Review

Pharmacotherapy of bipolar disorder: current status and emerging options

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Practice Points

- For the treatment of acute mania there are several available agents that include lithium, carbamazepine, valproic acid, aripiprazole, asenapine, chlorpromazine, paliperidone, olanzapine, quetiapine, risperidone and ziprasidone.
- Agents being investigated for acute mania include the partial agonist antipsychotic, cariprazine and the sodium channel-blocking anticonvulsant, eslicarbazepine.
- Agents with potential antimanic effect include the potassium channel agonist anticonvulsant, ezogabine and the *N*-methyl-D-aspartate antagonist, memantine.
- Agents currently approved by the US FDA for the treatment of bipolar depression include quetiapine, lurasidone and the olanzapine–fluoxetine combination.
- Agents that show efficacy for the treatment of bipolar depression include pramipexole, modafinil and armodafinil, tamoxifen and ketamine.
- The controversy regarding the use of antidepressants in bipolar depression has not been resolved. Nonetheless, this class of medications appears to be effective when used in monotherapy (type II) or when combined with an antipsychotic (e.g., olanzapine–fluoxetine combination), but not when combined with a mood stabilizer (multiple negative adequately-powered randomized clinical trials).

SUMMARY In the treatment of bipolar depression, the debate regarding the utility and safety of antidepressants continues. There are several agents that are available for the treatment of bipolar depression, including US FDA-approved agents such as quetiapine and lurasidone, and non-FDA-approved agents such as lamotrigine, pramipexole, modafinil and armodafinil, and ketamine. Efficacy studies for the use of antidepressants are lacking, but

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safety concerns are quite real with an increased risk of manias, cycling and chronic irritable dysphoria. Many agents are effective in acute mania, including lithium, several anticonvulsants and every antipsychotic examined. All newer agents being studied for mania are anticonvulsants or second-generation antipsychotics. Most agents, which are effective for acute treatment, appear to be effective in maintenance. Despite many advances in the treatment of bipolar illness, the condition remains severe, with a guarded prognosis.

Bipolar illness is a chronic, disabling and frequently destructive disease. In its more severe form, it afflicts over 1% of the population, and in its spectral form, it may affect one out of 20 people [1,2]. The acute episodes of both mania and depression are nearly always disruptive, and can create dysfunction in the patients' lives. The recurrence of these episodes is frequently disabling in nearly all aspects of life. Bipolar patients have high rates of substance abuse comorbidity, are more likely to divorce, less likely to maintain employment, develop cognitive difficulties and have earlier onset of dementia, and are at a higher risk for suicide. Diagnosis can be challenging with over two-thirds of bipolar patients initially misdiagnosed [3], with both under-detection [3] and over-inclusion [4]. However, even after an appropriate diagnosis is made, treatment is still a challenge. The diversity of presentation of bipolar patients increases the level of complexity of treatment. Patients may be euthymic (i.e., without a mood episode), or may have subsyndromal depressive or manic (i.e., hypomanic) symptoms, or may have full syndromal mania or depression, or combined manic and depressive symptoms (mixed states).

Several types of bipolar disorder are recognized. Patients who have experienced at least one full manic episode at some point in their lives, are diagnosed with type I illness. Patients who have only experienced hypomanic episodes (i.e., never a full syndromal mania) and at least one major depression are diagnosed with type II illness. Patients who never experience full syndromal manias or depression, but only experience hypomanias and subsyndromal depressive symptoms are classified as cyclothymic. Some patients experience frequent recurrence of episodes; should these patients have at least four distinct episodes in a 12-month period, they are diagnosed with rapid cycling – a modifier that is associated with poorer prognosis.

High rate of comorbid substance abuse is associated with poor prognosis. In addition, response rates are generally suboptimal with a large number of patients remaining symptomatic for the majority of their lives despite being on multiple medications [5,6]. Furthermore, lack of consensus regarding some treatments, such as antidepressants, increases the uncertainty of interventions.

Treatment is frequently partitioned into acute treatment of mania and depression, and chronic recurrence prevention maintenance strategies. The current review provides a very brief synopsis of currently available pharmacologic approaches to both acute and maintenance treatments since other excellent reviews have already summarized this topic [7]. Furthermore, existing treatments are critically reviewed in multiple treatment guidelines (e.g., [8–10]). More importantly, this review explores potential future options and the direction of exploration in strategies for the management of bipolar disorder.

Bipolar depression

Patients with both type I and type II bipolar illnesses spend a large fraction of time with depressive symptoms [5,6]. Nonetheless, the duration of a typical depressive bipolar episode, at approximately 2 months, is shorter than a unipolar depressive episode (~3 months) or subthreshold depressive symptoms (3.2 months) [11]. However, the severity of these episodes can be quite paralyzing. Recurrent depressions in bipolar illness are more common, and in approximately 20% of patients are atypical with features such as excessive sleep, excessive appetite and weight gain. Evidence-based therapeutic options for the acute management of bipolar depression are few. The US FDA has approved only three agents for the treatment of bipolar depression **(Table 1)**.

FDA-approved treatments

Quetiapine, in both the immediate-release and extended-release formulations, has been shown to be effective in short-term studies of 8 weeks for the treatment of acute bipolar depression at doses

Table 1. Agents approved by the US FDA for treatment in bipolar I illness.

Treatment	Mania	Bipolar depression	Maintenance
Lithium†	✓		✓
Lamotrigine			✓
Carbamazepine and ER	✓		
Divalproex and ER	✓		
Aripiprazole	✓		✓
Asenapine	✓		
Chlorpromazine	✓		
Paliperidone	✓		
Olanzapine	✓	✓‡	✓
Quetiapine and XR†	✓	✓	✓
Lurasidone		✓	
Risperidone	✓		✓
Ziprasidone	✓		✓

†Not approved for mixed mania.
‡Approved for bipolar depression in combination with fluoxetine.
ER: Extended release; XR: Extended release.

of 300–600 mg/day [12,13]. When quetiapine is added to either lithium or divalproex, the combination is associated with a significant reduction in both mania and depression compared with placebo added to lithium or divalproex over the 2-year study period [14].

Lurasidone has been only recently approved by the FDA for bipolar depression. Lurasidone is a new second-generation antipsychotic (SGA) that has high affinity to the serotonin 7 ($5HT_7$) receptor. In at least two unpublished short-term randomized, placebo-controlled trials of acutely depressed bipolar I patients, lurasidone demonstrated efficacy both as a monotherapeutic agent [15] and as an add-on to a mood stabilizer [16]. A submission for a new drug indication is currently being reviewed by the FDA. The presumed mechanism of action of this effect is the blockade of $5HT_7$ [17–19]. Risperidone, another SGA with high affinity to the $5HT_7$ receptor, has shown antidepressant activity in open naturalistic reports [20,21], but a randomized trial was nonconfirmatory [22].

The combination of olanzapine and fluoxetine (Symbiax™, Lilly, IN, USA) has also been found to be effective in depressed bipolar I patients not receiving a mood stabilizer [23]. A 24-week open extension found that the risk for manic induction due to the coadministration of fluoxetine was low, but 27.4% relapsed into depression [24].

All SGAs carry the potential for weight gain and aggravation of the metabolic syndrome. In addition, all of the agents currently approved for the treatment of depression are also sedating to various degrees. Approximately 10% of patients receiving quetiapine discontinue the drug due to sedation.

Non-FDA-approved treatments

In addition to approved agents, there are other pharmaceuticals that have shown efficacy in the treatment of bipolar depression **(Table 2)**. The majority of these agents are already in use to varying degrees in depressed bipolar subjects. The most commonly used class of agents is antidepressants [25,26]. This is despite a dearth of evidence regarding the efficacy of antidepressants in bipolar illness [27]. All randomized, controlled trials in which antidepressants were added to mood stabilizers have demonstrated that the combination is not superior to the mood stabilizer alone in treating the depression [28]. However, in studies in which antidepressants were used alone or in combination with an antipsychotic, they were effective [29]. One study in which fluoxetine was added to olanzapine included over 900 patients. Owing to its large size, meta-analyses that examine the efficacy of antidepressants are nearly always supportive for the use of antidepressants because they include this large study (e.g., [30]). Nonetheless, this particular meta-analysis has been very influential because it matches clinicians' impression that antidepressants are effective. Current expert opinion tends to support the use of antidepressants in bipolar illness [31].

Studies performed in the era of the third edition of the Diagnostic and Statistical Manual [32,33], when patients with type II bipolar illness were diagnosed with major depression, included

Table 2. Agents that display efficacy in the treatment of bipolar depression in randomized, placebo-controlled trials.

Agent	Bipolar I	Bipolar II
Olanzapine + fluoxetine	✓	
Quetiapine	✓	✓
Lithium	✓	
Lamotrigine[†]	✓	✓
Pramipexole[‡]	✓	✓
Modafinil[§] and armodafinil	✓	✓
Fluoxetine monotherapy[¶]		✓
Venlafaxine monotherapy[¶]		✓
Ketamine[#]	✓	

[†]Lamotrigine reduces rapid cycling in type II bipolar patients.
[‡]Mean effective dose 1.7 mg/day.
[§]Mean effective dose 177 mg/day.
[¶]*Post hoc* analyses of type II bipolar patients included in placebo-controlled trials of unipolar major depressive illness before the creation of the type II bipolar diagnostic category. In these studies, manic induction could appear as improvement in depressive illness.
[#]Single acute dose is effective for 7–10 days.

depressed bipolar II patients in controlled studies examining the efficacy of fluoxetine and venlafaxine. In these placebo-controlled studies, both fluoxetine and venlafaxine were as effective in type II patients as in unipolar patients [32,33]. Measures of mania were not performed in these studies since the studies were not designed to examine bipolar illness. Consequently, it is not clear if the antidepressant treatment was associated with manic induction in those studies. However, in a randomized, uncontrolled study of bipolar patients in the Stanley Network, depressed bipolar patients were randomized to sertraline, bupropion, or venlafaxine, as adjuncts to mood stabilizers. At 10 weeks 9.1% experienced switches into hypomania or mania (another 9.1% had hypomania with no-to-minimal dysfunction) [34]. While manic induction rates were low, only 23.3% had a sustained remission at 6 months [35]. Thus, there was no sustained beneficial effect. Similarly, when patients who appeared to have responded well to an antidepressant, were randomized to either staying on the antidepressant or discontinuing the drug in an open fashion, individuals with a history of cycling were twice as likely to experience a depression over the subsequent year of observation if they stayed on the antidepressant [36]. Similarly, people with a history of rapid cycling were ninefold more likely to experience chronic irritable dysphoria over the subsequent year when they received an antidepressant compared with those not receiving an antidepressant in a naturalistic study [37].

Agomelatine is an antidepressant that works by stimulating melatonin M1 and M2 receptors and blocking 5-HT2C receptors. It is used as an antidepressant in Europe (Valdoxan, Melitor, Thymanax) but will not be approved in the USA. In a small, open add-on study to lithium or valproic acid, agomelatine demonstrated efficacy for bipolar depression [38]. Ramelteon is a sleep aid that is available in the USA and also is an agonist of M1 and M2 receptors. In small, single-site, studies of insomnia in bipolar patients it demonstrated significant antidepressant [39] and maintenance efficacy [40]. While these drugs are both very well tolerated, gastrointestinal disturbances are the most common adverse consequences.

The data for antidepressants can be summarized as: antidepressants are effective when used as monotherapy in type II patients [27], but their safety is not clear. Antidepressants are ineffective in type I patients when added to a mood stabilizer [29], but may be effective when added to an antipsychotic [23]. Ramelteon may be important to study further.

There are nonantidepressant, non-FDA-approved treatments for bipolar depression (Table 2). Lamotrigine is FDA-approved for the prevention of recurrences of mania and depression, with particular efficacy for preventing depressive episodes [41]. It also works synergistically when coadministered with valproate [42]. In addition, lamotrigine does have documented efficacy in treating acute bipolar depressive episodes, and is more effective in more severely depressed subjects [43]. Despite these positive studies, some authors do not recommend lamotrigine for acute depression [44]. Lamotrigine is perhaps the best

tolerated mood stabilizer available with almost no sedation and minimal cognitive issues. However, lamotrigine can cause a toxic (nonallergic) reaction in approximately one in 3000 individuals known as toxic epidermal necrolysis or Steven–Johnson syndrome, in which the skin can actually be sloughed. Slow titration of dose can reduce the risk to one in 7000.

Modafinil is a nonstimulant agent that is used to increase alertness in subjects with daytime sleepiness due to a variety of conditions. In a randomized, placebo-controlled, 6-week study, (n = 41) or placebo (n = 44) were added to ongoing treatment in depressed bipolar patients [45]. Response, defined as at least 50% improvement, was twice as great in modafinil-treated subjects (44%) compared with placebo (23%; $p < 0.05$) [45]. There were no manic or hypomanic switches [45]. Armodafinil, the purified active enantiomer of modafinil, was also examined in an 8-week randomized, placebo-controlled study of 157 depressed bipolar patients [46]. The combination of armodafinil with a mood stabilizer was minimally superior to placebo added to a mood stabilizer [46]. One of the problematic side effects with these agents in bipolar subjects is anxiety.

The dopamine D2 and D3 agonist, pramipexole, was studied in two 6-week placebo-controlled studies [47,48]. A total of 15 patients with type I, and 28 with type II, bipolar disorder were studied. Response occurred in 60–67% of patients taking pramipexole and 9–20% taking placebo [47,48]. The 6-week duration or the studies is too brief to determine long-term safety, but in a 48-week follow-up in which subjects could also be receiving antidepressants, of 23 patients (12 with major depression and 11 with bipolar disorder), 27% experienced a switch (two subjects developed hypomania and one developed psychotic mania) [49]. Similarly, in a naturalistic, retrospective chart review of 16 patients with bipolar I or II disorders, pramipexole was well tolerated and maintained its efficacy [50].

Lisedexamfetamine is an FDA-approved prodrug of amphetamine, used in attention deficit disorder, and marketed as Vyvance® (Shire, PA, USA). Both amphetamine [51] and methylphenidate [52,53] have both been used for bipolar depression in open studies. A double-blind, placebo-controlled study of lisedexamfetamine in bipolar depression was started in January 2010 and is ongoing at this point in time with an anticipated completion date of December 2013 [101]. Anxiety and insomnia are the major side effects of stimulants.

Proof-of-concept studies have been performed with ketamine, a *N*-methyl-D-aspartate (NMDA) antagonist that is often abused. Most of these studies utilized one intravenous dose (0.5 mg/kg) [54,55]. Open naturalistic reports in outpatient youths utilized intranasal ketamine with similar results [56]. The mechanism may be directly through antagonism of the NMDA receptor or perhaps by effects on the rapamycin (mTOR; a regulatory protein kinase) signaling pathway [57]. Interestingly, memantine, a partial antagonist of the NMDA receptor that is approved for use in moderately to severely demented individuals, has shown efficacy in a preclinical model of mania [58], and in a small (n = 29), randomized, placebo-controlled exploratory study of adjunctive use treatment of depressed bipolar subjects [59]. Finally, riluzole is a sodium channel antagonist that may also modify NMDA activity [60]. It has been approved as an orphan drug by the FDA for amyotrophic lateral sclerosis [61]. In a small, open, 8-week study, 66% of those receiving riluzole doses of 200 mg/day or greater responded, but only 33% of those receiving lower doses responded [62]. Use of ketamine may be problematic because it is a substance of abuse, but these results suggest that manipulation of the NMDA receptor may prove to be a novel antidepressant mechanism in the future.

Nonpharmacologic approaches include electroconvulsive therapy, transcranial magnetic stimulation (TMS), cranial electrical stimulation, and the ketogenic diet. Bipolar depression may be more responsive to electroconvulsive therapy than unipolar depression and is a reasonable clinical option [63]. TMS is FDA approved for unipolar, treatment-resistant depression; additionally, both rapid (>10 mHz) [64] and slow (1–5 mHz) [65] TMS may be useful in bipolar depression. Cranial electrical stimulation is an older electrotherapy that is FDA-approved for the treatment of depression, anxiety and insomnia. In a small retrospective chart review it reduced overall symptoms in chronically symptomatic bipolar patients [66], suggesting that future controlled studies are warranted. Finally, the ketogenic diet has been hypothesized to be useful in bipolar illness [67], but is very difficult to adhere to over prolonged time periods [68]. Two recent case reports of bipolar II patients on the

ketogenic diet monotherapy for at least 2 years, showed that this may be a potent treatment for type II patients [69].

Pharmacotherapy: mania

Many agents are FDA-approved for the treatment of acute mania in type I patients **(Table 1)** [70]. Nearly all of the SGAs have been examined in placebo-controlled studies as monotherapy and adjunctive treatments **(Table 1)** [71,72]. In meta-analyses, monotherapy with SGAs is equivalent to [72] or more effective than mood stabilizers alone [73], and when combined with mood stabilizers, the combination is more effective than a mood stabilizer alone [72,74]. Other agents are under study **(Table 3)**.

Antiepileptic agents and lithium are frequently used in the treatment of bipolar disorder, particularly in the control of mania. Frequently collectively referred to as 'mood stabilizers', these agents all appear to share the mechanism of reducing intracellular sodium accumulation in an activity-dependent manner [75]. In other words, these agents inhibit the fastest and most frequently firing neurons preferentially. These agents remain the foundation for treatment of bipolar patients. However, adjunctive use of SGAs does increase the antimanic efficacy of mood stabilizers **(Table 1)**.

Potassium channel genes have been associated with bipolar disorder in genome-wide linkage analyses [76]. Furthermore, the membrane potential of ill patients may be deporlarized [77]. Consequently, it is reasonable to examine ezogabine (previously known as retigabine, Potiga™ [GlaxoSmithKline, UK; Valeant Pharmaceuticals, QC, Canada]), a potassium channel agonist that stabilizes the channel in the open conformation and thereby promotes the M-current (due to the efflux of potassium ions) [78]. The M-current is the potassium current that is mediated by the potassium channel and is responsible for the repolarization of electrically active cells (e.g., neurons) after depolarization. In other words, ezogabine is a potassium channel agonist that would help re-hyperpolarized neurons after firing. This effect is very similar to the common effect of mood stabilizers of inhibiting sodium entry, thereby increasing the hyperpolarization of neurons [75]. Ezogabine was effective in animal models of mania [79–81]. In an open study, three out of ten manic patients responded to ezogabine monotherapy over a 3-week period [82]. Ezogabine would be expected to be additive to other mood stabilizers in its effect. Randomized trials are in the planning stages.

Similarly, the gene for the α1C subunit of the L-type voltage-gated calcium-channel (*CACNA1C*), located on chromosome 12p13.3, has been associated with bipolar disorder in a genome-wide association study [83,84]. MEM-1003 blocks this channel. Unfortunately, in a Phase IIa study by its manufacturer, Memory Pharmaceuticals (NJ, USA), 84 patients with acute mania did not improve significantly compared with placebo [102]. The drug is still in development for Alzheimer's disease. This study is sobering in that it is evidence that genetic association with bipolar illness does not necessarily translate into clinical utility.

Eslicarbazepine (Stedesa™ in the USA; Zebinix®, Exalief® in Europe; chemical name: (*S*)-(–)-10-acetoxy-10,11-dihydro-*5H*-dibenz[*b,f*] azepine-5-carboxamide; development name: BIA 2–093) is a new dibenzazepine antiepileptic drug closely related to oxcarbazepine [85]. Eslicarbazepine shares similar affinity to the sodium channel as carbamazepine and oxcarbazepine [85]. Positive case reports exist [86], and studies for bipolar disorder are currently underway but the results are not yet available.

Cariprazine (RGH-188) is a dopamine D3/D2 receptor partial agonist antipsychotic [87]. It has been found to be effective in animal models for mania [88]. When administered in randomized, placebo-controlled trials, cariprazine is significantly more effective than placebo [89]. Placebo-controlled studies in bipolar depression are still underway [103].

The NMDA glutamate receptor is a target for several new neurotropic agents, many of which are failing clinical trials. However, memantine (Nemenda™, Forest Laboratories, NY, USA) a moderate-affinity, uncompetitive NMDA receptor antagonist [90], has been approved for moderate-to-severe Alzheimer's disease [91]. It has been found to reduce manic symptoms in

Table 3. Agents being studied for bipolar mania.

Agent	Status	Ref.
Ezogabine	Minimally effective in an open study	[81]
Cariprazine	Effective in two placebo-controlled studies	[88]
Eslicarbazepine	Case reports and ongoing placebo-controlled studies	[85]
Memantine	Small open study	[92]
Tamoxifen	Effective in three placebo-controlled studies	[95–97]

an animal model of mania [58]. Despite its failure in the treatment of bipolar depression [58], it was effective in a small (n = 33) open study of manic patients (in which patients receiving 20–30 mg/day improved more than those receiving 10–20 mg/day) [92].

Lithium and valproate both inhibit the second messenger effector, PKC [93]. Tamoxifen (Nolvadex™, Istubal™, Valodex™ [all AstraZeneca, UK]), which is used to treat breast cancer, is an estrogen receptor antagonist that also inhibits PKC. Tamoxifen antagonizes manic-like behavior in a rat model of mania [94], and manic bipolar behavior as monotherapy [95,96] and adjunctive to lithium [97]. However, because of its antiestrogen properties, it is unlikely to be used in bipolar patients except in very unique circumstances.

Conclusion

Over the recent years there have been multiple advances in the treatment of bipolar illness. Despite this, debate continues regarding the use of antidepressants in bipolar depression. Alternative agents that do not affect the serotonin reuptake system are available, and have good efficacy data but limited long-term safety data. More advances have occurred in the treatment of acute mania, with a variety of anticonvulsants and nearly all SGAs demonstrating efficacy in acute mania. With the exception of antidepressants, agents with demonstrated acute antimanic or antidepressant efficacy, appear to be useful for maintenance treatments aimed at recurrence prevention. Despite the investment in investigating new agents, there has not been a similar investment in comparative studies. Examination of effect sizes suggests that there are real differences among the SGAs and possibly the mood stabilizers [73]. Direct head-to-head randomized clinical trials need to be performed to examine these differences.

Future perspective

While many of the agents being examined work by mechanisms similar to currently available drugs, there appears to be an increase in the examination of pharmaceuticals that work by novel mechanisms. These include ketamine and memantine, which work through the NMDA receptor; ezogabine, which is an agonist of the potassium channel; modafinil and armodafinil, which may be prohistamine drugs; and agomelatine and ramelteon, which are melatonin agonists. The development of such novel agents bodes well for the future of the treatment of bipolar illness. Use of novel agents such as pramipexole and ketamine is already gaining acceptance. Within 5 or 10 years, such agents, and others currently in development, may be used routinely to treat bipolar patients.

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