Extrapyramidal Symptoms and Tolerability of Olanzapine Versus Haloperidol in the Acute Treatment of Schizophrenia

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Background: A relative lack of extrapyramidal symptoms (EPS, i.e., the syndromes of dystonia, parkinsonism, akathisia, dyskinesia) is one criterion used to determine whether an antipsychotic is "atypical." The extrapyramidal symptom profiles of the novel antipsychotic olanzapine and the conventional antipsychotic haloperidol were compared in a population of 2606 patients from three well-controlled prospective clinical trials.

Method: Extrapyramidal symptom data were analyzed for 1796 patients treated with olanzapine (5 to 20 mg/day) and 810 patients treated with haloperidol (5 to 20 mg/day) for up to 6 weeks of therapy. Patients were monitored weekly by three methods of extrapyramidal symptom assessment: (1) detection of extrapyramidal adverse events (signs and symptoms) by casual observation, nonprobing inquiry, and spontaneous report; (2) objective rating scale scores; and (3) use of concomitant anticholinergic medications. Emergence of EPS was assessed by (1) analysis of the incidence of extrapyramidal syndrome categories based on adverse events, (2) the incidence of extrapyramidal syndromes based on categorical analysis of rating scale scores, (3) analysis of mean maximum change in rating scale scores, and (4) categorical analysis of anticholinergic medication use. Outcome of EPS was assessed by (1) analysis of mean change in rating scale scores at endpoint and (2) mean anticholinergic use at endpoint.

Results: Olanzapine was statistically significantly ($p = .014$, $p < .001$) superior to haloperidol in all four analyses related to emergence of EPS and in the two analyses related to outcome. Furthermore, during acute treatment, statistically significantly fewer patients treated with olanzapine (0.3%) discontinued the study because of any extrapyramidal adverse event than patients treated with haloperidol (2.7%, $p < .001$).

Conclusion: Olanzapine exhibited a statistically significantly lower extrapyramidal symptom profile than the conventional antipsychotic haloperidol at comparably effective antipsychotic doses. The lower extrapyramidal symptom profile with olanzapine was evident despite statistically significantly more frequent use of anticholinergic drugs among haloperidol-treated patients. Fewer olanzapine-treated than haloperidol-treated patients discontinued because of EPS, suggesting that olanzapine should contribute to better compliance with longer term maintenance treatment, with minimal anticholinergic-associated events.
(J Clin Psychiatry 1997;58:205–211)

Conventional antipsychotic agents such as haloperidol have been used widely to treat schizophrenia and other psychotic disorders for the last several decades. These agents principally target the dopamine D_2 receptor with little selectivity between mesolimbic (A10) and striatal (A9) pathways.[1] Consequently, antipsychotic efficacy is often accompanied by undesirable neurologic side effects such as extrapyramidal symptoms (EPS; i.e., the syndromes of dystonia, parkinsonism, akathisia, dyskinesia), which complicate the clinician's ability to treat the disorder. EPS contribute to drug intolerance and poor compliance, increasing the probability of relapse.[2–4] More persistent forms of EPS may also compromise patients' well-being, self-image, and social life. In addition, antipsychotic-induced acute EPS reportedly increase the risk of later emerging tardive dyskinesia.[5,6]

The criteria for an "atypical" antipsychotic include a lower incidence of EPS than observed with conventional antipsychotic agents. The reported incidence of EPS associated with conventional antipsychotics has been around 40%.[7,8] Clozapine was the first agent to demonstrate that antipsychotic effects could be disassociated from EPS.[9] Patients treated with clozapine rarely experienced dystonia, rigidity, or other events suggestive of EPS.[10,11] However, use of clozapine is limited by its potential to induce agranulocytosis. There are continuing efforts to find other novel antipsychotic agents that are efficacious and have a low extrapyramidal symptom liability like clozapine but with a superior safety margin.

Olanzapine is a new "atypical" antipsychotic agent of the thienobenzodiazepine class that is structurally related

to clozapine.[12] In vitro receptor binding studies have shown that olanzapine has high affinity for dopamine (D_4, D_3, D_1, D_2), serotonin (5-HT$_{2A/2C}$, 5-HT$_3$, 5-HT$_6$), muscarinic (particularly m_1), histamine H_1, and α_1-adrenergic receptors.[12] Olanzapine has a greater affinity for serotonin 5-HT$_{2A/2C}$ than dopamine D_1/D_2 receptors by a ratio of approximately 3:1[12]; it also has greater affinity for D_4 than D_2 receptors.[13]

In vivo behavioral studies have shown that the dose of olanzapine required to induce catalepsy substantially exceeds the doses required to inhibit conditioned avoidance in mice.[12,14,15] Electrophysiologic studies have shown that olanzapine decreases the number of spontaneously active A10, but not A9, dopamine neurons, suggesting mesolimbic specificity.[16]

In cebus monkeys previously sensitized to haloperidol, the dose of olanzapine necessary to induce EPS was much higher (10 times) than the clinical dose in humans (Casey DE. Oral personal communication, March 1996).

In vivo human neuroimaging corroborated this preclinical profile. In a positron emission tomography (PET) study[17] of a single oral dose (10 mg) in healthy volunteers, olanzapine was shown to produce a higher 5-HT$_{2A}$ than dopamine D_2 receptor occupancy. The percentage of radiolabel displaced from striatal D_2 binding sites (61%) was less than the threshold previously associated with EPS by this research group.[17] In addition, a single photon emission tomography (SPET) imaging study in schizophrenic patients showed that striatal D_2 occupancy was lower in olanzapine-responsive patients than in typical antipsychotic- and risperidone-responsive patients, while being comparable to that in clozapine-responsive patients.[18]

A phase 1 open-label study[19] of olanzapine with a flexible dose regimen starting with either 5 or 10 mg/day in 10 inpatients showed that after 4 weeks of treatment, patients experienced a decrease from baseline to endpoint in Simpson-Angus Scale,[20] Barnes Akathisia Scale,[21] and Abnormal Involuntary Movement Scale[22] scores. The median change in scores was –2, –1, and –2, respectively.[19] Results from a pilot study in patients with Parkinson's disease complicated by dopaminomimetic psychosis demonstrated that olanzapine was efficacious in controlling psychotic symptoms with little or no detrimental effect on motor symptoms.[23]

Experience in placebo-controlled clinical trials has shown further that the magnitude of EPS after acute treatment with olanzapine, as measured by formal rating scales such as the Simpson-Angus Scale and the Barnes Akathisia Scale, is comparable to the magnitude with placebo.[24,25] When olanzapine was compared with haloperidol, patients treated with olanzapine had improvement in Simpson-Angus and Barnes Akathisia Scale scores with respect to baseline while those treated with haloperidol had worsening in such scores.[24]

From the preclinical and the clinical findings it was hypothesized that olanzapine would have lower propensity to produce EPS than the commonly prescribed antipsychotic haloperidol. To test this premise, the incidence and severity of EPS were evaluated in a combined database from three large haloperidol-controlled acute clinical trials, representing a total sample of 2606 patients.

METHOD

Clinical Studies

Data were analyzed from three multicenter, double-blind, randomized trials comparing dosage ranges of olanzapine and haloperidol. In these studies, 1796 patients were treated with olanzapine and 810 patients were treated with haloperidol. All patients participating in the trials gave their informed consent after the procedures and possible side effects were fully explained.

Two of the trials were of similar design. One[24] was conducted in North America, and the other[26] was conducted in Europe, Australia, Israel, and South Africa. After a washout period of 4 to 7 days, both trials enrolled schizophrenic inpatients who were in acute exacerbation of their illness according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R)[27] and who had a minimum Brief Psychiatric Rating Scale (BPRS)[28] total score of at least 24 (items scored 0 to 6). The two trials compared three fixed-dose ranges of olanzapine (5.0 ± 2.5 mg/day, 10.0 ± 2.5 mg/day, 15.0 ± 2.5 mg/day) with one fixed-dose range of haloperidol (15.0 ± 5.0 mg/day). The North American trial also employed a placebo group, whereas the international trial substituted a fixed subtherapeutic dose (olanzapine 1.0 mg/day) group. Patients treated with olanzapine started with either 5.0, 10.0, or 15.0 mg/day of olanzapine, and patients treated with haloperidol started with 15.0 mg/day of haloperidol. Patients were treated for 6 weeks. Patients were allowed to receive anticholinergic medication for treatment-emergent EPS. Prophylactic use was discouraged but not proscribed. In the North American trial, patients could receive benztropine mesylate in doses up to 6 mg/day, and in the international trial, patients could receive biperiden up to 6 mg/day.

The third trial[29] was conducted in 17 countries under a single protocol. After a washout period of 2 to 9 days, inpatients or outpatients with DSM-III-R diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder were randomly assigned to one of two treatment groups for 6 weeks of acute therapy with olanzapine or haloperidol. The trial compared an identical dose range of olanzapine and haloperidol (5.0, 10.0, 15.0, or 20.0 mg/day). To be eligible for enrollment, most patients were required to have a minimum BPRS total score of at least 18 (items scored 0 to 6). Patients

who were intolerant to conventional antipsychotic treatment (excluding haloperidol) could be enrolled into the trial without having to meet the minimum BPRS total score requirement. Patients were randomly assigned in a 2:1 ratio of olanzapine to haloperidol and started with 5 mg of either study drug. Patients could receive benztropine mesylate or biperiden up to 6 mg/day to treat EPS and could continue the treatment after EPS resolved. Prophylactic use of these anticholinergics, however, was discouraged.

Assessments

In each trial, EPS were assessed weekly by three methods. First, extrapyramidal adverse events (signs and symptoms) detected by casual observation, nonprobing inquiry, and spontaneous report were collected. The adverse events were then mapped, classified, and recorded using a system based on the U.S. Food and Drug Administration *Coding Symbol and Thesaurus for Adverse Reaction Terms* (COSTART).[30] COSTART terms suggestive of EPS were assigned to one of the following five categories: dystonic events (dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis); parkinsonian events (akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor); akathisia events (akathisia, hyperkinesia); dyskinetic events (buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia); and residual events (movement disorder, myoclonus, twitching). Second, two objective, quantitative scales—the Simpson-Angus Scale for parkinsonism and the Barnes Akathisia Scale for akathisia—were used to assess EPS. Third, anticholinergic medication use was recorded.

To assess emergence of EPS, four analyses of data were carried out:

1. Incidence of extrapyramidal syndrome categories based on adverse events
2. Incidence of extrapyramidal syndromes based on categorical analysis of rating scale scores. The percentages of patients who experienced treatment-emergent parkinsonism and akathisia at any time using criteria based on Simpson-Angus Scale and Barnes Akathisia Scale scores were evaluated. Only patients with Simpson-Angus Scale and Barnes Akathisia Scale scores normal at baseline were included in these analyses.
3. Analysis of mean maximum change in rating scale scores
4. Categorical analysis of anticholinergic medication use

To assess outcome, two analyses of data were carried out:

1. Analysis of mean change in rating scale scores at endpoint (last observation carried forward; LOCF)
2. Analysis of mean anticholinergic use at endpoint

Table 1. Patient Characteristics

Characteristic	Olanzapine (N = 1796)	Haloperidol (N = 810)	Total (N = 2606)	p Value
Sex (%)				.628
Male	67.3	66.3	67.0	
Female	32.7	33.7	33.0	
Origin (%)				.556
Caucasian	80.7	77.7	79.7	
African descent	10.8	12.5	11.3	
East/South East Asian[a]	1.3	1.7	1.5	
Western Asian[b]	0.9	1.0	0.9	
Hispanic	3.7	4.7	4.0	
Other origin	2.6	2.5	2.5	
Age, mean ± SD y	38.0 ± 11.4	37.8 ± 10.9	38.0 ± 11.2	.667

[a]Examples include Burmese, Chinese, Japanese, Korean, Mongolian, Vietnamese.
[b]Examples include Pakistani, Indian subcontinent.

Statistical Methods

All statistical analyses were based on the intent-to-treat population, meaning all patients were included in the treatment groups to which they were randomly assigned, even if the patient did not strictly adhere to the protocol. All endpoint analyses used a last-observation-carried-forward algorithm; the last available visit served as endpoint. For analyses of change from baseline to endpoint, only patients with a baseline and at least one postbaseline visit were included. Treatment effects were tested at a two-sided significance level of .05. Statistical Analysis Software (SAS; version 6.07) was used to perform all statistical analyses.[31]

Treatment differences between olanzapine and haloperidol for demographic variables and reasons for study discontinuation were evaluated using the Pearson chi-square test. For the analyses of all other proportions (proportions of patients experiencing treatment-emergent extrapyramidal adverse events, proportions of patients meeting Simpson-Angus and Barnes Akathisia Scale criteria, and proportions of patients taking anticholinergic medication), incidence rates were compared between treatments by a two-sided Fisher's exact test.

The treatment effect between olanzapine and haloperidol for continuous data was assessed using an analysis-of-variance (ANOVA) model including the terms for treatment, study, and treatment-by-study interaction. The treatment effect on change from baseline to endpoint and on change from baseline to maximum for the Simpson-Angus Scale total score and the Barnes Akathisia global score, as well as the treatment effect on average daily anticholinergic use, was assessed using this ANOVA model.

RESULTS

Patient Characteristics

Characteristics of the patient population are summarized in Table 1. The treatment groups were comparable at

Table 2. Patient Disposition

Reason for Discontinuation	Olanzapine (N = 1796) %	Haloperidol (N = 810) %	Total (N = 2606) %	p Value
Completed	62.9	47.2	58.0	< .001
Satisfactory response	0.4	0.0	0.3	.075
Adverse event	5.5	8.1	6.3	.009
Lack of efficacy	21.0	30.5	24.0	< .001
Lost to follow-up	1.4	2.2	1.7	.124
Patient decision	4.9	7.7	5.8	.005
Criteria not met/ noncompliance	3.6	4.1	3.8	.572
Sponsor decision	0.2	0.2	0.2	.905

Table 3. Extrapyramidal Adverse Events Reported as Reason for Discontinuation

Event	Olanzapine (N = 1796) %	Haloperidol (N = 810) %	p Value
Hypertonia	0.1	0.2	.413
Akathisia	0.1	1.4	< .001
Dystonia	0.1	0.1	.563
Tremor	0.1	0.2	.183
Extrapyramidal syndrome	0.0	0.7	< .001
Any extrapyramidal event	0.3	2.7	< .001

Table 4. Treatment-Emergent Extrapyramidal Adverse Events Listed by Category of Event

Extrapyramidal Syndrome Category	Olanzapine (N = 1796) %	Haloperidol (N = 810) %	Fisher's Exact p Value
Dystonic[a]	1.4	6.3	< .001
Parkinsonian[b]	9.4	28.4	< .001
Akathisia[c]	7.0	21.5	< .001
Dyskinetic[d]	1.7	3.3	.014
Residual[e]	1.6	2.6	.086
Any extrapyramidal event	18.0	46.5	< .001

[a]Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[b]Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[c]Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
[d]Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[e]Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

baseline with respect to age, racial origin, and gender. Most patients were in their 30s (mean ± standard deviation [SD] = 38.0 ± 11.2 years), had a history of chronic schizophrenia, and had received antipsychotic treatment previously. Patients in the olanzapine-treated group had experienced the first acute episode of schizophrenia at a mean ± SD age of 24.0 ± 7.7 years with a mean ± SD duration of illness of 14.0 ± 10.2 years. Patients in the haloperidol-treated group had experienced the first acute episode of schizophrenia at a mean ± SD age of 23.2 ± 6.7 years with a mean ± SD duration of illness of 14.6 ± 9.9 years. The patient population studied included inpatients or outpatients; most had experienced a recent exacerbation of their psychosis and/or had been judged intolerant to their antipsychotic. Across all three trials, the mean modal maintenance dose of olanzapine was 12.8 ± 5.5 mg/day, and the mean modal maintenance dose of haloperidol was 12.7 ± 5.7 mg/day.

Patient Disposition

The reasons for discontinuation from the trials are listed in Table 2. The overall discontinuation rate was 37.1% for olanzapine-treated patients and 52.8% for haloperidol-treated patients, a statistically significant difference favoring olanzapine (p < .001). The percentage of olanzapine-treated patients (5.5%) who discontinued from the studies because of an adverse event was significantly lower than the percentage of haloperidol-treated patients (8.1%) who discontinued (p = .009). Furthermore, the percentage of patients who discontinued because of any extrapyramidal event (Table 3) was significantly lower with olanzapine (0.3%) than with haloperidol (2.7%; p < .001).

Incidence of Treatment-Emergent Extrapyramidal Symptoms

Treatment-emergent extrapyramidal adverse events. The percentages of patients who experienced treatment-emergent EPS, detected by casual observation, non-probing inquiry, and spontaneous report and recorded as adverse events in the olanzapine and the haloperidol groups are shown by syndrome category in Table 4. For this analysis, patients who reported extrapyramidal adverse events were tabulated in the following manner. If a patient experienced one or more extrapyramidal adverse events that mapped to one of these five categories, the patient was counted once in that category. If a patient experienced an extrapyramidal adverse event that mapped to more than one category, the patient was counted once in each applicable category. Since some patients could be counted more than once with this tabulation system, an additional category ("any extrapyramidal event") showing the percentage of patients who experienced at least one extrapyramidal adverse event (thus counted only once) was also provided.

Overall, the olanzapine group had a significantly lower incidence of any extrapyramidal event than the haloperidol group (46.5% haloperidol, 18.0% olanzapine; p < .001). The olanzapine group also had a statistically significantly lower incidence of dystonic events (p < .001), parkinsonian events (p < .001), akathisia events (p < .001), and dyskinetic events (p = .014) than the haloperidol group.

Categorical analysis of Simpson-Angus Scale. Evaluation of the percentages of patients who experienced a

Simpson-Angus Scale total score of > 3 at any post-baseline visit among patients with a baseline total score of ≤ 3, a criterion used to identify treatment-emergent parkinsonism,[20] showed that a significantly lower percentage of olanzapine-treated patients (14.3%) than haloperidol-treated patients (39.8%) experienced emergent parkinsonism (p < .001).

Analysis of mean maximum change in Simpson-Angus Scale. An increase in mean $\pm$ SD score from baseline to maximum score was observed in both groups, but the increase was less in the olanzapine group (0.59 $\pm$ 2.78, N = 1723) than in the haloperidol group (3.04 $\pm$ 5.03, N = 772), a significant difference (p < .001).

Categorical analysis of Barnes Akathisia Scale. Evaluation of the percentages of patients who experienced a global Barnes Akathisia Scale score of ≥ 2 at any postbaseline visit among patients with a baseline global score of < 2, a criterion used to identify treatment-emergent akathisia,[21] showed that a significantly lower percentage of olanzapine-treated patients (13.0%) than haloperidol-treated patients (40.2%) experienced emergent akathisia (p < .001).

Analysis of mean maximum change in Barnes Akathisia Scale. An increase in mean $\pm$ SD score from baseline to maximum score was observed in both groups, but the increase was less with olanzapine (0.22 $\pm$ 0.85, N = 1753) than with haloperidol (0.92 $\pm$ 1.26, N = 784), a statistically significant difference (p < .001).

Categorical analysis of anticholinergic medication use. Different anticholinergic medications were used to treat EPS in the three studies. All doses of anticholinergic medication were converted to benztropine equivalents through accepted conversion factors (Appendix 1). The percentage of patients taking any anticholinergic medication was significantly lower in the olanzapine group (15.5%) than in the haloperidol group (47.0%; p < .001).

Extrapyramidal Symptom Outcome Assessment

Analysis of mean change in Simpson-Angus Scale. Baseline mean $\pm$ SD scores on the Simpson-Angus Scale were 2.48 $\pm$ 3.93 for the olanzapine group and 2.83 $\pm$ 4.25 for the haloperidol group. A decrease in mean $\pm$ SD score from baseline to endpoint was observed in the olanzapine group (–0.86 $\pm$ 3.37, N = 1723) compared with an increase in the haloperidol group (1.08 $\pm$ 5.09, N = 772), a significant difference (p < .001) favoring olanzapine.

Analysis of mean change in Barnes Akathisia Scale. Baseline mean $\pm$ SD scores on the Barnes Akathisia Scale were 0.54 $\pm$ 0.89 for the olanzapine group and 0.59 $\pm$ 0.93 for the haloperidol group. A decrease in mean $\pm$ SD score from baseline to endpoint was observed in the olanzapine group (–0.19 $\pm$ 0.88, N = 1753) compared with an increase in the haloperidol group (0.39 $\pm$ 1.28, N = 784), a significant difference (p < .001).

Analysis of mean anticholinergic medication use. The mean daily use of anticholinergic medication was significantly greater in the haloperidol group (1.45 $\pm$ 2.59 mg/day, N = 810) than in the olanzapine group (0.31 $\pm$ 1.12 mg/day, N = 1796; p < .001).

DISCUSSION

The extensive database used for the analyses of EPS presented here, with data from 2606 patients from three well-controlled prospective clinical trials, provides substantial power to detect a potential difference in the extrapyramidal symptom profiles of olanzapine and haloperidol in inferential statistical analyses. Further, the integration of multiple assessment methods and analyses of both the emergence of extrapyramidal syndromes, as clinically recognized entities, and their outcome provides a means for validating the extrapyramidal symptom profile of olanzapine versus the profile of haloperidol statistically and clinically. In the studies, the detection of extrapyramidal adverse events by casual observation, nonprobing inquiry, and spontaneous report permitted assessment of physician's judgment and patients' subjective perception of extrapyramidal symptom–related experiences. The use of formal rating scales, the Simpson-Angus Scale and the Barnes Akathisia Scale, which require trained clinicians to classify EPS through predefined operational criteria, provided an objective, rigorous clinical evaluation of EPS. The assessment of concomitant anticholinergic medication use gave perspective on the incidence of troublesome EPS requiring countertherapy. These three assessment methods and six analyses, based on these assessment methods, along with the large sample size provide a comprehensive view of the emergence and outcome of EPS.

In considering the results of the analyses of extrapyramidal symptom data, it should be noted that the dosage ranges of haloperidol used in these trials were consistent with the optimal range as recommended in recent investigations.[32,33] Further, it should be noted that the use of dosage ranges rather than fixed doses in each of the three trials permitted flexibility to optimize the dose based on individual patient needs. Accordingly, the results should be generalizable to the larger clinical setting.

From these assessments, olanzapine was consistently observed to exhibit a markedly lower incidence of EPS than haloperidol across each of the extrapyramidal symptom dimensions. The difference in incidence of EPS was evident despite the fact that haloperidol-treated patients had received significantly more anticholinergic therapy than olanzapine-treated patients. To some extent, the greater tendency to employ an anticholinergic among haloperidol-treated patients may have lowered the true effect-size difference. This finding, enhanced by the large number of patients studied, provides support for the

hypothesis that therapeutically effective doses of olanzapine are associated with significantly less frequent and less severe emergent EPS than comparable doses of haloperidol.[24]

Additionally, the actual decrease over the course of treatment (baseline to endpoint) in Simpson-Angus and Barnes Akathisia Scale scores, reflecting improvement in parkinsonian and akathisia symptoms, indicates that emergent EPS observed in association with olanzapine were relatively transient. This was in contrast to the emergent EPS observed in haloperidol-treated patients where scores increased and remained increased over the course of treatment.

These results should be interpreted in light of the confounding features inherent in the research methodology applied in the protocols. EPS, because of residual antipsychotic effect, may persist after drug discontinuation and a short washout period, thus making it difficult to establish a drug-free baseline for EPS. Consequently, a drug-free baseline can be established only after a washout period of several weeks and will reflect only the motor symptoms related to the underlying psychotic disorder. Unfortunately, EPS caused by residual antipsychotic effect are difficult to eliminate because of the ethical considerations of denying treatment to chronic schizophrenic patients for an extended period of time and risking an exacerbation of their psychosis. Any baseline motor symptoms that might be related to the state of psychosis may also confound the estimation of the rate of EPS associated with therapy. It has been shown that approximately 17% of a group of severely ill antipsychotic-naive schizophrenic patients exhibited EPS, particularly rigidity, bradykinesia, and cogwheel rigidity.[34] However, it is quite likely that both confounds described above would have been equally distributed across each treatment arm. Therefore, these findings are likely to accurately reflect the relative differences in EPS associated with the different treatments.

A lower incidence of EPS and enhanced drug tolerability have important implications in the management of chronic mental disorders such as schizophrenia. The incidence of noncompliance with conventional antipsychotic drugs is high (7% to 57%, depending on studies) and is frequently related to unpleasant side effects such as EPS.[2,3] The discontinuation rate because of adverse events, e.g., EPS, provides an indication of how well patients tolerated the drugs. In the present analysis, patients treated with olanzapine were nine times less likely than their haloperidol counterparts to discontinue from the trials because of treatment-related EPS. Because patients treated with olanzapine tended to be maintained in the trials with fewer discontinuations because of EPS, it is reasonable to assume this could translate into better compliance, and therefore fewer relapses and, in turn, substantial economic savings. Last, the risk of tardive dyski-

nesia has been linked to earlier EPS treatment experiences.[5,6] If a novel antipsychotic demonstrates minimal EPS, it may also offer an extra benefit of causing a lower incidence of tardive dyskinesia.

Several hypotheses may explain the low extrapyramidal symptom profile of olanzapine. Olanzapine exhibits a broad-based receptor pharmacology. Behavioral studies have demonstrated that serotonin 5-HT_2-mediated activity predominates over dopamine D_2 activity. The lower D_2 to 5-HT_2 striatal receptor occupancy, as measured in a PET study[17] in human volunteers, corroborates the animal pharmacology and supports an interpretation that 5-HT_2 antagonism coupled with a lower striatal D_2 blockade may mitigate EPS. Another perspective is that olanzapine, with a high affinity for several muscarinic cholinergic receptors (particularly m_1), may modulate D_2 activity and minimize striatal dopamine imbalance.

In conclusion, the pooled safety results from three large double-blind, controlled trials in 2606 patients demonstrated that the novel antipsychotic olanzapine possesses a significantly lower EPS profile than the conventional D_2 antagonist haloperidol. This "atypical" feature of low EPS should contribute to a superior risk/benefit profile and, thus, represents a substantial advantage over conventional antipsychotics in the acute and long-term management of psychotic disorders.

Drug names: amantadine (Symadine, Symmetrel), benztropine (Cogentin), biperiden (Akineton), clozapine (Clozaril), dimenhydrinate (Dommanate), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), olanzapine (Zyprexa), orphenadrine (Banflex and others), procyclidine (Kemadrin), trihexyphenidyl (Artane, Pipanol).

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Appendix 1.
Conversion Factors for Anticholinergic Medications

Drug Name	Conversion Factor (X)	Drug Converted to This Equivalent
Amantadine	.01333	Benztropine
Benztropine	1.00000	Benztropine
Biperiden	1.00000	Benztropine
Dimenhydrinate	.01333	Benztropine
Diphenhydramine	.02667	Benztropine
Orphenadrine	.04000	Benztropine
Procyclidine	.50000	Benztropine
Trihexyphenidyl	.50000	Benztropine
Tropatepine	.40000	Benztropine