EXPERT OPINION

Treatment and prevention of mania in bipolar I disorder: focus on aripiprazole

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Abstract: Aripiprazole is a second-generation antipsychotic with a unique pharmacologic receptor profile that has efficacy in the treatment and prevention of mania in bipolar I disorder. This article reviews the evidence supporting treatment of adults with bipolar I disorder using aripiprazole as monotherapy or adjunctively during acute mania and its utility as an intramuscular agent for agitation in manic patients. Results from one of the longest bipolar maintenance trials which support aripiprazole as a prophylactic mood stabilizer, specifically against manic relapses, will be discussed as well as a post-hoc analysis that suggests efficacy for rapid cycling bipolar disorder. Safety and tolerability issues, patient-focused perspectives and aripiprazole's place in therapy for bipolar mania will be covered.

Keywords: bipolar disorder, mania, prevention, aripiprazole, rapid cycling

Introduction

The management of acute mania presents challenges to clinicians that extend beyond simple symptomatic reduction. Clearly, early recognition of manic states and early intervention pharmacologically is necessary in order to resolve the affective disturbance and to avoid serious negative consequences that may result from out-of-control manic behaviors. Fortunately, a growing number of antimanic medication treatment options have become available over the past decade which has fortified the armamentarium from which clinicians may select and patients may choose effective antimanic therapy. However it is quite important that a more far-sighted approach to managing acute mania is undertaken given the recurrent and sometimes chronic nature of bipolar disorder. While acutely treating mania, clinicians must take into consideration not only short-term efficacy and tolerability but begin laying the foundation of a safe and effective long-term prevention strategy.

This article seeks to review the treatment and prevention of mania in bipolar I disorder with a focus on aripiprazole. Only data related to adult bipolar disorder from large, randomized and controlled clinical trials will be included with an emphasis on studies related to aripiprazole's approved usages in the United States and clinical implications and patient-centered perspectives.

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The emergent use of atypical antipsychotics for mania

Manic episodes are often medical emergencies that require hospitalization in order to rapidly address abnormal affective symptomatology, restore behavioral control and

protect the individual with bipolar disorder and others from the consequences related to impulsive and often dangerous actions. Prior to the approval of olanzapine for the management of acute mania by the US Food and Drug Administration (US FDA) in 2000, only lithium, divalproex and chlorpromazine carried an anti-manic indication. Since then four other atypical or second-generation antipsychotics (SGAs) have received US FDA approval for the management of acute bipolar mania – risperidone (2003), quetiapine (2004), ziprasidone (2004), and aripiprazole (2004). Evidence of longer-term stabilization of mood provided by olanzapine, aripiprazole, and quetiapine (adjunctively with lithium or divalproex) – particularly against manic relapses and recurrences – led not only to their US FDA approval as maintenance therapies for bipolar I disorder but the emergence of atypical antipsychotics as common, first-line pharmacotherapies in clinical practice for the treatment and prevention of mania. Table 1 summarizes the strength of available data and US FDA indications for the antipsychotic medications in the treatment of mania and prevention of relapse in bipolar I disorder.[1] In addition to these antipsychotics, it should be noted that other mood stabilizers not reviewed here carry US FDA indications against mania (lithium, divalproex, divalproex extended-release, carbamazepine)

and for maintenance treatment of bipolar I disorder (lithium; lamotrigine – primarily for depressive relapse).

An overview of the pharmacology of aripiprazole

Aripiprazole is an SGA that belongs to the quinolinone class, available since the end of 2003, and available in a wide variety of formulations (tablets, oral solution, oral-disintegrating tablets, short-acting intramuscular injectable). To date, studies have consistently confirmed that this SGA is reasonably well tolerated, with low metabolic risks (induction of type 2 diabetes, weight gain, hyperlipidemia), little sedation, and generally mild extrapyramidal side effects (EPS).

As with psychosis, central dopaminergic hyperactivity has long been implicated as a causative factor in acute mania.[2] Dopamine D2 receptor antagonists, both typical and atypical antipsychotics, presumably exert both antipsychotic and antimanic effects by dampening hyper-dopaminergic brain activity. Although similar in many ways to other SGAs, aripiprazole's pharmacologic mechanism of action is unique among the atypical antipsychotics due to a complex receptor profile.[3–5] Its profile of partial agonist action at several G-protein coupled receptors (postsynaptic dopamine (D2), presynaptic dopamine autoreceptors, 5-HT1A) and antagonism at others

Table 1 Antipsychotic drugs for bipolar mania and maintenance, US-FDA indications and strength of data

Agent	Acute mania		Maintenance	
	US-FDA approved?	Strength of data	US-FDA approved?	Strength of data
SGAs				
Aripiprazole	Yes[a]	A	yes	A[b]
Asenapine	no	A	no	n/a
Olanzapine	yes[1]	A	yes	A
Paliperidone	no	n/a	no	n/a
Quetiapine	yes[a,c]	A	yes[a]	A
Risperidone	yes[1]	A	no	n/a
Ziprasidone	yes	A	no	n/a
Typical antipsychotics				
Chlorpromazine	yes	B	no	n/a
Haloperidol	no	A	no	n/a
Perphenazine	no	n/a	no	negative

[a]additionally indicated as adjunct to lithium or valproate; [b]no effectiveness against bipolar depression; [c]among the approved second-generation antipsychotics (SGAs) for acute mania, the only agent that does not also carry indication for mixed episodes.
Strength of data on basis of a modified POST method.[1]
Level A: Good research-based evidence, supported by at least one-placebo-controlled study of sufficient magnitude.
Level B: Fair research-based evidence, from at least one randomized, double-blind controlled trial but does not fulfill the level A criteria fully (eg, no placebo control or small sample size).
Negative: negative data; n/a: none available.
United States Food & Drug Administration (US FDA) data can be accessed at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

(5-HT2A) marks aripiprazole as the first functionally selective atypical antipsychotic. Lacking the conventional D2 receptor antagonism characteristics of other antipsychotics, aripiprazole most likely exerts antimanic efficacy by way of *partial* dopamine D2 receptor agonist activity, thus lowering intrinsic and excessive dopamine neurotransmission.[6] In addition, partial agonism at the dopamine D3 receptor may also contribute to aripiprazole's therapeutic action in bipolar disorder.[7]

Positron emission tomography (PET) studies support the proposed mechanism of receptor action for aripiprazole as a partial dopamine agonist.[8,9] Aripiprazole occupied 70% to 80% of striatal dopamine receptors in healthy subjects at doses of 2 mg/day, with dopamine occupancy at 95% when the dose was increased to 30 mg/day while EPS was not observed. A pure agonist would likely induce EPS at such high dopamine receptor occupancy levels. Aripiprazole has minimum affinity for histamine, muscarinic and alpha-1 adrenergic neuroreceptors which may explain the excellent tolerability of the drug in terms of sedation, heart rate and weight gain.[3,10]

Aripiprazole is rapidly absorbed and demonstrates linear pharmacokinetics with a mean elimination half-life of 75 hours, allowing for single daily dosing. The drug is highly protein bound in plasma. Elimination of aripiprazole occurs chiefly though hepatic metabolism via cytochrome P450-2D6 and 3A4. Clinically significant alterations in aripiprazole plasma levels may occur when co-administered with 3A4 inducers (ie, carbamazepine), inhibitors (ie, fluvoxamine, ketoconazole), or substrates (ie, nefazodone, haloperidol). Aripiprazole has safely been co-administered with valproic acid and lithium.[11]

Efficacy studies of aripiprazole for bipolar mania

Aripiprazole is approved by the US FDA for the management of acute manic or mixed episodes of bipolar disorder in adults, either as monotherapy or as an adjunctive therapy to either lithium or valproate. Aripiprazole monotherapy is indicated for maintenance treatment of manic and mixed episodes associated with bipolar I disorder. Additionally, aripiprazole has efficacy in the acute treatment of agitation associated with manic or mixed states. This article will not review aripirazole's approval for mania in children ages 10 to 17, for schizophrenia, or as adjunctive therapy for unipolar major depression.

Aripiprazole – monotherapy treatment of mania

The efficacy of aripiprazole monotherapy in the treatment of acute manic or mixed episodes was established in four 3-week, placebo-controlled trials (n = 268; n = 248; n = 480; n = 485) in hospitalized patients who met criteria for bipolar I disorder (US FDA Prescribing Information: http://www. accessdata.fda.gov/scripts/cder/drugsatfda/). Patients with or without psychotic features were included in all four trials, while patients with or without rapid cycling were included in two of the studies. Across all studies the primary outcome was change in degree of manic symptomatology as measured by the Young Mania Rating Scale (YMRS) with secondary outcome measurements including the Clinical Global Impression – Bipolar (CGI-BP) Scale. Aripiprazole was superior to placebo in the reduction of YMRS total score and CGI-BP Severity of Illness score for mania. As noted in the review by Garcia-Amador and colleagues, one unpublished monotherapy, placebo-controlled study was negative.[12] Among the positive studies, aripiprazole monotherapy was associated with a 10% to 20% greater response than placebo in the treatment of manic and mixed episodes.[13–15]

The seminal aripiprazole monotherapy trial by Keck and colleagues for bipolar mania utilized a starting daily dose of 30 mg aripiprazole or placebo while allowing for reduction to 15 mg/day for tolerability.[13] In this 3-week study, aripiprazole monotherapy demonstrated significantly greater efficacy compared with placebo in reduction of total YMRS scores from baseline to study endpoint (mean change in YMRS: aripiprazole −8.2, placebo −3.4). Statistically significant separation between active treatment and placebo effects on manic symptoms was noted as early as Day 4. Using the standard definition of antimanic response – reduction of baseline YMRS by ≥50% – aripiprazole monotherapy was associated with a 40% response rate, statistically superior to the 19% response rate observed with placebo. The mean aripiprazole dose at endpoint was 27.9 mg/day.

In a separate study of aripiprazole monotherapy employing similar design, 53% of aripiprazole-treated patients with bipolar I mania or mixed state responded to treatment by end of the 3-week placebo controlled study at a mean dose of 28 mg/day.[15] A statistically significant lower placebo response rate of 32% was observed in this study compared with active treatment. This study also demonstrated early onset of antimanic effects with aripiprazole monotherapy compared with placebo, again with separation between treatment arms on Day 4 and sustained throughout the 3-week study.

A post-hoc analysis of these two studies found that the antimanic response to aripiprazole was independent of baseline level of agitation, suggesting a specific antimanic effect.[16] In a separate post-hoc analysis of pooled efficacy

data from these two studies, Frye and colleagues examined individual manic symptoms measured by the 11-item YMRS to determine how individual symptom improvement relates to overall improvement in patients with bipolar I disorder with an acute manic or mixed episode.[17] Aripiprazole monotherapy (n = 259) significantly improved 10 of 11 YMRS manic symptom domains, statistically separating from placebo treatment (n = 254) on all YMRS line items with the exception of sexual interest by study endpoint (Figure 1). The antimanic effect of aripiprazole therefore was diffuse and widespread among manic patients and across various manic symptom domains, with the YMRS line items ranked with the highest percent change over placebo being disruptive–aggressive behavior (34%), insight (29%), and irritability (28%).

Further post-hoc analysis of these pooled data was conducted to determine whether any treatment differences existed among subpopulations of patients with acute manic or mixed episodes of bipolar I disorder given aripiprazole or placebo.[18] Aripiprazole significantly reduced mean YMRS total scores at end point compared with placebo irrespective of patient age, sex, or severity of illness. Importantly, aripiprazole also evidenced antimanic superiority

over placebo among bipolar I patients with mixed or manic episodes, with or without psychotic features, or with a history of rapid or non-rapid cycling (p < 0.01 for each subpopulation). These results support efficacy of aripiprazole across a broad range of bipolar subpopulations often associated with treatment resistance, such as psychotic or rapid cycling patients experiencing manic or mixed episodes of bipolar I disorder.

Vieta and colleagues compared aripiprazole and haloperidol monotherapy in a 12-week study of 347 patients with bipolar I disorder experiencing an acute manic or mixed episode.[19] This double-blind, randomized trial assigned patients to either aripiprazole or haloperidol monotherapy with the primary outcome measured as number of patients in response (≥50% reduction in YMRS) and still on treatment at week 12 – representing an "effectiveness measure of response." Aripiprazole was initiated at 15 mg/day and haloperidol at 10 mg/day, with dosage increased to 30 mg/day and 15 mg/day, respectively, at week 1 or 2 in patients showing poor response; reduction to initial starting dose was permitted for tolerability reasons if necessary with those patients not able to tolerate the minimum starting daily dosages discontinued from study. Both active treatments produced considerable and early reductions in
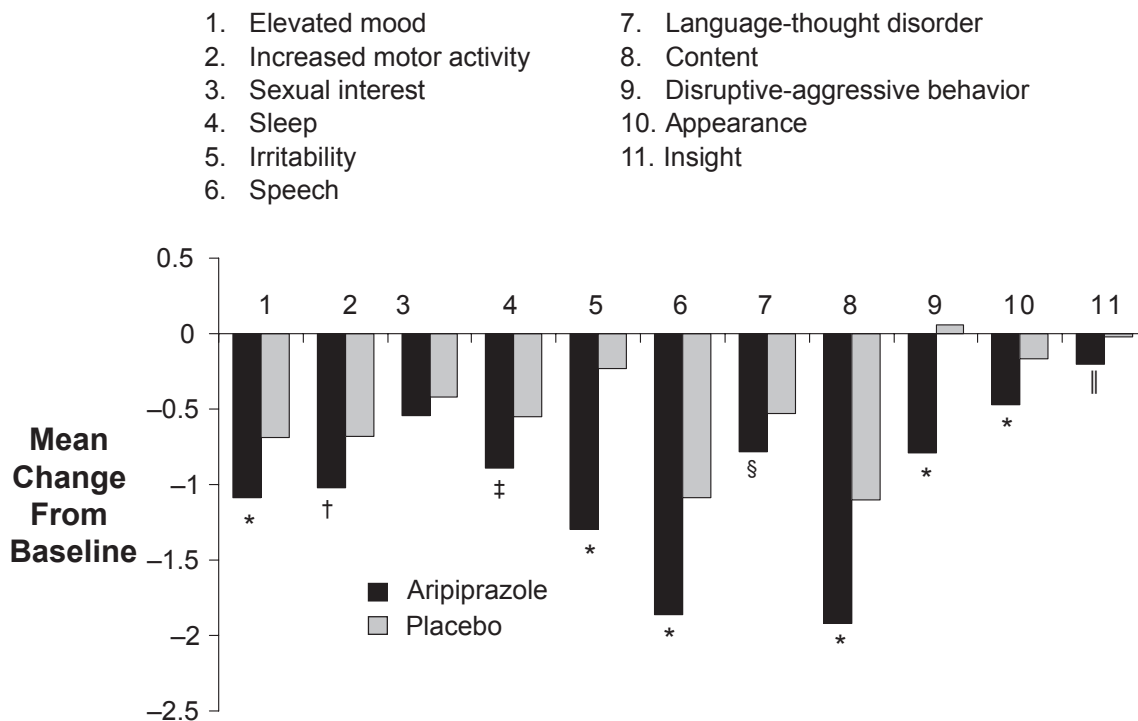
1. Elevated mood
2. Increased motor activity
3. Sexual interest
4. Sleep
5. Irritability
6. Speech
7. Language-thought disorder
8. Content
9. Disruptive-aggressive behavior
10. Appearance
11. Insight

Figure I Mean changes in individual YMRS line items of patients with an index of manic or mixed episode. [a]Item range of 0–4 for elevated mood, increased motor activity/energy, sexual interest, sleep, language/thought disorder, appearance, and insight. Item range of 0–8 for irritability, speech, content, and disruptive/aggressive behavior (2).
[a]Pooled data from 2 placebo-controlled trials (LOCF). *p < 0.001, †p = 0.002, ‡p = 0.001, §p = 0.003, ‖p = 0.006.
Reproduced with permission from Frye MA, Eudicone J, Pikalov A. et al. Aripiprazole efficacy in irritability and disruptive-aggressive symptoms: young mania rating scale line analysis from two, randomized, double-blind, placebo-controlled trials. *J Clin Psychopharmacol.* 2008;28:243–245.[17] Copyright © 2007 Lippincott Williams & Wilkins.

manic symptomatology with no statistically significant differences in effectiveness between the two groups at week 3: a 50.9% response with aripiprazole and 42.6% response with haloperidol (p = 0.126), as depicted in Figure 2. However, at week 12 significantly more patients randomized to aripiprazole were responders and still on therapy (49.7%) compared with those on haloperidol (28.4%) (p < 0.001). Patients given haloperidol during this study were nearly twice as likely as those given aripiprazole to discontinue their medication, primarily due to adverse events associated with treatment. Extrapyramidal symptoms occurred in 36% of haloperidol-treated patients compared to 9% of aripiprazole-treated patients. The results of this study suggest that aripiprazole's greater sustained response rates and better tolerability make it a more effective treatment for acute mania than haloperidol.

Aripiprazole has also been studied as monotherapy for bipolar I mania/mixed state with a randomized, double-blind, placebo- and lithium-controlled trial.[20] Patients were randomized to aripiprazole (15–30 mg/day; n = 155), placebo (n = 165) or lithium (900–1500 mg/day; n = 160) for 3 weeks, with continuation of blinded active treatment for an additional 9 weeks. Aripiprazole demonstrated significantly greate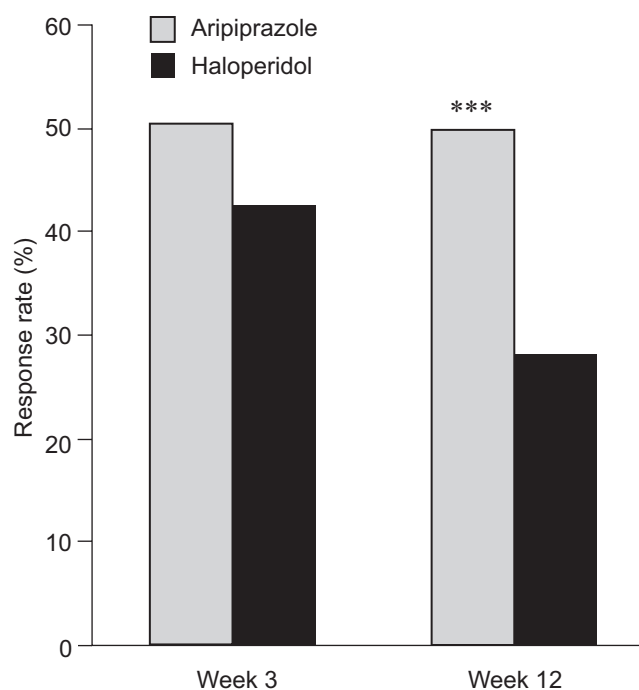r improvement than placebo in mean YMRS total score from baseline to Day 2 (−4.3 vs −2.8; p = 0.003), and up to week 3 (−12.6 vs −9.0; p < 0.001). Significant improvement in YMRS total score was first observed with lithium versus placebo at week 3 (−12.0 vs −9.0; p = 0.005). Improvements in YMRS total score were sustained through week 12 for both aripiprazole (−14.5) and lithium (−12.7). Response rates at week 3 were significantly higher with aripiprazole (46.8%) and lithium (45.8%) than placebo (34.4%; both p < 0.05); growing to week 12 with aripiprazole (56.5%) and lithium (49.0%). Aripiprazole led to statistically significant improvement of acute mania within 2 days, continuing over 3 weeks and maintained over 12 weeks. The magnitude of improvement in manic symptomatology was similar with aripiprazole and lithium through 12 weeks of treatment.

In summary, aripiprazole monotherapy at doses of 15 to 30 mg/day is efficacious in the treatment of acute manic and mixed states associated with bipolar I disorder. As an antimanic agent it compares favorably with lithium and haloperidol, with faster onset of action than lithium and with greater effectiveness of response than haloperidol.

Aripiprazole – adjunctive treatment of mania

A recent multicenter, randomized, placebo-controlled study of adjunctive aripiprazole added to either lithium or valproate treatment in manic/mixed bipolar I patients partially nonresponsive to lithium/valproate monotherapy has been reported.[21] This study consisted of 3 phases: a screening phase, an open-label treatment phase, and a double-blind phase. During the Phase 1 screening period, medications other than lithium or valproate were discontinued; patients were required to achieve serum levels of lithium (0.6 to 1.0 mmol/L) or valproate (50–125 µg/mL) in the therapeutic range yet remain manic at end of screening (YMRS ≥ 16). In Phase 2, open-label lithium or valproate was continued as monotherapy for 2 weeks. Those patients with partial nonresponse to mood stabilizer monotherapy at the end of Phase 2, defined as YMRS persisting at ≥16 with a decrease of ≤25% between Phases 1 and 2, were eligible for Phase 3 random assignment to double-blind adjunctive aripiprazole or placebo for 6 weeks. Adjunctive aripiprazole was initiated at 15 mg/day and could be increased to 30 mg/day after 1 week depending on clinical response or tolerability.

Adjunctive aripiprazole compared with placebo added to lithium or valproate was associated with significantly greater reduction in manic symptomatology as measured by YMRS at week 1 of double-blind treatment and at all study points through week 6. Six of 11 YMRS items were significantly

Figure 2 Response rates to monotherapy treatment with aripiprazole and haloperidol at weeks 3 and 12 among patients with bipolar I disorder, manic or mixed at baseline. ***p < 0.001 versus haloperidol.
Reproduced with permission from Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005;187:235–242.[19] Copyright © 2005 The Royal College of Psychiatrists.

improved with adjunctive aripiprazole relative to placebo: elevated mood, sexual interest, irritability, speech, disruptive/aggressive behavior and insight. Response rates with adjunctive aripiprazole were higher than placebo, separating statistically from placebo at week 5 and remaining significantly greater at week 6, 62.8% versus 48.5%, respectively (p < 0.01). Remission, defined as total YMRS ≤ 12, was observed in a significantly larger number of patients receiving adjunctive aripiprazole compared with placebo at weeks 1, 3, 4, 5, and 6; at week 6, the remission rate was 66.0% for adjunctive aripiprazole and 50.8% for placebo (p < 0.01). In addition, there was significant reduction in the emergence of depression as well as improvement in psychosocial functioning among the adjunctive aripiprazole group compared with placebo in this study.

Aripiprazole – acute agitation associated with bipolar mania

In a multicenter clinical trial, 301 agitated patients with bipolar I disorder in manic or mixed state were randomized in double-blinded fashion to receive intramuscular (IM) aripiprazole (9.75 or 15 mg IM), IM lorazepam (2 mg) or IM placebo. Up to 3 injections in the first 24 hours were permitted.[22] Based on mean change in Positive and Negative Syndrome Scale Excited Component scores, both doses of IM aripiprazole as well as IM lorazepam demonstrated significant improvement in agitation 2 hours post-injection compared with IM placebo. Oversedation during the first 2 hours after injection was significantly less with IM aripiprazole 9.75 mg and IM placebo compared with IM aripiprazole 15 mg and IM lorazepam. These results suggest that IM aripiprazole can be used to quickly and effectively reduce agitation in manic patients, with a tolerability advantage for the 9.75 mg IM dose over IM aripiprazole 15 mg or IM lorazepam 2 mg.

Aripiprazole – prevention of mania

Keck and colleagues conducted an initial 26-week placebo-controlled, double blind study that evaluated the long-term efficacy of aripiprazole in the prevention of mood episodes associated with bipolar I disorder.[22] This study was later extended by 74 weeks for a total of 100 weeks, thus comprising the longest maintenance study of bipolar disorder to date.[14] The study employed an enriched design, with patients first completing a stabilization treatment phase which included aripiprazole as therapy for an acute manic or mixed episode. During the 6- to 18-week stabilization phase, patients were given aripiprazole 15 to 30 mg/day and were eligible to enter the randomized maintenance study once remission of the acute mania/mixed episode was achieved (defined by YMRS

total scores ≤10 in 4 consecutive weeks or during 6 weeks, plus the absence of depression). The stabilized patients were then randomly assigned to double-blind treatment with aripiprazole or placebo and followed over 100 weeks with a primary study endpoint of relapse to any mood episode. Time to any relapse was significantly longer with aripiprazole monotherapy compared with placebo (p = 0.011). Further analysis demonstrated that this statistical superiority was present for aripiprazole over placebo only for the prevention of manic relapses; there were no significant differences in depressive relapses between treatment groups. Nearly half of the patients receiving aripiprazole monotherapy in the study were on 15 mg/day at end of study.

In a post-hoc analysis of this 100-week maintenance study, the impact of aripiprazole on the course of rapid cycling bipolar disorder was examined in comparison to placebo.[23] Among the small sample of patients (n = 28) with rapid cycling bipolar disorder who were initially stabilized from a manic or mixed episode during open label treatment that included aripiprazole and went on to be randomized to double-blinded treatment, time to any mood relapse was significantly longer with aripiprazole monotherapy compared with placebo at week 26 (p = 0.033) and at week 100 (p = 0.017).

Aripiprazole monotherapy is effective in the long-term treatment of bipolar disorder, with more robust prophylaxis against manic relapses than depressive relapses among recently manic patients who were stabilized acutely with aripiprazole. There is also evidence to suggest that aripiprazole monotherapy is effective in the prevention of relapse among patients with rapid cycling, which may represent a more refractory form of bipolar disorder with greater morbidity than non-rapid cycling illness. Long-term prevention of relapse among rapid cycling bipolar patients using a combination of aripiprazole with a second mood stabilizer has not been systematically investigated. Such an effort is warranted given these findings and an emerging consensus that patients with bipolar disorder on monotherapy, if followed for sufficiently long periods, will eventually require adjunctive or combination treatment to maintain a full remission.[24]

Safety and tolerability of aripiprazole

In the studies reviewed here with aripiprazole among patients with bipolar disorder for acute treatment of mania and for prevention of relapse, the drug was generally well tolerated. The most commonly observed adverse reactions associated with the use of aripiprazole in adult patients with bipolar disorder are noted in Table 2. Of particular clinical

Table 2 Commonly observed adverse reactions associated with the use of aripiprazole in patients with bipolar I disorder (incidence of ≥5% and at least twice the rate of placebo)[a]

Indications	Aripiprazole (%)	Placebo (%)
Monotherapy for mania		
Akathisia	13	4
Sedation	8	3
Tremor	6	3
Restlessness	6	3
Extrapyramidal disorder	5	2
Adjunctive for mania		
Akathisia	19	5
Insomnia	8	4
Extrapyramidal disorder	5	1
IM for agitation		
Nausea	9	3
Maintenance[b]		
Tremor	9	1
Akathisia	8	1
Dry mouth	8	1
Hypertension	8	4
Weight gain	6	0
Vaginitis	6	0
Flu syndrome	5	0
Pharyngitis	5	2
Abnormal thinking	5	2

[a]US FDA Prescribing Information for Abilify® (aripiprazole) available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ or http://packageinserts.bms.com/pi/pi_abilify.pdf
[b]Keck et al.[14]

concern with the use of any antipsychotic agent, including aripiprazole and other SGAs, is the risk of EPS, weight gain, induction of type II diabetes and elevation of lipids.

The incidence of EPS, including akathisia, is thought to be relatively low with aripiprazole and other SGAs in comparison with conventional antipsychotics. The rates of EPS reported in randomized controlled clinical trials of SGAs in bipolar disorder range between 5% and 15%, although this low figure has been challenged as non-representative of the rates observed in the "real world" clinical setting.[25] A recent review of antipsychotic-induced EPS relative to placebo from large randomized controlled trials in bipolar disorder and schizophrenia found that patients with bipolar disorder were more vulnerable to acute EPS than those with schizophrenia, even with SGAs.[26] It should be noted that this analysis revealed that among patients with bipolar disorder who experienced EPS from any antipsychotic agent, its occurrence was much more likely during the depressive

phase than when manic. However, the incidence of akathisia was significantly increased in manic patients receiving aripiprazole compared with other SGAs.

In the 100-week maintenance study of aripiprazole monotherapy, the mean weight change from baseline was +0.4 kg (± 0.8 kg) with aripiprazole and −1.9 kg (± 0.8 kg) with placebo.[14] However, some patients may be more sensitive to the risk of weight gain with 20% (12/60) of the aripiprazole-treated patients in this long-term study gaining clinically significant weight (≥+7% from baseline) compared with only 5% (3/61) of the placebo-treated patients (p = 0.01). Further analysis of mean weight change in this study by body mass index (BMI) at baseline is summarized in Table 3. No significant difference in weight change was observed between aripiprazole and placebo for patients in both the low baseline BMI (<23 kg/m^2) and high baseline BMI (>27 kg/m^2) categories at study end point.

The data from this long-term aripiprazole study also provide valuable information regarding the incidence of other clinically important changes in metabolic risk factors with treatment. No statistically significant differences were found in the change from baseline to week 100 in combined fasting and nonfasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, or triglycerides with aripiprazole treatment. In addition, there were no significant differences in the incidence of abnormal lipid or glucose levels between groups over the 100 weeks of treatment. These findings are consistent with the consensus statement from the American Diabetes Association/American Psychiatric Association/American Association of Endocrinologists collaborative conference on antipsychotic drugs and obesity and diabetes.[27] Their summary of scientific evidence indicated that among the SGAs both aripiprazole and ziprasidone carried the lowest risk for induction of weight gain, diabetes and lipid disorders.

There are case reports in the literature of aripiprazole induction of tardive dyskinesia or dystonia,[28,29] and neuroleptic malignant syndrome.[30] Aripiprazole has not been associated with elevation of prolactin[31] and has been reported to reverse hyperprolactinemia due to other antipsychotics or prolactinomas.[32] The risk for agranulocytosis and seizures is very low, although two case reports of isolated seizures on aripiprazole have been published.[33,34]

Aripiprazole – patient-focused perspectives

Increasingly, patients with bipolar disorder and their clinicians have come to recognize that the best medication management

Table 3 Mean weight change by body mass index (BMI) at baseline for aripiprazole monotherapy versus placebo in a 100-week maintenance study of recently manic patients with bipolar I disorder

BMI (kg/m²)	Aripiprazole (kg)	Placebo (kg)	p value
<23	+1.86	−1.91	ns
23–27	+3.04	−2.59	0.025
>27	−0.77	−1.81	ns

Abbreviations: ns, nonsignificant; p > 0.05.

strategies involve not just treatment of the acute episodes of mania but implementation of effective prevention early in the course of the illness as well as factoring in individual patient preferences and concerns. Several patient-focused perspectives and issues must be considered.

Acutely manic patients often lack insight into the presence of an active mood disorder and the need for treatment, with little improvement in level of insight upon discharge from psychiatric inpatient hospitalization and despite marked improvement in symptoms.[35] Impaired insight among patients with bipolar I disorder has been reported in 47% of remitted and 94% of symptomatic patients,[36] and is more commonly found in patients with bipolar disorder than those with unipolar major depression or anxiety disorders.[37] Manic patients with psychotic features are more likely to have poor insight into the need for treatment.[38] Impaired insight, particularly into need for treatment more so than into diagnosis, has a negative impact on clinical outcome.[37,39] Conversely, patients with bipolar disorder who have higher levels of insight may be at increased risk for suicide and more commonly report poorer overall quality of life.[40,41]

The cause for impaired insight is unknown and presents a very common problem during treatment of mania and in longer term maintenance. Although poorly studied in bipolar disorder, stigma related to mental illness as well as the stigmatizing effects of antipsychotic medications likely plays a significant role in non-adherence and may be difficult to tease apart from trouble with patient insight.[42] Evidence suggests that improving level of insight in patients with bipolar disorder represents an opportunity to improve adherence with treatment and ostensibly improve outcomes.[43] The negative effects of stigma and insight impairments can only be counteracted when they are addressed by caring clinicians through better understanding of individual patient factors and with support from the family and society as a whole. Psychoeducation, family-focused and other psychotherapies must all be utilized to support medication management efforts.

Patients in need of medication therapy, including those with bipolar disorder, ask practical questions related to

their decision to take medications such as aripiprazole: "Do I have to take medication?"; "Will it work?"; "Will I have side effects?"; "Will I have to take multiple medications?"; "Will I be able to return to work?"; and, "How long will I have to take it?"

The availability of an injectable form of aripiprazole provides a therapeutic option for those patients with bipolar disorder who are manic and agitated. In such a context, insight is often impaired, and the use of IM medication is often necessary for the protection of the patient and others. With rapid and effective control of acute manic symptoms, clinical experience suggests that patients are often better able to engage in a therapeutic alliance and to have informed consent discussions about therapeutic options to treat the mania and to plan for prevention of future episodes.

The data reviewed in support of aripiprazole for the treatment and prevention of mania allows clinicians to discuss the risks and benefits associated with aripiprazole therapy. Dosing aripiprazole appropriately is important, as a balance between rapid antimanic effects and avoidance of side effects is obviously desirable. Although combination therapy for acute mania if often considered first-line for many manic patients, the evidence supports the use of aripiprazole as either monotherapy or as an adjunct to a mood stabilizer such as lithium or valproate. Generally, aripiprazole should be started at 15 mg/day for acute mania, although the presence of concomitant antimanic therapy or patient history of medication sensitivity may dictate starting at a lower dose. For severely manic patients, starting with 30 mg/day may be necessary. Adjusting the dose during the first few weeks of aripiprazole therapy should then be based on response and tolerability.

Prompt attention to and effective management of treatment emergent side effects that appear early in the course of treating mania with aripiprazole is important. Dosage reduction may be necessary should akathisia develop. Akathisia may also be treated with beta-blockers, benzodiazepines, or anticholinergics. Reducing the dose of aripiprazole when nausea or vomiting is encountered as a side effect and later returning to the target dose is often

helpful, otherwise conventional antiemetic medications can be utilized. Insomnia secondary to aripiprazole can be minimized by taking the medication in the morning only and may also be ameliorated through the use of benzodiazepines or hypnotics. These and other practical guidelines can be used to minimize side effect burden for patients on aripiprazole and to maximize its efficacy.[44]

With long-term aripiprazole therapy, clinicians should be vigilant in their monitoring for metabolic perturbations that may be related to treatment. Although the risk for weight gain, diabetes and hyperlipidemia appears to be low with this SGA, some patients may be predisposed to these adverse events and so all patients should be routinely weighed and have laboratory assessments of fasting glucose and lipids. The frequency of such safety monitoring should be tailored to each patient's individual need based on personal and family risk factors. More specific guidelines for monitoring patients on aripiprazole and other SGAs can be found in the literature.[24]

Patients and their families should be continuously educated about the recurrent and sometimes chronic nature of bipolar disorder and the need for long-term medication and safety monitoring. The appropriate use of psychotherapies and community support groups should be encouraged, particularly given increasing evidence of benefit for delaying time to relapse. Symptomatic and syndromic recovery from acute mania is likely with adherence to medications such as aripiprazole, while full functional recovery and cautious preventive treatment should be the ultimate goal for all patients with bipolar disorder.

Conclusions/place in therapy

Aripiprazole is an effective and generally well-tolerated medication in the treatment and prevention of mania in bipolar I disorder. Its rapid onset of action for acute mania, either as monotherapy or in combination with a mood stabilizer, the availability of a fast-acting injectable formulation and excellent tolerability position this SGA as a first-line agent in the treatment of mania. The results from a 100-week study of aripiprazole for the prevention of bipolar I episodes represent the longest maintenance study since early lithium trials and support the use of aripiprazole as maintenance treatment, primarily against manic relapses. Given the lack of metabolic adverse effects with long-term aripiprazole relative to most other SGAs, it should also be considered a first-line prevention strategy, especially among bipolar I patients with highly recurrent manias. There is also evidence to support its long-term use in rapid cycling bipolar disorder

and sufficient data regarding safety of usage in combination with lithium or valproate. As monotherapy, aripiprazole should not be considered effective treatment for or prevention of bipolar depression. Prescription of aripiprazole for management of bipolar disorder should be accompanied by appropriate concern for individual patient preferences, acknowledgement of the importance of addressing stigma, insight and adherence, as well as psychotherapy and conservative caution when monitoring for the emergence of any treatment-related side effects or adverse events, particularly metabolic derangements.

Disclosures

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