Antimanic Response to Aripiprazole in Bipolar I Disorder Patients Is Independent of the Agitation Level at Baseline

Gary S. Sachs, M.D.; Bruce D. Gaulin, Pharm.D.; Rolando Gutierrez-Esteinou, M.D.; Robert D. McQuade, Ph.D.; Andrei Pikalov III, M.D., Ph.D.; Joseph A. Pultz, Ph.D.; Raymond Sanchez, M.D.; Ronald N. Marcus, M.D.; and David T. Crandall, Ph.D.

Objective: To examine the antimanic efficacy of the relatively nonsedating antipsychotic aripiprazole in patients with bipolar I disorder and high or low baseline levels of agitation.

Method: Data were pooled for this post hoc analysis from two 3-week, placebo-controlled trials of aripiprazole in acute mania (DSM-IV). Patients randomly assigned to aripiprazole 30 mg/day (N = 259) or placebo (N = 254) were classified as having either high (Positive and Negative Syndrome Scale [PANSS] Excited Component [PEC] score of ≥ 14 and a score of ≥ 4 on at least one PEC item) or low (PEC < 14) levels of agitation at baseline. Efficacy measures were changes in Young Mania Rating Scale (YMRS) scores, Clinical Global Impressions–Bipolar (CGI-BP) scores, and PEC scores. Efficacy and agitation measurements were assessed by analysis of covariance.

Results: From the first week of therapy onward, aripiprazole-treated subjects had significantly greater reduction from baseline in YMRS total scores than placebo-treated subjects in both the high- and low-agitation groups ($p < .05$ for both groups) and significantly improved CGI-BP scores vs. placebo at end point ($p < .05$ for both). In highly agitated patients receiving aripiprazole, PEC scores were significantly decreased versus placebo at end point ($p < .05$). In patients with low agitation receiving aripiprazole, no increases in PEC scores were seen, and a significant reduction in agitation symptoms was apparent after adjustment for baseline PEC scores.

Conclusions: Aripiprazole was superior to placebo in reducing the severity of both mania and agitation in highly agitated patients with bipolar I disorder and showed significant antimanic activity in patients with low levels of agitation without increasing agitation. These findings suggest that aripiprazole's antimanic effect is specific and not limited to control of agitation through sedation.

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Corresponding author and reprints: Gary Sachs, M.D., Massachusetts General Hospital, 50 Stanford St., Boston, MA 02114 (e-mail: sachsg@aol.com).

Agitation is a common symptom component in manic or mixed episodes of bipolar disorder[1,2] and is a factor associated with hospitalization.[3] For bipolar disorder patients with mania and agitation, treatments may ameliorate symptoms through nonspecific (sedative effects) and through specific antimanic effects. Sedating medications are often used to advantage for treatment of acute agitation in the emergency setting. However, the clinician's ultimate goal, full restoration of function, can be frustrated by impairment caused by excessive sedation.[4,5] A specific treatment for agitation and mania would ameliorate these symptoms without causing sedation. Although the pathophysiology of agitation and mania is complex and not completely understood, a body of evidence suggests that dopaminergic neurotransmitter system dysregulation underlies the symptoms of agitation[6] and mania.[7] Clinical support for the efficacy of dopamine antagonists in these patients began with a seminal study comparing the dopamine D_2 receptor antagonist chlorpromazine with lithium.[8] The study showed signifi-

cant superiority of the antipsychotic chlorpromazine for reducing mania in highly active (i.e., agitated) patients, with a more rapid onset of effect. Atypical antipsychotics, including risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, have demonstrated efficacy for treatment of manic or manic/mixed episodes and are associated with an improved adverse-event profile when compared with the conventional agents.[9–21] They have also been shown to reduce agitation in several psychiatric disorders.[22–31] Atypical antipsychotics are now recommended for the treatment of episodes of acute or mixed mania associated with bipolar I disorder.[21,32,33] Excessive sedation is considered an unwanted side effect of treatment for agitated patients because it may compromise a patient's ability to participate in his or her care.[4] However, the contribution of the nonspecific sedating properties relative to specific antimanic effects of most atypical antipsychotics in managing agitated mania remains unclear. Nonsedating agents may be perceived as being less efficacious or as actually causing an increase in agitation.

Aripiprazole is a dopamine D_2 and serotonin 5-HT_{1A} receptor partial agonist, as well as a serotonin 5-HT_{2A} receptor antagonist with minimal sedating properties.[34–38] It is the most recently approved antipsychotic in the United States for the treatment of bipolar I disorder (indicated for acute manic and mixed episodes and maintaining efficacy).[39] Although the general antimanic properties of aripiprazole are well-established, its effects in agitated patients have yet to be explored. This post hoc analysis was initiated at the request of a group of psychiatrists who led a 2005 American Psychiatric Association (APA) symposium examining the impact of agitation on the response to atypical antipsychotics.[40] Their purpose was to evaluate the impact of baseline agitation status on treatment outcomes in adequately powered placebo-controlled treatment trials across psychiatric disorders. The present analysis considers only data from aripiprazole acute mania studies.

METHOD

Efficacy data were pooled from two 3-week aripiprazole registrational trials conducted at 67 U.S. sites.[18,20] These trials were conducted according to Good Clinical Practice and conformed to the regulations of the Declaration of Helsinki. Written informed consent was obtained from all participants and institutional review board approval was given at each study site.

Inclusion/Exclusion Criteria and Study Design

Eligibility criteria, study design, and procedures were similar for the 2 trials. Prospective patients had to be aged ≥ 18 years with a current diagnosis of DSM-IV bipolar I disorder (current episode manic or mixed) requiring hospitalization. A baseline score of ≥ 20 on the Young Mania Rating Scale (YMRS) was required prior to being randomly assigned.[18,41] Patients with a diagnosis or history of delirium, dementia, amnestic or other cognitive disorders, schizophrenia, schizoaffective disorders, or first-break manic episode were excluded. Other exclusion criteria included current manic episode duration of more than 4 weeks; nonresponse to clozapine; the probable need for prohibited medication during the trial (other antipsychotic agents, fluoxetine, carbamazepine, divalproex sodium, valproic acid, valproate, lithium, benzodiazepine [except lorazepam], and all other psychotropic drugs); or a substance use disorder. In addition, patients with a significant risk of committing suicide or homicide, those with a history of neuroleptic malignant syndrome or seizure disorder, and those who had been previously enrolled in an aripiprazole trial were ineligible.

Concomitant use of psychotropic medications was not allowed during the trials (including screening periods) except for lorazepam. Lorazepam treatment was allowed on days 1–4 (≤ 6 mg/day), 5–7 (≤ 4 mg/day), and 8–10 (≤ 2 mg/day). No lorazepam was allowed after day 10. After a 1- to 7-day screening period, during which all psychotropic drugs were discontinued, baseline assessments were completed, and patients were randomly assigned to aripiprazole 30 mg/day or placebo for a 3-week treatment period. If necessary, the dose of aripiprazole could be decreased to 15 mg/day for tolerability reasons. Two hundred sixty-two patients were randomly assigned in the first study (aripiprazole, N = 130; placebo, N = 132), and 272 patients were randomly assigned in the second study (aripiprazole, N = 137; placebo, N = 135).[18,20]

Study Population

At the request of the organizers (G. Sachs, M.D., S. Marder, M.D., and J. Mintzer, M.D.) of the 2005 APA symposium, the efficacy populations of both trials were dichotomized into groups experiencing either high or low agitation based on a medium split of the baseline Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score across psychiatric disorders (schizophrenia, Alzheimer's disease, and bipolar mania). For this post hoc analysis, high agitation was defined as a PEC score of ≥ 14 and a score of ≥ 4 on at least one PEC item.[24,31] Low agitation was defined as a PEC score < 14 and no PEC item score ≥ 4. The PEC is a subscale of the PANSS and consists of the following 5 items rated from 1 (absent) to 7 (extremely severe): excitement, hostility, tension, uncooperativeness, and poor impulse control. It is calculated as the sum of the 5 PANSS items. The PEC scale has been validated in clinical trials of bipolar disorder, acute mania, and schizophrenia.[23,24,30,42]

Assessments

The efficacy of study medication in reducing symptoms of mania within high- and low-agitation groups

Table 1. Baseline Characteristics of the Pooled Patient Subpopulations

Characteristic	High Agitation	Low Agitation	Total	p Value (high vs low agitation)
Subjects, N	213	300	513	
Sex, N (%)				
Male	100 (46.9)	137 (45.7)	237 (46.2)	
Female	113 (53.1)	163 (54.3)	276 (53.8)	.774 NS*
Age group, N (%)				
< 48 y	157 (73.7)	234 (78.0)	391 (76.2)	
≥ 48 y	56 (26.3)	66 (22.0)	122 (23.8)	.261 NS*
Race/ethnicity, N (%)				
White	159 (74.6)	222 (74.0)	381 (74.3)	
Black	33 (15.5)	57 (19.0)	90 (17.5)	
Other	21 (9.9)	21 (7.0)	42 (8.2)	.346 NS*
YMRS total at baseline, mean (SD)	31.2 (5.9)	26.9 (4.8)		< .0001
CGI-BP score at baseline, mean (SD)	5.0 (0.7)	4.4 (0.6)		< .0001
PEC score at baseline, mean (SD)	17.7 (3.2)	10.5 (2.1)		< .0001

*Test for association between group (low agitation/high agitation) and characteristic.
Abbreviations: CGI-BP = Clinical Global Impressions-Bipolar, NS = not significant, PEC = Positive and Negative Syndrome Scale (PANSS) Excited Component, YMRS = Young Mania Rating Scale.

was defined as the mean change from baseline to study end point in the YMRS total score and the mean score on the Clinical Global Impressions–Bipolar Mania (CGI-BP) scale. Changes in agitation status within treatment groups were assessed by measuring the mean change from baseline to end point in PEC total scores. For this analysis, assessments were made at baseline and at days 7, 14, and 21 for YMRS and CGI-BP and at baseline and day 21 for PEC. An additional analysis was conducted to measure the percentage of benzodiazepine use across treatment groups and within agitation cohorts.

Statistical Evaluations

Efficacy and agitation measurements in the intent-to-treat, high- and low-agitation cohorts were analyzed using the last observation carried forward (LOCF) approach. Efficacy measures (YMRS total scores, CGI-BP scores, and PEC scores) were assessed by analysis of covariance (ANCOVA). Because, as expected, highly agitated patients had higher baseline symptomatology (Table 1), additional statistical analyses were performed following adjustment for baseline YMRS total, CGI-BP, and PEC scores. In the case of CGI-BP, severity was used as a covariate. Analyses were conducted at weeks 1, 2, and 3 (end point).

RESULTS

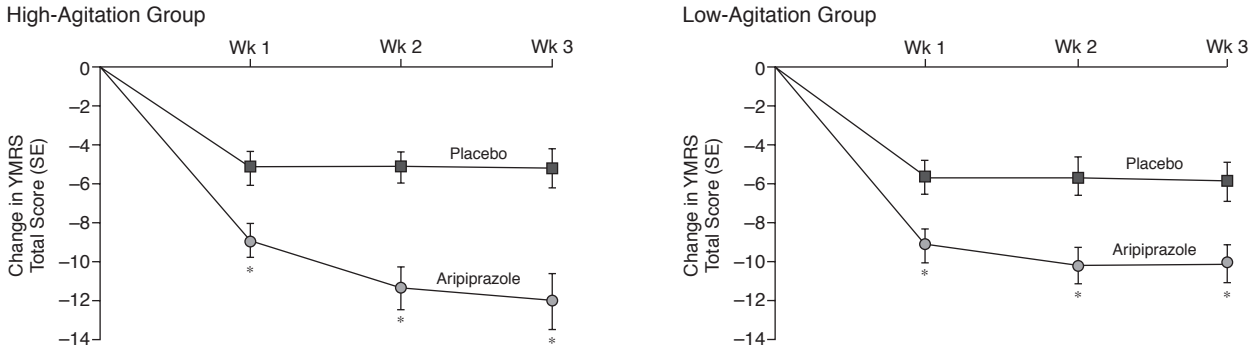
The efficacy population consisted of 513 hospitalized patients receiving aripiprazole (N = 259) or placebo (N = 254). The high-agitation group included 213 patients, and the low-agitation group included 300 patients; baseline agitation status was balanced across treatment groups (high-agitation group: aripiprazole, N = 100; placebo, N = 113; low agitation group: aripiprazole, N = 159; placebo, N = 141). At study end point, the mean dose of aripiprazole was 27.8 mg, and 85% of patients remained on the starting dose of 30 mg. Baseline characteristics for the pooled inpatient subpopulations are shown in Table 1. There were no significant differences in demographic characteristics (age, race, sex) between the high- and low-agitation groups. However, patients in the high-agitation groups had significantly higher severity scores (YMRS and CGI-BP) compared with those in the low-agitation group ($p < .0001$ for all) (Table 1).

Effect of Aripiprazole on Manic Symptoms

In both the high- and low-agitation groups, aripiprazole treatment resulted in a significant reduction in mania symptoms (YMRS total scores) from baseline to end point compared with placebo. For both high- and low-agitation cohorts, treatment with aripiprazole produced improvements in YMRS total scores that were significantly greater than placebo within the first week of therapy and that were sustained through study end point ($p < .05$ at all time points) (Figure 1). At end point, aripiprazole-treated patients from the high-agitation cohort had a mean reduction of 12.0 points on the YMRS compared with a mean reduction of 5.3 points in the placebo patients ($p < .05$). Aripiprazole-treated patients from the low-agitation cohort had a mean reduction of 10.1 points at end point compared with a reduction of 5.9 points for patients receiving placebo ($p < .05$).

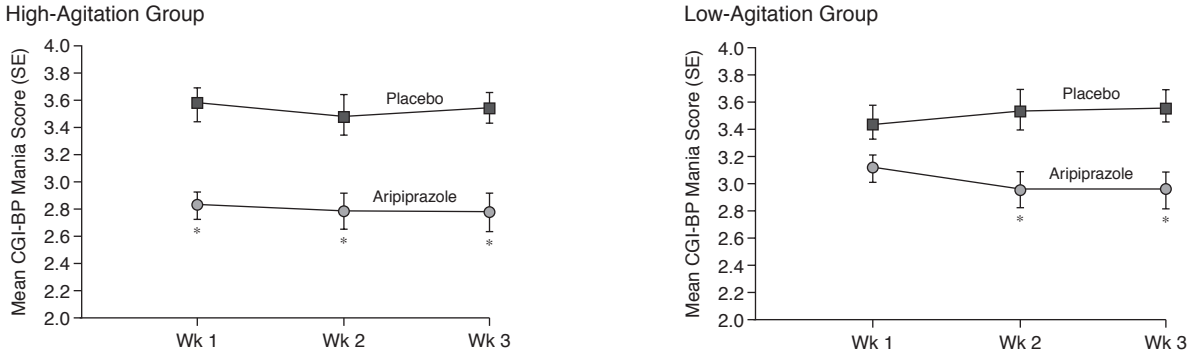
Aripiprazole-treated patients also had significantly improved CGI-BP (mania) scores compared with placebo-treated patients in either low- or high-agitation groups ($p < .05$) at all time points except for week 1 in the low-agitation group (Figure 2). At end point, the high-agitation cohort treated with aripiprazole had a mean CGI-BP score of 2.9 points compared with 3.7 points for placebo-treated patients ($p < .05$). In the low-agitation cohort, the aripiprazole treatment group had a mean score of 3.0 points on the CGI-BP scale compared with 3.6 points

Figure 1. Mean Change From Baseline to Study End Point in YMRS Total Scores for Acutely Manic Bipolar I Disorder Patients Experiencing High or Low Agitation



*p < .05, unadjusted means.
Abbreviation: YMRS = Young Mania Rating Scale.

Figure 2. Mean CGI-BP Scores for Acutely Manic Bipolar I Disorder Patients Experiencing High or Low Agitation



*p < .05, unadjusted means.
Abbreviation: CGI-BP = Clinical Global Impressions–Bipolar.

for the placebo group (p < .05). After adjusting for baseline YMRS and CGI-BP scores, aripiprazole-treated patients in both groups continued to show significant differences compared with placebo-treated patients at end point (p < .005 for YMRS total and CGI-BP scores).

Effect of Aripiprazole on Agitation Symptoms

The mean baseline PEC score was 17.7 ± 3.2 in the high-agitation group and 10.5 ± 2.1 for the low-agitation group (p < .0001). Patients in the high-agitation cohort receiving aripiprazole showed a significant reduction of agitation symptoms at end point vs. placebo (Figure 3). PEC agitation scores decreased 5.1 points in the aripiprazole group compared with 2.5 points in the placebo group (p < .05). For patients who were experiencing low levels of agitation at baseline, agitation scores decreased 0.9 points in the aripiprazole group and increased 0.4 points in the placebo group (p = NS). However, in the low-agitation cohort, the response of agitation symptoms to aripiprazole was significantly different from placebo after adjusting for baseline PEC values (p < .05).

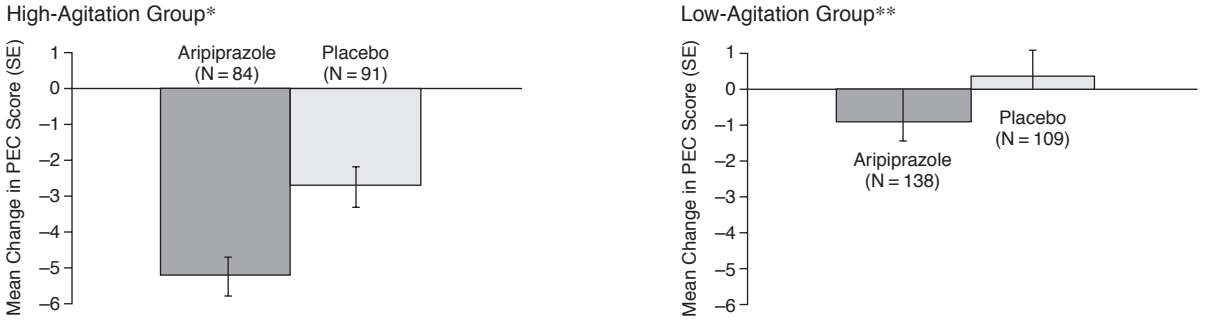
Benzodiazepine Usage

The percentage of patients who required lorazepam treatment in the first 10 days was comparable between the aripiprazole- and placebo-treated cohorts regardless of agitation status at baseline (p = NS). In all 4 groups, 80% to 84% of patients used lorazepam during week 1. The percentage of patients using lorazepam dropped to 46% to 59% in week 2. Although it was discouraged in the respective clinical trial protocols, a few patients (4% to 7%) in each group inadvertently received lorazepam off protocol in week 3; this was also comparable across groups.

Adverse Events

The treatment-emergent adverse events that occurred in ≥ 5% of patients in any group and ≥ 2 times the

Figure 3. Mean Change From Baseline to Study End Point in PEC Scores for Acutely Manic Bipolar I Disorder Patients Experiencing High or Low Agitation at Baseline



*p < .05, unadjusted means.
**p = NS; unadjusted means.
Abbreviation: PEC = Positive and Negative Syndrome Scale (PANSS) Excited Component.

Table 2. Incidence of Treatment-Emergent Adverse Events in Acutely Manic Bipolar I Disorder Patients Experiencing High or Low Agitation at Baseline[a]

	High Agitation		Low Agitation	
Adverse Event	Aripiprazole N = 100	Placebo N = 113	Aripiprazole N = 159	Placebo N = 141
Somnolence	21.0	5.3	21.4	10.6
Dyspepsia	19.0	7.1	NA	NA
Constipation	13.0	6.2	NA	NA
Vomiting	NA	NA	14.5	6.4
Anxiety	12.0	5.3	NA	NA
Accidental injury	10.0	1.8	8.2	2.1
Pain extremity	9.0	4.4	NA	NA
Akathisia	NA	NA	18.9	5.7
Dry mouth	7.0	2.7	NA	NA
Infection	6.0	0	NA	NA
Salivation increased	NA	NA	5.7	0.7
Blurred vision	NA	NA	5.7	0.7

[a]Criteria: Incidence (%) of treatment-emergent adverse events occurring in ≥ 5% of any group and more frequent (≥ 2 times the incidence) in the aripiprazole group than in the placebo group. Adverse events that do not meet these criteria are marked NA (not applicable).

placebo rate are reported in Table 2 for both high- and low-agitation cohorts.

DISCUSSION

Data from this post hoc analysis demonstrated that aripiprazole was superior to placebo in the treatment of patients with acute or mixed mania associated with bipolar I disorder regardless of agitation status at baseline. Aripiprazole significantly improved manic/mixed symptoms as early as the first week of therapy in patients with high or low agitation at baseline, as demonstrated by significant decreases in YMRS total scores. Additionally, aripiprazole was associated with significant and sustained overall clinical improvements in both the high- and low-agitation cohorts as measured by CGI-BP.

The data show that, compared with placebo, aripiprazole significantly reduced the level of agitation for subjects in the high-agitation group and did not exacerbate the level of agitation in the low-agitation group. To the contrary, the observation of a statistically significant difference after adjusting for baseline PEC scores suggests that aripiprazole was most likely effective in reducing agitation, even in subjects who started with low levels of agitation.

These trials permitted use of lorazepam as a concomitant medication until day 10. The effects of lorazepam include calming and sedation. Potentially, our findings might be attributable to differential use of lorazepam; however, the percentage of patients prescribed lorazepam was similar across treatment groups as well as across agitation status. Therefore, the significant improvements in the symptoms of agitation attributed to aripiprazole appear to be in addition to any improvements provided by lorazepam. Clinical trials have shown that aripiprazole is associated with a low potential to cause sedation,[18,20,43] and the present findings further suggest that aripiprazole's effects were specific to treating the core symptoms of mania and agitation in these patients.

Although based on large placebo-controlled, randomized clinical trials, the post hoc nature of this analysis is a limitation. In addition, PEC scores could only be assessed at baseline and end point because the scale was only administered at those 2 time points. It should also be noted that the requirement of informed consent in clinical trials inherently excludes the most extremely ill patients. However, the cutoff criteria used for the high agitation group are consistent with at least some moderate symptoms on the PANSS items that comprise the PEC. Also, some patients may have experienced agitation as a result of depression (e.g., patients with mixed mania). Further research is needed to assess the effect of aripiprazole on agitation at intermediate time points and to confirm the

findings of this study. Nevertheless, this post hoc analysis demonstrated the effectiveness of aripiprazole for the treatment of acute manic/mixed episodes of bipolar I disorder regardless of baseline agitation status. In addition, the findings suggest that the efficacy of aripiprazole as an antimanic therapy for patients with bipolar I disorder is specific rather than limited to the control of agitation through sedation.

In summary, aripiprazole was effective and well-tolerated in patients with bipolar I disorder experiencing an acute manic or mixed episode regardless of agitation level at baseline. Aripiprazole significantly reduced the symptoms of mania and agitation and significantly improved the overall clinical condition in patients with a moderate to high level of agitation. Agitation was not exacerbated in these patients. Therefore, it appears that the beneficial effects of aripiprazole were specific to treating the core symptoms of mania and agitation and not limited to a sedation effect in acute patients with bipolar I disorder.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

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