

# Aripiprazole in the acute and maintenance phase of bipolar I disorder

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**Abstract:** Bipolar affective disorder is a disabling illness with substantial morbidity and many management challenges. Traditional mood stabilizers such as lithium, valproate, and carbamazepine are often inadequate in controlling symptoms both during the acute and maintenance phase of treatment. Aripiprazole is a second-generation antipsychotic with a unique mechanism of action. Evidence suggests that it is effective in acute manic and mixed states. There are limited data to suggest its efficacy as a maintenance agent. Future studies will be needed to better define the role of aripiprazole relative to other traditional pharmacologic agents.

**Keywords:** aripiprazole, bipolar disorder, acute treatment, maintenance treatment

## Introduction

Amongst people aged 15–44 years, bipolar affective disorder (BPAD) is the sixth leading cause of medical disability worldwide and associated with a greater degree of impairment than chronic medical conditions such as osteoarthritis, asthma, and diabetes.<sup>1</sup> Patients report significant levels of impairment in family relationships, social relationships, and employment.<sup>2</sup> BPAD patients have higher levels of impairment and rates of rehospitalization relative to unipolar depression patients.<sup>3</sup> Cost of care has been estimated at USD\$45 billion.<sup>4</sup> The monthly cost per patient of treating this illness have been estimated at USD\$1600, and exceeds that of coronary artery disease, unipolar depression, and diabetes.<sup>5</sup>

## Epidemiology

BPAD is a rare yet severe psychiatric illness with an estimated lifetime prevalence of 1.6%.<sup>6</sup> However, estimates from community samples frequently miss milder forms of BPAD resulting in the underestimation of prevalence rates.<sup>1</sup> Expanding the diagnostic criteria to include subthreshold symptoms of mania and hypomania has resulted in prevalence estimates as high as 11.5%.<sup>7</sup> An estimated 40% of patients diagnosed with major depressive disorder are reported to have subthreshold hypomanic symptoms.<sup>8,9</sup> Baseline hypomanic symptoms are associated with younger age at onset, a family history of BPAD, greater levels of impairment, and increased psychiatric comorbidity.<sup>9</sup> An estimated 20% of patients initially diagnosed with major depressive disorder will eventually go on to have a manic or hypomanic episode and the baseline presence of subthreshold hypomanic symptoms is a significant predictor of subsequent mania or hypomania.<sup>10</sup>

There is no gender partiality, although women have been reported to experience more depressive episodes over the course of illness as opposed to manic episodes.<sup>11–13</sup>

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Typical age of onset is between the ages of 15 and 19 years, and more than 50% of patients experience their first affective symptoms during childhood or adolescence.<sup>12,14</sup>

The elevated cost of care of this disorder is in part due to the extensive comorbidity of this population. The Epidemiologic Catchment Area Survey found an estimated 46% of patients used alcohol or were alcohol dependent, 41% used drugs or were drug dependent, 21% had panic disorder, and 21% had obsessive-compulsive disorder.<sup>15–17</sup>

## Diagnostic and management challenges

Accurate diagnosis continues to be a barrier to adequate treatment. The high rate of comorbidity with substance use makes it difficult to distinguish between mood lability secondary to drug and alcohol use versus a true bipolar spectrum. In the setting of substance abuse, bipolar disorder may be overdiagnosed. Goldberg et al found that only 33% of patients with active substance abuse suspected of having bipolar disorder met criteria after formal interview.<sup>18</sup> High rates of misdiagnosis of unipolar depression have been reported.<sup>19</sup>

However, additional literature suggests that bipolar disorder may be underdiagnosed. Ghaemi et al found that 40% of bipolar patients were initially misdiagnosed, most commonly with major depressive disorder, and waited an average of 7.5 years before an accurate diagnosis was given.<sup>20</sup> Other studies have also reported high rates of misdiagnosis with patients most commonly labeled with unipolar depression.<sup>2</sup> Impediments to accurate diagnosis include failure to recognize hypomanic symptoms and frequent initial presentation with depressive features.<sup>21</sup> Over 50% of BPAD patients will initially present with a depressive episode.<sup>22</sup>

Failure to accurately diagnose bipolar disorder can lead to improper treatment. Most frequently, patients are given antidepressants without mood stabilizers placing them at increased risk for switching into mania and/or rapid cycling as well as poor response to depressive symptoms.<sup>21</sup> Additionally, bipolar disorder is associated with a higher risk of suicide than any other axis I disorder. An estimated 25%–50% of bipolar patients attempt suicide, with the majority of attempts occurring during depressive episodes.<sup>22,23</sup>

Maintenance therapies have traditionally focused on mood stabilizers including lithium, valproic acid, carbamazepine, and, recently, lamotrigine. All agents have been shown to be effective relative to placebo in preventing relapses and typically need to be used in combination to control symptoms.<sup>24</sup> Lithium has long been considered the gold standard of therapy. Relative to placebo, lithium use

reduces the rates of manic or hypomanic episodes by 64% and depressive episodes by 30%–50%.<sup>25</sup> However, relapse rates on lithium have ranged from 20% to 40%.<sup>26</sup> Given the high relapse rate and extensive morbidity associated with this illness, additional therapies are needed.

The atypical antipsychotics have increasingly been used as an add-on and even monotherapy in bipolar spectrum disorders. Olanzapine was the first agent to gain US Food and Drug Administration approval for bipolar maintenance therapy. Relative to placebo, the relative risk of relapse on olanzapine for any episode has been estimated to be 0.6 and the number needed to treat, 4.2.<sup>27</sup> Olanzapine has shown similar efficacy to lithium and divalproex.<sup>27</sup> However, concerns about the metabolic side effects of olanzapine can lead to treatment discontinuation or adverse health outcomes.<sup>27</sup>

## Pharmacodynamics and pharmacokinetics of aripiprazole

Aripiprazole, a quinolinone antipsychotic, is currently the only US Food and Drug Administration–approved atypical antipsychotic that is characterized uniquely as a partial agonist at the dopamine D<sub>2</sub> receptor and serotonin 5-HT<sub>1A</sub> receptor.<sup>28</sup> Agonism of the 5-HT<sub>1A</sub> receptor is thought to activate a cascade that results in inhibition of cortical pyramidal neurons, hormonal regulation, and may affect depression, anxiety, and cognition.<sup>29</sup> Agonism of D<sub>2</sub> receptor is thought to mediate psychosis and the dopamine-reward system in the brain. Antagonism of the D<sub>2</sub> receptor is thought to be responsible for antipsychotic efficacy, as well as undesired effects including affective blunting, worsening cognition, akathisia, parkinsonism, and hyperprolactinemia. Conventional and other atypical antipsychotics are full dopamine D<sub>2</sub> receptor and serotonin 5-HT<sub>1A</sub> receptor antagonists that do not allow receptor output.<sup>29</sup> Aripiprazole, as a partial agonist, can partially activate the receptor to a lesser extent than a full agonist, yet attenuate, but not completely block, the receptor output.<sup>29</sup> Through this mechanism, it creates a stabilizing balance between the D<sub>2</sub> receptor and 5-HT<sub>1A</sub> receptor output.<sup>29</sup> Similar to other atypical antipsychotics, aripiprazole antagonizes serotonin 5-HT<sub>2A</sub> receptors, which balances D<sub>2</sub> receptor blockade and attenuates extrapyramidal side effects. Aripiprazole exhibits high receptor-binding affinity to dopamine D<sub>2</sub>, D<sub>3</sub>, serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>7</sub> receptors.<sup>28–30</sup> This activity is thought to mediate psychosis, depression, anxiety, cognition, sleep, mood, learning, and memory.<sup>30</sup> It has moderate affinity for  $\alpha$ -adrenergic  $\alpha_1$ ,  $\alpha_{2C}$ , and histamine H<sub>1</sub> receptors, which are associated with balancing

dopamine blockade, hypotension, sedation, and cognitive impairment.<sup>28,30</sup> Aripiprazole has no appreciative affinity for muscarinic M<sub>1</sub> cholinergic receptors that relate to low anticholinergic side-effect potential.<sup>28,30</sup>

Aripiprazole is metabolized hepatically primarily via cytochrome P-450 (CYP) 2D6 and 3A4 isoenzymes to its active metabolite, dehydroaripiprazole.<sup>28</sup> This metabolite is thought to have receptor activity similar to that of aripiprazole but has an extended half-life. Steady-state serum concentrations consist of approximately 60% aripiprazole and 40% dehydroaripiprazole. The recommended adult dose for aripiprazole monotherapy treatment of bipolar I is 15 mg once daily, which may be titrated to 30 mg once daily if needed.<sup>28</sup> Children aged >10 years may be initiated at 2 mg aripiprazole daily and titrated to a target maintenance dose of 10 mg aripiprazole daily.<sup>28</sup> Concomitant therapy with CYP 3A4 inducers, including carbamazepine, may increase clearance and lower serum concentrations of aripiprazole and dehydroaripiprazole by approximately 70%.<sup>28</sup> Effective doses of aripiprazole may need to be titrated to double the recommended maintenance dose when coadministered with strong CYP 3A4 inducers. Coadministration with CYP 2D6 inhibitors including quinidine and fluoxetine may increase serum concentrations of aripiprazole by approximately 112% and reduce serum concentrations of dehydroaripiprazole by 35%.<sup>28</sup> To compensate for these effects, effective doses of aripiprazole may need to be reduced by half when coadministered with CYP 3A4 inhibitors, such as ketoconazole and some antiretrovirals, or when coadministered with 2D6 inhibitors such as quinidine and fluoxetine. Currently, no dose adjustments are recommended for the elderly or individuals with hepatic or renal impairment.

Aripiprazole drug labeling currently includes pharmacogenomic dosing recommendations based on CYP 2D6 isoenzyme polymorphisms. Poor metabolizers at CYP 2D6 would result in an 80% increase in exposure to aripiprazole, and these individuals should have initial doses reduced by half.<sup>28</sup> No initial dose adjustment is recommended for extensive metabolizers at CYP 2D6. The average half-life of aripiprazole is 75 hours for extensive CYP 2D6 metabolizers and 146 hours for poor metabolizers.<sup>28</sup> The long half-life of aripiprazole allows for once-daily dosing of the drug. Steady-state serum concentrations can be reached in approximately 2 weeks but time to reach steady state may be doubled in CYP 2D6 poor metabolizers. Individuals' time to steady state may be considered when assessing efficacy and appropriate dose titrations of aripiprazole.

## Clinical data

Aripiprazole stands apart from other atypical antipsychotics because of its unique mechanism of action through partial agonism at the D<sub>2</sub> and D<sub>3</sub> receptors as well as its 5HT<sub>2A</sub> antagonist properties and partial agonism at the 5HT<sub>1A</sub> receptor. It is less commonly associated with the metabolic side effects of olanzapine.<sup>31</sup> Consequently, it is a good candidate for acute and maintenance treatment of BPAD.

Several studies have demonstrated aripiprazole to be effective in the acute treatment of mania and mixed states (summarized in Table 1).<sup>32–37</sup> Sachs et al randomized 272 hospitalized patients with manic or mixed episodes to aripiprazole or placebo in a 3-week trial. Response was significantly higher with aripiprazole (53%) relative to placebo (32%) and this difference was evident as early as day 4. Discontinuation of treatment due to adverse effects was similar between the two groups. Target dosing was 30 mg/day of aripiprazole and was maintained in 85% of patients.<sup>33</sup> Similarly, in a 12-week trial of 347 manic or mixed patients, Vieta et al found superior rates of response and tolerability in aripiprazole treated patients compared to those randomized to haloperidol. Response rates for aripiprazole treated patients were 50% compared to 28% of haloperidol patients.<sup>32</sup> By week 12, 51% of aripiprazole-treated patients, compared with 29% of haloperidol-treated patients, remained on therapy. Extrapyramidal side effects were also significantly higher in the haloperidol-treated group. Vieta et al showed aripiprazole produces significantly higher rates of response and remission compared with placebo when used as an adjuvant therapy to lithium and valproate during a 6-week double-blind placebo-controlled study involving 384 manic or mixed patients. At the end of 6 weeks, 50% of aripiprazole-treated patients were classified as remitters based on a Young Mania Rating Scale score <12 versus 36% of placebo-treated patients. Mean aripiprazole dose was 19 mg/day. Aripiprazole-treated patients reported higher incidence of extrapyramidal symptoms. There were no differences between the aripiprazole and placebo groups on metabolic parameters.<sup>34</sup> In a randomized double-blind placebo-controlled comparative study with lithium, aripiprazole-treated patients demonstrated significantly greater response rates than placebo and similar rates to those observed with lithium at the 3-week end point.<sup>35</sup>

The data on the use of aripiprazole in the maintenance phase are sparse. Following the 6–18 week stabilization phase, Keck et al<sup>38</sup> randomized 161 recently manic or mixed patients to receive monotherapy with aripiprazole (78) or placebo (83) for an additional 100 weeks. The only

**Table 1** Aripiprazole in the acute treatment of bipolar affective disorder, manic, and mixed states

Study (reference number)	Patients, n	Length	Treatment	Endpoint	Result
30	347 manic or mixed	12 weeks	Aripiprazole, haloperidol (double blind)	Response via YMRS	Aripiprazole showed significantly greater response rate relative to haloperidol. Greater incidence of EPS in haloperidol group
31	272 manic or mixed	3 weeks	Aripiprazole or placebo (double blind)	Mean change in YMRS, response via YMRS	Significantly greater YMRS reductions and response observed with aripiprazole. No difference between groups in discontinuation secondary to adverse effects
33	480 manic or mixed	3 weeks	Aripiprazole, lithium, or placebo (double blind)	Mean change in YMRS	Significantly greater reduction in YMRS in aripiprazole vs placebo, similar reductions in aripiprazole relative to lithium
34	485 manic or mixed	3 weeks	Aripiprazole, placebo, or haloperidol (double blind)	Mean change in YMRS	Significant reductions in YMRS relative to placebo, similar to haloperidol. Aripiprazole associated with lower incidence of EPS than haloperidol
35	262 manic or mixed	3 weeks	Aripiprazole or placebo (double blind)	Mean change in YMRS, response via YMRS	Aripiprazole treated patients had significantly greater mean reductions/response rates. Discontinuation secondary to adverse effects did not differ between groups
39	384 manic or mixed	6 weeks	Adjunctive aripiprazole vs placebo to lithium/valproate (double blind)	Reductions in YMRS, Response/remission via YMRS	Significant reductions in YMRS, significantly greater response/remission in aripiprazole treated patients

**Abbreviations:** EPS, Extrapyramidal symptoms; YMRS, Young Mania Rating Scale.

concomitant medications allowed were lorazepam 2 mg/day during the first month, 1 mg/day during the second month, and 1 mg/day up to four times per week for the remainder of the study. Anticholinergics were also allowed. Primary endpoint was time to relapse for a mood episode. Relapse was defined as hospitalization due to mood episode and/or addition or increase in psychotropic medication other than the study drug for mood symptoms. Mean dose of aripiprazole was 24 mg. On data analysis, aripiprazole-treated patients had a significantly longer time to relapse into mania than placebo-treated patients. No differences were observed for depressive episodes. Fifty two percent of the aripiprazole- versus 33% of placebo-treated patients experienced a relapse.<sup>38</sup> No differences were observed between the groups in lipid, glucose, or weight changes. In a 46-week open-label extension following a 6-week double-blind phase of adjunctive aripiprazole to lithium or valproate in partial responders with bipolar mania, Vieta et al found adjunctive aripiprazole to lead to significant improvements in Young Mania Rating scores and

Montgomery-Asberg Depression Scale.<sup>39</sup> Mean aripiprazole dose was 18 mg/day. Other studies have also demonstrated aripiprazole to be effective as adjunctive therapy in patients with an inadequate response to lithium or valproic acid.<sup>40</sup>

## Conclusion and future directions

The use of aripiprazole in the acute phase of manic and mixed episodes seems to be supported by the literature and is in line with common practice patterns where a primary mood stabilizer and antipsychotic are often started simultaneously. However, the dearth of data on aripiprazole as maintenance agents makes it difficult to recommend this during the maintenance phase over more established prophylactic agents such as lithium, valproic acid, and carbamazepine.

Although studies to date have demonstrated the potential for aripiprazole in the acute treatment phase and maintenance treatment of BPAD, additional data are needed to better clarify its role in the treatment of this disabling disorder, particularly in the maintenance phase. Due to the lesser incidence of

metabolic side effects, aripiprazole is an attractive alternative to olanzapine, yet there are no head-to-head trials comparing either these two agents or aripiprazole to other atypical agents used in BPAD such as quetiapine or risperidone. Long-term maintenance studies comparing aripiprazole to lamotrigine and carbamazepine are also lacking. Additionally, no studies have been done comparing aripiprazole in combination with a mood stabilizer with two primary mood stabilizers such as lithium and valproate or carbamazepine. No research has examined its role in BPAD II.

## Disclosure

The authors report no conflicts of interest in this work.

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