Comparative Assessment of the Incidence and Severity of Tardive Dyskinesia in Patients Receiving Aripiprazole or Haloperidol for the Treatment of Schizophrenia: A Post Hoc Analysis

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Objective: To comparatively assess the incidence of tardive dyskinesia in patients with schizophrenia receiving either aripiprazole or haloperidol.

Method: Data from 2 controlled, long-term trials of subjects meeting DSM-IV criteria for schizophrenia treated with aripiprazole (N = 861, 20–30 mg/day) or haloperidol (N = 433, 5–10 mg/day) were analyzed. The primary outcome measure was the rate of new-onset tardive dyskinesia. The analysis was limited to patients without baseline tardive dyskinesia. There were no significant differences between treatment groups in demographic or disease characteristics. The Abnormal Involuntary Movement Scale (AIMS) and Research Diagnostic Criteria for tardive dyskinesia were used to define the comparative incidence rates of long-term treatment-emergent tardive dyskinesia.

Results: A significantly lower percentage of aripiprazole-treated patients developed new-onset tardive dyskinesia compared with haloperidol-treated patients ($p < .0001$). The annualized rate of treatment-emergent tardive dyskinesia was significantly lower in aripiprazole-treated versus haloperidol-treated patients. In patients without a baseline diagnosis of tardive dyskinesia, aripiprazole significantly improved AIMS scores compared with haloperidol ($p \leq .0001$).

Conclusion: These findings support the potential for a significantly lower risk of tardive dyskinesia with aripiprazole than with haloperidol among patients requiring maintenance antipsychotic treatment.

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Tardive dyskinesia is an often persistent and potentially debilitating movement disorder and is the principal iatrogenic adverse effect of long-term conventional antipsychotic treatment.[1,2] Schizophrenia spectrum disorders appear to be associated with an inherent tendency to develop dyskinetic movements[1,3,4]; however, first-generation antipsychotics appear to exaggerate this tendency and may predispose certain individuals to develop tardive dyskinesia.[5,6] Factors related to antipsychotic use that may increase this risk include higher drug doses, increased treatment length, and increased striatal dopamine D_2 receptor occupancy.[3,7,8] Additional risk factors may include increased age, female gender, the presence of acute and early-onset extrapyramidal symptoms, the use of anticholinergic agents, substance abuse, greater cognitive impairment, higher ratings on negative symptom scales, and diabetes mellitus comorbidity.[4,8–11]

Data from clinical trials suggest that patients receiving treatment with second-generation antipsychotic medications have a lower propensity to develop movement disorders than those receiving treatment with the older, first-generation agents.[10,12–15] Comparative trials have demonstrated that the incidence of tardive dyskinesia is lower with the newer medications; when signs of tardive dyskinesia do occur, they appear to be less pronounced with the newer medications.[16–19] In addition, there is evidence suggesting that certain second-generation antipsy-

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chotics may lead to a significant, persistent reduction of preexisting tardive dyskinesia.[20–22]

Aripiprazole is a second-generation antipsychotic with a mechanism of action distinct from that of other second-generation antipsychotics, which act primarily as mixed dopamine D_2/serotonin 5-HT_{2A} antagonists.[23,24] Aripiprazole has been shown to act as a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors and as an antagonist at serotonin 5-HT_{2A} receptors.[25] The drug's unique pharmacologic profile may protect against the emergence of extrapyramidal symptoms.[26,27] In clinical trials, aripiprazole was associated with a relatively low incidence of acute extrapyramidal symptoms in a range of disorders, including schizophrenia spectrum disorders,[28–32] bipolar I disorder,[33–35] borderline personality disorder,[36] and Alzheimer's disease.[37] This favorable extrapyramidal symptom profile suggests that aripiprazole may share with other atypical antipsychotics a reduced risk of inducing tardive dyskinesia compared with conventional antipsychotics.

This post hoc analysis was designed to assess the incidence rates of treatment-emergent tardive dyskinesia during the long-term administration of aripiprazole or the first-generation antipsychotic haloperidol in patients with schizophrenia.

METHOD

Trial Design

Post hoc analyses were performed on pooled data from the acute and extension phases of 2 double-blind, randomized controlled trials,[30] involving aripiprazole- and haloperidol-treated patients with schizophrenia (defined by DSM-IV criteria) who did not have tardive dyskinesia prior to trial entry and/or at baseline. A total of 1452 patients were enrolled in the 2 studies; 1294 of these patients, 758 men (59%) and 536 women (41%) between 18 and 65 years of age, were randomly assigned to double-blind treatment groups.

Tardive Dyskinesia Diagnosis

The Abnormal Involuntary Movement Scale (AIMS)[38] and the cross-sectional Research Diagnostic Criteria (RDC) for tardive dyskinesia suggested by Schooler and Kane[39] were used to define treatment-emergent tardive dyskinetic syndromes. The AIMS consists of 12 items, of which items 1 through 7 specifically measure involuntary movements on a scale of 0 to 4 (0 = none; 1 = minimal, may be extreme normal; 2 = mild; 3 = moderate; 4 = severe). Those 7 items were used as a basis for the application of the Schooler and Kane[39] research criteria (at least moderate dyskinetic movements in 1 body area or mild dyskinetic movements in 2 body areas). The AIMS total score is the sum of items 1 through 7.

Study Group

Of the 1294 patients (aripiprazole, N = 861; haloperidol, N = 433) in the original study sample, 1290 subjects were included in the safety sample. Of these, 14 subjects (9 treated with aripiprazole and 5 treated with haloperidol) were excluded from the analysis due to missing AIMS ratings. Of the remaining 1276 evaluable subjects, 1177 met criteria for inclusion in the post hoc analyses, including 786 patients receiving aripiprazole and 391 patients receiving haloperidol. Because the primary outcome of interest for this post hoc analysis was the rate of new-onset tardive dyskinesia, the study sample excluded patients with tardive dyskinesia at baseline (N = 99). The absence of tardive dyskinesia at baseline was determined by the AIMS rating at baseline using the Schooler and Kane[39] criteria.

Dosages

During the studies, subjects received either aripiprazole (20–30 mg/day) or haloperidol (5–10 mg/day).

Patients randomly assigned to the aripiprazole treatment group were initiated at 30 mg/day. Those patients randomly assigned to receive haloperidol treatment were to take a 5-mg dose for days 1 to 3 and then a 10-mg dose from day 4 onward. After the first week of treatment, a 1-time dose decrease was allowed if needed for tolerance (to 20 mg/day for aripiprazole patients and 7 mg/day for haloperidol patients).

Comparative Post Hoc Analyses of Treatment-Emergent Tardive Dyskinesia

The numbers and percentages of patients with treatment-emergent tardive dyskinesia for each group were tabulated at each visit and at study end point (last observation carried forward [LOCF]). The annualized incidence of tardive dyskinesia (as a percentage) was calculated according to the following formula[12]: annualized incidence = percent incidence of tardive dyskinesia at the last 2 visits (dyskinesia present at both visits) × 365/mean days of exposure.

The change from baseline to each evaluation point (data not shown) and end point (week 52, LOCF analysis) was determined, along with the change from baseline to the maximum AIMS score. In addition, the overall severity of treatment-emergent tardive dyskinesia was assessed. Severity was defined by the LOCF end point AIMS score on item 8 (global assessment, score range 1–4; 1 = minimal, 2 = mild, 3 = moderate, 4 = severe). A frequency distribution of severity scores was determined for each treatment arm.

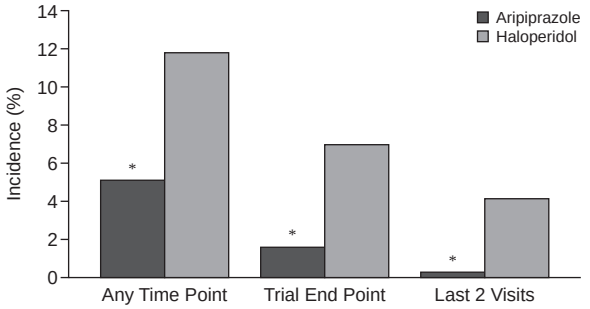
Statistical Analysis

For all analyses, the treatment effect was tested at a 2-tailed significance level of $p \leq .05$. An analysis of variance (ANOVA) was used to evaluate change from

Table 1. Incidence of Treatment-Emergent Tardive Dyskinesia in Patients Without Current or Historical Dyskinesia at Baseline

	Aripiprazole (N = 786)		Haloperidol (N = 391)		
Period	%	N	%	N	p Value
Any time point during 52 wk	5.09	40	11.76	46	< .0001
Trial end point, wk 52	1.53	12	6.91	27	< .0001
Last 2 visits	0.25	2	4.09	16	< .0001
Annualized incidence, %	0.45		9.09		

Figure 1. Incidence of Treatment-Emergent Tardive Dyskinesia in Patients Without Current or Historical Dyskinesia at Baseline



*p < .0001 versus haloperidol.

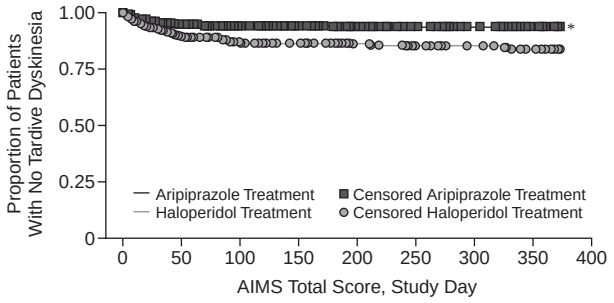
baseline to end point. Change from baseline to end point within each pooled group was evaluated on the basis of the overall integrated database. Time to first onset of RDC-defined tardive dyskinesia was compared between treatment arms using Cox proportional hazards model. Rates of antiparkinsonian medication use were compared between treatment arms using χ^2 analysis.

RESULTS

Incidence of Treatment-Emergent Tardive Dyskinesia

The mean ± SD medication dosages were as follows: haloperidol, 9.12 ± 1.17 mg; aripiprazole, 28.83 ± 2.53 mg. Table 1 summarizes the incidence of treatment-emergent tardive dyskinesia for patients without current or historical dyskinesia at baseline. A significantly lower percentage of aripiprazole-treated patients developed new-onset tardive dyskinesia at any time point during the 52-week trial compared with haloperidol-treated patients (5.09% [40 of 786 patients] vs. 11.76% [46 of 391 patients], respectively; p < .0001). New-onset tardive dyskinesia rates at study end point (week 52) were also significantly lower in aripiprazole-treated patients versus haloperidol-treated patients (1.53% [12 of 786 patients] and 6.91% [27 of 391 patients], respectively; p < .0001). The frequency of tardive dyskinesia at the last 2 visits (dyskinesia present at both visits) was significantly lower

Figure 2. Survival Analysis of Time to First Onset of Tardive Dyskinesia Safety Sample



*p < .0001.
Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

in the aripiprazole-treated patients (0.25% [2 of 786 patients]) versus the haloperidol-treated patients (4.09% [16 of 391 patients], p < .0001) (Figure 1). The annualized incidence of tardive dyskinesia in both treatment groups was calculated as 0.45% for patients treated with aripiprazole and 9.09% for patients treated with haloperidol. Time to first onset of tardive dyskinesia was significantly greater in aripiprazole-treated compared to haloperidol-treated patients (hazard ratio = 0.396, p < .0001, Figure 2). Antiparkinsonian medications were used in 57.54% of haloperidol-treated patients versus 23.16% of aripiprazole-treated patients (p < .0001).

Change From Baseline in Maximum AIMS Score

The change from baseline in the maximum AIMS total score was significantly greater in haloperidol-treated patients compared with aripiprazole-treated patients (1.0 vs. 0.4, respectively; p < .001).

Overall Severity of Treatment-Emergent Tardive Dyskinesia

Each of the 2 aripiprazole-treated patients with dyskinesia present at the last 2 visits experienced mild signs. The haloperidol-treated patients with dyskinesia present at the last 2 visits (N = 16) presented with severity ratings of mild (N = 11), moderate (N = 2), and severe (N = 3).

Change in AIMS Scores (baseline to end point, week 52)

Table 2 summarizes the change in AIMS scores from baseline to trial end point at 52 weeks. In the LOCF analysis (aripiprazole, N = 786; haloperidol, N = 391), the difference (mean ± SD) in AIMS total scores was significantly greater in haloperidol-treated patients (0.64 ± 0.14) compared with aripiprazole-treated patients (0.01 ± 0.09, p = .0001). In the observed cases analysis (aripiprazole, N = 316; haloperidol, N = 111), aripiprazole significantly improved AIMS total scores in aripiprazole-treated pa-

Table 2. Change in Total AIMS Scores (baseline to end point) for Patients With Schizophrenia or Schizoaffective Disorder Without Baseline Tardive Dyskinesia

	Last Observation Carried Forward			Observed Cases		
Variable	Aripiprazole (N = 786)	Haloperidol (N = 391)	p Value	Aripiprazole (N = 316)	Haloperidol (N = 111)	p Value
Score change, mean ± SD	0.01 ± 0.09	0.64 ± 0.14	.0001	–0.32 ± 0.07	0.52 ± 0.12	< .0001

Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

tients (–0.32 ± 0.07) compared with haloperidol-treated patients (0.52 ± 0.12, p < .0001).

DISCUSSION

Motor dysfunction is inherent to schizophrenia spectrum disorders.[40] It is, therefore, important not to confuse drug-induced motor dysfunction with psychiatric symptoms associated with schizophrenia and schizoaffective disorders.[41] Evidence from clinical trials indicates that first-generation antipsychotic medications may induce or aggravate motor dysfunction,[13,15,18,42] while some of the newer, second-generation antipsychotics appear to have a lower propensity to induce motor dysfunction or to improve signs and symptoms associated with preexisting tardive dyskinesia.[16–21,43–45]

Our results demonstrate that, when compared with haloperidol, aripiprazole was significantly less likely to cause treatment-emergent tardive dyskinesia over 52 weeks of treatment in patients who were not experiencing tardive dyskinesia at baseline. The rate of new-onset tardive dyskinesia was significantly lower in aripiprazole-treated patients compared with haloperidol-treated patients. Aripiprazole was also associated with significant improvements in AIMS total scores from baseline to end point compared with haloperidol. The annualized rate of new-onset tardive dyskinesia was found to be 0.45% for aripiprazole and 9.09% for haloperidol. The rate for aripiprazole is similar to the annualized rates reported by Correll and colleagues[12] for risperidone,[46] olanzapine,[47] and quetiapine.[48] The annualized rate of new-onset tardive dyskinesia of 9.09% for haloperidol is somewhat higher than the annualized rates for haloperidol of 5.9% in the report by Rein and L'Héritier,[49] 7.4% by Beasley et al.,[47] and 4.1% by Csernansky et al.[46] It is unclear why the rate was higher because the mean age, gender distribution, duration of illness, and haloperidol mean daily dose in the current study were similar to those in these other studies. The use of antiparkinsonian medications in over half of the haloperidol-treated patients may have induced or exacerbated dyskinetic movements, leading to higher reporting rates. Another possibility is that extrapyramidal symptoms were mistaken for signs of tardive dyskinesia. However, any such bias would be controlled by the randomized double-blind design of the trial. The use of lower doses of haloperidol may have led to reduced rates of treatment-emergent tardive dyskinesia. However, the mean dose of 9.12 mg/day is not excessive and may have even been considered somewhat low at the time of the trial. All of these limitations are inherent to the retrospective, post hoc nature of this study.

In a similar analysis by Tollefson et al.,[19] which compared the incidence of tardive dyskinesia among patients receiving olanzapine with those receiving haloperidol, a significantly lower risk of tardive dyskinesia was observed with olanzapine treatment. At the final 2 AIMS assessments, 1.0% of the patients in the olanzapine treatment group exhibited a new onset of tardive dyskinesia; this compares with 4.6% of the patients in the haloperidol treatment group. The percentage of haloperidol-associated treatment-emergent cases of tardive dyskinesia was 4 times higher than that found in olanzapine-associated treatment-emergent cases of tardive dyskinesia, a difference that was statistically significant.

Among the available antipsychotic medications, aripiprazole has a unique receptor-binding profile and mechanism of action.[50] Clinical trials have consistently demonstrated that aripiprazole treatment is associated with low potential for inducing treatment-emergent movement disorders.[28–37] Although the occurrence of extrapyramidal side effects is less frequent, it is important to note that the risk for developing these problems may still exist in some vulnerable individuals.[51–55] This low incidence of treatment-emergent extrapyramidal symptoms occurs even in the presence of high occupancy of striatal dopamine D_2 receptors.[56]

Sustained D_2 receptor antagonism in the nigrostriatal system may induce functional overactivity and lead to an upregulation of D_2 receptors[57]; this occurs rapidly and universally in response to haloperidol treatment in both animal[58–60] and human models.[61] D_2 upregulation has also been demonstrated in response to olanzapine and risperidone treatment, but not quetiapine treatment, in animal models.[62] However, the emergence of tardive dyskinesia is not directly correlated to an alteration in the functional status (e.g., number and sensitivity) of the D_2 receptor.[63,64] D_2 upregulation may be a necessary but *insufficient* proximal step in a process that may lead to other changes, including excitotoxic and/or oxidative striatal cell death. Genetic and medical risk factors may enhance vulnerability for secondary cell death or influence compensatory/

protective neural processes.[57] A complex cascade of neurochemical changes appears to be required to be manifest as abnormal movements. Aripiprazole treatment does not upregulate rat striatal D_2 receptors following long-term administration, while repeated haloperidol treatment results in marked D_2 receptor upregulation in rat striatum.[65] This may explain the very low incidence of treatment-emergent tardive dyskinesia in the patients treated with aripiprazole compared with those treated with haloperidol.

One of the limitations of this post hoc analysis is the lack of historical data on prior exposure to antipsychotic treatment (lifetime cumulative exposure data). Long-term observational studies are needed to adequately address this important issue.

CONCLUSION

The treatment-emergent tardive dyskinesia rate observed in aripiprazole-treated patients was significantly lower than the rate observed in haloperidol-treated subjects over 52 weeks of treatment. Improvements in motor function, assessed by AIMS, were observed with aripiprazole, but not with haloperidol, in subjects who finished the study and had no baseline tardive dyskinesia.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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