An Integrated Analysis of Acute Treatment-Emergent Extrapyramidal Syndrome in Patients With Schizophrenia During Olanzapine Clinical Trials: Comparisons With Placebo, Haloperidol, Risperidone, or Clozapine

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Background: The frequency and severity of extrapyramidal syndrome (EPS) were evaluated in patients with DSM-III or DSM-IV schizophrenia in the acute phase (≤ 8 weeks) of randomized, double-blind, controlled trials from the integrated olanzapine clinical trial database.

Method: This retrospective analysis included 23 clinical trials and 4611 patients from November 11, 1991, through July 31, 2001. Incidences of dystonic, parkinsonian, and akathisia events were compared using treatment-emergent adverse-event data. Categorical analyses of Simpson-Angus Scale and Barnes Akathisia Scale (BAS) scores, use of anticholinergic medications, and baseline-to-endpoint changes in Simpson-Angus Scale and BAS scores were compared.

Results: A significantly smaller percentage of olanzapine-treated patients experienced dystonic events than did haloperidol- ($p < .001$) or risperidone-treated patients ($p = .047$). A significantly greater percentage of haloperidol-treated patients experienced parkinsonian ($p < .001$) and akathisia ($p < .001$) events than did olanzapine-treated patients. Categorical analysis of Simpson-Angus Scale scores showed significantly more haloperidol- ($p < .001$) or risperidone-treated patients ($p = .004$) developed parkinsonism than did olanzapine-treated patients. Olanzapine-treated patients experienced significantly greater reductions in Simpson-Angus Scale scores than did haloperidol- ($p < .001$), risperidone- ($p < .001$), or clozapine-treated ($p = .032$) patients. Categorical analysis of BAS scores showed significantly more haloperidol-treated patients experienced treatment-emergent akathisia versus olanzapine-treated patients ($p < .001$). Significantly greater reductions in BAS scores were experienced during olanzapine treatment versus placebo ($p = .007$), haloperidol ($p < .001$), and risperidone ($p = .004$) treatments. A significantly smaller percentage of olanzapine-treated patients received anticholinergic medications compared with that of haloperidol- ($p < .001$) or risperidone-treated patients ($p = .018$). Compared with that in olanzapine-treated patients, the duration of anticholinergic cotreatment was significantly longer among haloperidol- ($p < .001$) or risperidone-treated patients ($p = .040$) and significantly shorter among clozapine-treated patients ($p = .021$).

Conclusion: This analysis of available data from olanzapine clinical trials lends additional support to olanzapine's favorable EPS profile.

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Despite their efficacy in reducing symptoms among patients with schizophrenia, some antipsychotic drugs, especially conventional antipsychotics, are associated with significant incidences of extrapyramidal syndrome (EPS) during treatment. Acute EPS generally includes dystonia, parkinsonism, and akathisia. EPS may be further classified depending on the timing and circumstances of the onset of symptoms. Acute EPS usually develops within hours or days after beginning medication or increasing the dose, and acute dystonia may be particularly distressing to patients in an acute psychotic episode or patients inexperienced with antipsychotic therapy. It has been suggested that occurrence of acute EPS, particularly severe acute EPS, may predict future vulnerability to parkinsonism and tardive dyskinesia,[1,2] and patients treated long term with atypical antipsychotics that have a favorable EPS profile may experience less tardive dyskinesia.[2]

Severe EPS may be physically painful and emotionally traumatic to patients with schizophrenia. The severity of EPS can range from mild tremor to life-threatening acute dystonic reactions that may impair breathing or swallowing. The social stigma associated with EPS may hinder social reintegration by limiting personal contacts and reducing employment opportunities. The distressing effects

of acute EPS, particularly acute dystonia, on patients may also lead to a lack of confidence in future therapy and decreased compliance with medication,[3,4] potentially resulting in relapse and poor long-term outcome. In addition, drugs associated with higher rates of EPS often require concomitant use of anticholinergic agents that may be associated with additional side effects or adverse events. The lower rate and severity of EPS observed during treatment with atypical antipsychotics have greatly increased their use as first-line treatments of schizophrenia.

Patients treated with atypical antipsychotics have generally experienced lower levels of EPS compared with those in patients treated with conventional antipsychotics.[5,6] It has been estimated that 50% to 90% of patients taking conventional antipsychotics will experience some form of EPS.[7] In a cross-sectional study of outpatients with schizophrenia who were treated with antipsychotics, the frequency of overall adverse extrapyramidal reactions was 78.3% with haloperidol, 55.1% with risperidone, 39.5% with quetiapine, and 35.8% with olanzapine.[8] The relative frequency of EPS during antipsychotic treatment may depend on different factors, including the means used to assess and report EPS (different rating scales, baseline-to-endpoint changes, maximum scores during therapy, anticholinergic use), the patient population under examination, and the dose of antipsychotic.

The lower rates of EPS during treatment with some atypical antipsychotics may be due to the more selective dopamine blockade in mesolimbic versus nigrostriatal tracts of the brain[9] in contrast to the nonselective dopamine blockade by conventional antipsychotics. In addition, the higher affinity of atypical antipsychotics for serotonin receptors may offer some protection against dopamine antagonist–mediated EPS.[10,11] The relatively low incidence of EPS during olanzapine and clozapine therapies may be mediated by their intrinsic anticholinergic activity at muscarinic receptors.[10–13]

In this retrospective analysis, we examined data from an integrated clinical trial database of randomized, double-blind, controlled trials investigating the use of olanzapine and its comparators for the acute-phase treatment of schizophrenia (≤ 8 weeks). The incidence and severity of EPS occurring during treatment with olanzapine compared with placebo, haloperidol, risperidone, or clozapine were assessed using treatment-emergent adverse-event data and mean baseline-to-endpoint changes in and categorical analyses of objective scale scores evaluating parkinsonism and akathisia. Concomitant use of anticholinergic medication was also considered an indicator of treatment-emergent EPS.

METHOD

Study participants were inpatients or outpatients aged 18 to 65 years who met the DSM-III or DSM-IV criteria for a diagnosis of schizophrenia or related disorders and had provided written informed consent after study designs and possible adverse events were described. Data from the acute phase (≤ 8 weeks) of olanzapine clinical trials from November 11, 1991, through July 31, 2001, (23 clinical trials and 4611 total patients) investigating the treatment of schizophrenia were retrospectively analyzed after subdividing the head-to-head trials into groups by comparator (placebo, haloperidol, risperidone, or clozapine). Assessments of EPS were made between patients treated with individual comparator drugs or placebo and olanzapine-treated patients within the trials that compared the 2 treatments. Treatment-emergent EPS was evaluated using adverse-event data, categorical data derived from the Simpson-Angus Scale[14] and Barnes Akathisia Scale[15] (BAS), mean baseline-to-endpoint changes in Simpson-Angus Scale and BAS total scores, and data on concomitant use of anticholinergic medication.

Antipsychotic Dose

All antipsychotics were administered orally. Dose ranges for olanzapine in placebo or haloperidol comparison trials were 2.5 to 20 mg/day and were 5 to 20 mg/day in risperidone or clozapine comparison trials. Doses of comparator drugs were as follows: haloperidol, 1 to 20 mg/day; risperidone, 4 to 12 mg/day; and clozapine, 25 to 625 mg/day. Patients in the risperidone group were divided into 2 subgroups: patients receiving modal doses of ≤ 6 mg/day and patients receiving modal doses of > 6 mg/day. The 2 subgroups were compared and showed no significant differences in any of the treatment-emergent EPS measures. However, given the relationship between EPS and increasing dose of risperidone,[16,17] only the patients receiving modal doses of ≤ 6 mg/day were included in the comparisons with the olanzapine group. The dose range for the clozapine group was relatively broad; however, the lower doses were administered during the period of dose titration, and more than 80% of the clozapine-treated patients received a modal dose between 100 and 400 mg/day.

Event Category Analysis

Treatment-emergent extrapyramidal adverse events were subdivided into dystonic, parkinsonian, and akathisia events. The event category data were assessed for differences between olanzapine and comparator treatments. The following COSTART terms were used to identify patients with dystonic events: *dystonia*, *oculogyric crisis*, *opisthotonos*, and *torticollis*. The COSTART terms used for identification of parkinsonian events were *akinesia*, *cogwheel rigidity*, *extrapyramidal syndrome*, *hypertonia*, *hypokinesia*, *masked facies*, and *tremor*. Akathisia events were identified using the COSTART terms *akathisia* and *hyperkinesia*.

If a patient exhibited 1 or more extrapyramidal treatment-emergent events that mapped to 1 of the 3 extra-

Table 1. Patient Demographics From Clinical Trials of Olanzapine Versus Placebo (3 trials), Haloperidol (13 trials), Risperidone (6 trials), or Clozapine (4 trials)

	Placebo Comparator		Haloperidol Comparator		Risperidone Comparator		Clozapine Comparator	
Variable	Olanzapine	Placebo	Olanzapine	Haloperidol	Olanzapine	Risperidone	Olanzapine	Clozapine
Total N	388	153	2110	1059	400	279	235	233
Sex, N (%)								
Women	87 (22.4)	35 (22.9)	687 (32.6)	356 (33.6)	127 (31.8)	104 (37.3)	84 (35.7)	94 (40.3)
Men	301 (77.6)	118 (77.1)	1423 (67.4)	703 (66.4)	273 (68.3)	175 (62.7)	151 (64.3)	139 (59.7)
Ethnic origin, N (%)								
White	309 (79.6)	113 (73.9)	1625 (77.0)[a]	758 (71.6)	272 (68.0)	191 (68.5)	188 (80.0)	185 (79.4)
Nonwhite	79 (20.4)	40 (26.1)	485 (23.0)	301 (28.4)	128 (32.0)	88 (31.5)	47 (20.0)	48 (20.6)
Age, mean ± SD, y	37.0 ± 10.2	36.2 ± 8.5	37.9 ± 11.1	37.6 ± 10.6	36.4 ± 10.0	37.8 ± 9.3	36.6 ± 10.6	37.5 ± 10.3

[a]$p < .001$.

pyramidal categories, the patient was counted once in that category. If a patient exhibited events that mapped to more than 1 extrapyramidal category, the patient was counted once in each applicable category. The "any of the above" category consisted of the total number and percentage of patients who exhibited at least 1 extrapyramidal treatment-emergent adverse event (regardless of the category). Even though a patient may have been counted in more than 1 extrapyramidal category, the patient was counted only once in the "any of the above" row.

Categorical Analysis of Simpson-Angus Scale and Barnes Akathisia Scale Scores

The numbers and percentages of patients with a Simpson-Angus Scale baseline score of ≤ 3 whose total score exceeded 3 anytime during treatment were compared.[14] A similar categorical analysis of the BAS data was performed. The numbers and percentages of patients with a BAS baseline score of < 2 whose total score equaled or exceeded 2 anytime during treatment were compared.[15]

Anticholinergic Medication Use

The numbers and percentages of patients administered concomitant anticholinergic medications to treat EPS were compared across therapies. Additionally, among the patients who required anticholinergic medications, the mean number of days of exposure and the mean doses (converted to benztropine equivalents) were compared between treatment groups.

Statistical Analysis

Pairwise, between-group differences in the frequency of patients with treatment-emergent adverse events and categorical increases in parkinsonism and akathisia were compared using a Fisher exact test, and 2-tailed p values were calculated. Mean baseline-to-endpoint changes in Simpson-Angus Scale and BAS scores were evaluated between treatment groups using an analysis-of-covariance (ANCOVA) model that included baseline score as a covariate. All tests of hypothesis were done at a 2-sided 5% level of significance, and Statistical Analysis System (SAS), versions 6.09 and 8, was used to perform all analyses.

RESULTS

Patient Demographics

The number of clinical trials pooled and the number and distribution of randomized patients between treatment groups with respect to sex, ethnic origin, and age are summarized in Table 1. There were no statistically significant differences in the patient populations with respect to sex, ethnic origin, or age between the olanzapine and placebo, risperidone, or clozapine groups. In the haloperidol group, there were no significant differences compared with the olanzapine group with respect to sex or age. The olanzapine treatment group had a significantly greater percentage of white patients in comparison with the haloperidol group ($p < .001$). However, inclusion of ethnic origin (white vs. nonwhite) as an independent variable in the logistic regression model examining categorical treatment-emergent adverse extrapyramidal events in the olanzapine and haloperidol groups revealed no significant differences in the incidence of akathisia, dystonic, parkinsonian, or "any of the above" events (data not shown).

Mean Modal Daily Antipsychotic Dose

The mean modal daily doses (the average of the doses most frequently administered during the observation period) of antipsychotics received by patients that took at least 1 dose of study drug in each treatment group are presented in Table 2.

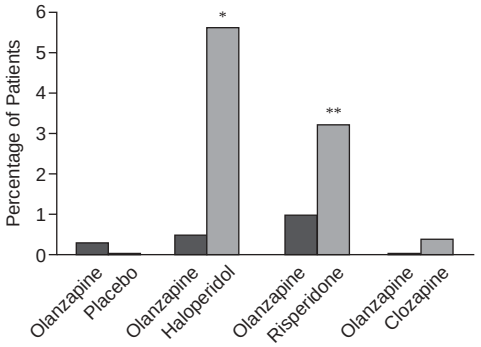
Dystonic Events

There were no significant differences in the percentage of patients experiencing dystonic events during treatment between the olanzapine group and the placebo or clozapine groups (Figure 1). A significantly smaller percentage of olanzapine-treated patients experienced dystonic events during treatment compared with that of haloperidol- (5.6% vs. 0.5%, $p < .001$) or risperidone-treated patients (3.2% vs. 1.0%, $p = .047$).

Table 2. Mean Modal Antipsychotic Dose by Treatment Group in Clinical Trials of Olanzapine

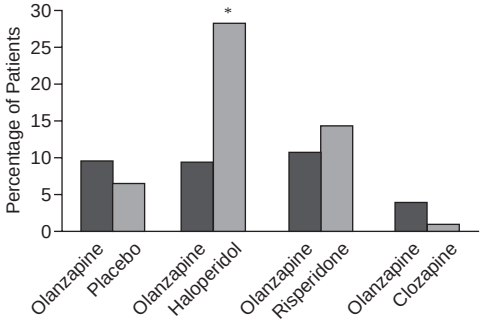
	Placebo Comparator		Haloperidol Comparator		Risperidone Comparator		Clozapine Comparator	
Variable	Olanzapine	Placebo	Olanzapine	Haloperidol	Olanzapine	Risperidone	Olanzapine	Clozapine
N	387	153	2078	1046	400	279	231	225
Modal dose, mean ± SD, mg/day	11.6 ± 5.5	…	12.3 ± 5.5	11.6 ± 5.6	14.8 ± 4.2	4.9 ± 1.2	17.7 ± 5.0	255 ± 106

Figure 1. Treatment-Emergent Dystonic Events for Olanzapine and Comparator Treatment



*p < .001.
**p = .047.

Figure 2. Treatment-Emergent Parkinsonian Events for Olanzapine and Comparator Treatment



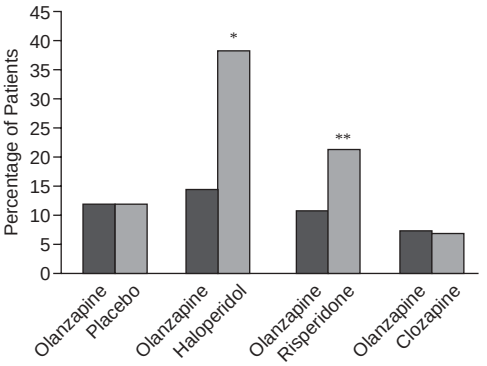
*p < .001.

Parkinsonian Events

Treatment-emergent parkinsonian event analysis. There were no significant differences in the percentage of patients experiencing parkinsonian events during treatment between the olanzapine group and the placebo, risperidone, or clozapine groups (Figure 2). A significantly greater percentage of haloperidol-treated patients experienced parkinsonian events during treatment compared with that of olanzapine-treated patients (28.3% vs. 9.3%, p < .001).

Categorical analysis of Simpson-Angus Scale scores. Compared with patients treated with olanzapine, a significantly greater percentage of patients treated with haloperidol (38.5% vs. 14.5%, p < .001) or risperidone (21.3% vs. 10.9%, p = .004) developed parkinsonism (according to Simpson-Angus Scale total score criteria) at any time during treatment (Figure 3). The percentage of patients treated with placebo (12.0% vs. 11.9%) or clozapine (7.0% vs. 7.5%) who developed parkinsonism was not significantly different than that of patients treated with olanzapine.

Figure 3. Percentage of Patients Taking Olanzapine or Comparator Drug With a Simpson-Angus Scale Total Score of ≤ 3 at Baseline and > 3 Anytime Thereafter



*p < .001.
**p = .004.

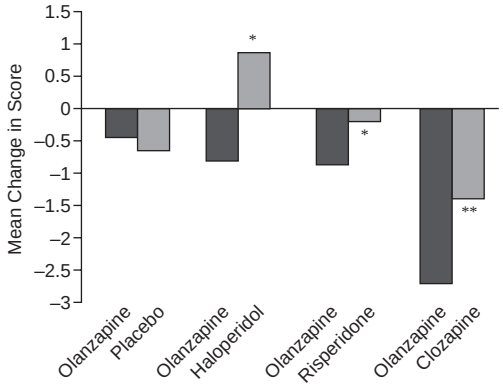
Mean baseline-to-endpoint changes in Simpson-Angus Scale scores. Olanzapine-treated patients had significantly greater reductions in mean Simpson-Angus Scale scores at endpoint than did haloperidol- (p < .001), risperidone- (p < .001), or clozapine-treated patients (p = .032; Figure 4). There were no significant differences in the mean baseline-to-endpoint changes in Simpson-Angus Scale scores among patients treated with olanzapine compared with patients treated with placebo.

Akathisia Events

Treatment-emergent akathisia event analysis. There were no significant differences in the percentage of placebo-, risperidone-, or clozapine-treated patients who experienced akathisia events during therapy compared with that of olanzapine-treated patients (Figure 5). The percentage of haloperidol-treated patients who experienced akathisia during treatment was significantly greater than the percentage of patients experiencing akathisia in the olanzapine-treatment group (20.4% vs. 6.7%, p < .001).

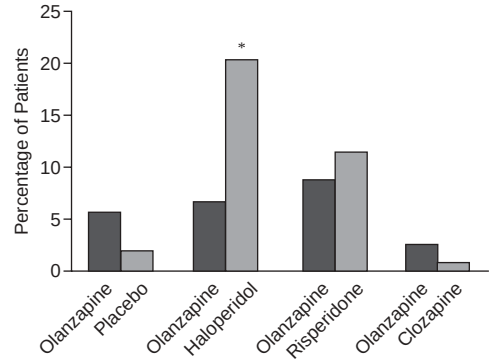
Categorical analysis of akathisia. Categorical analysis of BAS scores demonstrated that a significantly

Figure 4. Mean Change in Baseline-to-Endpoint Simpson-Angus Scale Total Scores for Treatment-Emergent Parkinsonism in Patients Taking Olanzapine or Comparator Drug[a]



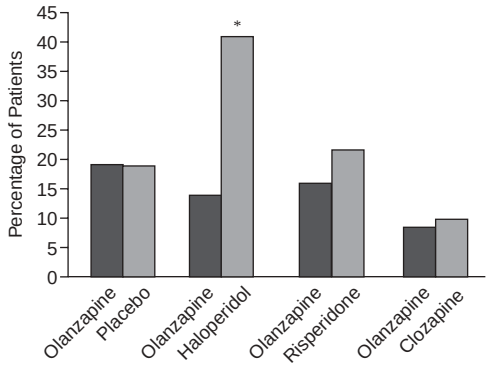
[a]Mean baseline-to-endpoint changes in Simpson-Angus Scale total scores were evaluated among treatment groups using an analysis-of-covariance model that included baseline score as a covariate.
*p < .001.
**p = .032.

Figure 5. Treatment-Emergent Akathisia Events for Olanzapine and Comparator Treatment



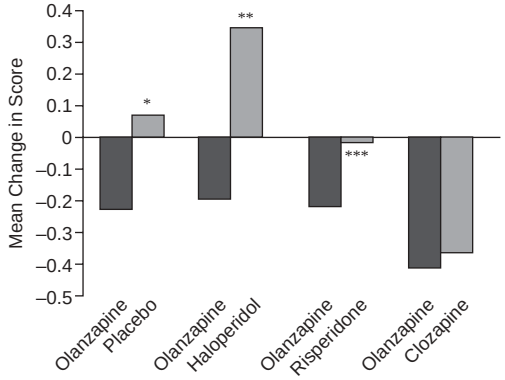
*p < .001.

Figure 6. Percentage of Patients Taking Olanzapine or Comparator Drug With a Barnes Akathisia Scale Total Score of < 2 at Baseline and ≥ 2 Anytime Thereafter



*p < .001.

Figure 7. Mean Changes in Baseline-to-Endpoint Barnes Akathisia Scale Total Scores for Treatment-Emergent Akathisia in Patients Taking Olanzapine or Comparator Drug[a]



[a]Mean baseline-to-endpoint changes in Barnes Akathisia Scale total scores were evaluated among treatment groups using an analysis-of-covariance model that included baseline score as a covariate.
*p = .007.
**p < .001.
***p = .004.

greater percentage of patients treated with haloperidol developed akathisia (according to BAS total score criteria) at any time during treatment compared with that of patients treated with olanzapine (41.0% vs. 13.7%, p < .001; Figure 6). There were no significant differences in the percentage of patients who developed akathisia during treatment with olanzapine versus placebo (19.2% vs. 19.0%), olanzapine versus risperidone (15.8% vs. 21.7%), or olanzapine versus clozapine (8.3% vs. 9.9%).

Mean baseline-to-endpoint changes in Barnes Akathisia Scale scores. At endpoint, patients treated with olanzapine had a significantly greater mean reduction in BAS scores from baseline compared with that of patients treated with placebo (p = .007), haloperidol (p < .001), or risperidone (p = .004; Figure 7). The small, nonsignificant increase in mean ± SD BAS scores (0.08 ± 0.86, p = .325) within the placebo group may have been due to withdrawal akathisia following abrupt discontinuation of previous medications. There were no significant differences in the mean baseline-to-endpoint change in BAS scores between olanzapine- and clozapine-treated patients.

Overall Incidence of Any Extrapyramidal Event

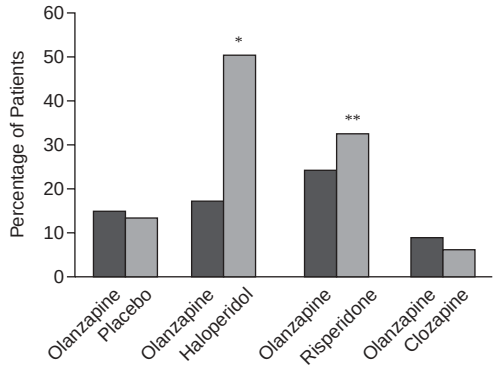
With respect to the overall incidence of any extrapyramidal adverse event, there were no significant differences in the percentage of patients who experienced a treatment-

Table 3. Percentage of Patients Exhibiting at Least 1 Extrapyramidal Treatment-Emergent Adverse Event (regardless of category) With Olanzapine or Comparator Treatment[a]

Clinical Trial	Olanzapine N (%)	Comparator N (%)	p Value
Olanzapine vs.			
Placebo	60 (15.5)	14 (9.2)	.070
Haloperidol	341 (16.2)	470 (44.4)	< .001
Risperidone	76 (19.0)	69 (24.7)	.087
Clozapine	16 (6.8)	6 (2.6)	.047

[a]Even if a patient was counted in more than 1 extrapyramidal event category, the patient was counted only once in this analysis.

Figure 8. Percentage of Patients Using Anticholinergic Medications for Extrapyramidal Syndrome During Treatment With Olanzapine or Comparator Drug



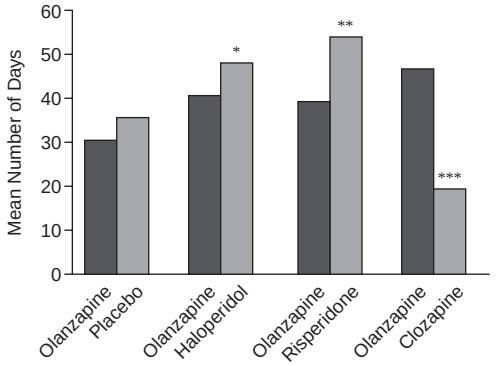
*p < .001.
**p = .018.

emergent EPS event among patients treated with olanzapine compared with those taking placebo (15.5% vs. 9.2%) or among patients treated with olanzapine compared with those taking risperidone (19.0% vs. 24.7%; Table 3). A significantly greater percentage of haloperidol-treated patients had a treatment-emergent EPS event compared with that of patients treated with olanzapine (44.4% vs. 16.2%, p < .001). A significantly lower percentage of patients treated with clozapine experienced a treatment-emergent EPS event than did that of olanzapine-treated patients (2.6% vs. 6.8%, p = .047).

Anticholinergic Medication Use

Another means to determine the occurrence and general severity of treatment-emergent EPS was to assess concomitant anticholinergic therapy at any time during treatment. Comparison of the percentage of patients who were administered at least 1 dose of anticholinergic medication during treatment showed that significantly fewer olanzapine-treated patients were administered anticholinergic drugs than were patients treated with haloperidol (17.0% vs. 50.4%, p < .001) or risperidone (23.7% vs. 32.3%, p = .018; Figure 8). There were no significant differences in the percentage of patients treated with anticholinergic agents among patients treated with olanzapine compared with patients treated with placebo (14.7% vs. 13.1%) or clozapine (8.5% vs. 6.0%).

Figure 9. Mean Number of Days of Anticholinergic Cotreatment During Treatment With Olanzapine or Comparator Drug



*p < .001.
**p = .040.
***p = .021.

There were no significant differences in mean number of days of anticholinergic medication cotreatment between the olanzapine group and the placebo group (Figure 9). The mean number of days of anticholinergic medication cotreatment was significantly greater in haloperidol- (p < .001) or risperidone-treated patients (p = .040) compared with olanzapine-treated patients. The clozapine treatment group was administered anticholinergic medications for significantly fewer days than was the olanzapine treatment group (p = .021).

There were no significant differences in the amount of anticholinergic medication equivalents administered to patients treated with olanzapine compared with patients treated with placebo, risperidone, or clozapine (data not shown). Olanzapine-treated patients were administered significantly less anticholinergic equivalents than were patients treated with haloperidol (mean ± SD dose = olanzapine, 2.50 ± 1.60 mg/day vs. haloperidol, 3.04 ± 1.64 mg/day; p < .001).

DISCUSSION

Early in the era of conventional antipsychotic therapy, EPS was viewed as a necessary part of effectively treating the symptoms of psychosis. This concept had to be reassessed after the introduction of clozapine.[18,19] Clozapine therapy was associated with a markedly lower incidence of treatment-emergent EPS while still having efficacy in treating psychotic symptoms.[19,20] Because of the de-

creased incidence of EPS, lack of effect on prolactin secretion, and increased efficacy at treating negative symptoms compared with conventional antipsychotics, clozapine was termed the first "atypical" antipsychotic.

However, despite early reports that clozapine treatment was devoid of EPS, it has been estimated that up to 20% of patients treated with clozapine experience EPS.[21] One study described higher rates of tremor and bradykinesia among patients treated with clozapine than did earlier reports.[22] Another study reported that after 1 year of clozapine treatment, 33% of patients had parkinsonian symptoms, and 14% and 7% had psychic and motor akathisia symptoms, respectively.[23] Although these studies reported higher rates of parkinsonism and akathisia than did initial trials, they also reported virtually no dystonia in clozapine-treated patients.[22,23] Following the introduction of clozapine to the marketplace were several other "atypical" antipsychotics (olanzapine, risperidone, and quetiapine) that had a more favorable adverse-event profile, particularly with respect to EPS, compared with that of conventional antipsychotics.[16,17,19,20,24–33]

To some degree, all antipsychotic medications bind to or act as antagonists at central nervous system dopamine receptors. Based on positron emission tomography (PET) studies, most antipsychotics occupy approximately 40% to 80% of striatal dopamine receptors at therapeutic doses.[20,32,33] When excessive blockade (greater than 80% receptor occupancy) of striatal dopamine receptors occurs during treatment with antipsychotic agents, control over voluntary and involuntary muscle movements may be compromised, producing EPS in some patients.[32]

The reduced occurrence of EPS during treatment with atypical antipsychotic agents is thought to occur due to their unique receptor-binding profiles. For example, olanzapine's favorable EPS profile may result in part from a greater regionally selective blockade of mesolimbic versus striatal dopamine receptors.[9] In addition, some of the atypical antipsychotics have a greater in vitro affinity for serotonin receptors than for dopamine receptors[10,11] and occupy a greater percentage of serotonin receptors in vivo.[19] Therefore, some degree of protection from dopamine antagonist–mediated EPS may be provided by simultaneous blockade of serotonin receptors. When patients administered dopamine-blocking conventional antipsychotics were concomitantly treated with the 5-HT_2-receptor–selective serotonin antagonist ritanserin, a decrease in EPS was observed.[34] However, the protection from EPS afforded by atypical antipsychotic blockade of serotonin receptors is not absolute. At clinically relevant doses of olanzapine, clozapine, and risperidone, in vivo PET data suggest that while serotonin receptors in the prefrontal cortex are almost completely occupied in all patients,[18] a number of patients still experience some EPS during treatment with atypical antipsychotics, albeit with some variability.

The relatively low incidence of EPS during olanzapine and clozapine therapy may be explained by their intrinsic ability to block muscarinic cholinergic receptors.[10–13] In support of this hypothesis, our data show that a significantly smaller percentage of olanzapine-treated patients were administered concomitant anticholinergic medications to alleviate EPS symptoms compared with that of haloperidol- and risperidone-treated patients. Furthermore, even though more patients treated with haloperidol and risperidone were administered concomitant anticholinergic medications, haloperidol- and risperidone-treated patients also experienced more treatment-emergent dystonic adverse events and parkinsonism (defined by a categorical increase in Simpson-Angus Scale score) than did patients treated with olanzapine.

Results of this analysis should be viewed in the context of other independent head-to-head clinical trials of olanzapine versus other antipsychotics. One small (N = 42), open-label, head-to-head trial of olanzapine and risperidone showed, like this analysis did, that after a mean of 4 weeks of treatment, olanzapine-treated patients had a significantly greater reduction of BAS total scores from baseline. Their study and our analysis also showed a significantly smaller percentage of olanzapine-treated patients required concomitant anticholinergic medications than did risperidone-treated patients.[35] In contrast to our findings, these investigators found no significant differences between olanzapine- and risperidone-treated patients in the mean baseline-to-endpoint changes in Simpson-Angus Scale total scores.[35]

Another head-to-head clinical trial that investigated the use of risperidone and olanzapine for treatment of schizophrenia[36] reported no significant differences in akathisia scores or total scores for parkinsonism and dyskinesia between the olanzapine- and risperidone-treated groups. These investigators also did not detect any differences in Extrapyramidal Symptom Rating Scale (ESRS) total scores. The ESRS total score contains parkinsonism, dyskinesia, and akathisia items[37] and is analogous to the "any of the above" event category analysis in this study. Our analysis of this category failed to show any differences between olanzapine- and risperidone-treated patients. In contrast to this integrated analysis, Conley and Mahmoud[36] reported no significant difference in concomitant use of anticholinergic medication between the olanzapine- and risperidone-treated groups.

In a cross-sectional, nonintervention study of outpatients with schizophrenia, a significantly lower percentage of olanzapine-treated patients experienced akathisia, rigidity, hypokinesia/akinesia, tremor, and an overall incidence of EPS compared with haloperidol- or risperidone-treated patients.[8] Olanzapine-treated patients also experienced significantly less dystonia and hyperkinesia than did haloperidol-treated patients. In addition, a significantly smaller percentage of both olanzapine- and

clozapine-treated patients were administered anticholinergic medications than were haloperidol-treated patients.[8]

A double-blind trial comparing the efficacy of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder and a suboptimal treatment response showed no significant between-group differences in total ESRS score, dyskinesia, or akathisia.[38] However, a significantly smaller percentage of both olanzapine- and clozapine-treated patients were administered anticholinergic medications than were risperidone-treated patients.

The limitations of the current study include the retrospective nature of the analysis. Data from multiple trials designed to determine the efficacy of olanzapine versus placebo or active comparators in treating psychotic symptoms of schizophrenia as the primary outcome were pooled and divided by individual comparator. The database was then retrospectively analyzed for between-group differences in EPS (a secondary outcome). In addition, the patient populations in these trials were mainly composed of males with a long course of illness (more than 10 years) and years of prior antipsychotic therapy. Therefore, the incidence of dystonia reported here might be lower than expected because dystonia occurs more frequently in young males treated with antipsychotics.[39]

This analysis of data available from olanzapine clinical trials lends additional support to olanzapine's favorable EPS profile, particularly in comparison with the conventional antipsychotic haloperidol. Treatment with an antipsychotic possessing a favorable EPS profile may be advantageous for several reasons. Keepers and Casey[40] have shown that a relatively low incidence of EPS during the first 5 years of antipsychotic treatment was associated with a reduced liability for future EPS. It has also been proposed that the reduced acute EPS burden associated with atypical antipsychotics will potentially result in a lower long-term risk for tardive dyskinesia.[2] However, long-term studies are required before a definitive conclusion can be reached about the relationship between acute EPS and long-term development of tardive dyskinesia. In addition, an antipsychotic with a favorable EPS profile will require fewer anticholinergic agents, thus decreasing the amount of concomitant medications and consequently reducing the potential for additional adverse events and drug-drug interactions.

Acute EPS, especially acute dystonia, may hinder patients' commitment to future drug therapy and may contribute to noncompliance. Social interactions and social reintegration may also be enhanced in patients who lack embarrassing and disturbing EPS side effects. Therefore, an atypical antipsychotic with a relatively low EPS adverse-event profile, such as olanzapine, may not only reduce psychotic symptoms but also potentially provide long-term benefits through increased treatment compliance and social integration.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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