

Safety of Olanzapine

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Clinical safety data for treatment of acute schizophrenia with olanzapine, a new atypical antipsychotic agent, are summarized. The primary clinical trial safety database included 2500 patients treated with olanzapine, 810 with haloperidol, and 236 with placebo. The overall discontinuation rate from olanzapine treatment was low. Significant adverse events included somnolence, weight gain, and asymptomatic treatment-emergent transaminase elevation. Minimal parkinsonism and akathisia with rare dystonia were noted. No hematotoxicity was noted. The incidence of seizures and sexual dysfunction was rare.
(J Clin Psychiatry 1997;58[suppl 10]:13-17)

Olanzapine is a member of the thienobenzodiazepine class of serotonin-dopamine antagonists which have potent 5-HT₂ and weaker D₂ receptor binding properties. This pharmacologic profile is similar to that of the atypical antipsychotic agent clozapine, which has been noted to effect a reduction in the negative symptoms of schizophrenia, enhanced cognitive function in the treatment of this disease, and a significantly reduced rate of extrapyramidal symptoms (EPS), compared to typical, primarily D₂ binding neuroleptics. We present pivotal clinical trial data concerning the safety of olanzapine.

The safety profile of olanzapine, based on the primary clinical trial safety database, is derived from data evaluated from five clinical trials: the U.S. Clinical Trial (Study 1),¹ the North American Study (Study 2),² the Eastern Hemisphere Study (Study 3),³ the International Study (Study 4),⁴ and the U.S. Alzheimer's Study (Eli Lilly and Company, data on file). The primary clinical trial safety database included 2500 patients who received olanzapine, 810 who received haloperidol, and 236 who received placebo. The total duration of exposure to each therapy was as follows: olanzapine, 1122 patient-years; haloperidol, 193 patient-years; and placebo, 27 patient-years. The data for olanzapine include patients randomly assigned to receive olanzapine in the acute treatment phase of clinical trials, as well as those who elected to cross over to olanzapine therapy in extension phases of the studies. These include

data for patients in controlled efficacy trials, open-label trials, and patients who crossed over from either haloperidol or placebo to olanzapine in both types of trials.

OLANZAPINE VERSUS PLACEBO

Methods. Patients received olanzapine or placebo treatment in two double-blind pivotal studies. These included the U.S. Clinical Trial (Study 1)¹ and the North American Clinical Trial (Study 2).² Study 1¹ included 152 acute schizophrenic inpatients with a Brief Psychiatric Rating Scale (BPRS) score on a 0-6 rating scale of at least 24. Patients with serious medical or neurologic illness were excluded from the study. After discontinuation of oral neuroleptic for at least 2 days and depot neuroleptic for a minimum of 2 weeks, patients entered a single-blind placebo lead-in phase of 4-9 days. Eligible patients in 12 investigative sites were then randomly assigned to one of three double-blind treatment groups: olanzapine 1.0 mg/day (Olz 1.0), olanzapine 10.0 mg/day (Olz 10.0), and placebo. During the placebo lead-in phase and for a maximum of 21 days of the study, patients could receive up to 10 mg/day of lorazepam. Benzotropine mesylate, up to 6 mg/day, was allowed during study participation. The use and dosage of these two medications were determined on clinical grounds by the individual investigators. Patients could be discharged from the hospital after 2 weeks of double-blind therapy if their BPRS₀₋₆ total score had been reduced by ≥ 25% from baseline or was < 24, if they were capable of functioning as outpatients. While the double-blind acute phase of therapy lasted 6 weeks, those patients who failed to show a substantial response could cross over to open-label olanzapine after more than 3 weeks' participation in the double-blind trial. All patients who completed the 6-week acute phase of treatment were eligible to receive open-label olanzapine 5-20 mg/day, a dosage range that was higher than the double-blind doses.

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Presented at the closed symposium "Practical Issues in Using Olanzapine," held August 1-3, 1996, in Boston, Massachusetts, and made possible by an educational grant from Eli Lilly and Company.

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Table 1. Adverse Events: Olanzapine vs. Placebo ($p \leq .05$ and $\geq 2\%$) in Studies 1 and 2

Event	Olanzapine (%)	Placebo (%)
Study 1 ^a		
Anorexia	0	10
Delusions	0	8
Study 2 ^b		
Somnolence	39.1	16.2
Dizziness	17.4	2.9
Constipation	14.5	0.0
Pharyngitis	10.1	1.5
Paresthesia	0.0	5.9

^aOlanzapine 10 mg/day.^bOlanzapine 12.5–17.5 mg/day.

At entry, patients underwent psychiatric and physical examinations, ECG, chest x-ray, urinalysis, serum chemistry, hematology, hepatitis B serology, and drug screen evaluation. Urinalysis, serum chemistry, and hematology values were obtained weekly during acute treatment and at discontinuation. Serum prolactin was measured at the start of double-blind therapy and at discontinuation. The ECG was repeated at Week 6 of the study or at discontinuation. Acute EPS, parkinsonism, and akathisia, were assessed with the Simpson-Angus Scale⁵ and the Barnes Akathisia Scale,⁶ respectively. Dyskinesias were systematically assessed with the Abnormal Involuntary Movement Scale (AIMS).⁷

Adverse events were recorded at every visit, including study entry and baseline, through nondirected, open-ended questioning, spontaneous complaint, and clinical observation. Adverse events were recorded, regardless of potential relationship to treatment, using the COSTART⁸ dictionary of adverse event terms.

Study 2² included 335 acute schizophrenic inpatients with entry criteria similar to those in Study 1, who were required to discontinue use of oral neuroleptic for at least 2 days and depot neuroleptic for at least 6 weeks prior to study entry. They first entered a single-blind placebo lead-in phase of 4–7 days. Those eligible to continue were randomly assigned to five double-blind treatment arms: olanzapine 5.0 ± 2.5 mg/day (Olz-L); olanzapine 10.0 ± 2.5 mg/day (Olz-M); olanzapine 15.0 ± 2.5 mg/day (Olz-H); haloperidol 15 ± 5 mg/day (Hal); or placebo. Patients were started in the middle of the dosage ranges, with the options of adjusting upward or downward, as clinically indicated. Use of lorazepam and benztropine mesylate was permitted as described in Study 1. Laboratory tests, EPS rating scales, and adverse events were recorded as in Study 1. Serum prolactin was repeated every 2 weeks and at discontinuation.

Results. In Study 1, which employed a fixed 10-mg dose of olanzapine versus placebo, discontinuation because of an adverse event in the Olz 10 group was 4% versus 0% in the placebo group. In this study, only two adverse events were noted for which there was both statis-

tical separation between Olz 10 and placebo ($p < .05$), and the rate of the events was $\geq 2\%$ in either group. These are anorexia and delusions, both of which were more associated with placebo and both of which are considered manifestations of the underlying schizophrenia (Table 1). Results from Study 2, in which the Olz-H group started on 15 mg/day of olanzapine and quickly moved to 17.5 mg, shows that 5.8% of the Olz-H-treated patients discontinued because of adverse events, compared to 10.3% of the placebo group. Many of the events that led to discontinuation among the placebo-treated patients included manifestations of the schizophrenic disease process, i.e., delusions, hallucinations, worsening of psychosis.

OLANZAPINE VERSUS HALOPERIDOL

Methods. The Eastern Hemisphere Trial, Study 3,³ included 431 acute schizophrenic inpatients who were randomized to five treatment groups that compared three dosage ranges of olanzapine, (Olz-L, 5.0 ± 2.5 mg/day; Olz-M, 10.0 ± 2.5 mg/day, Olz-H, 15 ± 2.5 mg/day) with a very low dose of olanzapine (Olz 1.0, 1.0 mg/day) and one dosage range of haloperidol (Hal 15.0 ± 5 mg/day). After a 4- to 7-day placebo lead-in period, patients were randomly assigned to a 6-week period of acute, double-blind treatment. Treatment responders could continue double-blind therapy for up to 1 year. Continued responders could continue treatment beyond 1 year, and, when unblinded, those who were receiving olanzapine could receive open-label treatment for an indefinite period. Collection of safety data and use of concomitant medications were similar to the protocol described for Studies 1 and 2.

The international, multicenter, double-blind parallel trial, Study 4,⁴ compared olanzapine in a single dose range, 5–20 mg/day, to a single dose range of haloperidol, 5–20 mg/day, in the treatment of 1996 inpatients and outpatients with a DSM-III-R diagnosis of schizophrenia (83.1%), schizophreniform disorder (1.9%), and schizoaffective disorder (15.0%). Patients entered with a BPRS₀₋₆ total score of at least 18 or were intolerant of current therapy. They were assigned in a 2:1 olanzapine to haloperidol ratio. Safety evaluation and use of concomitant medication were similar to the protocol described for Studies 1 and 2 above.

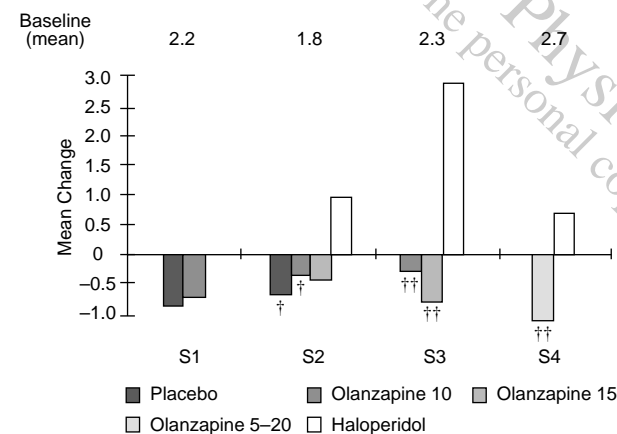
Results. Rates of early discontinuation of patients in Study 4 (1336 patients on olanzapine and 660 on haloperidol) are shown in Table 2. The overall result was 4.5% for treatment with olanzapine, compared to 7.3% for haloperidol; this represented a statistically significant difference. Adverse events which occurred in at least 2% of cases and reached statistical significance are also shown in Table 2. In the olanzapine-treated group, dry mouth, weight gain, and increased appetite were more prevalent. In the haloperidol-treated group, extrapyramidal syndrome (the

Table 2. Adverse Events: Olanzapine vs. Haloperidol ($p \leq .05$ and $\geq 2\%$) in Study 4*

Adverse Event	Olanzapine Group	Haloperidol Group
	(N = 1336) %	(N = 660) %
Dry mouth	7.5	4.2
Weight gain	4.6	1.8
Increased appetite	4.0	0.9
Akathisia	6.6	22.0
Insomnia	10.4	13.6
Tremor	3.6	12.6
Hypertonia	3.4	9.2
Nervousness	5.6	9.1
Extrapyramidal syndrome	2.0	7.6
Increased salivation	2.2	6.4
Vomiting	3.1	6.1
Joint disorder	1.9	4.7
Amblyopia	2.3	4.4
Anorexia	1.6	3.3
Dystonia	0.4	2.9
Weight loss	0.5	2.1

*Olanzapine, 5–20 mg/day; haloperidol, 5–20 mg/day. Data on file, Eli Lilly and Company.

Figure 1. Mean Change (LOCF) in Simpson-Angus Scale Scores for Extrapyramidal Symptoms Occurring in Acute Phases of Studies 1 to 4 (S1 to S4)



† $p \leq .050$ vs haloperidol; †† $p \leq .001$ vs haloperidol.

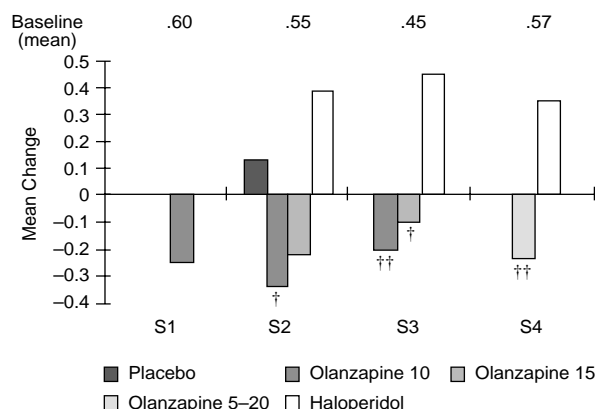
COSTART dictionary of adverse events term for a global diagnosis of parkinsonism), psychomotor activation, vomiting, anorexia, and weight loss occurred at a statistically significantly higher rate.

SAFETY EVALUATIONS

Clinical Events

Extrapyramidal symptoms. The Simpson-Angus Scale was used to measure acute parkinsonism in Studies 1 to 4. The scale was administered at baseline and at scheduled intervals throughout each study. Akathisia was determined by the Barnes Akathisia Scale, which was administered in a similar fashion. For the acute phase of therapy, an improvement in Simpson-Angus Scale scores over baseline

Figure 2. Mean Change (LOCF) in Barnes Akathisia Scale Scores for Acute Extrapyramidal Symptoms Occurring in Acute Phases of Studies 1 to 4 (S1 to S4)



† $p \leq .010$ vs haloperidol; †† $p \leq .001$ vs haloperidol.

is shown in the placebo-controlled trials (Figure 1). Approximately the same number of olanzapine-treated patients received anticholinergic medication for treatment of EPS as did the placebo-treated patients. For olanzapine in all four trials, both at mid- and high-dose, there is an improvement over baseline in the Simpson-Angus Scale analyses for EPS, compared to the haloperidol-treated groups, in which an increase over baseline EPS is seen. The results are similar to those for akathisia, as measured by the Barnes Akathisia Scale analyses, except for an increase in symptoms over baseline in the placebo group in Study 2 (Figure 2). Dystonia was rare.

Weight gain. Weight gain, a common side effect with antipsychotic agents, particularly the atypical agents, was noted in the olanzapine-treated group. Weight gain in the amount of 2 to 3 kg was seen in comparison to both placebo and haloperidol during the acute phases of these four trials. Further relationship is noted between the patients' baseline body mass index (BMI) and the incidence of weight gain (Table 3); the most significant increases in weight occurred in those patients who were the most underweight prior to beginning treatment with olanzapine. For the entire database, with treatment varying between 2 days and 3½ years, 40.5% of the patients treated with olanzapine gained 7% or more of body weight (Table 4). Of these, only 7 patients discontinued olanzapine due to weight gain.

Vital signs and ECGs. Seven different vital sign measurements were analyzed in the physical assessments of patients in each protocol, including supine systolic and diastolic blood pressure, standing systolic and diastolic blood pressure, supine and standing pulse rate, and body temperature. For postural vital signs in Study 2, a slight increase in orthostatic heart rate was noted in the Olz-H group. A 17% incidence in the rates of complaints of dizziness was noted, compared to the placebo group; however,

Table 3. Incidence of Weight Gain ($\geq 7\%$) by BMI Category in Acute Phases of Studies 1 to 4

BMI Category	N	%	p Value ^a
Underweight (< 23 kg/m ²)	575	31.7	< .001
Normal (23–27 kg/m ²)	623	17.8	
Overweight (> 27 kg/m ²)	584	11.1	

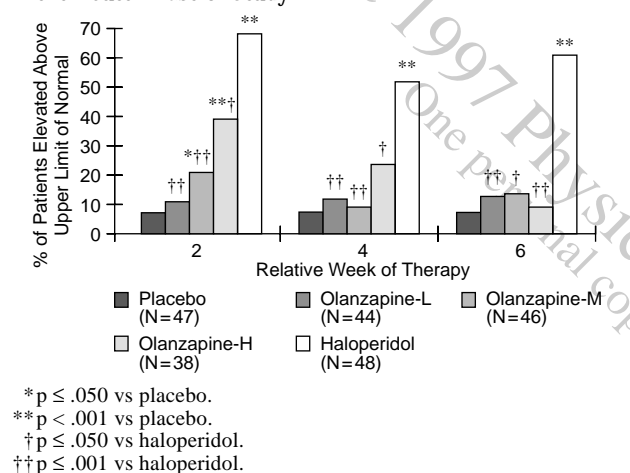
^aCorresponds to overall p value from two-tailed Fisher's exact test.

Table 4. Incidence of Weight Change $\geq 7\%$ in the Overall Integrated Database

% Change	Placebo (N = 226)	Olanzapine (N = 2418 ^a)	Haloperidol (N = 777)
Weight gain	3.1	40.5	12.4
Weight loss	6.6	6.4	8.4

^aIncludes patients that crossed over to olanzapine from placebo or haloperidol treatment groups.

Figure 3. Treatment-Emergent Prolactin Elevation in Males in the Acute Phase of Study 2



* p \leq .050 vs placebo.
 ** p < .001 vs placebo.
 † p \leq .050 vs haloperidol.
 †† p \leq .001 vs haloperidol.

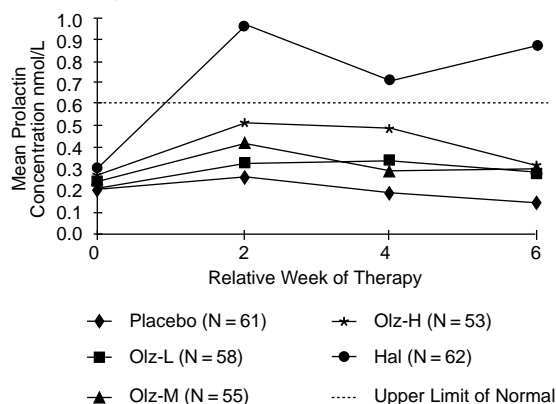
evaluation of postural blood pressure changes failed to reveal a statistically significant increase in orthostatic decrease. Olanzapine appeared to have no consistent effect on blood pressure or body temperature.

Review of ECG data in olanzapine-treated patients showed a slight but statistically significant increase in sinus rate, with a corresponding decrease in absolute QT interval. The magnitude of these changes was not considered clinically significant. Based on analysis of ECGs, olanzapine therapy did not adversely affect cardiac conduction or rhythm.

Laboratory Data

Liver enzymes. Transient treatment-emergent elevation in hepatic serum transaminase (ALT/SGPT) was noted at a rate of 9.4% in the olanzapine-treated patients (N = 2075). This event generally began within the first or second week of treatment, with a median time to peak of 28 days. Absolute values over 200 IU/L occurred in 2.1%

Figure 4. Mean Prolactin Concentration in Males (Observed Case) in Study 2



of the olanzapine-treated patients, and the median elevation for all olanzapine-treated patients was 34 IU/L (N = 2381). None of the patients evidenced signs or symptoms of clinical hepatitis. Fewer patients treated with olanzapine (0.2%) experienced substantial elevations, i.e., > 400 IU/L, compared to those who received haloperidol (0.4%).

Hematology. Analysis of hematologic parameters, particularly leukocytes, did not suggest a clinically significant adverse impact on the bone marrow. No evidence of hematotoxicity was seen in the olanzapine-treated group. In the entire database, 32 patients who had prior hematotoxicity associated with clozapine treatment had no recurrence when treated with olanzapine.

Serum prolactin. As with other drugs that antagonize 5-HT₂ and/or dopamine D₂ receptors, olanzapine may induce elevated serum prolactin levels in some patients. Figure 3 shows a dose-related elevation in serum prolactin in male patients in the acute treatment phase of Study 2. Olanzapine-treated patients had normal prolactin levels at baseline, then showed elevations that were tapering off by the end of 6 weeks. The mean elevation (Figure 4) in the olanzapine-treated group as a whole never exceeded the upper limit of normal, whereas elevation above normal levels persisted in the haloperidol-treated patients.

DISCUSSION

Olanzapine had been studied in over 2500 schizophrenic patients at the time of submission to regulatory agencies for approval in the United States. Safety evaluations in this significant database showed that olanzapine is generally well tolerated. Compared to placebo, olanzapine-treated patients experienced mild sedation and some anticholinergic effects. EPS was not significantly higher on olanzapine compared with placebo and generally did not cause discontinuation. Patients treated with olanzapine also complained of dizziness, but this did not appear to be

due to objective orthostatic hypotension. Weight gain was expected, given the drug's serotonin antagonism, and studies consistently showed a tendency toward increase over baseline weight. Although 40.5% of olanzapine-treated patients gained 7% or more of their body weight, this effect appeared to be largest in that group of patients who began treatment in an underweight state. Compared to the haloperidol-treated group, olanzapine-treated patients experienced significantly fewer EPS and very rare dystonia. Hematotoxicity was not found in the olanzapine group, which included a cohort of 32 patients who had experienced neutropenia during prior treatment with clozapine. Serum prolactin elevations were mild and transient in the olanzapine-treated group, compared to those treated with haloperidol. Early, asymptomatic hepatic transaminase elevations occurred in some patients treated with olanzapine. The overall clinical experience with olanzapine has been one of high tolerability.

Drug names: benzotropine (Cogentin and others), clozapine (Clozaril), haloperidol (Haldol and others), lorazepam (Ativan and others), olanza-

pine (Zyprexa).

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