Aripiprazole Effects in Patients With Acute Schizophrenia Experiencing Higher or Lower Agitation: A Post Hoc Analysis of 4 Randomized, Placebo-Controlled Clinical Trials

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Objective: Patients with acute schizophrenia who are agitated typically manifest worse overall symptomatology and are generally more challenging to treat than nonagitated patients. In order to determine whether baseline agitation level influences treatment response, the effects of oral aripiprazole in acute patients with schizophrenia experiencing either higher or lower levels of agitation were examined.

Method: A post hoc analysis of pooled data from the first 4 or 6 weeks of 4 randomized, double-blind, placebo-controlled aripiprazole trials was conducted. Patients with a DSM-IV diagnosis of acute schizophrenia randomly assigned to treatment with either aripiprazole 10, 15, 20, or 30 mg/day (N = 790) or placebo (N = 397) were divided into groups experiencing higher or lower agitation at baseline. Higher agitation was defined as a baseline Positive and Negative Syndrome Scale (PANSS)–Excited Component (PEC) score of ≥ 14 and a score of ≥ 4 on at least 1 PEC item (excitement, hostility, tension, uncooperativeness, or poor impulse control). Analysis of covariance was used to evaluate PANSS total, Clinical Global Impressions-Improvement scale (CGI-I), and PEC scores between aripiprazole and placebo within the higher and lower agitation groups.

Results: In both the higher and lower agitation groups, aripiprazole treatment produced significantly lower PANSS total, CGI-I, and PEC scores at weeks 2 to 6, compared with placebo ($p < .05$ for each measure). Percentage of concomitant benzodiazepine use was similar at end point for aripiprazole and placebo, and adverse events were generally mild across groups.

Conclusions: Aripiprazole significantly improved the core symptoms of acute schizophrenia regardless of baseline agitation level. In particular, agitation symptoms were significantly decreased in patients with higher baseline agitation. Improvements appeared to be independent of benzodiazepine use or excessive sedation effects. These results suggest that oral aripiprazole is an effective and safe treatment option for patients with acute schizophrenia who manifest agitation symptoms.

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Frequently, patients with acute schizophrenia manifest symptoms of agitation, such as excitement, hostility, aggressive behavior, destructive behavior, verbal abuse, and extreme personal distress.[1–3] These symptoms may delay appropriate psychiatric assessment, hinder diagnosis and treatment, and prevent or disrupt physician-patient alliances.[4] Symptoms of agitation can contribute to the poor quality of life for patients with schizophrenia.[5] In addition, patients with psychotic agitation tend to be uncooperative[6] and potentially dangerous to self and others.[6,7] For instance, approximately one third of aggressive acts committed by patients with schizophrenia occur during an acute exacerbation of the illness.[8]

Although the precise etiology of psychotic agitation is not known, symptoms that result in a distorted perception of reality, including thought disturbances, hallucinations, and paranoid delusions, may be contributing factors.[7,9] Poor impulse control related to neuropsychiatric deficits may also facilitate the discharge of aggressive tendencies.[9] Moreover, agitation or motor restlessness has been shown to be a significant risk factor for suicide in patients with schizophrenia.[10]

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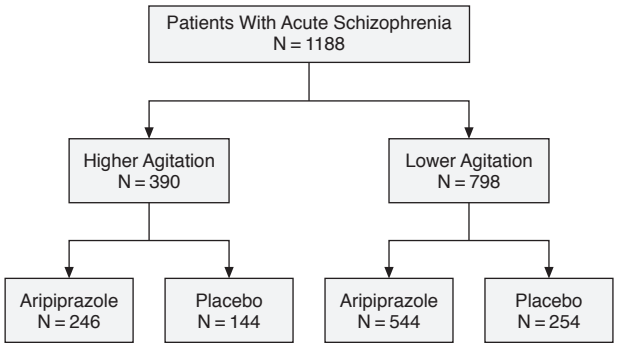
Table 1. Clinical Trials Providing Data for This Post Hoc Analysis[a]

Trial	Duration, wk	Fixed Doses of Aripiprazole, mg/d	Patients, N	
			Aripiprazole	Placebo
1	6	10, 15, 20	303	107
2	6	10	94	86[b]
3	4	15, 30	199	102
4	4	20, 30	194	103

[a]Data on file, Bristol-Myers Squibb (Trial 1), Cutler et al.[25] (Trial 2), Kane et al.[22] (Trial 3), and Potkin et al.[23] (Trial 4).
[b]One patient in the placebo group (with baseline higher agitation) had a postbaseline efficacy assessment after study drug discontinuation and thus was included in the safety summary but not the efficacy analysis.

Figure 1. Distribution of Patients Included in the Analysis



Atypical antipsychotic medications, including risperidone, olanzapine, ziprasidone, and aripiprazole (either alone or in combination with benzodiazepines), have been shown in clinical trials to be effective and safe for the rapid control of acute agitation.[11–17] However, it is unclear what effect, if any, baseline levels of agitation may have on overall symptom improvement following the initiation of atypical antipsychotic therapy, especially during maintenance with oral therapies.

Aripiprazole is a dopamine D_2[18] and serotonin 5-HT_{1A} partial receptor agonist,[19,20] as well as a serotonin 5-HT_{2A} receptor antagonist.[21] Several randomized, double-blind, placebo-controlled trials have shown that aripiprazole is an effective, safe, and well-tolerated treatment for acute schizophrenia and schizoaffective disorder.[22–24] Somnolence rates from the clinical trials were comparable with those of placebo (11% vs. 8%),[23] suggesting that aripiprazole treatment effects are not likely related to generalized sedation. The purpose of this post hoc analysis was to determine the treatment response to oral aripiprazole in patients with acute schizophrenia with different levels of agitation at baseline who were pooled from 4 randomized, double-blind, placebo-controlled trials (data on file, Bristol-Myers Squibb, and references 22, 23, 25).

METHOD

The following analyses were performed as part of a larger data request made by a group of clinical research physician experts who convened a 2005 American Psychiatric Association (APA) symposium examining the impact of agitation on the response to atypical antipsychotics across several DSM-IV disorders.[26] Efficacy data were pooled from the first 4 weeks of 4 randomized, double-blind, placebo-controlled trials (two 4-week and two 6-week trials) of fixed oral dose aripiprazole (10 mg/day–30 mg/day) (Table 1) (data on file, Bristol-Myers Squibb, and references 22, 23, 25). In addition, efficacy data were pooled from weeks 5 and 6 of the two 6-week trials. A total of 1188 randomly assigned patients with a DSM-IV diagnosis of acute schizophrenia was pooled from the 4 trials; 1187 of these were included in the post hoc efficacy analysis. (One patient in the placebo group [with baseline higher agitation] had a postbaseline efficacy assessment after study drug discontinuation and thus was not included in the efficacy analysis but was included in the safety summary.)

Patients were divided into groups experiencing higher or lower levels of agitation at baseline. Of the 390 patients in the higher agitation group, 246 received aripiprazole and 144 received placebo. Of 798 patients in the lower agitation group, 544 received aripiprazole and 254 received placebo (Figure 1). Higher agitation was defined as a Positive and Negative Syndrome Scale (PANSS)[27]–Excited Component (PEC) score ≥ 14 and a score of ≥ 4 on at least 1 PEC item. These cutoffs were chosen based on the request from the aforementioned panel of experts who convened the APA 2005 symposium. The PEC subscale score is the sum of 5 PANSS items (excitement, hostility, tension, uncooperativeness, poor impulse control). Each of the items is scored on the following scale: 1 = absent; 4 = moderate; 7 = extreme. PEC scores can, therefore, range from a minimum score of 5 to a maximum score of 35. The use of PEC scores to stratify patients with higher or lower levels of agitation has been validated in multiple clinical trials in patients with schizophrenia or bipolar disorder.[11,12,28–30]

Lorazepam (up to 4 mg/day) was permitted for the treatment of anxiety, emergent agitation, or insomnia but only if deemed absolutely necessary by the investigator. If needed, an additional 1 to 2 mg could be administered at night as a sleep aid.

Statistical Analysis

Mean changes from baseline to analysis end point (i.e., week 4) in PANSS total, Clinical Global Impressions-Improvement (CGI-I), and PEC scores were assessed for all treatment groups. Unadjusted means were used for statistical comparisons between aripiprazole and placebo for

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Table 2. Patient Demographics and Baseline Characteristics

Characteristic	Higher Agitation, N (%)	Lower Agitation, N (%)	Total, N (%)	p Value (includes all agitation groups)
All patients	389 (32.8)	798 (67.2)	1187 (100)	
Aripiprazole	246 (63.2)	544 (68.2)	790 (66.6)	
Placebo	143 (36.8)	254 (31.8)	397 (33.4)	
Sex				.089
Male	276 (71.0)	603 (75.6)	879 (74.1)	
Female	113 (29.0)	195 (24.4)	308 (25.9)	
Age group				.456
< 46 years	284 (73.0)	566 (70.9)	850 (71.6)	
≥ 46 years	105 (27.0)	232 (29.1)	337 (28.4)	
Race				.174
White	223 (57.3)	415 (52.0)	638 (53.7)	
Black	110 (28.3)	266 (33.3)	376 (31.7)	
Other	56 (14.4)	117 (14.7)	173 (14.6)	
Baseline PANSS score	Mean (SD)	Mean (SD)		p Value (higher vs lower agitation)
Total	107.7 (20.1)	87.1 (13.1)		< .001
Excited Component	18.1 (3.9)	9.9 (2.3)		< .0001
Baseline CGI-S score	5.2 (0.8)	4.6 (0.7)		< .0001

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

Table 3. Patient Disposition

	Lower Agitation Group		Higher Agitation Group	
Reason for Discontinuation	Placebo, N = 254	Aripiprazole Combined Doses, N = 544	Placebo, N = 144	Aripiprazole Combined Doses, N = 246
Withdrew consent, N (%)	35 (13.8)	91 (16.7)	22 (15.3)	47 (19.1)
Lack of efficacy, N (%)	46 (18.1)	69 (12.7)	30 (20.8)	30 (12.2)
Adverse event, N (%)	35 (13.8)	43 (7.9)	17 (11.8)	20 (8.1)
Noncompliance with protocol, N (%)	1 (0.4)	2 (0.4)	1 (0.7)	5 (2.0)
Lost to follow-up, N (%)	0 (0)	3 (0.6)	1 (0.7)	2 (0.8)
Other, N (%)	3 (1.2)	3 (0.6)	1 (0.7)	4 (1.6)
Completed study, N (%)	134 (52.8)	333 (61.2)	72 (50.0)	138 (56.1)

each agitation group. Additional statistical analyses were performed following adjustment for baseline PANSS total, CGI-Severity of Illness scale (CGI-S), and PEC scores. Analysis of covariance (ANCOVA) was used to evaluate differences within agitation groups (aripiprazole–higher agitation vs. placebo–higher agitation; aripiprazole–lower agitation vs. placebo–lower agitation) for each dependent measure.

The percentage of patients who used lorazepam was assessed for each agitation group in order to determine if the improvements in PANSS total, PEC, and CGI-I scores associated with aripiprazole were independent of the sedating effects of lorazepam.

RESULTS

Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the higher and lower agitation groups are presented in Table 2. There were no statistically significant differences in patient demographics between the higher and lower agitation groups. Patients were predominately white, male, and under 46 years of age. As expected, there were significant differences between agitation groups in baseline symptomatology as measured by the PANSS total, CGI-S, and PEC (Table 2).

Patient Disposition

In the lower agitation group (N = 798), 467/798 (58.5%) patients completed the trials (Table 3). The reasons for discontinuation were withdrew consent (126/798 [15.8%]); lack of efficacy (115/798 [14.4%]); adverse events (78/798 [9.8%]); lost to follow-up (3/798 [0.4%]); noncompliance with protocol (3/798 [0.4%]); and reasons listed as "other" (6/798 [0.8%]).

In the higher agitation group (N = 390), 210/390 (53.9%) completed the trials. The reasons for discontinuation were withdrew consent (69/390 [17.7%]); lack of efficacy (60/390 [15.4%]); adverse events (37/390 [9.5%]); noncompliance with protocol (6/390 [1.5%]); lost to follow-up (3/390 [0.8%]); and reasons listed as "other" (5/390 [1.3 %]).

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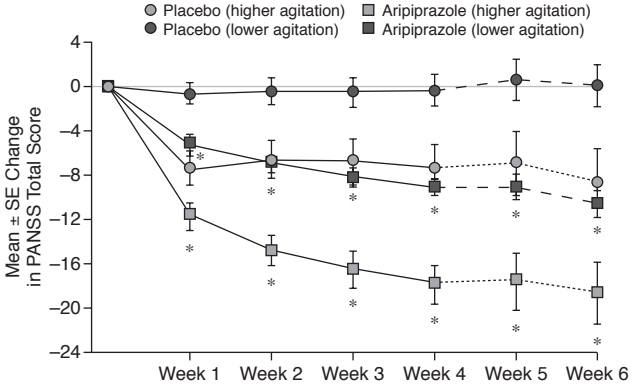
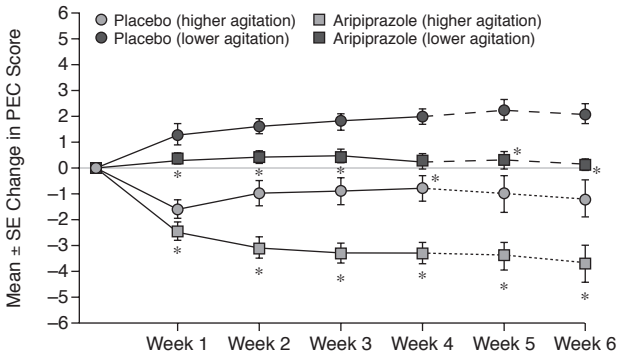
Figure 2. PANSS Total Scores: Mean Change From Baseline Over Time



*p ≤ .05 compared with placebo (unadjusted means). Data from the two 6-week trials only are represented by dotted lines (aripiprazole, N = 109; placebo, N = 67) and dashed lines (aripiprazole, N = 288; placebo, N = 67).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 3. Mean Change in PEC Scores From Baseline to End Point



*p ≤ .05 compared with placebo (unadjusted means). Data from the two 6-week trials only are represented by dotted lines (aripiprazole, N = 109; placebo, N = 67) and dashed lines (aripiprazole, N = 288; placebo, N = 67).
Abbreviations: PANSS = Positive and Negative Syndrome Scale, PEC = PANSS-Excited Component.

Efficacy

Aripiprazole was associated with significant decreases in mean PANSS total scores at all time points and 4-week study end point ($p < .05$; Figure 2). A significant separation from placebo, observed as early as the first week of treatment with aripiprazole, was sustained across trial weeks (Figure 2). Similar significant differences vs. placebo were obtained at end point (week 4) for both the higher and lower agitation groups receiving aripiprazole when the mean scores were adjusted to control for baseline differences in PANSS total scores (higher agitation: aripiprazole, –15.1 ± 1.5; placebo, –4.9 ± 1.9; lower agitation: aripiprazole, –10.5 ± 1.0; placebo, –1.5 ± 1.4; $p < .0001$ at end point for both higher and lower agitation). Further analysis of pooled data from the 6-week trials revealed that the separation from placebo was maintained at weeks 5 and 6 in both the higher and lower agitation groups treated with aripiprazole ($p < .05$ vs. placebo; Figure 2).

Patients with higher agitation receiving aripiprazole were observed to have significantly reduced PEC scores from week 2 to study end point (week 4) compared with patients with higher agitation receiving placebo ($p < .05$; Figure 3). Aripiprazole-treated patients in the lower agitation group had significantly lower PEC scores at all time points (including week 1) compared with the patients receiving placebo ($p < .05$) (Figure 3). PEC scores continued to decrease in both the higher and lower agitation groups of patients treated with aripiprazole compared with placebo, and this decrease continued to be statistically significantly greater than placebo ($p < .05$ vs. placebo; Figure 3). Similar significant differences vs. placebo were obtained at end point (week 4) for both the higher and lower agitation groups receiving aripiprazole when the mean scores were adjusted for baseline PEC scores (higher agitation: aripiprazole, –1.2 ± 0.4; placebo, 1.1 ± 0.5; lower agitation: aripiprazole, –0.7 ± 0.3; placebo, 1.1 ± 0.3; $p < .0001$ at end point for both higher and lower agitation).

Aripiprazole was associated with significantly improved CGI-I scores at all time points in both the higher and lower agitation groups, compared with placebo ($p < .05$). A significant separation from placebo, observed as early as the first week of treatment with aripiprazole, was sustained throughout the study (4-week end point). Similar significant differences vs. placebo were obtained at end point (week 4) for both the higher and lower agitation groups receiving aripiprazole when the mean scores were adjusted for baseline CGI-S scores (higher agitation: aripiprazole, 3.3 ± 0.1; placebo, 4.0 ± 0.1; lower agitation: aripiprazole, 3.4 ± 0.1; placebo, 4.0 ± 0.1; $p < .0001$ at end point for both higher and lower agitation).

An additional analysis determined that there were modest effect sizes related to the efficacy outcomes of .32 and .34 for the higher and lower agitation groups, respectively, at week 4.

Benzodiazepine (lorazepam) Use

Lorazepam use declined in all groups over time (Table 4). At end point, 41.3% of placebo-treated patients and 44.7% of aripiprazole-treated patients in the higher agitation group had used lorazepam (p = not significant [NS]). In the lower agitation group at end point, 40.6% of placebo-treated patients and 47.6% of aripiprazole-treated patients had used lorazepam (p = NS).

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Table 4. Benzodiazepine Use in Patients Treated With Aripiprazole or Placebo in the Higher and Lower Agitation Groups by Week

Group	Week 1	Week 2	Week 3	Week 4
Higher agitation				
Aripiprazole, N/N (%)	179/244 (73.4)	147/246 (59.8)	127/245 (51.8)	110/246 (44.7)
Placebo, N/N (%)	113/143 (79.0)	97/143 (67.8)	70/143 (49.0)	59/143 (41.3)
p Value[a]	.21	.11	.58	.51
Lower agitation				
Aripiprazole, N/N (%)	387/541 (71.5)	345/543 (63.5)	300/544 (55.1)	259/544 (47.6)
Placebo, N/N (%)	177/253 (70.0)	138/254 (54.3)	123/254 (48.4)	103/254 (40.6)
p Value[a]	.65	. 01	.08	.06

[a]Aripiprazole vs. placebo, χ^2 analysis.

Table 5. Incidence of Adverse Events in Aripiprazole Group ≥ 5% and at Twice Rate of Placebo Group in the Higher and Lower Agitation Groups

	Treatment Group	
Adverse Event	Aripiprazole, N = 246	Placebo, N = 144
Higher agitation group, N (%)		
Abdominal pain	15 (6.1)	4 (2.8)
Asthenia	14 (5.7)	2 (1.4)
Infection	14 (5.7)	4 (2.8)
Akathisia	22 (8.9)	6 (4.2)
Somnolence	16 (6.5)	3 (2.1)
Lower agitation group, N (%)	N = 544	N = 254
Light-headedness	64 (11.8)	12 (4.7)

Adverse Events

Adverse events reported for aripiprazole- and placebo-treated patients within the higher and lower agitation groups were generally mild and infrequent (Table 5).

DISCUSSION

The purpose of this post hoc analysis was to assess the efficacy of oral aripiprazole (10–30 mg/day) in patients with acute schizophrenia and higher or lower levels of baseline agitation. Statistically significant differences between aripiprazole-treated and placebo-treated patients were observed in total psychopathology (as assessed by changes in PANSS total scores), overall severity of illness and clinical condition (as assessed by changes in CGI-I scores), and agitation (as assessed by changes in PEC scores). These results suggest that aripiprazole effectively treated the core symptoms of acute schizophrenia, including agitation symptoms, regardless of patients' baseline level of agitation.

Significantly less agitation was associated with aripiprazole compared with placebo in both the higher and lower agitated patients. Specifically, aripiprazole effectively decreased agitation in patients with higher baseline agitation, whereas agitation symptoms did not change in those with relatively lower baseline agitation. These findings appear to contrast a published case example describing increased agitation following adjunctive treatment with aripiprazole in 2 schizophrenia patients with extensive histories of aggressive behavior and psychotic symptoms.[31] It should be noted, however, that the acute patients in the aripiprazole clinical trials were capable of providing informed consent and were not in need of emergency behavioral intervention.

Other studies have examined the efficacy of oral atypical antipsychotic medications in treating agitation symptoms. Post hoc analyses of short-term (4–6 weeks) and long-term (up to 52 weeks) studies have suggested that oral aripiprazole significantly improves the symptoms of excitement and hostility in patients with acute schizophrenia.[32,33] In post hoc analyses of 6-week, double-blind, placebo-controlled studies, quetiapine and olanzapine were associated with reduced agitation among patients experiencing acute schizophrenia.[34,35] Additionally, a recent, open-label, observational study examined patients with acute schizophrenia treated with risperidone and stratified by the severity of agitation on the agitation subscale of the PANSS. In this study, significant improvements in PANSS total, CGI, and Brief Psychiatric Rating Scale scores were more pronounced in the patients with "high" agitation.[36]

Further examination of the post hoc aripiprazole data also showed significantly greater symptom improvement on the PANSS total after adjusting for baseline values in the higher agitation patients compared with the lower agitation patients (–15.1 vs. –10.5, $p < .02$), despite the fact that CGI improvement ratings appeared to be similar for both groups throughout the study. Nevertheless, the higher agitation patients were still more symptomatic than the lower agitation patients at study end point (PANSS mean scores: 90.4 vs. 78.2, $p < .05$). Additional analyses determined that there were modest effect sizes for both the higher and lower agitated groups which supports the clinical significance of the efficacy results. These findings underscore the clinical observation that patients with greater levels of agitation tend to have more severe illness even after a period of symptom improvement. Agitated patients may take longer to achieve a level of symptom improvement that approximates the level achieved by patients with lower levels of agitation.

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This analysis was focused on a pooled population with acute schizophrenia from 4 well-controlled studies involving large numbers of patients. Although prospective analyses may generally be more definitive, pooling data from similarly designed trials, while not ideal, may reveal significant treatment differences that would otherwise be masked due to insufficient statistical power. In addition, these pooled analyses may potentially provide valuable insight into key issues related to the target patient population of agitated patients, which in turn may improve the treatment practice employed in the routine clinical setting. While these patients, based on the baseline criteria, were moderately agitated, they were still required to sign an informed consent. The original intent of this trial was not to measure the effectiveness of aripiprazole in agitated patients, and the trial design prevented the recruitment of patients who were extremely agitated. However, the most stringent criteria available in pivotal trials were used to define high agitation.

Analyses were performed to determine whether the sedating effects of lorazepam may have contributed to the significant reduction in agitation associated with aripiprazole. This seems unlikely given that the percentage of lorazepam use did not differ significantly at study end point between aripiprazole-treated and placebo-treated patients within the higher and lower agitation groups. Therefore, aripiprazole-associated, significant improvements in the symptoms of agitation appear to be independent of potential lorazepam effects. Furthermore, incidence of somnolence was low, implying that treatment effects were also independent of excessive sedation.

CONCLUSION

Results demonstrated that aripiprazole effectively treated patients with acute schizophrenia, regardless of their baseline agitation status. Aripiprazole effects appeared to be specific improvements in psychiatric symptoms, including agitation, and not nonspecific effects attributed to sedation. Results appeared to be independent of benzodiazepine use, and adverse events were generally mild in both the higher and lower agitated patients. These results suggest that oral aripiprazole is an effective and safe treatment option for patients with acute schizophrenia who manifest agitation symptoms.

Drug names: aripiprazole (Abilify), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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