepine, lamotrigine) • Antipsychotics: quetiapine, aripiprazole, olanzapine, risperidone

ACUTE MANAGEMENT OF EPISODES OF BIPOLAR DISORDER

Mania and Hypomanic Episodes

Manic or hypomanic episodes tend to be easier to manage than depressive episodes in bipolar disorder, with more rapid resolution of symptoms in naturalistic practice.[2] There is also a broad range of treatments that have demonstrable efficacy in treating mania. The oldest of these is lithium, first shown to have antimanic properties by John Cade in 1949.[3] A number of antiepileptic medications also have demonstrable antimanic properties, most prominently valproate but also carbamazepine. However, this is not a class effect of antiepileptics with there being negative data for example for topiramate, gabapentin and lamotrigine. Conversely, it appears that antipsychotics as a class all have antimanic properties including both first- and second-generation drugs and dopamine receptor partial agonists.

All antimanic drugs appear to be of very similar efficacy. There are relatively few studies that have included more than one antimanic treatment, but those that have tend to show little if any difference in effect size between treatments (e.g., lithium versus valproate or aripiprazole vs. haloperidol). However, network meta-analyses have attempted to rank the efficacy of treatments.[4] It is important to recognize that such meta-analyses can be quite influenced by individual studies investigating different populations of patients. For example, the Cipriani network meta-analysis ranked risperidone as the second most efficacious and acceptable antimanic treatment. This was in large part due to one study conducted in India that showed a particularly large effect size and very low dropout rates.[5] This was in contrast to another study of risperidone in acute mania conducted in the United States of America (USA) that showed an effect size very similar to other studies of other second-generation antipsychotics.[6] However, this second study included less severely ill patients, used lower doses of risperidone and had lower completion rates than the one conducted in India. Most studies of antimanic treatments have been conducted in patient cohorts similar to this USA study.

The main factor to consider when choosing between antimanic agents is their side effect profiles. First- and second-generation antipsychotics are associated with different problems. However, it is important not to simply extrapolate data from studies in schizophrenia. For example, the risk of treatment emergent parkinsonism with first-generation antipsychotics appears to be higher in patients with bipolar disorder compared to those with schizophrenia. This has led to the preferential use of second-generation antipsychotics for the management of mania. Other factors may also influence choice of antimanic agent. Most notable is the concern regarding the

risks of valproate in women of childbearing potential of causing polycystic ovary syndrome, teratogenicity and intellectual impairment in infants exposed in-utero. In addition, there are some suggestions that the characteristics of a patient's illness might influence treatment. For example, a very old study suggested that chlorpromazine is more effective than lithium in patients with high levels of behavioral activation.[7] This study has been influential in leading guidelines to recommend antipsychotics ahead of lithium for patients with mania. Perhaps slightly less clear-cut is data suggesting that patients who have had a large number of lifetime manic episodes (10 or more) may be more likely to respond to valproate rather than lithium.[8] This may be of particular relevance in parts of the world where manic, rather than depressive, episodes predominate.

For patients with mania that do not respond to monotherapy, there is evidence that a range of second-generation antipsychotics added to lithium or valproate are more effective than lithium or valproate alone. Beyond this, there is limited data regarding the management of treatment-resistant mania. There is data regarding the use of clozapine, though most of this is observational open-label data. Similarly, there is data supporting the use of electroconvulsive therapy (ECT) for mania, with an apparently similar effect size to that seen in bipolar depression, though again much of the data is nonrandomized.

Depressive Episodes

Naturalistically, bipolar depressive episodes are much harder to treat than manic episodes with longer times to remission. This is compounded by major deficiencies in the evidence base around the treatment of bipolar depression, in particular the role that antidepressants play.

There are extremely few (<10) randomized placebo-controlled studies of antidepressants in bipolar depression in comparison to those in unipolar disorder (hundreds). It is therefore difficult to know whether evidence of efficacy in unipolar depression can be extrapolated to bipolar depression. A meta-analysis of old, mainly very small, studies of a heterogeneous mix of various antidepressants found a nonsignificant effect in bipolar depression.[9] To date, there are only three large/largish placebo-controlled randomized trials of antidepressants in bipolar disorder. The oldest of these was a study that compared olanzapine monotherapy with the combination of olanzapine plus fluoxetine with placebo.[10] This found a significant benefit of olanzapine monotherapy though this related to significant improvements in "inner tension", "reduced sleep" and "reduced appetite" on the Montgomery-Asberg Depression Rating Scale (MADRS) but not on other items such as apparent and reported sadness and pessimistic thoughts. This raises a suspicion that the effect was a nonspecific one and not a true antidepressant

effect. Conversely, the combination of olanzapine plus fluoxetine also significantly separated from placebo but also had a significant effect on most MADRS items. It should be noted that while there were over 350 patients in each of the placebo and olanzapine treatment arms, there were only 82 in the olanzapine plus fluoxetine arm. Given that there was no fluoxetine only arm, it is impossible to know how much the effect seen was due to fluoxetine alone or synergy between fluoxetine and olanzapine. We also do not know if the effect might generalize to olanzapine plus other antidepressants or fluoxetine plus other antipsychotics. However, the two more recent studies of antidepressants for bipolar depression showed no significant effect. The first of these examined the effect of bupropion or paroxetine added to a broad range of "mood stabilizers" versus a mood stabilizer alone.[11] No benefit of the antidepressants was seen in either bipolar I or bipolar II patients. Interpretation of the study is complicated by the fact that many of the patients had been newly started on mood stabilizers shortly prior to randomization to placebo or antidepressant, and that these mood stabilizers include antipsychotics and lamotrigine that may have bipolar antidepressant properties (see below). Nevertheless, the findings are consistent with a study that compared paroxetine with placebo (and quetiapine), as monotherapy and found the paroxetine to be ineffective.[12]

In addition to this lack of support for the efficacy of antidepressants for the treatment of bipolar depression, there is concern that they may be associated with adverse consequences in bipolar disorder. Old data suggests that tricyclic antidepressants may be associated with an increased risk of switching to mania, an effect not apparently seen with selective serotonin reuptake inhibitors (SSRIs). This is supported by a randomized trial that compared bupropion, sertraline and venlafaxine. There have also been suggestions that antidepressant use is associated with accelerated cycling into episodes of illness and the induction of "irritable dysphoria".

It is hard to make sense of this data. Despite the lack of evidence for efficacy and possible adverse effects associated with treatment, audits of patients with bipolar disorder find nearly 50% are treated with antidepressants in naturalistic practice. Many psychiatrists remain convinced that some individual patients with bipolar depression respond to antidepressants and that SSRI-induced mania is seen, in both instances contrary to the data. It may be that there is great heterogeneity in the effects of antidepressants in bipolar disorder. Beneficial or adverse effects seen in a small proportion of patients may be lost within the larger groups studied in trials. In support of this, there is data suggesting that in patients in whom they and their psychiatrist believe antidepressants have been beneficial, more remain well if they stay on antidepressants compared to those who have the drug withdrawn. Nevertheless, current guidance

is to avoid antidepressants in the first instance in patients with bipolar depression.[1]

In terms of alternatives to antidepressants for the acute treatment of bipolar depression, there is equivocal data with regards to lithium, valproate and lamotrigine. A large randomized placebo-controlled trial found there to be no significant difference between lithium monotherapy and placebo,[12] though there is some evidence for it in combination with lamotrigine (see below). Nevertheless, it is recommended to optimize lithium treatment in patients already on this if they experience a depressive episode.[1] It should also be remembered that lithium has been demonstrated to have antisuicidal effects and this may be a specific reason for its use in its own right. With regards to valproate, there are a small number of small trials in bipolar depression with a meta-analysis suggesting a significant benefit. However, this may be driven by an anxiolytic, rather than a true antidepressant, effect since reduction in anxiety symptoms appears to be much greater than reduction in depressive symptoms. Lamotrigine has been more extensively studied for bipolar depression. Five randomized controlled trials (RCTs) of lamotrigine monotherapy have been conducted with only one positive, though a meta-analysis suggests a modest positive effect.[13] This may be somewhat offset by the need for slow dose titration to avoid dangerous skin reactions. A larger and more clinically significant effect has been observed in a trial of lamotrigine augmentation of lithium for bipolar depression.[14]

The major options for the management of bipolar depression are currently antipsychotics,[1] though it is important to note that this is not a class effect of these drugs. Indeed it should be remembered that antipsychotics, perhaps especially first-generation drugs, can induce a "deficit syndrome" that includes worsening of low mood. In addition, antipsychotics may have nonspecific effects such as sedation and anxiolysis that may "mascaraed" as an antidepressant effect, such as described above in the trial of olanzapine and olanzapine plus fluoxetine. The effect of olanzapine in bipolar depression has been replicated in another study in an Asian population[15] and while it is not clear that this is more than just a nonspecific effect, it has been sufficient for olanzapine to be included as an option (either as monotherapy or in combination with fluoxetine) in guidelines. The data for quetiapine is, however, much clearer with multiple positive placebo-controlled randomized trials with evidence of effects across depressive symptoms. Importantly, quetiapine does not cause switching into mania, as might be expected from its known antimanic effects. It is also important to note that an antidepressive effect of quetiapine is seen at lower doses than those needed to treat either mania or psychosis. Quetiapine is now the first-line recommendation for the treatment of bipolar depression in

the British Association for Psychopharmacology guidelines.[1] It has potentially been joined by lurasidone which is supported by positive RCTs both as monotherapy and in combination with lithium or valproate.[16] Lurasidone has a potential advantage over quetiapine by virtue of being less likely to induce metabolic disturbances. Most recently is emerging data suggesting that the dopamine D2 and D3 receptor partial agonist cariprazine has efficacy in bipolar depression.[17] This is of interest given findings that the D2 partial agonist, aripiprazole, is ineffective in bipolar depression, despite the evidence supporting it as an augmentation agent in unipolar depression, once again emphasizing the importance of the need for great caution in extrapolating from unipolar to bipolar disorder in the absence of evidence.

In summary, the data suggests a strategy for the treatment of bipolar depression of optimizing mood stabilizers, if the patient is on these and using quetiapine, lurasidone, possibly olanzapine (either alone or with fluoxetine), cariprazine and lurasidone, while generally avoiding antidepressants. If such strategies fail, there is some evidence for the combination of lithium plus lamotrigine (see above) and quetiapine and lurasidone in combination with lithium or valproate. There is also data suggesting that the addition of lamotrigine to quetiapine improves outcomes. Beyond this, guidelines tend to recommend using treatment strategies that might be employed in unipolar depression combined with good antimanic treatment and only after evidence-based treatments have been exhausted.[1] The use of ECT should also be considered for treatment-resistant bipolar depression. There is some data for augmentation with modafinil, pramipexole and ketamine, but these treatments remain under investigation.

Mixed Episodes

Most data regarding the pharmacological management of bipolar disorder come from patients defined as meeting criteria for mania or depression. However, it is now recognized that some degree of "mixity" of symptoms is the norm rather than the exception. For example, in a study of 1,380 bipolar patients meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for a depressive episode, only 31% had no manic symptoms even though just 15% met criteria for suffering from a DSM-IV mixed episode (i.e., meeting full criteria for a depressive and manic episode simultaneously). Such findings influenced DSM-5 to introduce the concept of a "mixed specifier" that can be added to a diagnosis of either a depressive or manic episode to indicate the presence of symptoms of the "opposite" pole. However, this presents a major challenge for the conduct of randomized trials given an almost infinite number of combinations of varying

levels of depressive and manic symptoms. It is therefore not surprising that there is extremely limited evidence regarding the management of mixed episodes.

The majority of data to guide the management of mixed episodes come from post hoc analysis of studies in patients with manic episodes who also met DSM-IV criteria for a depressive episode. This suggests that olanzapine, aripiprazole and asenapine all seem to be as effective in reducing manic symptoms in patients with mixed, compared to those with pure manic, episodes. In addition, they appear to, if anything, also improve depressive symptoms. There is some old data suggesting that valproate may have similar efficacy in manic and mixed episodes, while lithium may be less effective in mixed versus manic episodes.

On the basis of the data described above, guidelines usually recommend treating mixed states as manic episodes and avoiding antidepressants.[1] This may be very appropriate for patients with manic episodes with mixed features. However, there is much less to guide depressive episodes with mixed features. It might be assumed that the use of antipsychotics such as quetiapine, lurasidone and cariprazine for such situations would be a reasonable starting point in that as antipsychotics it would be expected they would have efficacy against the manic symptoms as well (though it should be noted that there is no data for lurasidone in mania). A study that also may be of relevance is one in depressed patients who had mixed symptoms though did not meet the criteria for bipolar disorder that showed a large significant benefit for lurasidone.[18] Further research in patients with bipolar disorder and suffering from depressive episodes with mixed features is required.

LONG-TERM PROPHYLAXIS FOR BIPOLAR DISORDER

Much of the data supporting the use of long-term treatments in bipolar disorder come from "continuation" rather than true "prophylaxis" studies. The former involves treating patients in an acute episode with a particular treatment, taking the responders and then randomizing them to either continue on the treatment or be switched to placebo. This design probably biases the data in favor of the treatment preventing relapse into the pole of illness the patient has just recovered from. Either because of this, or genuinely because long-term prophylactic efficacy reflects acute efficacy, there is a strong correlation between these two apparent properties of medications used in bipolar disorder. It is also reflected in the so-called "polarity index" that described the relative ability of a drug to prevent episodes of depression versus mania.

Lithium is the oldest long-term treatment option and still the "gold standard" long-term agent preventing relapse into

both mania and depression. It is also important to remember the potential antisuicidal effect of lithium. The major downside of lithium, aside from the need for frequent checks of the plasma level and adverse effects on thyroid and renal function, is the risk of discontinuation mania if it is abruptly stopped. There is reportedly around a 50% risk of mania in the first 3 months following a sudden discontinuation, with the risk being lower if it is withdrawn more slowly. This is a higher risk than the average naturalistic relapse rate with no medication which led to recommendations to avoid using lithium unless the patient is likely to take it consistently for at least 2 years. This problem though can be militated against through a tapered withdrawal probably over a couple of months or more.

While valproate has been used as a long-term prophylactic agent for bipolar disorder for many decades, the level of evidence supporting its evidence is not great, with the most recent study, BALANCE, finding that valproate is not as effective as lithium in preventing relapse into any type of episode.[19] Valproate is therefore not a major alternative to lithium and additionally given the recommendations to avoid valproate in women of childbearing potential. Similarly, there is very limited data regarding carbamazepine with one study showing superiority of lithium.[20] There is better data supporting lamotrigine, which predominantly prevents relapse into depression with a smaller effect preventing manic relapse and so it is recommended for patients with a predominantly depressive pattern of their illness.[1]

The data regarding the use of second-generation antipsychotics closely mirrors their acute efficacy with quetiapine having efficacy in preventing relapse into both depression and mania, olanzapine having greater potency in preventing manic relapse and aripiprazole appearing to only be effective in preventing manic relapse, though a recent study on long-acting injectable (LAI) aripiprazole has recently suggested that it is effective in preventing relapse into any mood episode. There is some data showing risperidone also has prophylactic efficacy, probably mainly preventing mania.

For patients not responding to monotherapy, the combination of lithium plus valproate does not seem to add a great deal to lithium alone. However, in combination with lithium or valproate, quetiapine, aripiprazole and ziprasidone have been shown to reduce relapse. In one study of lurasidone augmentation of lithium or valproate, its efficacy appeared to be predominantly preventing depressive relapse.[21]

If medication adherence is an issue, there is data supporting the efficacy of LAI aripiprazole, as well as for LAI risperidone as an adjunct to "treatment as usual". Another option that might be considered in some patients is implantable vagus nerve stimulation (VNS) for which 5-year follow-up data shows around

a 70% response rate, with over 50% of patients reaching criteria for response remaining responders through the remaining duration of the follow-up, in bipolar as well as unipolar patients.

PRINCIPLES OF TREATMENT OF BIPOLAR DISORDER

The pharmacological management of patients with bipolar disorder requires great art to apply the evidence base described above to the complexity of the presentations of patients. However, there are a number of principles that can help guide the clinician (Box 1).

The first of these is that it is important, where ever possible, to treat to full remission of symptoms, since residual interepisode symptoms greatly increase the risk of relapse. A common such residual symptom is sleep disturbance with a variety of problems including insomnia, hypersomnia and circadian sleep disturbance seen in patients. Such sleep problems are associated with worse mood symptoms and low probability of response to medication.

Secondly, it is important to think "long-term" rather than overly focusing on acute episodes. Clearly, any risks associated with acute episodes need to be managed. However, many episodes will be mild and self-limiting. At most, all that will be needed will be to address any stressors if they are present and optimize long-term treatment. It is important to guard against interpreting an episode of illness as indicating that the long-term treatment that the patient is on is ineffective. No treatment is 100% perfect—all they do is decrease the probability of relapse. To really understand if ongoing treatment is having a prophylactic effect or not requires considering the course of the patient's illness over the long-term. This can be most robustly done if patients are encouraged to complete mood diaries or regular mood rating scales. If a change in acute treatment is indicated by the severity and/or duration of symptoms, then consideration should be given to the potential long-term consequences of using the drug that is chosen. This is because of the maxim "what gets you well keeps you well"; if a treatment instigated for an acute episode is effective in bringing symptoms under control it is likely that this medication should be continued long-term.

BOX 1 Principles of treating bipolar disorders.

- Treat to full remission of symptoms as residual interepisode symptoms greatly increase the risk of relapse
- Think "long-term" rather than overly focusing on acute episodes
- Ensure adherence as medications work when patients are adherent to them
- For comorbid substance use disorder or psychiatric disorders, address both the problems

Thirdly, medications only work if patients are adherent to them, and patients are much more likely to be adherent to medication if they understand the reasons for taking them, especially over the long-term. It is therefore no surprise that psychoeducation, related to the nature of bipolar disorder and the need for and nature of, treatments, has been shown to highly significantly decrease risks of relapse over the long-term. Such psychoeducation has been shown to be associated with more consistent lithium plasma levels which may be critical given the risk of rebound mania with sudden lithium discontinuation. Additionally, an element of psychoeducation can be to help patients identify their "relapse signatures". Identification of early warning signs of relapse, together with associated plans of action to implement in such situations, can also decrease risks of relapse.

Finally, while there is little data regarding the management of bipolar disorder with comorbid substance misuse or other psychiatric illness, the general rule is to actively address both problems.

CONCLUSION

The pharmacological management of bipolar disorder is complex. While there are a range of different treatment options for mania and hypomania (any antipsychotic, lithium, valproate), there are many fewer options for bipolar depression. Some, but certainly not all, antipsychotics may be helpful (quetiapine, lurasidone, possibly olanzapine and preliminary data for cariprazine). Aside from this, there is data for lamotrigine, possibly lithium, and olanzapine plus fluoxetine. There is no other high-quality data supporting any other antidepressants for bipolar depression. There is least evidence for mixed episodes, especially depression with mixed mania. For long-term prophylaxis the key is "what get the patient well keeps the patient well". The ability of a drug to prevent depressive and manic relapse relates to its ability to treat depressive and manic episodes acutely. Most important is how treatments are used, with some key principles detailed in Box 1.

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