Blind, Controlled, Long-Term Study of the Comparative Incidence of Treatment-Emergent Tardive Dyskinesia With Olanzapine or Haloperidol

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Objective: *Tardive dyskinesia is a serious and common complication of neuroleptic treatment. Olanzapine is a novel antipsychotic agent exhibiting regional mesolimbic dopaminergic selectivity and a broad-based pharmacology encompassing serotonin, dopamine, muscarinic, and adrenergic receptor binding affinities. The authors' goal was to compare the incidence of tardive dyskinesia among patients receiving olanzapine and those receiving the conventional dopamine 2 antagonist haloperidol.* *Method:* *Data were analyzed from three actively controlled and blind long-term responder studies of subjects meeting DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with olanzapine (N=707, up to 20 mg/day, 237 median days of exposure) or haloperidol (N=197, up to 20 mg/day, 203 median days of exposure) who did not have evidence of tardive dyskinesia at baseline. All of the subjects had a chronic disease course (mean greater than 10 years), and there were no significant between-treatment group differences in demographic or disease characteristics. The Abnormal Involuntary Movement Scale and research diagnostic criteria for tardive dyskinesia were used to define the comparative incidence rates of long-term treatment-emergent tardive dyskinesia.* *Results:* *The incidence of newly emergent tardive dyskinesia at any visit after baseline, at the final visit, and at the final two clinical assessments was statistically significantly lower among olanzapine-treated patients than among haloperidol-treated patients.* *Conclusions:* *These findings support an atypical extrapyramidal symptom profile and the potential of a significantly lower risk of tardive dyskinesia with olanzapine than with haloperidol among patients requiring maintenance antipsychotic treatment.*

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Neuroleptic drugs have been the treatment of choice for psychotic disorders. The term "neuroleptic" literally means "taking control of the neuron" (1). However, this control may result in treatment-emergent tardive dyskinesia, which is characterized by involuntary hyperkinetic movements during or shortly after stopping pharmacotherapy, most often with neuroleptic agents. Approximately 25% of patients receiving extended neuroleptic treatment will manifest treatment-emergent tardive dyskinesia associated with varying degrees of social and/or functional impairment (2).

Past cumulative exposure to neuroleptic drugs is directly associated with the risk of developing tardive dyskinesia (3). Across a series of investigations, increasing age (4) and the development of acute extrapyramidal symptoms (5) have also been associated with development of tardive dyskinesia. Thus, the likelihood of experiencing neuroleptic-induced tardive dyskinesia may be positively related to drug dose, treatment duration, and a drug's striatal dopamine 2 (D_2) receptor potency (6).

Olanzapine is a novel antipsychotic agent that has been extensively characterized in preclinical models (7–10). These data illustrate a number of atypical features similar to the prototypical antipsychotic clozapine. Furthermore, several double-blind, controlled clinical investigations have demonstrated an extremely low risk of acute extrapyramidal symptoms with olanzapine, a risk that is comparable to the risk with placebo and significantly less than that with haloperidol (11–13). Therefore, an important research question is how does olanzapine compare with a conventional neuroleptic

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drug in the incidence of treatment-emergent tardive dyskinesia during chronic administration? To answer this question, we conducted several analyses from three double-blind, multicenter, long-term, controlled clinical trials to determine the comparative incidence rates of treatment-emergent tardive dyskinesia in ambulatory, chronically ill, adult schizophrenic subjects randomly assigned to treatment with either olanzapine or haloperidol. We hypothesized that the unique pharmacologic profile of olanzapine would be associated with a lower incidence of treatment-emergent tardive dyskinesia than seen with haloperidol, the conventional standard for neuroleptic drugs.

METHOD

Study Group and Assessments

The incidence of treatment-emergent dyskinetic symptoms in olanzapine-treated and haloperidol-treated patients was collected from three actively controlled, long-term longitudinal studies (11–13) in patients meeting DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. The study protocols were approved by each site's institutional or ethical review board and a signed informed consent was obtained from all eligible patients after procedures and possible side effects were explained to them. The Abnormal Involuntary Movement Scale (AIMS) (14) and the cross-sectional research diagnostic criteria for tardive dyskinesia suggested by Schooler and Kane (15) were used to define treatment-emergent tardive dyskinetic syndromes.

The AIMS consists of 12 items. Items 1 through 7 measure specific involuntary movements (i.e., facial, extremities, and trunk) on a scale from 0 to 4, with higher scores indicative of more severe disorders. The AIMS total score is the sum of items 1 through 7, and items 1 through 7 of the AIMS were the basis for application of the Schooler and Kane research criteria (a score of 3 or greater on any one of the AIMS categorical items 1 through 7 or a score of 2 or greater on any two of the categorical items that were not present at baseline). Of the remaining items on the AIMS, only item 8 (global assessment) was examined.

Data from the three research studies included patients who had responded during acute pharmacotherapy (40% or greater improvement from baseline on the Brief Psychiatric Rating Scale [BPRS] [16] or BPRS extracted from the Positive and Negative Syndrome Scale [17] or a final BPRS score less than 18) and entered the maintenance phase of the study. Only subjects without a historical diagnosis of tardive dyskinesia and without evidence of tardive dyskinesia (15) at entry into these randomized trials were included in the database. The study methodologies have been outlined previously (11–13). During the studies, subjects received either olanzapine (2.5–20 mg/day) or haloperidol (5–20 mg/day). In these three actively controlled studies, AIMS assessments were conducted weekly during the first 6 treatment weeks, biweekly for a short segment of visits, and then monthly (two studies) or every other month (one study).

Data Analyses

Comparisons between olanzapine and haloperidol were based on pooled data from the acute and extension phases of the three actively controlled studies. Data from the placebo group (two of three trials) and the 1.0-mg olanzapine treatment group (present in only one of the three studies) were excluded. This was related to the relatively small number of subjects entering maintenance treatment for either assignment.

SAS (versions 6.07 and 6.08) (18) was used to perform all statistical analyses. For all analyses, the treatment effect was tested at a two-tailed significance level of 0.05. PROC GLM was used for analysis of variance (ANOVA), which was used to evaluate change from baseline to endpoint. Most comparisons between olanzapine-treated and haloperidol-treated patients in mean change from baseline to endpoint score or baseline to maximum score were made by using an ANOVA model containing the terms treatment, protocol, and treatment-by-protocol interaction. The primary inference was based on the ANOVA of the raw data. Secondary efficacy analysis was also conducted by using the ANOVA logarithmic transformation family (19). Change from baseline to endpoint within each pooled group was evaluated on the basis of the overall integrated database. For analysis of proportions, incidence rates were compared between groups by using a two-tailed Fisher's exact test.

A patient was defined as having treatment-emergent tardive dyskinesia if he or she met the Schooler-Kane criteria (15). The numbers and percentages of patients with treatment-emergent tardive dyskinesia symptoms for each group were tabulated at 1) any visit after random assignment, 2) a last study visit (final AIMS assessment), and 3) the final two AIMS assessments. In addition, the distribution of scores on item 8 (scored 1–4) was examined to determine the presence of mild (score 2 or more), moderate (score of 3), and severe (score of 4) treatment-emergent tardive dyskinesia.

RESULTS

The three integrated studies included a total of 904 subjects without historical and/or baseline evidence of tardive dyskinesia who entered long-term maintenance therapy (78.3% of all maintenance-eligible subjects [N=1,155]). Individuals with baseline tardive dyskinesia according to Schooler-Kane criteria and/or a historical diagnosis of dyskinesia or tardive dyskinesia (including presence of symptoms at their baseline) were excluded. At baseline, the demographic and clinical descriptors of the eligible study subjects who received olanzapine or haloperidol were comparable. Haloperidol-treated patients had a longer length of current episode and earlier onset; however, duration of illness was comparable between the two groups.

Table 1 summarizes the baseline characteristics of the patients who were given haloperidol and those who were given olanzapine. On average, all of the patients had received a substantial previous course of conventional antipsychotic medication; however, exact cumulative exposure history was not available. This underscored that the subjects were at a substantial risk at entrance to the study for the emergence of tardive dyskinesia. The median days of exposure to the study drugs was 237 days (range=42–964 days) for the olanzapine-treated patients and 203 days (range=42–540 days) for haloperidol-treated patients. Mean endpoint doses were 14.41 mg/day (SD=10.69) and 14.67 mg/day (SD=12.06), respectively.

The first evaluation was based on change in AIMS total score irrespective of the tardive dyskinesia criterion. The changes from baseline to endpoint and from baseline to maximum in AIMS total score (any visit) for all study subjects in actively controlled studies are summarized in table 2. Mean baseline scores were 0.59 (SD=1.26) for the olanzapine treatment group and 0.66 (SD=1.30) for the haloperidol treatment group. The significant decrease in scores from baseline to endpoint indicated improvement in the olanzapine treatment

TABLE 1. Characteristics of Patients With Schizophrenia Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol

Characteristic	Patients Treated With Olanzapine (N=707)		Patients Treated With Haloperidol (N=197)		Analysis[a]		
	N	%	*N*	%	*p*		
Sex					0.68		
Male	450	63.6	129	65.5			
Female	257	36.4	68	34.5			
Origin					0.83		
Caucasian	594	84.0	164	83.3			
African descent	60	8.5	17	8.6			
East or Southeast Asian	10	1.4	3	1.5			
Western Asian	5	0.7	2	1.0			
Hispanic	25	3.5	5	2.5			
Other origin	13	1.8	6	3.1			
Diagnosis type					0.37		
Schizophrenia	612	86.6	175	88.8			
Schizoaffective	75	10.6	20	10.2			
Schizophreniform	20	2.8	2	1.0			
	Mean	*SD*	*Mean*	*SD*	*F*	*df*	*p*
Age (years)	37.1	11.0	36.4	10.3	0.76	1, 898	0.38
Age at onset of psychosis (years)[b]	24.5	7.8	22.9	6.4	2.35	1, 895	0.13
Duration of illness (years)[b]	12.6	9.6	13.6	9.2	0.05	1, 895	0.82
Length of current episode (days)[c]	470.3	1167.3	873.0	1956.3	1.12	1, 759	0.29

[a]p values for analyses of categorical variables are from a two-tailed Fisher's exact test; p values for analyses of continuous variables are from an ANOVA model containing the terms treatment, protocol, and treatment-by-protocol interaction.
[b]N=705 for olanzapine-treated patients; N=196 for haloperidol-treated patients.
[c]N=603 for olanzapine-treated patients; N=162 for haloperidol-treated patients.

group, but the increased scores in the haloperidol treatment group indicated worsening (table 2). The change from baseline to maximum score at any study visit after random assignment was statistically significantly lower in the olanzapine treatment group than in the haloperidol treatment group (table 2). The change from baseline to endpoint and the change from baseline to maximum score remained statistically significant across a wide range of additive parameters (7.5–20.0) when the analysis was based on the logarithmic transformation.

Among the 904 study subjects eligible for analysis (as defined by the absence of baseline tardive dyskinesia according to the Schooler-Kane criteria), 50 (7.1%) of 707 patients in the olanzapine treatment group and 32 (16.2%) of 197 patients in the haloperidol treatment group manifested research-based criteria of treatment-emergent tardive dyskinesia symptoms at any visit after baseline (table 3). The percentage of haloperidol-treated patients experiencing treatment-emergent tardive dyskinesia symptoms at any visit after baseline was statistically significantly higher than that observed among olanzapine-treated patients (table3).

Sixteen (2.3%) of the patients in the olanzapine treatment group and 15 (7.6%) of the patients in the haloperidol treatment group manifested treatment-emergent tardive dyskinesia at their last study visit. The percentage of haloperidol-treated patients experiencing treatment-emergent tardive dyskinesia symptoms at endpoint was also statistically significantly greater than the percentage of olanzapine-treated patients (table 3).

In the third analysis of treatment-emergent tardive dyskinesia symptoms—at the subject's final two AIMS assessments—seven (1.0%) of the patients in the olanzapine treatment group, compared with nine (4.6%) of the patients in the haloperidol treatment group exhibited a new onset of tardive dyskinesia. The percentage of haloperidol-associated treatment-emergent cases of tardive dyskinesia was four times higher and statistically significantly greater than the olanzapine-associated treatment-emergent cases of tardive dyskinesia (table 3).

Examination of the overall severity of treatment-

TABLE 2. Change in Abnormal Involuntary Movement Scale Total Score for Patients With Schizophrenia Without Current or Historical Dyskinesia at Baseline Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol

	Change in Total Score on Abnormal Involuntary Movement Scale						
	Patients Treated With Olanzapine (N=707)		Patients Treated With Haloperidol (N=197)		Analysis[a]		
Period	Mean	SD	Mean	SD	F	df	p
Baseline to endpoint	–0.13	1.59	0.36	2.04	9.02	1, 898	0.003
Baseline to maximum score (any visit)	0.80	1.93	1.52	2.52	7.92	1, 898	0.005

[a]Test of treatment from an ANOVA model containing the terms treatment, protocol, and treatment-by-protocol interaction.

TABLE 3. Long-Term Treatment-Emergent Dyskinesia in Patients With Schizophrenia Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol

	Patients With Tardive Dyskinesia[a]				
	Patients Treated With Olanzapine (N=707)		Patients Treated With Haloperidol (N=197)		
Time	N	%	N	%	p[b]
Any assessment after baseline	50	7.1	32	16.2	<0.001
Final Abnormal Involuntary Movement Scale (AIMS) assessment	16	2.3	15	7.6	0.001
Final two AIMS assessments	7	1.0	9	4.6	0.003

[a]Tardive dyskinesia was defined according to research diagnostic criteria for tardive dyskinesia (15) as a score of 3 or greater on any one of the AIMS categorical items 1 through 7 or a score of 2 or greater on any two of the categorical items that were not present at baseline. The median exposure to olanzapine was 237 days (range=42–964 days) and the median exposure to haloperidol was 203 days (range=42–540 days).
[b]Two-tailed Fisher's exact test.

emergent tardive dyskinesia based on item 8 of the AIMS showed that when treatment-emergent tardive dyskinesia was present (N=16), it was generally mild (11 patients) or moderate (four patients). The difference between the two treatment groups with respect to severity revealed that one of seven olanzapine-treated patients and four of nine haloperidol-treated patients had a moderate or severe score on item 8.

DISCUSSION

Previous research on tardive dyskinesia has often been limited by cross-sectional or open study designs. Our study design included a prospective, longitudinal, and controlled (haloperidol) comparison to address the potential of a novel antipsychotic (olanzapine) in reducing the incidence of new treatment-emergent tardive dyskinesia in at-risk subjects. In addition, the study used a multi-item rating scale (the AIMS) (14) for the assessment of treatment-emergent tardive dyskinesia, a necessity in good tardive dyskinesia research. With the use of objective research diagnostic criteria for treatment-emergent tardive dyskinesia (15) and their application by experienced clinical investigators, the present observations are likely valid.

The use of two consecutive AIMS ratings to identify a case of treatment-emergent tardive dyskinesia, which introduced a degree of persistence, helped diminish the considerable variability inherent in the course of tardive dyskinesia by reducing the risk of false positive case identification. This conservative definition (last two visits) best approximates the true comparative incidence rates of persistent treatment-emergent tardive dyskinesia. Validating the present study's design and choice of subjects, the use of this definition of treatment-emergent tardive dyskinesia revealed a 4.6% incidence of new cases among haloperidol-treated subjects, a rate remarkably consistent with predicted exposure-adjusted treatment-emergent tardive dyskinesia rates for conventional neuroleptic drugs reported in the literature (20). The annual rate of new cases per year, in similar at-risk patients, has been estimated at approximately 5% in several analyses (3, 21–23). It is not clear whether the incidence of treatment-emergent tardive dyskinesia is linear over a 12-month period, but, if it is, the annualized haloperidol incidence here approaches 8%. Direct comparison with data in previous studies is limited by study group and methodologic differences.

In contrast, the treatment-emergent tardive dyskinesia rate observed among olanzapine-treated subjects (1.0%) was both several times and statistically significantly lower than that seen among haloperidol-treated subjects. The observation that the rate exceeded zero was not surprising. At least two factors may have contributed. As reviewed by Casey (24), both Kraepelin and Bleuler described spontaneous dyskinesias among psychotic individuals. A prevalence of 1%–5% among never-medicated psychotic subjects has been reported (24, 25). Chakos et al. (26) prospectively evaluated 118 patients experiencing their first episode of schizophrenia who had been ill for up to 8.5 years and reported evidence of spontaneous dyskinesia in neuroleptic-naive patients. Second, the present group of patients typically had an extended treatment history with antipsychotic medication before random assignment in the present study. Thus, they entered the trial with an accumulated lifetime risk for tardive dyskinesia exceeding zero.

Exposure to neuroleptic drugs is among the best established pathogenic factors in the development of tardive dyskinesia (3, 6). Several possible explanations may account for the significantly lower incidence of treatment-emergent tardive dyskinesia among olanzapine-treated than haloperidol-treated patients. Lifetime cumulative exposure data were not available. Although nonsignificant, the mean duration of illness was 1 year longer among the haloperidol-treated than the olanzapine-treated subjects (13.6 versus 12.6 years). It is unlikely that this would have materially contributed to the differential incidence rates observed. Subjects were randomly assigned to each drug in a blind manner at baseline. Given that both groups had a very long duration of illness, it is not likely that relative risks between the two groups were biased.

Although no definitive explanation for the underly-

ing pathophysiology of tardive dyskinesia exists, dopamine receptor hypersensitivity has been frequently cited (27). This hypothesis proposes that prolonged neuroleptic-induced antagonism of striatal D_2 receptors induces a functional overactivity (27). However, much of the support rests on preclinical evidence. In contrast, recent positron emission tomography investigations, such as that by Andersson et al. (28), failed to demonstrate a neuroleptic-associated change in D_2 receptor binding density among schizophrenic patients with tardive dyskinesia. An alternative explanation may be a modification of D_2-receptor-mediated response at a related site, e.g., the D_1 receptor. Observations with the atypical antipsychotic clozapine have led to a hypothesis that an imbalance between D_1 and D_2 receptor activity in the basal ganglia may underlie tardive dyskinesia (29). Several studies support a distinctly different $D_{1–4}$ binding profile relative to conventional neuroleptic drugs for both olanzapine and clozapine (7–10, 30–34). Regardless, the existing data suggest at least a secondary or modulatory role for dopamine in the pathophysiology of tardive dyskinesia.

Tardive dyskinesia involves motor irregularities. This likely implicates dopamine A_9 pathways innervating the basal ganglia. In contrast to conventional neuroleptic drugs, chronic administration of olanzapine is not associated with an alteration in dopamine A_9 firing rates (9, 10). A bedrock of the D_2 receptor hypothesis has been the observation that dopamine agonist challenge exaggerates stereotypical behavior. In contrast to haloperidol, olanzapine, in the presence of an amphetamine challenge, is associated with negligible blockade of amphetamine-induced hyperactivity (30). More recently, a model of spontaneous vacuous chewing movements has been proposed as a proxy for tardive dyskinesia. Gao et al. (33) reported that olanzapine, unlike conventional neuroleptic drugs, did not induce vacuous chewing movements. In support of these preclinical data, in vivo human imaging studies have demonstrated lower D_2 striatal receptor occupancy with olanzapine than with haloperidol (34). Each of these observations, consistent with regional dopamine selectivity, may explain the observed study results differentiating the motor profiles of olanzapine and haloperidol.

The above observations should translate into a significantly lower acute and chronic risk of extrapyramidal symptoms in human studies. Data integrated from the acute phase (6 weeks) of two double-blind, placebo-controlled studies (11, 35) in patients meeting DSM-III-R criteria for schizophrenia treated with olanzapine (N=248) (2.5–17.5 mg/day, mean modal maintenance dose of 11.0 mg/day) or placebo (N=118) support such a hypothesis. Evaluation of treatment-emergent extrapyramidal symptoms in the two trials was based on the analysis of scores on the Simpson-Angus Rating Scale (36), the Barnes Akathisia Scale (37), or the AIMS (14). No statistically significant differences between olanzapine and placebo on baseline to endpoint or baseline to maximum change on the Simpson-Angus Rating Scale, Barnes Akathisia Scale, or AIMS ratings were observed except for a statistically significant decrease in the baseline to endpoint Barnes Akathisia Scale score favoring the olanzapine treatment group. Thus, these outcomes, in studies using well-validated scales for drug-induced parkinsonism, akathisia, and dyskinesia, corroborate the preclinical prediction that olanzapine should exhibit a favorable extrapyramidal symptoms profile. Furthermore, the relevance of these differences in acute extrapyramidal symptoms to the present investigation of treatment-emergent tardive dyskinesia relate to the findings of Chouinard et al. (38), who observed that acute and severe extrapyramidal symptoms "appeared to be a precursor of tardive dyskinesia development."

Several nondopaminergic factors also warrant brief consideration. Olanzapine exhibits a polyvalent receptor profile and exhibits high affinity binding at $m_{1–5}$ sites (7). Muscarinic cholinergic receptors modulate Ch_5 and Ch_6 dopaminergic tone (39). Second, although olanzapine is not directly active at glutamatergic binding sites, it blocks *N*-methyl-D-aspartic-acid-antagonist-induced behaviors (40). This mechanism may protect against cytotoxic free radicals routinely generated during catecholamine degradation. The basal ganglia are especially sensitive to such damage, e.g., lipid peroxidation (27). Furthermore, the chronic administration of olanzapine is not associated with an increase in dopamine turnover in striatal A_9 pathways (10). This may bestow a relatively lower risk regarding the level of free radical byproducts generated. Third, consistent evidence for an underlying serotonergic disruption in tardive dyskinesia is lacking (27), but a modulatory effect on dopamine neurons is also plausible. Finally, an increase in dopamine β-hydroxylase activity and CSF norepinephrine concentration support a noradrenergic hypothesis of tardive dyskinesia (27). Both olanzapine and clozapine are active at α_1 adrenoceptors. However, so, too, are a number of the older phenothiazines, diminishing the likelihood of this explanation. In summary, the actual mechanistic explanation for the differences between haloperidol and olanzapine reported in the present study are as hypothetical as our understanding of the basis of tardive dyskinesia itself.

The present study was limited to the neuroleptic haloperidol, but the comparative differences seen here likely will generalize to other conventional D_2 antagonists. Casey (6) has indicated that any one of the conventional D_2 receptor blocking agents is "more or less likely" to cause tardive dyskinesia. The relative advantages of olanzapine reported here approximate the anecdotal experience to date with clozapine, which shares similar pharmacologic properties with olanzapine (7–10). Uncontrolled postmarketing surveillance with clozapine suggests a considerably lower risk of treatment-emergent tardive dyskinesia than seen with conventional neuroleptic drugs (27). This provides some validation for the controlled study results reported here with olanzapine.

If a favorable difference in treatment-emergent tardive dyskinesia for olanzapine or another atypical antipsychotic is confirmed, the clinical impact will be substantial. Although the risk of tardive dyskinesia is likely related to an individual's total cumulative past drug exposure, implying chronicity, several special populations exhibit a tardive dyskinesia risk that "increases rapidly within the first year of total lifetime neuroleptic use" (41). Older patients are such an at-risk population. Saltz et al. (42) reported an incidence of neuroleptic-induced tardive dyskinesia that was six times higher than usual (31% after only 43 weeks of cumulative treatment) in a naturalistic study of 160 subjects over the age of 55 (mean age=77 years). Other groups may include those with affective features, women, individuals with diabetes, and others (6).

The medical, psychological, and social sequelae of tardive dyskinesia are significant drivers highlighting the need for safer antipsychotic treatment options. Olanzapine, with a novel pharmacologic profile, offers a theoretical foundation supportive of a lower treatment-emergent tardive dyskinesia risk. In view of the encouraging present trial results suggesting a lower dyskinetic profile for olanzapine, additional prospective, well-controlled, comparative studies of this drug are awaited.

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