Treating Bipolar Disorder in the Primary Care Setting: The Role of Aripiprazole

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Objective: The objective of this article is to present practical strategies for detecting and diagnosing bipolar disorder in the primary care setting and to review the evidence for the efficacy and safety of aripiprazole treatment for bipolar disorder.

Data Sources: A review of the literature from 1980 to 2007 was conducted from November 2006 through February 2007 using a MEDLINE search and the key words *bipolar disorder*, *primary care, detection*, *diagnosis*, and *aripiprazole*.

Study Selection: A total of 100 articles that focused on the accurate detection and diagnosis of bipolar disorder and the evidence of the efficacy and safety of aripiprazole in the treatment of bipolar disorder were selected.

Data Synthesis: Patients with bipolar disorder often present to primary care physicians with depressive or mixed symptoms as opposed to purely hypomanic or manic symptoms. Accurate diagnosis of bipolar disorder is essential in order to provide timely and appropriate treatment. One treatment option available is aripiprazole, a partial agonist of dopamine $(D)_2$ and D_3 and serotonin $(5-HT)_{1A}$ receptors and an antagonist of the $5-HT_{2A}$ receptor. Clinical trial data have shown aripiprazole to be effective in treating manic and mixed episodes associated with bipolar I disorder, both in the acute phase and over an extended period of treatment lasting from 6 months to 2 years.

Conclusions: Accurate diagnosis and treatment of bipolar disorder are challenges increasingly faced by primary care physicians. Strategies geared toward detection, diagnosis, and management of bipolar I disorder and other bipolar spectrum disorders may improve the treatment outcome for patients. Aripiprazole may be considered as another first-line choice for the treatment of bipolar I disorder; however, its utility in patients with bipolar spectrum disorders is yet to be determined.

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Bipolar disorder is one of the leading causes of disability worldwide.[1,2] Once thought to have a prevalence of between 1% and 1.5%,[3] new research suggests that, when the full spectrum of the illness is considered (often referred to as bipolar spectrum disorder), the actual prevalence may be as much as 5-fold to 6-fold higher.[3,4] Patients with bipolar disorder experience difficulties in virtually every aspect of life, including work, social, and family interactions, and have a much higher risk of suicide than the general population.[5] Employees with bipolar disorder cost employers significantly more in missed work time and health care expenses in nearly every health benefit category annually compared with employees without bipolar disorder.[6–9] In 1991, direct and indirect expenditures associated with bipolar disorder cost the US economy as much as $45 billion (1991 values).[10]

Since most mental health services are administered predominantly in the primary care setting, it is likely that primary care physicians will encounter many, if not the majority, of the patients with bipolar disorder.[11] Several practice-based studies conducted in the primary care setting have found bipolar disorders are common, clinically significant, and underrecognized and that as many as 30% of outpatients treated for depression in primary care settings may have bipolar spectrum disorder.[12–15]

In this article, practical strategies for the recognition and accurate diagnosis of bipolar spectrum disorders in the primary care setting will be briefly summarized. An overview of the key efficacy and safety data for the atypical antipsychotics in treating bipolar disorder will be presented, with a focus on aripiprazole as the newest of these agents, including practical considerations for use of aripiprazole in the primary care setting.

METHOD

A review of the literature from 1980 to 2007 was conducted from November 2006 through February 2007 using a MEDLINE search (PubMed) and the key words *bipolar disorder*, *primary care*, *detection*, *diagnosis*, and *aripiprazole*. A total of 100 articles were selected on the basis of their informative value in providing guidance for primary care physicians both in the accurate detection and diagnosis of bipolar disorder, as well as the evidence for the efficacy and safety of aripiprazole in the treatment of bipolar disorder. Articles that focused on bipolar disorder

included population-based studies, epidemiology studies, and reviews that summarized strategies to detect and accurately diagnose bipolar disorder in the primary care setting. Aripiprazole articles included randomized, double-blind, placebo-controlled trials, open-label trials, and post hoc analyses evaluating the efficacy and safety of aripiprazole as a treatment for bipolar disorder. Additionally, preclinical pharmacologic studies were chosen to investigate the receptor-binding profiles of antipsychotics as the basis of their efficacy and safety profiles. Finally, a brief overview of the pivotal randomized, double-blind clinical trials for the other atypical antipsychotics was also included to provide context of evidence for the new data on aripiprazole, which this review seeks to cover in detail.

PRESENTATION AND DIAGNOSIS OF BIPOLAR DISORDER IN THE PRIMARY CARE SETTING

The Phenomenology of Bipolar Spectrum Disorder Symptoms, Complaints, and Diagnostic Criteria

The presentation of bipolar spectrum disorder symptoms falls between syndromal mania with psychotic features and hypomanic symptoms on the one hand and major depressive disorder with psychotic features and dysthymic symptoms on the other.[3] Importantly, these 2 dimensions of symptoms can alternate and co-occur in various ways that may be difficult to distinguish from normal mood fluctuations and other psychiatric disorders.[3]

One factor contributing to the difficulty in diagnosis is lack of familiarity with the phenomenology and course of the wider bipolar spectrum, including diagnostic subtypes within this spectrum beyond those of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*).[13,16] Thus, bipolar spectrum disorder includes the *DSM* diagnoses bipolar I and bipolar II disorders, cyclothymia, and bipolar disorder not otherwise specified (NOS) but also may include antidepressant-induced hypomania, highly recurrent (> 7 episodes) unipolar depression, and depressive mixed states (described later).[11,16] Patients manifesting symptoms of the depressive state of bipolar II disorder, various bipolar mixed states, and mood states described as bipolar I disorder may be more likely than patients with symptoms of mania to present to a primary care physician.[11,17–19] Moreover, current categorical

diagnostic classifications for hypomania exclude dimensional characteristics of the syndrome and as such may not accurately define more clinically subtle but valid manifestations. For example, one emerging view is that periods of overactivity associated with elevated or irritable mood (often combined with risk taking) should be considered as important indicators of hypomania even if relatively brief.[21,22]

In a study conducted by Angst and colleagues,[20] *DSM-IV*[21] criteria of hypomania were widened to incorporate the Zurich criteria and included (1) euphoria, irritability, or overactivity; (2) patients who experienced problems or received comments from others suggesting that something must be wrong with them (consequences); and (3) the presence of 3 of the 7 signs and symptoms of *DSM-IV* hypomania. The prevalence rate of bipolar II disorders found in this study doubled, indicating that using these criteria enabled more sensitive detection.

Although mania or hypomania are required for a diagnosis of bipolar disorder, depressive symptoms dominate the course of both bipolar I and II disorders.[23–25] These symptoms also dominate other forms of bipolar spectrum disorder, such as highly recurrent "unipolar" depression and recurrent brief hypomania with depression, as well as many mixed presentations, especially depressive mixed states (in which depression is more prominent than manic symptoms) and mixed manic states, in which mania is more prominent than depressive symptoms. Moreover, hypomania and even mania can be difficult to identify in clinical practice (Table 1),[5,11,13,26] especially if the patient is not experiencing these symptoms during an office visit. Significantly, a recent large systematic investigation of the nature of hypomania suggests that hypomania is often mixed with depressed mood, especially in women.[27] This quality of hypomania tends to be expressed as activated or agitated depression and may further hinder bipolar recognition.

Importantly, the diagnostic accuracy of hypomania and mania can be enhanced through the use of screening tools such as the Mood Disorder Questionnaire (MDQ), structured diagnostic clinical interviews, and interviews with patients' significant others (with permission).[18–20,26,28–30]

Although bipolar disorder is most often misdiagnosed as unipolar depression, a number of features may aid primary care physicians in the accurate diagnosis of bipolar

Table 1. Criteria for Detecting Bipolar Disorder

Criteria for Hypomanic Episode[19,20]

A distinct period of persistently elevated, expansive, or irritable mood occurs that lasts at least 4 days and is clearly different from the usual nondepressed mood

During the period of mood disturbance, 3 (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a substantial degree:

    Inflated self-esteem or grandiosity

    Decreased need of sleep

    More talkative than usual or pressure to keep talking

    Flight of ideas or subjective experience that thoughts are racing

    Distractibility

    Increase in goal-directed activity or psychomotor agitation

    Excessive involvement in pleasurable activities that have a high potential for painful consequences

The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic

The disturbances in mood and the change in functioning are observable by others

The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization, and there are no psychotic features

The symptoms are not due to direct physiologic effects of a substance or a general medical condition

Interepisode features suggestive of bipolar disorder[26]

Impaired attentional and executive function

Continued low sense of well-being

Intrusiveness of illness

Novelty seeking

Impulsivity

Substance abuse

Anxiety disorders

Manifestations of temperaments associated with risk of bipolar disorder, including:

    Hyperthymic (early-onset, habitual nonimpairing hypomanic features: cheerful, full of plans and activity, and outgoing and social, often with habitual short sleeping— ≤ 6 hours/d even on weekends)

    Dysthymic (early-onset, habitual nonimpairing depressive features: gloomy, pessimistic, and tendency toward being guilt ridden and anxious, often with habitual short sleeping— > 9 hours/d)

    Cyclothymic (early-onset, habitual, and nonimpairing alternation— typically for 1–2 weeks at a time—between hyperthymic and dysthymic temperamental manifestations)

    Irritable (early-onset, habitual, and nonimpairing blending of hyperthymic and dysthymic temperamental patterns: irascible, ill humored, sarcastic, cynical, and often with restless activity)

disorder in patients presenting with depressive symptoms. These features include early age at onset (< 25 years), family history of bipolar disorder, highly recurrent mood disruptions (particularly major depressive episodes), and certain depressive features, especially so-called atypical symptoms such as hyperphagia, weight gain, and hypersomnia. In addition, antidepressant-induced mania or hypomania, postpartum onset of depressive course or postpartum psychosis, a lack of response to antidepressants, and marked seasonality of episodes may also help primary care physicians differentiate bipolar disorder from major depressive disorder.[11,26]

Psychiatric Comorbidities With Bipolar Disorder

Another important way in which bipolar disorder may present is related to psychiatric comorbidity. Psychiatric

disorders that commonly co-occur with bipolar disorder include anxiety, substance abuse, and behavioral and eating disorders (Table 2).[31–36] Importantly, this comorbidity may be pronounced and/or complex and complicate the diagnosis of associated bipolar disorder by masking its presence (eg, mixed mania presenting as panic attacks or panic states).[5,35] Comorbidity is associated with poorer outcome.

General Medical Comorbidities

Bipolar disorder also frequently co-occurs with general medical disorders. These disorders include diabetes, hyperlipidemia, metabolic syndrome, migraine, thyroid illness, hypertension, lower back pain, asthma, chronic bronchitis, gastric ulcers, and obesity.[33,35–46] It is important to remember that bipolar disorder may present with complaints related to any of these conditions.

Comorbid obesity in bipolar disorder has recently received much attention. An evaluation of 644 outpatients with *DSM-IV* bipolar disorder in the Stanley Foundation Bipolar Treatment Outcomes Network found that 58% were overweight, 21% were obese, and 5% were extremely obese.[47] The observed prevalence rates may reflect a trend toward weight gain and obesity in the general population; however, persons with bipolar disorder appear to be at greater risk of being obese than the general population.[42–44,47]

Obesity in bipolar disorder is likely to be multifactorial in origin, involving various combinations of a more sedentary lifestyle, endogenous illness-related physiologic mechanisms, medication-related effects, and comorbid eating disorders.[44,49–51] Whatever its origin, comorbid obesity is associated with increased medical morbidity and poorer psychiatric outcome in bipolar disorder.[44,48–50]

ROLE OF ARIPIPRAZOLE IN THE TREATMENT OF BIPOLAR DISORDER

Approved Treatments and the Need for Evidence-Based Treatment

The treatment of bipolar disorder is a field in flux. A growing number of treatments are available for bipolar I disorder, and several sets of guidelines have been developed in the hope of establishing a standardized, evidenced-based approach to treatment.[53–57] The US Food and Drug Administration (FDA)–approved treatments for bipolar disorder include lithium, 3 anticonvulsant drugs (valproate, lamotrigine, and carbamazepine), 5 antipsychotics, and 1 combination medication (olanzapine/fluoxetine) (Table 3).[58] Guidelines for the treatment of bipolar disorder and its spectrum conditions vary significantly and often become outdated shortly after their publication; however, most primary care physicians recommend lithium or valproate, or a combination of both, as first-line treatment for patients with bipolar I and II disorder with manic or hypomanic symptoms.[54–57]

Table 2. Medical and Psychiatric Comorbidities Associated With Bipolar Disorder

Medical Comorbidity	Psychiatric Comorbidity
Metabolic syndrome	Anxiety disorders
Diabetes	Behavioral disorders
Hyperlipidemia	Substance abuse
Migraine	Eating disorders
Thyroid illness	
Hypertension	
Lower back pain	
Asthma	
Chronic bronchitis	
Gastric ulcers	
Weight gain	
Obesity	

Table 3. US Food and Drug Administration–Approved Treatments for Bipolar Disorder[58]

Medications	Manic	Mixed	Maintenance	Depression
Mood stabilizers				
Lithium	✓	…	✓	…
Carbamazepine extended release	✓	✓	…	…
Valproate	✓	…	…	…
Valproate extended release	✓	✓	…	…
Lamotrigine	…	…	✓[a]	…
Antipsychotics				
Chlorpromazine	✓	…	…	…
Olanzapine	✓	✓	✓	…
Risperidone	✓	✓	…	…
Quetiapine	✓	✓[b]	✓[c]	✓
Ziprasidone	✓	✓	…	…
Aripiprazole	✓	✓	✓	…
Combination				
Olanzapine/ fluoxetine	…	…	…	✓

[a]Indication is for prevention of manic, hypomanic, mixed, and depressive episodes.
[b]The extended-release version is now approved for bipolar mixed states.
[c]Approved as the maintenance treatment for patients with bipolar I disorder, as adjunctive to lithium or divalproex.
Symbol: … = not approved in this indication.

There is increasing evidence supporting the use of second-generation antipsychotics in the treatment of bipolar I disorder.[59] Second-generation antipsychotics, including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, have all been approved for treatment of acute mania. These drugs are increasingly considered important options for the treatment of acute mania and for continuing maintenance therapy, as either monotherapy or in conjunction with mood stabilizers.[60–63] Although psychiatrists are the main prescribers of these agents, their efficacy, safety, and tolerability profiles do not preclude initiation in primary care settings. Collaborative treatment and clear communication between primary care physicians and psychiatrists is often essential for optimal treatment strategies designed to improve patients' symptoms while minimizing exacerbation of comorbid conditions.

Antipsychotics in the Treatment of Bipolar Disorder

The efficacy, safety, and tolerability profile of antipsychotics is related to their receptor-binding profiles in the brain. Antipsychotics have varying binding affinities for dopaminergic, adrenergic, α1-adrenergic, histamine (H)1, and muscarinic (M) receptors.[64,65] Potent antagonist activity at dopamine (D)$_2$ receptors in mesolimbic areas is believed to account for the therapeutic efficacy of first-generation antipsychotics such as haloperidol and second-generation antipsychotics such as risperidone, olanzapine, quetiapine, and ziprasidone in schizophrenia and possibly mania.[65,66] However, antagonist activity at D$_2$ receptors in striatal areas is thought to cause extrapyramidal symptoms (EPS) such as akathisia, dystonia, pseudoparkinsonism, and tardive dyskinesia.[67–78] Second-generation antipsychotics antagonize serotonin (5-HT)$_{2A}$ receptors and generally have a less potent affinity than first-generation antipsychotics for D$_2$ receptors.[75] It is the balance between D$_2$ and 5-HT$_{2A}$ antagonism that is believed to define the profile of these agents. Serotonin inhibits the release of dopamine in the striatum.[75] Reduced D$_2$ receptor binding in the striatum in conjunction with 5-HT$_{2A}$ antagonism is thought to lessen motor symptoms as compared with first-generation antipsychotics (pure 5-HT$_{2A}$ antagonism is not associated with therapeutic antipsychotic activity).[79] With the possible exception of clozapine in schizophrenia and, potentially, bipolar disorder, it is unclear if second-generation antipsychotics offer a broader range of clinical efficacy; however, they are associated with fewer EPS.[80–82]

It is thought that the receptor-binding profiles of second-generation antipsychotics are responsible for a variety of adverse events (AEs) associated with their use (eg, weight gain, dyslipidemia, diabetes, sedation/somnolence, neuroleptic malignant syndrome, hyperprolactinemia, and sexual dysfunction) and their propensity to cause some of these events.[81,83] Knowledge of these events and the side effects of other drugs used in bipolar disorder is important when considering treatment options, particularly in view of the substantial burden of medical comorbidities associated with bipolar disorder.

Aripiprazole: A Receptor-Partial Agonist

Unlike other second-generation antipsychotics, aripiprazole is a partial agonist at D$_2$ and D$_3$ receptors and 5-HT$_{1A}$ receptors.[84–88] A partial agonist exhibits lower activity at the target receptor than would occur with a full agonist and therefore has the capability to treat behavioral states that include both excessive and deficient neurotransmitter activity. Theoretically, therefore, aripiprazole has the ability to reduce dopamine transmission in states of dopamine excess (eg, bipolar mania) and to increase dopamine transmission in states of dopamine deficiency. Hypodopaminergic tone would predict agonist activity at

Table 4. Efficacy Summary of Atypical Antipsychotics in Acute Bipolar Mania: Short-Term, Randomized, Placebo-Controlled Trials

Drug	Duration, wk	N	Screening/ Washout, d	Population	Change in YMRS Total Score (baseline to week 3)			Response Rates at Week 3, %[b]		
					Active	Placebo	P Value[a]	Active	Placebo	P Value[a]
Aripiprazole[92]	3	272	1–7	Manic/mixed	−12.5	−7.2	≤ .001	53	32	≤ .001
Aripiprazole[93]	3	262	1–7	Manic/mixed	−8.2	−3.4	≤ .01	40	19	≤ .01
Aripiprazole[94]	3 + 9	480	2–14	Manic/mixed	−12.64	−9.01	≤ .001	47	34	< .05
Aripiprazole[95]	3 + 9	485	2–14	Manic/mixed	−11.98	−9.7	< .05	47	38	NS
Olanzapine[96]	3	139	2–4	Manic/mixed	−10.3	−4.8	< .05	49	24	≤ .01
Olanzapine[97]	4	115	≥ 1	Manic/mixed	−14.8	−8.1	≤ .001	65	43	< .05
Risperidone[98]	3	259	3	Manic	−10.6	−4.8	≤ .001	43	24	≤ .01
Risperidone[99]	3	290	3	Manic/mixed	−22.7	−10.5	≤ .001	73	36	≤ .001
Risperidone[100]	3	438	3	Manic	−15.1	−9.4	≤ .001	48	33	≤ .01
Quetiapine[101]	3 + 9	302	7	Manic	−12.3	−8.3	≤ .01	43	35	NS
Quetiapine[102]	3 + 9	302	7	Manic	−14.6	−6.7	≤ .001	53	27	≤ .001
Ziprasidone[103c]	3	210	1–7	Manic/mixed	−12.4	−7.8	≤ .01	50	35	< .05
Ziprasidone[104c]	3	202	2–10	Manic/mixed	−11.1	−5.6	≤ .01	46	29	< .05

[a]P value vs placebo.
[b]Responders = percentage of patients achieving ≥ 50% decrease in Mania Rating Scale score from baseline to week 3.
[c]Ziprasidone efficacy measured on Mania Rating Scale.
Abbreviations: NS = not significant, YMRS = Young Mania Rating Scale.

presynaptic D_2 receptors by aripiprazole (eg, dopamine synthesis) and antagonism at postsynaptic D_2 receptors in the context of hyperdopaminergic tone (eg, locomotor stimulatory effects).[86,89]

In this context, the partial agonist actions of aripiprazole at the D_2 and D_3 receptors can be likened to a dimmer switch preset at a certain level of brightness.[90] A state of excessive dopamine neurotransmission, a component of mania, results in a situation analogous to a brightly lit room. If the dimmer switch in such a case is set at 30%, the action of the "dimmer" would be a net decrease of light relative to the initially brightly lit room. By analogy, dopamine transmission is reduced but not completely antagonized. If the room is initially dark, as in a state of depleted dopaminergic transmission, such a "dimmer" would result in a 30% brightness level—a net increase in light relative to an initially dark room—with dopamine transmission increased by up to 30% of full dopamine transmission.

As with other second-generation antipsychotics, aripiprazole is an antagonist at 5-HT$_{2A}$ serotonin receptors. Aripiprazole displays low-to-moderate affinity for α1-adrenergic and H1 receptors and no appreciable affinity for M1 receptors. This pharmacodynamic profile may explain the drug's lesser propensity to cause sedation, orthostatic hypotension, cognitive impairment, and metabolic side effects when compared with other second-generation antipsychotics.[85,86,91]

EFFICACY OF ATYPICAL ANTIPSYCHOTICS

Overview of Efficacy Evidence From Key Clinical Trials

Before reviewing the evidence base for aripiprazole in bipolar disorder, we first review the pivotal randomized, double-blind clinical trials for the atypical agents conducted to gain FDA approval. A total of 13, short-term, randomized, placebo-controlled trials, ranging from 3 to 4 weeks, have been conducted using atypical antipsychotic monotherapy in patients with bipolar disorder in acute manic or mixed episodes (4 studies with aripiprazole, 3 studies with risperidone, and 2 studies each with olanzapine, quetiapine, and ziprasidone)[92–104] (Table 4). At 3 weeks, treatment with atypical antipsychotics was shown to be efficacious in reducing manic symptoms, assessed using either the change in Young Mania Rating Scale (YMRS) total score or, for the studies using ziprasidone, the change in Mania Rating Scale scores. Response to treatment was generally defined as at least a 50% improvement from baseline in YMRS total score from baseline to week 3. The trial findings showed response rates ranging from 40% to 73% (Table 4), with all treatments showing a significantly greater response versus placebo.

Seven of the 13 placebo-controlled studies described above were continued for a total of 12 weeks, during which patients were treated with blinded atypical antipsychotics or active controls.[94,95,100–102,105,106]

Data from studies longer than 12 weeks are limited. A total of 4 studies have reported on monotherapy with atypical antipsychotics for a period greater than 12 weeks, 3 with olanzapine and 1 with aripiprazole, with 26-week and 100-week results being reported separately.[61,107–110] On the basis of findings from these clinical trials, olanzapine and aripiprazole have been approved for long-term maintenance therapy. Quetiapine is approved as an adjunctive to lithium or divalproex for the maintenance treatment of patients with bipolar I disorder.

To date, 7 trials have reported on combination therapy with atypical antipsychotics with mood stabilizers.[111–116] Most studies assessed the use of atypical antipsychotics

Figure 1. Mean Change From Baseline in Young Mania Rating Scale (YMRS) Total Score (last-observation-carried-forward analysis) During a 3-Week Randomized, Double-Blind, Placebo-Controlled Study[a,b]
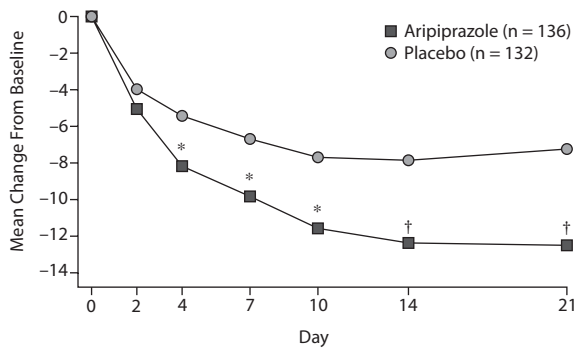
[a]Reprinted with permission from Sachs et al.[93]
[b]Mean baseline values: aripiprazole: 28.8 and placebo: 28.5.
*$P \leq .01$ vs placebo.
†$P \leq .001$ vs placebo.

as adjunctive therapy to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy. Studies were either 3 or 6 weeks in duration, with the primary endpoint defined as the change from baseline in the YMRS at study end—in the olanzapine and risperidone trials, this corresponded to the last available postbaseline assessment. Although an overall improvement in the reduction in mania symptoms was observed across all trials, 1 of the 2 risperidone studies[114] and 1 of the 3 quetiapine studies[116] failed to separate the primary efficacy parameter from placebo.

Atypical Antipsychotics in Bipolar Depression

A total of 8 randomized, double-blind studies have evaluated the efficacy and safety of atypical antipsychotic monotherapy or olanzapine/fluoxetine combination.[117–123] Overall, not all treatments achieved statistical significance versus placebo at the end of the study despite early improvements.[117,121,123] However, 2 8-week trials with quetiapine,[118,119] 1 study with olanzapine,[122] and 2 studies with olanzapine/fluoxetine combination[120,122] showed an improvement in symptoms, generally assessed as an improvement in Montgomery-Asberg Depression Rating Scale (MADRS) total scores, with significant differences versus placebo. The following section focuses on the efficacy findings conducted with aripiprazole.

Aripiprazole in the Acute Treatment Setting

Clinical trial data have demonstrated the safety and efficacy of aripiprazole in patients with bipolar I disorder in acute manic or mixed episodes.[61,92–95,105] To date, 6

double-blind, randomized, parallel-group, short-term trials in mania have been conducted. Four of these trials were 3-week placebo-controlled studies,[92–95] 2 of which continued with aripiprazole and active comparator (either lithium or haloperidol) for a total of 12 weeks.[94,95] A fifth 3-week, placebo-controlled study was a fixed-dose study. Another 12-week study compared aripiprazole with haloperidol.[105] Two of the placebo-controlled, 3-week, flexible-dose trials assessed treatment with aripiprazole at an initial dose of 30 mg/d (with the option to decrease to 15 mg/d based on tolerability) in hospitalized patients with bipolar I disorder experiencing an acute manic or mixed episode (n = 262 and n = 272).[92,93] In both trials, aripiprazole was efficacious in reducing manic symptoms, as demonstrated by significant improvements in YMRS total scores by day 4, which continued through study endpoint (Figure 1). Subanalyses showed that aripiprazole was equally efficacious in patients with manic or mixed episodes, in those with or without psychotic symptoms, and in those with or without rapid cycling. Separation between treatment groups was not demonstrated in the fifth placebo-controlled trial (Data on file; Otsuka America Pharmaceutical, Inc, Rockville, Maryland, April 2003).

Since we conducted our search, 2 12-week studies have reported on the efficacy of aripiprazole for acute bipolar mania in patients randomly assigned to placebo, aripiprazole, or an active comparator (either haloperidol or lithium) for 3 weeks,[94,95] followed by an additional 9 weeks of blinded treatment with aripiprazole and active comparator to examine maintenance of effect. In the study by Young et al,[95] 167 patients received aripiprazole (15 or 30 mg/d, starting dose 15 mg/d), 153 patients received placebo, and 165 patients received haloperidol (5–15 mg/d) for 3 weeks. Mean change in YMRS total score (primary endpoint) at week 3 was significantly greater with aripiprazole (–12.0, P < .05) and haloperidol (–12.8, P < .01) than placebo (–9.7).

Similarly, in the study conducted by Keck et al,[94] patients were randomly assigned to double-blind aripiprazole (15 or 30 mg/d, starting dose 15 mg/d, n = 155), placebo (n = 165), or lithium (900–1500 mg/d, n = 160) (1:1:1) for 3 weeks. Mean change in YMRS total score (primary endpoint) at week 3 was significantly greater with aripiprazole (–12.6, P < .001) and lithium (–12.0, P < .005) than placebo (–9.0).[94] Aripiprazole demonstrated significantly greater improvement than with placebo in mean YMRS total score as early as day 2 and through study endpoint (Figure 2). In both studies, improvements in response rates were maintained to week 12 (Keck et al: aripiprazole 57% and lithium 49% and Young et al: aripiprazole 72% and haloperidol 74%).[94,95]

In a separate active comparator trial (without placebo control) in 347 patients experiencing acute manic or mixed episodes, aripiprazole 15 mg/d (n = 175) or halo-

Figure 2. Mean Change From Baseline in Young Mania Rating Scale (YMRS) Total Score (last-observation-carried-forward analysis) During a 12-Week Randomized, Double-Blind, Placebo- and Lithium-Controlled Study[a,b,c]
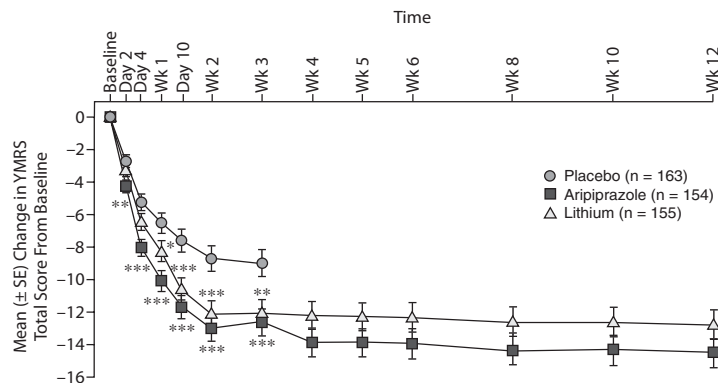
[a]Reprinted with permission from Keck et al.[94]
[b]Baseline mean (SE) YMRS scores: placebo: 28.9 (0.4), lithium: 39.2 (0.4), and aripiprazole: 28.5 (0.4).
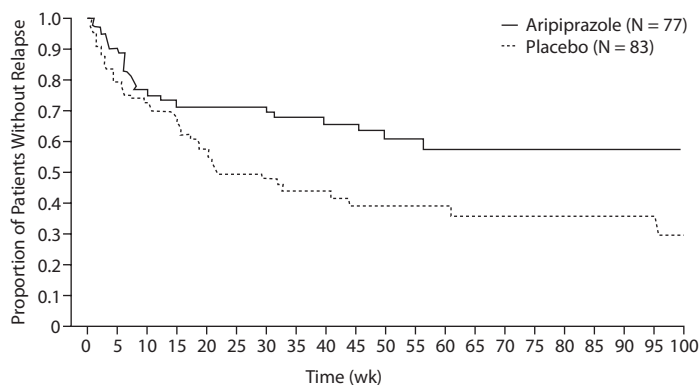[c]After the initial 3-week period, patients in the placebo group were switched in a blind manner to double-blind aripiprazole for the remaining 9 weeks of the study (data not shown).
*$P < .05$ vs placebo.
**$P < .01$ vs placebo.
***$P < .001$ vs placebo.

Figure 3. Aripiprazole vs Placebo: Kaplan-Meier Survival Curves Demonstrating Time From Randomization to Relapse for Any Reason[a,b]

[a]Reprinted with permission from Keck et al.[107]
[b]Log rank $P = .011$; hazard ratio = 0.53 (95% CI, 0.32–0.87).

peridol 10 mg/d (n = 172) administered for 12 weeks was similarly effective.[105] Mean reductions from baseline in YMRS total scores at week 12 were –19.9 for aripiprazole and –18.2 for haloperidol (last-observation-carried-forward analysis, P = .226). However, patients taking aripiprazole had a significantly greater response rate (defined as at least a 50% improvement from baseline in YMRS score and continuation of therapy from week 3) compared with those taking haloperidol at week 12

(49.7% vs 28.4%, $P < .001$). In addition, completion rates significantly favored aripiprazole (weeks 4–12: aripiprazole 50.9% vs haloperidol 29.1%, $P < .001$).[105] The proportion of patients in remission (defined as a YMRS score < 12) was also significantly higher in the aripiprazole group than in the haloperidol group (50% vs 27%, respectively; $P < .001$) at week 12.

Aripiprazole in Combination Therapy

A recent randomized, placebo-controlled study reported on the efficacy and safety of adjunctive aripiprazole in outpatients with bipolar I disorder partially nonresponsive to lithium/valproate monotherapy.[111] Patients with partial nonresponsiveness to lithium/valproate monotherapy were randomly assigned in a 2:1 ratio to adjunctive aripiprazole (n = 253, 15 or 30 mg/d, starting dose of 15 mg/d) or adjunctive placebo (n = 131) for 6 weeks. The primary efficacy endpoint (mean improvement from baseline in YMRS total score at week 6) was significantly greater with aripiprazole (–13.3) compared with lithium or valproate alone (–10.7), with significant improvements observed from the first week of treatment.[111]

Aripiprazole in the Maintenance Treatment Setting

In a double-blind, placebo-controlled maintenance trial,[61] patients with bipolar I disorder with a recent manic or mixed episode (N = 161) who met stabilization criteria (YMRS score ≤ 10 and MADRS score ≤ 13) for at least 6 consecutive weeks were randomly assigned to receive aripiprazole (15 or 30 mg/d) or placebo and monitored for relapse for 26 weeks. Aripiprazole was superior to placebo in delaying the time to overall relapse (P = .020) and the time to manic relapse (P = .01), but not depressive relapse. The proportion of aripiprazole patients not experiencing overall relapse by week 26 was 72%, compared with 49% of placebo patients. Aripiprazole-treated patients also experienced significantly fewer relapses than patients taking placebo (25% vs 43%, P = .013).[61] In addition, aripiprazole treatment resulted in significantly fewer relapse episodes of mania than placebo (8% vs 23%, respectively; P = .009).

This same trial was designed to prospectively continue monitoring patients in a double-blind, placebo-controlled fashion for an additional 74 weeks.[107] Over 100 weeks of treatment, aripiprazole monotherapy continued to delay the time to overall relapse (hazard ratio [HR] = 0.53; 95% CI, 0.32–0.87; P = .011) and manic relapse (HR = 0.35;

Table 5. Most Commonly Occurring Adverse Events in Aripiprazole-Treated Patients (at least 10% and twice that of placebo)

Adverse Event, n (%)	Keck et al, 2003[92]		Sachs et al, 2006[93]		Keck et al, 2009[94]		Young et al, 2009[95]	
	Placebo (n = 127)	Aripiprazole (n = 127)	Placebo (n = 133)	Aripiprazole (n = 136)	Placebo	Aripiprazole	Placebo	Aripiprazole
Accidental injury	3 (2)	15 (12)	…	…	…	…	…	…
Akathisia	3 (2)	14 (11)	6 (5)	24 (18)	5 (3.0)	17 (11.0)	…	…
Constipation	7 (6)	17 (13)	7 (5)	16 (12)	…	…	…	…
Dyspepsia	13 (10)	28 (22)	9 (7)	21 (15)	…	…	…	…
Extrapyramidal disorder	…	…	…	…	…	…	1 (0.7)	12 (7.2)
Nausea	13 (10)	29 (23)	…	…	…	…	…	…
Sedation	…	…	…	…	8 (4.9)	18 (11.7)	…	…
Somnolence	6 (5)	26 (20)	…	…	…	…	…	…
Vomiting	6 (5)	20 (16)	…	…	…	…	…	…

Symbol: … = adverse events did not occur in > 10% of aripiprazole patients and twice that of placebo patients.

95% CI, 0.16–0.75; *P* = .005) in patients initially stabilized with aripiprazole for 6 consecutive weeks (Figure 3).[107] However, no significant differences were observed in time to depressive relapse (HR = 0.81; 95% CI, 0.36–1.81; *P* = .602).

Aripiprazole in Acute Bipolar Depression

In 2 identically designed, 8-week, multicenter, randomized, double-blind, placebo-controlled studies, Thase and colleagues[117] evaluated the efficacy and safety of aripiprazole monotherapy in outpatients with bipolar I disorder experiencing a major depressive episode without psychotic features. Aripiprazole was initiated at 10 mg/d (5 mg twice daily) and then flexibly dosed to 5–30 mg/d based on clinical effect and tolerability. In the first (study 1) and second (study 2) studies, 186 and 187 patients, respectively, were randomly assigned to aripiprazole, and 188 and 188 patients, respectively, to placebo. Statistically significant differences in MADRS total scores (primary endpoint) were observed during weeks 1–6 in study 1 and during weeks 1, 2, 3, and 5 in study 2; however, aripiprazole did not achieve statistical significance versus placebo on the MADRS at week 8 in either study.

SAFETY AND TOLERABILITY OF ATYPICAL ANTIPSYCHOTICS

Overview of Safety Evidence From Clinical Trials

Overall, safety data with the atypical antipsychotics involving patients with mania showed that most AEs occurred early in treatment and were mild or moderate in severity. The AE profiles of quetiapine and olanzapine in the bipolar depression studies reflect those already established in the bipolar mania studies, with the exception that quetiapine is associated with EPS significantly more often than placebo in depression trials. In terms of effects on metabolic parameters, all of the atypical antipsychotics have been associated with weight gain[92–102,104,106]; however, levels varied according to the different atypical antipsychotics.[66,93–95,97,106]

Compared with haloperidol, atypical antipsychotics (olanzapine and quetiapine) were associated with lower rates of akathisia in monotherapy trials of 12 weeks.[101,106] Atypical antipsychotics (olanzapine, risperidone, and aripiprazole) were also associated with greater improvements in EPS rating scales (Simpson-Angus Scale and Barnes Akathisia Scale SAS and BAS for olanzapine[106] and aripiprazole[95] and EPS rating scale for risperidone[100]) than haloperidol in 12-week trials. The remainder of this review focuses on the safety and tolerability data for aripiprazole, with a final section on practical considerations when administering this treatment for bipolar disorder.

Safety and Tolerability of Aripiprazole

In the 2 3-week pivotal mania trials,[92,93] treatment-emergent AEs (at least 10% of aripiprazole patients and twice those of placebo) included nausea, dyspepsia, somnolence, vomiting, constipation, and akathisia (Table 5). Similarly, in the recently published 12-week comparator trials,[94,95] aripiprazole demonstrated a similar incidence of AEs when compared with the 3-week trials. The most commonly reported AEs (at least 5% of aripiprazole patients and twice those of placebo) in the 26-week trial included tremors (9.1% vs 1.2%), akathisia (6.5% vs 1.2%), vaginitis (6.4% vs 0%), and pain in extremities (5.2% vs 1.2%).[61] During the course of 100 weeks of treatment with aripiprazole, the most commonly reported AEs included tremors (9.1% vs 1.2%), akathisia (7.8% vs 1.2%), hypertension (7.8% vs 3.6%), dry mouth (7.8% vs 1.2%), weight gain (6.5% vs 0%), and vaginitis (6.4% vs 0%).[107] Overall, data from clinical trials involving patients with mania show that most AEs associated with aripiprazole, either as monotherapy or in combination with lithium/valproate, occur early in treatment, are mild or moderate in severity, are generally transient, and either resolve or are manageable with intervention.

Regarding depression, in the study conducted by Ketter and colleagues,[124] mild sedation, nausea, and constipation were the most common AEs. In the study

Table 6. Long-Term Effects of Aripiprazole on Metabolic Parameters

Patient Population	Study Duration	Metabolic Parameter	Change From Baseline (mg/dL) (aripiprazole vs placebo)	Study
Bipolar mania	26 wk	Fasting glucose (median)	Aripiprazole 4 vs placebo 6	Keck et al, 2006[61]
		Fasting HDL cholesterol (median)	Aripiprazole 3 vs placebo 2	
		Fasting LDL cholesterol (median)	Aripiprazole 16 vs placebo 15	
Bipolar mania	100 wk	Total cholesterol[a]	Aripiprazole 3.7 ± 3.5 vs placebo 1.8 ± 3.4	Keck et al, 2007[107]
		LDL cholesterol[a]	Aripiprazole 4.5 ± 2.8 vs placebo 4.4 ± 2.8	
		HDL cholesterol[a]	Aripiprazole 1.6 ± 1.0 vs placebo 0.3 ± 1.0	
		Triglycerides[a]	Aripiprazole –23.8 ± 9.0 vs placebo –16.9 ± 8.9	
		Glucose[a]	Aripiprazole 1.6 ± 2.8 vs placebo 1.0 ± 2.7	

[a]Values expressed as mean ± SE and pooled as fasting and nonfasting.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 7. Weight Change Data From Clinical Trials

Patient Population	Study Duration	Mean Weight Change From Baseline	Percentage of Patients With Clinically Significant (≥ 7%) Weight Gain	Study
Bipolar mania	3 wk	Aripiprazole 0.1 kg vs placebo 0.0 kg	Aripiprazole 2% vs placebo 3%	Abilify package insert[128]
Bipolar mania	12 wk	Aripiprazole 0.27 kg vs Haloperidol –0.10 kg	Not available	Vieta et al, 2005[105]
Bipolar mania	26 wk	Aripiprazole 0.5 kg vs placebo –1.7 kg	Aripiprazole 13% vs placebo 0%	Keck et al, 2006[61]
Bipolar mania	100 wk	Aripiprazole 0.4 kg vs placebo –1.9 kg	Aripiprazole 20% vs placebo 5%	Keck et al, 2007[107]
Bipolar depression	Mean: 84 d	Aripiprazole 3.7 kg (open label)	Aripiprazole 13%	Ketter et al, 2006[124]
Bipolar depression	8 wk	Aripiprazole 0.8 kg (open label)	Not available	McElroy et al, 2007[125]
Bipolar depression	8 wk	Study 1: aripiprazole 1.1 kg vs placebo 0.01 kg	Study 1: Aripiprazole 6.7% vs placebo 3.5%	Thase et al, 2008[117]
		Study 2: aripiprazole 0.01 kg vs placebo –0.07 kg	Study 2: Aripiprazole 2.9% vs placebo 2.6%	

by McElroy and colleagues,[125] the most common AE was akathisia, which occurred in 11 patients (35%). In the chart review conducted by Kemp et al,[126] newly developed akathisia occurred in 5 of 12 patients (42%).

In summary, although aripiprazole has a low propensity for causing EPS, EPS associated with aripiprazole treatment may be more common in clinical practice than in those participating in clinical trials and in patients with bipolar depression than in patients with mania. In the controlled clinical trials, discontinuation rates because of AEs in the aripiprazole group were generally comparable to rates in the placebo group among patients with mania[92–95]; however, among patients with depression, these rates were higher in the aripiprazole group than in the placebo group.[117] The observed higher incidence of EPS in clinical practice may be due to a number of factors, including the use of concomitant medications, titration and dosing issues, and patient-related factors. Indeed, bipolar patients in general may have a heightened sensitivity to EPS that may be even more pronounced when they are depressed than when they are manic.[127]

Aripiprazole Effects on Metabolic Parameters

Aripiprazole has been shown to have a relatively benign AE profile related to metabolic parameters in bipolar disorder. Weight changes in placebo-controlled trials and open-label trials were typically modest, and clinically significant effects on glucose tolerance and lipid levels were not detected (Tables 6 and 7).*

PRACTICAL CONSIDERATIONS WHEN USING ARIPIPRAZOLE TO TREAT BIPOLAR DISORDER

Aripiprazole is recommended for the acute and maintenance treatment of acute manic and mixed episodes associated with bipolar I disorder, with or without psychotic features.[128] The dose of aripiprazole currently approved for the acute and maintenance treatment of acute manic and mixed episodes in bipolar I disorder is 15–30 mg/d. Aripiprazole injection is recommended for the treatment of agitation associated with bipolar mania. More recently, aripiprazole was approved as an adjunctive treatment to antidepressants for patients with major depressive disorder in a dose range of 2–15 mg/d and as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episode of bipolar I disorder.

Importantly, patients seen in clinical practice often differ from those in clinical trials and may require different dosing strategies in both acute and outpatient settings. Aripiprazole at a starting dose of 15 mg/d, with the

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*References 61, 105, 107, 117, 124, 125, 128.

option to increase to a maximum of 30 mg/d, is effective and well tolerated in acute bipolar mania but may be too high for patients with bipolar depression,[125,126] who may experience higher rates of akathisia. Thus, it has been suggested that lower initial doses of aripiprazole, in the range of 2–5 mg/d, may be necessary to minimize EPS in bipolar patients in depressive states.[126]

Aripiprazole is available in 2-, 5-, 10-, 15-, 20-, and 30-mg tablets and oral solution (1 mg/mL), an orally disintegrating tablet (10- and 15-mg doses) and a single-dose vial (9.75 mg/1.3 mL). Patients may initially require a lower dose in order to reduce the risk of AEs, but this dose needs to be balanced against a delayed onset of therapeutic effect. Primary care physicians should inform patients of any AEs that they are likely to experience and reassure patients that when specific AEs are encountered, various approaches (pharmacologic if needed) are available for treatment. Aripiprazole may be especially helpful for patients with bipolar disorder with existing metabolic issues or those deemed at risk for adverse metabolic effects. Such patients may include overweight or obese patients, as well as those with impaired glucose tolerance, type 2 diabetes mellitus, or hyperlipidemia. It should be noted, however, that metabolic parameters should be assessed before initiating aripiprazole and periodically reassessed during treatment in all patients.[129,130]

Several circumstances may warrant a consultation with a psychiatrist, including diagnostic confusion, treatment refractoriness, illness severity beyond the scope of primary care practice, or patient/clinician preference. Aripiprazole dose adjustments or switches from other atypical antipsychotics for efficacy, tolerability, or management of AEs may also warrant psychiatric consultation.

CONCLUSION

Primary care physicians, like their psychiatrist colleagues, are experiencing challenges in diagnosing and treating patients with bipolar disorder. The consequences of misdiagnosis can have serious morbidity and mortality implications.[21] Efforts are needed to educate primary care physicians concerning the detection and management of bipolar I disorder as well as the other bipolar spectrum disorders.

Aripiprazole may be considered to be another first-line choice for the treatment of bipolar I disorder patients managed in the primary care setting. However, the drug's utility in patients with softer bipolar spectrum disorders remains to be determined. Aripiprazole is effective in patients with manic or mixed episodes, including patients with or without psychotic symptoms and those with or without rapid cycling. It has a rapid onset of action in acute mania (by 4 days). Aripiprazole is also effective in delaying the time to relapse and reducing the risk of relapse over the long term (up to 100 weeks). Finally,

aripiprazole has a favorable metabolic and tolerability profile in the acute and long-term treatment setting.

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