

Bipolar Disorder for Family Physicians *Part 2: Management—A Focus on the Role of Atypical Antipsychotics*

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As with the identification and diagnosis of bipolar disorder (BD), covered in Part 1 of this two-part series (earlier in this issue), management of BD is complex and can be difficult. Intervention strategies must be considered to address each distinct acute phase of the disorder, and to provide protection against relapse once the patient has achieved remission. This can be a complex task and may require consultation with a psychiatrist. An individual patient might not respond optimally to initial treatment that worked well for the last patient with the same diagnosis, but could do very well on a different treatment, suggesting the likelihood of neurobiological heterogeneity between patients. One always needs to consider the possibility of poor adherence. As with most chronic conditions, it may not be easy to convince patients to continue taking their medication once they are feeling better.

Part 1 of this article reviewed the epidemiology and diagnosis of BD. The present review (Part 2) provides a discussion of treatment options for patients diagnosed with BD, discussing the most recent (2009) management recommendations for BD from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) Collaborative guidelines³ along with additional information on the use of atypical antipsychotics in BD, with a particular focus on aripiprazole. One of the most recent atypical antipsychotics to become available to Canadian physicians and their patients, aripiprazole is indicated in Canada in adults for the treatment of

manic or mixed episodes in bipolar I disorder (as acute monotherapy or co-therapy with lithium or divalproex) and as co-therapy with lithium or divalproex for relapse prevention in the maintenance of bipolar I disorder. It is also indi-

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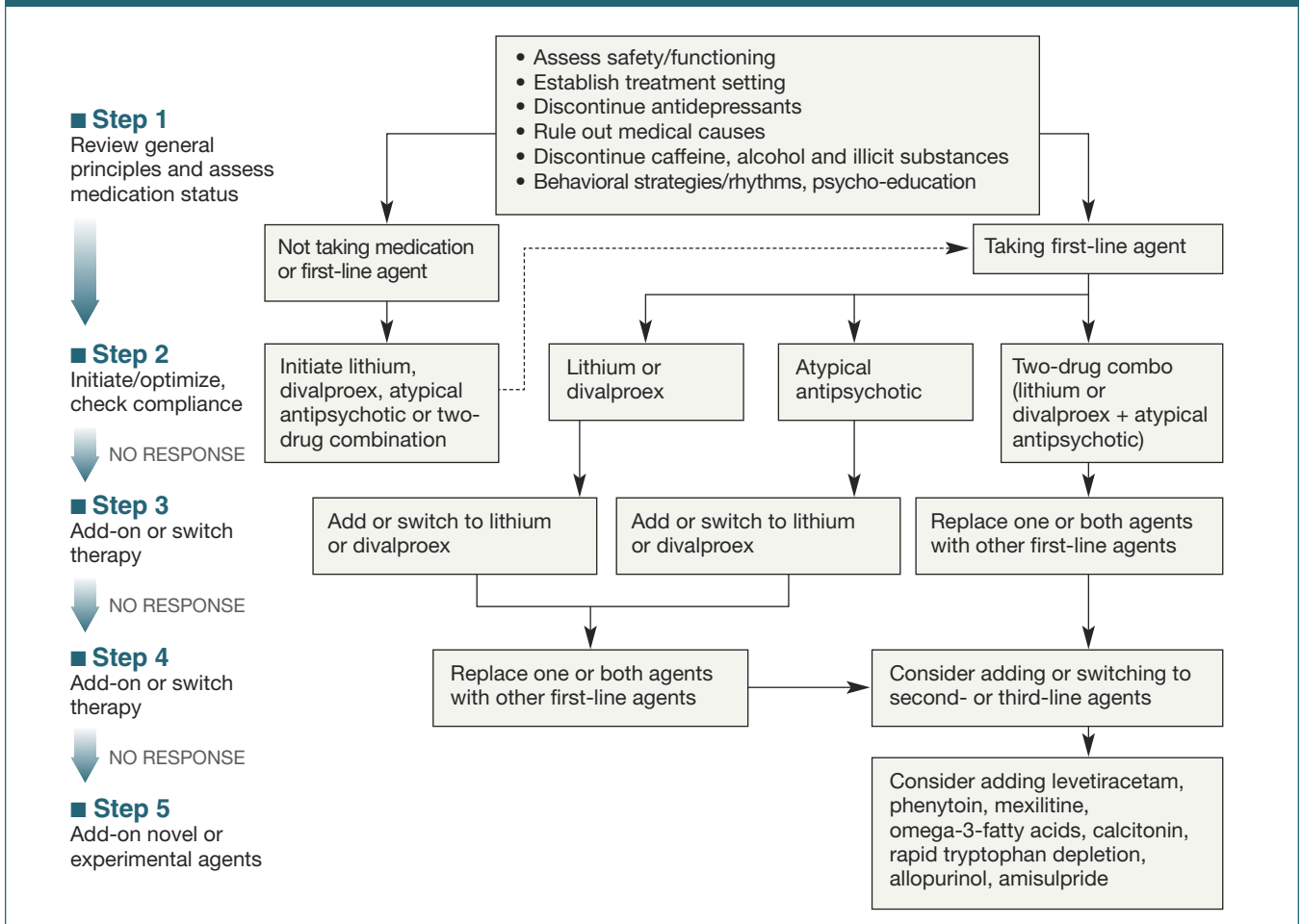
cated for the treatment of schizophrenia and related psychotic disorders in adults, and for the treatment of schizophrenia as well as the acute treatment of manic or mixed episodes in bipolar I disorder in adolescents (aged 15-17 years).

Canadian Guidelines for Managing Bipolar Disorder

The 2009 CANMAT/ISBD guidelines provide extensive evidence-based recommendations for the management of BD.¹ The goals of therapy overall are straightforward (but not necessarily easy to achieve): full remission of acute episodes and prevention of future episodes.

FIGURE 1.

2009 CANMAT/ISBD Recommendations for Treatment of Acute Mania¹



For acute mania (*i.e.*, bipolar I), the guidelines recommend initiating therapy with lithium, divalproex, an atypical antipsychotic or a combination of two agents. Should initial monotherapy fail (after having been optimized and compliance assessed), the guidelines recommend adding another first-line agent. Should initial combination therapy fail, the recommendation is to substitute one or both agents with other first-line agents (Figure 1).¹

For acute depression in bipolar I disorder, the recommendations are somewhat more complex. The course of treatment is highly dependent on which agent(s) the patient is taking at the onset of the depressive episode. Mood stabilizers, atypical antipsychotics, antidepressants and

electroconvulsive therapy all have a potential role in treating bipolar depression. The recommended first-line strategies are lithium, lamotrigine, quetiapine, quetiapine XR, lithium or divalproex + a selective serotonin reuptake inhibitor (SSRI), olanzapine + SSRI, lithium + divalproex, and lithium or divalproex + bupropion. For acute depression in bipolar II, the recommendations are different. The recommended first-line agent is quetiapine; second-line treatments include lithium, lamotrigine, divalproex, lithium/divalproex ± antidepressant, or atypical antipsychotic + antidepressant.¹

Of note, the risk for antidepressants to cause a switch into mania or hypomania—and possibly worsen the course of BD

TABLE 1.

2009 CANMAT/ISBD Recommendations for Maintenance Pharmacotherapy of Bipolar Disorder¹

	Recommended Therapies
First-line	Lithium, lamotrigine monotherapy (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, lithium or divalproex + quetiapine, risperidone LAI, adjunctive risperidone LAI, aripiprazole (mainly for preventing mania), adjunctive ziprasidone
Second-line	Carbamazepine, lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third-line	Adjunctive phenytoin, adjunctive clozapine, adjunctive ECT, adjunctive topiramate, adjunctive omega-3-fatty acids, adjunctive oxcarbazepine, or adjunctive gabapentin
Not recommended	Adjunctive flupenthixol, monotherapy with gabapentin, topiramate or antidepressants

by inducing mixed states and/or rapid cycling—must be considered in bipolar I and II. Patients with known BD should never be prescribed an antidepressant without first being established on adequate doses of mood stabilizers (lithium or divalproate) and/or atypical antipsychotics to minimize the risk of switching, which can be particularly disastrous if the patient becomes manic (bipolar I).

For maintenance therapy, first-line agents recommended by the CANMAT/ISBD guidelines are: lithium, lamotrigine monotherapy (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, lithium or divalproex + quetiapine, risperidone long-acting injection (LAI), adjunctive risperidone LAI, aripiprazole (mainly for preventing mania) and adjunctive ziprasidone (Table 1).¹ These recommendations are substantially different from those in the previous guidelines, particularly with respect to the inclusion of the atypical antipsychotics. Recently, Health Canada granted a new indication for aripiprazole in maintenance of bipolar I disorder in combination with a mood stabilizer.

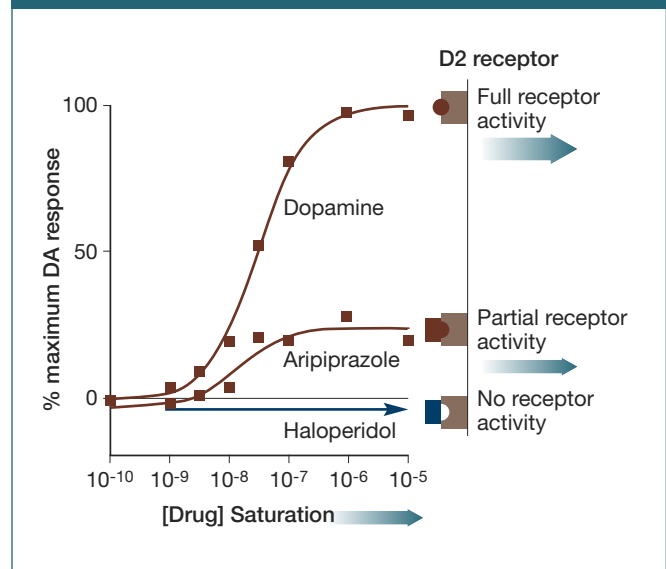
For each of these phases of BD, the evidence for the use of atypical antipsychotics is explored in greater detail below, with a particular focus on aripiprazole.

Atypical Antipsychotics as Pharmacotherapy for Bipolar Disorder

With respect to the atypical antipsychotics, there are many important differences between the agents that can impact upon efficacy and tolerability from patient to pa-

FIGURE 2.

Mechanisms of Action of Dopamine, Aripiprazole and Haloperidol

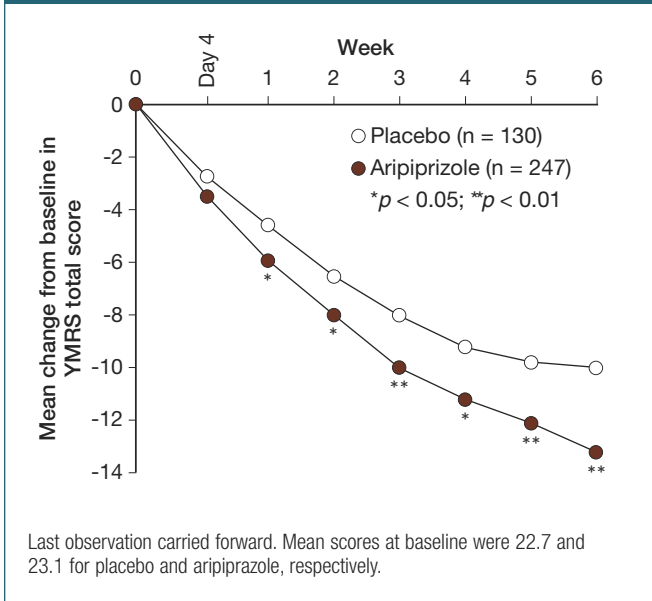


tient. One should not make the assumption that all patients will respond to each of these agents in the same fashion, either in terms of efficacy or adverse events.

Aripiprazole, for example, has a unique mechanism of action: partial dopamine (DA) agonism (20-30% intrinsic dopaminergic activity). This agent acts to maintain dopamine activity when DA activity levels are low (e.g., in the striatum, minimizing the likelihood of blocking D2 re-

FIGURE 3.

Mean Change From Baseline in Young Mania Rating Scale (YMRS) Total Score for Bipolar Mania Patients Randomly Assigned to Adjunctive Treatment With Aripiprazole or Placebo²



ceptors beyond 70-80% to decrease the risk of extrapyramidal symptoms), but inhibits activity of dopamine when the DA levels are high (Figure 2). During mania or psychosis, presumably DA levels are too high in the limbic lobes. Aripiprazole, which has a high affinity for D2 receptors, could be helpful by blocking these receptors and decreasing dopaminergic activity by 70-80% in this region. In schizophrenia, negative symptoms such as amotivation, affective flattening avolition and alogia may relate to levels of dopamine that are too low in the pre-frontal cortex as may also be the case in depression. Aripiprazole could potentially benefit patients with negative symptoms, cognitive symptoms or depression by increasing dopaminergic activity in this area.

Evidence in acute mania. Each of the atypical agents has demonstrated efficacy in treating acute mania—as monotherapy or in combination with mood stabilizers.²⁻¹³ As an adjunct, aripiprazole was evaluated among 384 pa-

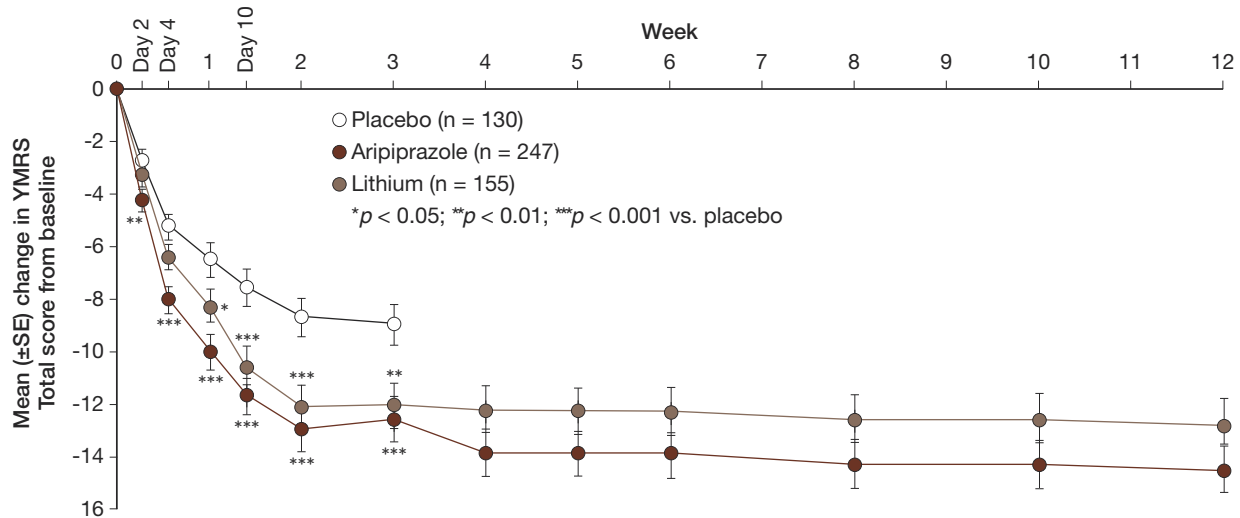
tients with bipolar I disorder mania incompletely responsive to mood-stabilizer (lithium or valproate) monotherapy.² Patients with a Young Mania Rating Scale (YMRS) total score of at least 16 were randomized to either aripiprazole 15 or 30 mg daily or placebo for six weeks. For the primary endpoint of improvement in YMRS, significant improvement was observed in those randomized to aripiprazole therapy compared to placebo (-13.3 vs. -10.7; Figure 3). Aripiprazole was also associated with a rapid onset of action, with separation from placebo evident as early as day 2 in this study. There was no significant difference in weight gain between aripiprazole and placebo.

An analysis of pooled safety data from short- and long-term trials of aripiprazole¹⁴ showed that, among patients with bipolar I disorder, akathisia occurred in 18% of aripiprazole-treated patients and 5% of patients taking placebo. The akathisia was generally mild to moderate in severity and tended to resolve within 1-2 weeks. The rate of discontinuation due to akathisia was low (aripiprazole 2.3%, placebo 0%), and was not associated with poorer clinical response.

A retrospective analysis of an American insurance claims database compared the time to hospitalization for BD patients treated with an adjunctive atypical antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone).¹⁵ In this analysis, adjunctive aripiprazole was associated with a longer time until hospitalization than adjunctive therapy with ziprasidone, olanzapine, quetiapine, or risperidone.

In terms of monotherapy for acute mania, aripiprazole's efficacy and safety have been evaluated in two recently published comparative studies.^{2,3} A total of 480 patients suffering with acute bipolar I mania (baseline YMRS \geq 20) were randomized to double-blind therapy with aripiprazole (15 or 30 mg daily), placebo or lithium (900-1500 mg/day) for three weeks, with aripiprazole- and lithium-treated patients continuing their blinded treatment for an additional nine weeks. On the primary outcome measure of mean change in YMRS total score from baseline to week 3, aripiprazole demonstrated significantly greater improvement than placebo (-12.6 vs. -9.0; $p < 0.001$; Figure 4). There was no significant difference between aripiprazole and lithium at week 3 (lithium: -12.0 at week 3). The significant benefit of aripiprazole vs. placebo

FIGURE 4.

Aripiprazole, Lithium or Placebo for Monotherapy Among Patients with Acute Bipolar Mania^{2,3}

Baseline YMRS scores (SE): placebo 28.9 (0.4); lithium 29.2 (0.4); aripiprazole 28.5 (0.4)

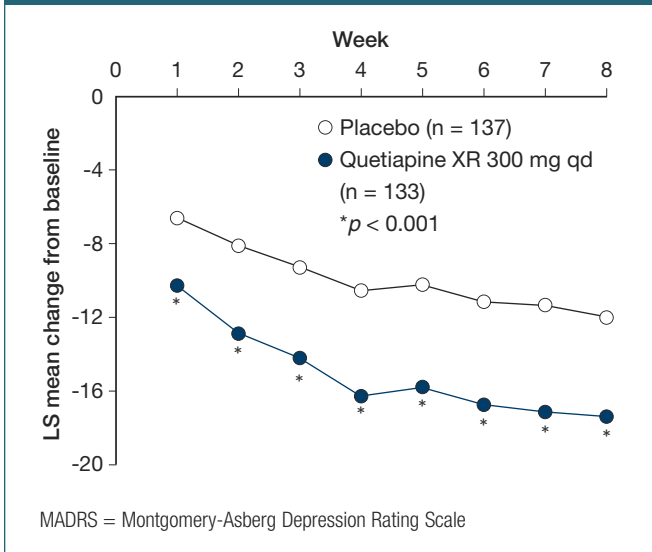
was seen as early as day 2 (-4.3 vs. -2.8; $p = 0.003$). Improvements in YMRS total score were maintained to week 12 for both aripiprazole (-14.5) and lithium (-12.7). The most common adverse events seen in the aripiprazole group were headache, nausea, akathisia, sedation, and constipation. The most common adverse events with lithium were nausea, headache, constipation, and tremor.

In a comparison with the first-generation antipsychotic, haloperidol, in patients with acute bipolar mania, a total of 485 patients were randomized to aripiprazole (15 or 30 mg/day), placebo or haloperidol (5-15 mg/day) for three weeks, with the active treatment groups continuing for an additional nine weeks of therapy.⁴ For the primary endpoint of mean change in YMRS total score, aripiprazole and haloperidol were associated with significantly greater improvements than placebo (-12.0 for aripiprazole, -12.8 for haloperidol and -9.7 for placebo; $p < 0.05$ for each active treatment vs. placebo); improvements were maintained at week 12 for both antipsychotic groups. In this study, extrapyramidal adverse events were significantly more frequent with haloperidol than aripiprazole (53.3% vs. 23.5%).

Evidence in acute depression. There have been mixed results with atypical antipsychotics for the treatment of acute bipolar depression. To date, the best evidence for efficacy has been shown by quetiapine. The extended-release (XR) formulation of this agent was evaluated in a double-blind, placebo-controlled study in acutely depressed adults with bipolar I disorder or bipolar II disorder.¹⁶ Patients were randomized to eight weeks of treatment with either quetiapine XR 300 mg daily or placebo. The primary outcome measure was change from baseline to week 8 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Quetiapine XR was associated with an improvement of 17.4 points, significantly greater than the 11.9-point improvement in the placebo group ($p < 0.001$; Figure 5). Response and remission rates at week 8 were also significantly higher with quetiapine XR compared to placebo (p values for both < 0.05). The most common adverse events associated with quetiapine XR were dry mouth (37.2%), somnolence (29.2%), and sedation (23.4%). Greater weight gain was also observed in patients taking quetiapine XR relative to those taking placebo (+ 1.3 kg vs. -0.2 kg, respectively).

FIGURE 5.

Quetiapine vs. Placebo for the Treatment of Acute Bipolar Depression: Change in MADRS Scores¹⁶



Olanzapine, alone or in combination with fluoxetine, was evaluated in 788 patients with acute bipolar depression.¹⁷ In this study, the monotherapy and combination therapies were associated with significant improvements in the MADRS total score compared to placebo. However, analysis of the effects of therapy on the individual MADRS items revealed that there were only three items for which there was a significant difference between olanzapine monotherapy and placebo: reduced sleep, reduced appetite and inner tension. Improvements in reduced sleep and reduced appetite were likely related to the adverse-event profile of olanzapine, which is known to be sedating and to increase appetite. Therefore, in terms of antidepressant efficacy, olanzapine may have only separated itself from placebo in terms of inner tension. For the other five core depressive symptoms included on the MADRS (apparent sadness, reported sadness, lassitude, inability to feel and pessimistic thoughts), there were no significant differences between olanzapine monotherapy and placebo.

An open-label study demonstrated significant improvements in bipolar depressive symptoms with aripiprazole.¹⁸ In this 16-week study of 85 bipolar patients with acute

depression inadequately responsive to one mood stabilizer, patients were assigned to aripiprazole either as monotherapy or adjunctive therapy. Monotherapy patients received a mean aripiprazole dose of 12.5 mg/day, while the mean dose was 10.2 mg/day among adjunctive-therapy patients. The investigators observed significant decreases in mean MADRS and Clinical Global Impression Severity (CGI-S) scores, and 52 patients (65%) met criteria for response ($\geq 50\%$ reduction in MADRS total score) while 30 (37.5%) met criteria for remission (final MADRS total score ≤ 12).

Aripiprazole monotherapy was also investigated in two identically designed, double-blind, placebo-controlled studies in bipolar depression.¹⁹ In each study, patients ($n = 373$ and $n = 376$) were randomized to placebo or aripiprazole, initiated at 10 mg daily and then flexibly dosed at 5-30 mg daily based on clinical effect and tolerability. Although there were significant differences in favor of aripiprazole (for the primary endpoint of change in total MADRS score from baseline) at weeks 1 through 6 in one study and at weeks 1, 2, 3 and 5 in the other study, no statistically significant differences were noted for this endpoint at week 8 in either study. Nevertheless, there was a trend towards a difference between aripiprazole and placebo. Aripiprazole was associated with a higher incidence of adverse events and discontinuations relative to placebo.

Notably, in subgroup analyses, aripiprazole monotherapy was associated with a significant benefit in the MADRS total and MADRS-6 (core depressive symptoms) scores among patients with more severe depression at baseline (Bech-6 score ≥ 15), but not among those with milder symptoms (Bech-6 score < 15).

It is somewhat puzzling that the aripiprazole curve for MADRS total score in the overall trial populations separates early and significantly from placebo and continues to diverge for the first five weeks of the studies, only to converge with the placebo curve in the subsequent weeks. There are, however, possible explanations for this phenomenon.

The dosing of aripiprazole may not have been appropriate in these studies. Study physicians were allowed to dose the agent up to 30 mg/day, and the higher end of that dose range is likely too high for the treatment of bipolar depression. Analysis of the mean MADRS change by aripiprazole dose shows that the difference between aripiprazole and

placebo was greatest for patients taking low doses (5 or 10 mg; -2.47 and -2.54 points in the two studies) and was lower among those taking 15 or 20 mg (-1.86 and +0.35), and that placebo was superior to the higher doses (25 or 30 mg; +1.93 and +0.35). Of note, the dose of aripiprazole given in the study did not appear to be dependent on symptom severity at baseline. In fact, among those with a Bech-6 score of < 15 (milder symptoms), 34% of patients received a dose of 25 or 30 mg, while among those with a Bech-6 score of ≥ 15 (more severe symptoms), 21% received the 25- or 30-mg dose.

Evidence in maintenance therapy. The goals of maintenance therapy are to reduce the incidence of episodes of acute mania and acute depression. The majority of the research conducted with atypical agents in maintenance therapy has shown that these agents are most useful in preventing manic recurrences, with aripiprazole, olanzapine and quetiapine having the most compelling data in this regard.²⁰⁻²⁵

The utility of aripiprazole as maintenance therapy was evaluated in a 100-week study²⁰ (26-week core study with a prospective 74-week extension study; both phases were double blind) involving 161 patients with bipolar I disorder who had achieved stabilization (YMRS score of ≤ 10 and MADRS score of ≤ 13 for six consecutive weeks). The subjects were randomized to receive either aripiprazole (15 or 30 mg/day) or placebo, with the primary endpoint being time to relapse into a mood episode. The authors reported that the time to any relapse was significantly longer with aripiprazole compared to placebo (HR 0.53; 95% CI 0.32-0.87; $p = 0.011$), driven by a significant improvement in delaying time to manic relapse (HR 0.35; 95% CI 0.16-0.75; $p = 0.005$). The difference between the groups was not significant with respect to delaying time to depressive relapse (HR 0.81; 95% CI 0.36-1.81; $p = 0.602$).

Another long-term study compared aripiprazole 15-30 mg/day to lithium 900-1500 mg/day in maintenance therapy.²² Patients with acute bipolar mania were initially randomized to double-blind aripiprazole, lithium or placebo for three weeks, after which the placebo arm was eliminated and patients were treated with aripiprazole or lithium for an additional nine weeks in the core double-

blind phase. Patients could then enter an additional 40-week, double-blind extension. At week 52, mean changes from baseline in YMRS total scores for the aripiprazole and lithium groups were -26.4 and -22.5, respectively. The majority of patients in both treatment groups sustained remission (YMRS ≤ 12) from week 12 to 52.

In another study—whose design was perhaps more reflective of clinical practice, where patients with BD are more likely to receive adjunctive treatment than monotherapy—aripiprazole added to lithium or valproate was compared to placebo added to either of these agents, as maintenance therapy for patients with bipolar I disorder who had an inadequate response to lithium or valproate monotherapy.²³ Patients with a current

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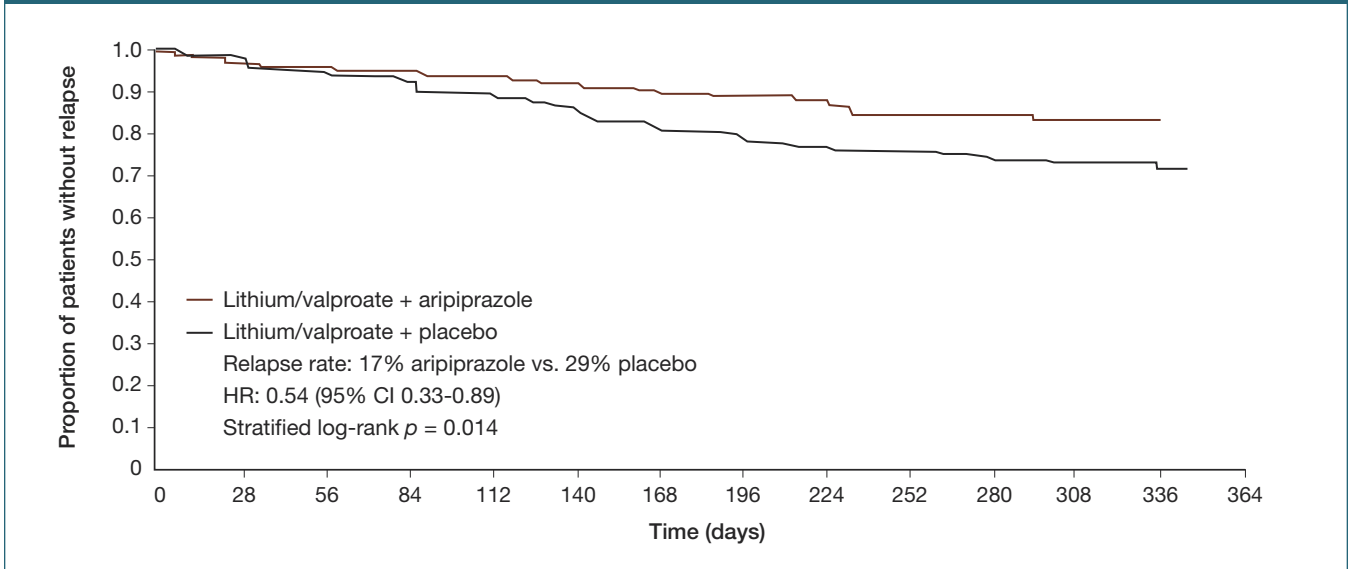
manic/mixed episode received lithium or valproate for at least 2 weeks, and those with YMRS total score ≥ 16 and $\leq 35\%$ decrease from baseline at 2 weeks received adjunctive aripiprazole. Patients who achieved stability for 12 consecutive weeks were randomized to aripiprazole or placebo, each added to lithium or valproate. Adjunctive aripiprazole significantly delayed time to any relapse compared to adjunctive placebo (relapse rate 17% vs. 29%; HR 0.54; 95% CI 0.33-0.89; $p = 0.014$; Figure 6).

For the prevention of recurrences of acute depression, quetiapine has demonstrated the most favorable efficacy.^{24,25} A study by Vieta et al,²⁴ published in 2008 ($n = 703$), showed that stable patients treated with twice-daily immediate-release quetiapine were significantly less likely to relapse into depression compared to those who received placebo (HR 0.26; 95% CI 0.17-0.41; $p < 0.001$).

Dosing. In BD, the rule of thumb for atypical agents is to start with the lowest potentially effective dose and

FIGURE 6.

Aripiprazole vs. Placebo (Both Adjunctive to Lithium or Valproate) for Maintenance Therapy: Time from Randomization to Relapse²³



slowly titrate the agent based on tolerability and response. A lower initial dose reduces the risk of treatment-emergent adverse events. For example, with aripiprazole, starting at a dose of 5 or 10 mg daily (or lower if the patient is not manic) is an effective method of minimizing the risk of antipsychotic-related akathisia, which with aripiprazole tends to be short-lived (1-2 weeks).²⁶

In my clinical practice I often use aripiprazole to treat bipolar depression and as an add-on to antidepressants for treatment-resistant unipolar depression (off-label and not endorsed in Canada by the manufacturer). For bipolar depression or the depressive mixed state of bipolar II, I usually start with 2 mg in the morning either as monotherapy or added to a mood stabilizer. Since aripiprazole has a half-life of 72 hours, I tend to leave the dose at 2 mg until blood levels reach steady state at day 15 (five half-lives). Rarely do I see any side effects when starting at 2 mg, except for the occasional patient who finds it too activating. In these cases, simply increasing the dose to 5 mg AM will often stop the excess activation. I had one patient with an intention tremor at 2 mg that stopped with an increase in dose

to 5 mg/day. About 7% of patients will find aripiprazole sedating. In these cases, I have the patient take the aripiprazole at bedtime. Many patients notice improvement in their mood, interest, pleasure, energy and sometimes cognition within the first two weeks at 2 mg. Usually the final dose to bring about the best antidepressant response in my practice is 5, 7.5 or 10 mg/day. Exceeding 10 mg/day, for some patients, seems to have a depressogenic effect, likely because of the high affinity for and potential blockade of D2 receptors, which probably contributes to effective antimanic and antipsychotic properties between 15-30 mg/day.

My bipolar II and bipolar NOS patients, who usually have comorbid anxiety disorders (as I discussed in Part 1 of this article), often do best with a combination of a low dose of an atypical antipsychotic and lamotrigine (anti-glutamatergic, antidepressant, anxiolytic) which I start at 25 mg/day and titrate up (to minimize the risk of Stevens-Johnson syndrome) by 25 mg every 1-2 weeks, usually up to 100-200 mg bid. Often, once their mood is stabilized, the anxiety symptoms decrease substantially or remit (even without a serotonergic antidepressant) and

other comorbid medical disorders such as migraine, fibromyalgia syndrome, chronic fatigue syndrome and irritable bowel syndrome improve significantly. Once the patient is stabilized and is doing well, as long as their regimen is well tolerated, I recommend they continue the effective treatment indefinitely.

Although lithium may help with depression, which is so prominent in bipolar II, it has little if any anxiolytic efficacy and decreased effectiveness in mixed episodes. Valproic acid, on the other hand, tends to be anxiolytic and helpful in mixed episodes but may not have much antidepressant efficacy (studies have shown mixed results).

Adverse events. Each atypical antipsychotic has a unique receptor-binding profile, which results in markedly different adverse-event profiles among these agents. Given the increased risk of cardiometabolic risk factors and complications in this population (even before treatment), one of the considerations for therapy needs to be whether the pharmacotherapy used to treat the BD has any impact on these parameters. The receptor-binding profiles of aripiprazole, ziprasidone and aripiprazole, for example, make these agents far less likely to induce metabolic adverse effects (*e.g.*, dyslipidemia, weight gain, increased risk of diabetes). In contrast, clozapine, olanzapine, risperidone and possibly quetiapine are likely associated with greater metabolic risk. Aripiprazole is not typically associated with daytime sedation, which is a common effect of therapy with other atypical agents (*e.g.*, quetiapine and olanzapine). In fact, aripiprazole can be activating, for some patients in a positive energizing way and for some patients activating to the point of agitation and restlessness, particularly if started at higher doses. Usually, this resolves with dose reduction or over time (1-2 weeks).

Antipsychotic-related akathisia is also a potential adverse event of note, and bipolar patients are particularly predisposed to this. In a recently published review of antipsychotic-related akathisia, Kane et al analyzed data from 77 trials of antipsychotics in schizophrenia or BD in adults.²⁷ The incidence of akathisia was generally higher in BD trials than in schizophrenia trials, and the incidence was consistently higher with first-generation antipsychotics than with second-generation agents. It should be noted, however, that there may be wide variability in reporting of akathisia be-

tween clinical trials. This is an adverse effect that may be difficult to distinguish from agitation or anxiety. The reporting of akathisia rates is therefore dependent on the experience and training of study personnel in its identification.


To reduce the risk of antipsychotic-related akathisia in patients with BD, one should start with a low dose and titrate slowly.²⁸ If akathisia develops, there are several options for management. Reducing the dose of the an-

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tipsychotic may be effective.²⁸ If it is not, the addition of an adjunctive agent is indicated.^{27,28} Benzodiazepines may be the most effective option, while beta-blockers and anticholinergic agents are other useful possibilities. Evidence also exists for managing akathisia with other agents, including mirtazapine.^{29,30} With mirtazapine specifically, however, consideration must also be given to the risk of weight gain (particularly after prolonged therapy) and sedation associated with this agent. It is noteworthy that additive use of aripiprazole has been shown to neutralize or reduce the increased weight gain induced by mirtazapine.³¹

Conclusions

BD is a highly variable disorder with a high risk of relapse and recurrence. To optimally manage patients diagnosed with BD, clinicians need to familiarize themselves with the recommendations of evidence-based guidelines for each of the disorder's distinct phases. Atypical antipsychotics have demonstrated efficacy for the treatment of acute bipolar mania and depression, in addition to maintenance therapy.

The recent accumulation of evidence in these phases of BD has led to the inclusion of atypical antipsychotics as treatment options recommended by the CANMAT/ISBD bipolar guidelines. Aripiprazole, the newest addition to the antipsychotic armamentarium available to Canadian physicians, has demonstrated efficacy in treating acute mania or mixed episodes (either as an adjunctive therapy with a mood stabilizer or as monotherapy) and in preventing relapse as a maintenance agent. Like ziprasidone and asenapine, this agent also has an adverse-effect profile distinct from the other available antipsychotics (in particular, decreased risk of weight gain and metabolic syndrome), which should provide clinicians with even greater flexibility in tailoring a therapeutic regimen to best suit each individual patient. 

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