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Olanzapine versus Placebo and Haloperidol

Acute Phase Results of the North American Double-Blind Olanzapine Trial

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Olanzapine is a potential new "atypical" antipsychotic agent. The double-blind acute phase of this study compared three dosage ranges of olanzapine (5 ± 2.5 mg/day [Olz-L], 10 ± 2.5 mg/day [Olz-M], 15 ± 2.5 mg/day [Olz-H]) to a dosage range of haloperidol (15 ± 5 mg/day [Hal]) and to placebo in the treatment of 335 patients who met the DSM-III-R criteria for schizophrenia. In overall symptomatology improvement (Brief Psychiatric Rating Scale [BPRS]-total), Olz-M, Olz-H, and Hal were significantly superior to placebo. In positive symptom improvement (BPRS-positive), Olz-M, Olz-H, and Hal were comparable and significantly superior to placebo. In negative symptom improvement (Scale for the Assessment of Negative Symptoms [SANS]-composite), Olz-L and Olz-H were significantly superior to placebo and Olz-H was also significantly superior to Hal. The most common treatment-emergent adverse events included somnolence, agitation, asthenia, and nervousness. No acute dystonia was observed with olanzapine. Treatment-emergent parkinsonism occurred with Olz-H at approximately one-third the rate of Hal, and akathisia occurred with Olz-H at approximately one-half the rate of Hal. Prolactin elevations associated with olanzapine were not significantly greater than those observed with placebo and were also significantly less than those seen with haloperidol.
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KEY WORDS: *Olanzapine; Placebo; Haloperidol; Acute; Double-blind; Atypical; Schizophrenia; Antipsychotic*

Olanzapine, a thienobenzodiazepine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno<2,3-B> <1,5>benzodiazepine), is a potential new "atypical" antipsychotic agent. The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic (e.g., haloperidol) (Casey 1992; Meltzer 1992). Clozapine, the prototypical "atypical" antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics, (2) greater efficacy in the treatment of negative symptoms of schizophrenia, and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy.

Olanzapine has a high affinity for a variety of monoamine receptors. It binds potently to both the 5-HT_{2A} as well as the D_2 receptors, but more potently to the 5-HT_{2A} receptor by a factor of approximately 3:1 (Tye et al. 1992; Moore et al. 1993; Wong et al. 1993). It also binds potently to the D_4, D_1, 5-HT_{2C}, muscarinic (especially m_1), α_1-adrenergic, and H_1 histaminic re-

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ceptors (Tye et al. 1992; Moore et al. 1993; Seeman and Van Tol 1993; Wong et al. 1993). The K_is for these affinities are less than 50 nM. The affinities for the D_4 (27 nM) and D_2 (45 nM) receptors are comparable (Seeman and Van Tol 1993).

Neurochemically, acute olanzapine administration increases levels of the DA metabolite 3-4-dihydroxyphenylacetic acid (DOPAC) in rat nucleus accumbans and increases levels of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG-SO_4) in rat hypothalamus (Hemrick-Luecke et al. 1993).

Neuroendocrine challenge studies have demonstrated that olanzapine is both a serotonin (5-HT) antagonist (blocks quipazine-induced corticosterone elevations) and a DA antagonist (blocks pergolide-induced corticosterone elevations) but is more potent at antagonizing the 5-HT-mediated response, similar to clozapine (Fuller and Snoddy 1992; Moore et al. 1993).

Electrophysiologic studies have also revealed that acute administration of olanzapine increases the firing of dopamine A10 neurons, but not the firing of dopamine A9 neurons. On repeated administration, A10 neuronal firing is decreased and A9 neuronal firing is increased in a dose-dependent manner. These acute and chronic effects resemble those of clozapine (Rasmussen and Stockton 1993; Stockton and Rasmussen 1993).

Behavioral pharmacologic study results are consistent with the receptor affinity profile and suggest the potential for atypical antipsychotic activity. Olanzapine blocks both apomorphine-induced climbing behavior and 5-hydroxytryptophan (5-HTP)-induced head twitch in a dose-dependent manner but with greater potency in blocking the 5-HTP head twitch (Moore et al. 1992; Tye et al. 1992; Moore et al. 1993; Wong et al. 1993). These findings indicate 5-HT and DA antagonism in vivo with greater 5-HT potency. Olanzapine also blocks oxotremorine-induced tremor in a dose-dependent manner, indicating cholinergic antagonism in vivo (Moore et al. 1992; Tye et al. 1992; Moore et al. 1993). The dose of olanzapine required to induce catalepsy substantially exceeds the dose required to inhibit conditioned avoidance (ratio of 8:1 in one study and 4:1 in another study) (Moore et al. 1992; Tye et al. 1992; Moore et al. 1993; Wong et al. 1993). These findings suggest antipsychotic activity with minimal potential for induction of acute extrapyramidal symptoms. Unlike typical antipsychotics, olanzapine increases punished responding in a conflict model, similar to clozapine (Moore et al. 1992; Tye et al. 1992; Moore et al. 1993; Wong et al. 1993; Moore et al. 1994). Finally, olanzapine substitutes in animals trained to discriminate clozapine, suggesting similar pharmacologic profiles (Moore et al. 1992; Tye et al. 1992; Moore et al. 1993; Wong et al. 1993).

An earlier open-label study suggested that olanzapine at doses between 5 and 20 mg/day had significant antipsychotic activity against both positive and negative symptoms of schizophrenia. Minimal extrapyramidal symptoms were observed; at endpoint no patient (n = 10) had a serum prolactin concentration elevated above baseline level (Montgomery et al. 1992).

We report here the results of the acute phase of a study comparing three dosage ranges of olanzapine to a dosage range of haloperidol and to placebo in the treatment of patients with schizophrenia. This double-blind study included 335 patients and was conducted at 22 study sites in the United States and Canada between November 1991 and September 1993.

METHODS AND SUBJECTS

Study Design

Patients comprised men and women between the ages of 18 and 65. Female patients of childbearing potential were allowed to enter the study only after approximately two-thirds of enrollment had been completed. All patients enrolled met the DSM-III-R (APA 1987) criteria for schizophrenia with an acute exacerbation, as established by clinical interview and chart review. In addition, patients were required to have a minimum Brief Psychiatric Rating Scale-Anchored (BPRS) (Woerner et al. 1988) total score (items scored 0 to 6) of 24. Patients with a diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry were excluded as were patients at serious suicidal risk. Also excluded were patients with serious, unstable medical illness; Parkinson's disease; myasthenia gravis; illness contraindicating use of anticholinergic medication; a history of seizures; a history of leukopenia without known etiology; and significantly elevated (greater than two times conventional laboratory upper limit of normal) liver function test results, active hepatitis B, or jaundice. Patients were required to be off oral neuroleptics for at least 2 days and off depot neuroleptics for at least 6 weeks prior to starting the study. All patients gave written informed consent prior to entering the study. The study protocol was approved by the institutional review boards responsible for the individual study sites.

Patients first entered a single-blind placebo lead-in phase of 4 to 7 days. Patients whose BPRS-total score decreased ≥25% or whose BPRS-total score decreased to <24 during the placebo lead-in phase were discontinued as placebo responders. After the placebo lead-in phase, patients eligible to continue the study were assigned by random allocation to one of five double-blind treatment arms: olanzapine 2.5, 5, or 7.5 mg/day (Olz-L); olanzapine 7.5, 10, or 12.5 mg/day (Olz-M); olanzapine 12.5, 15, or 17.5 mg/day (Olz-H); haloperidol 10, 15, or 20 mg/day (Hal); or placebo.

Patients in the olanzapine and haloperidol treatment groups began on the middle dose within their assigned arms, and the dose could be adjusted upward

or downward as clinically indicated. The first upward adjustment could occur after approximately 4 days (visit 3) of double-blind therapy. An upward adjustment could occur at any regularly scheduled visit (3 to 4 days for the first and second visits after beginning double-blind therapy, then weekly). Downward adjustment could occur at any time.

Patients could receive up to 10 mg/day of lorazepam during the placebo lead-in and for a maximum of 21 days (any dose up to 10 mg/day) during the double-blind acute therapy phase. In addition, benztropine mesylate, up to 6 mg/day, was allowed during study participation. Prophylactic use of these two concomitant medications was discouraged but not proscribed. The use and dosage of both were determined on clinical grounds by the investigators.

Hospitalization was required during the placebo lead-in and the first 2 weeks of double-blind therapy. Patients could then be discharged to outpatient status if their BPRS-total score had decreased ≥25% from baseline or was <24, and were judged to be capable of functioning as outpatients and to be no risk to themselves or others. The double-blind acute therapy phase lasted 6 weeks (through visit 9). Responders (BPRS-total score decreased ≥40% from baseline or was ≤18) at the completion of the double-blind acute phase were eligible to enter a 46-week double-blind extension, the results of which will be reported separately after its completion.

At entry, patients underwent psychiatric, physical, and ophthalmologic examinations; ECG; chest x-ray (if not performed within 6 months prior to entry); urinalysis; serum chemistry; prolactin; hematology; hepatitis B serology; and drug screen evaluation. Severity of illness rating instruments included the BPRS, Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982), Clinical Global Impressions-Severity and Improvement Scales (CGI-S and CGI-I) (Guy et al. 1976), and Patient Global Impression (PGI) (Guy et al. 1976). Acute extrapyramidal symptoms, parkinsonism and akathisia, were assessed systematically with the Simpson-Angus Scale (Simpson-Angus) (Simpson and Angus 1970) and the Barnes Akathisia Scale (Barnes) (Barnes 1989), respectively. Dyskinesias were systematically assessed with the Assessment of Involuntary Movement Scale (AIMS) (Guy et al. 1976).

Adverse events were recorded at every visit (including entry [visit 1] and baseline [visit 2]) through nondirected, open-ended questioning; spontaneous complaint; and clinical observation. Adverse events were recorded irrespective of their potential relationship to treatment, using the COSTART dictionary of adverse event terms. Severity of illness ratings, extrapyramidal symptom ratings, urinalysis, serum chemistry, hematology, and serum prolactin were repeated immediately before beginning double-blind therapy, weekly throughout the acute therapy phase (prolactin measurement was repeated at weeks 2, 4, and 6), and at any early discontinuation. The ECG and the ophthalmology examination were repeated at week 6 and at any early discontinuation.

Investigators received training on administration and scoring of the BPRS and SANS, using videotaped interviews, at the study initiation meeting.

Statistical Analysis

The primary purpose of this study was to determine if one or more dosage ranges of olanzapine were superior to placebo in improving overall psychopathology (BPRS-total score, endpoint last-observation-carried-forward [LOCF] mean change) and positive psychotic symptoms (BPRS-positive score, endpoint LOCF mean change) and if one or more dosage ranges of olanzapine were superior to placebo and a conventional dosage range of haloperidol in improving negative psychotic symptoms (SANS-composite score, endpoint LOCF mean change).

All analyses were done on an intent-to-treat basis, meaning all patients were included in the groups to which they were randomly assigned, even when the patient did not strictly adhere to the protocol. All endpoint analyses used a LOCF algorithm; the last available visit of visits 3 to 9 served as endpoint. All weekly (visitwise) analyses used an observed-case algorithm such that only available data were used for a given week (visit). For analyses of change from baseline to endpoint, only patients with a baseline (last available visit, visit 1 or 2) and at least one postbaseline measure were included. Furthermore, analysis of baseline efficacy and extrapyramidal symptom rating scales included only those patients with a baseline (last available visit, visit 1 or 2) and at least one postbaseline measure to be consistent with the analysis of the change from baseline to endpoint. All patients randomly assigned to double-blind therapy (N = 335) were included in the analysis of baseline patient and illness characteristics as well as of the incidence of treatment-emergent adverse events. For those patients who had ≥1 dose of rescue antipsychotic medication more than a day immediately before their discontinuation visit, that visit was eliminated from all efficacy and extrapyramidal symptom rating scale analyses. In the computation of all total scores, if any of the individual items were missing, then the total score was treated as missing. SAS procedures were used to perform all statistical analyses (SAS Institute Inc. 1990).

Analysis of variance (ANOVA) was used to evaluate the continuous data, including terms for treatment, investigator, and treatment-by-investigator interaction. The only exception was the weekly analyses, which did not include the interaction term because of sparse data. Data were pooled from investigators who did not have at least two patients per treatment. Both the original scale data and rank-transformed data were fit to the

Table 1. Patient Characteristics

Characteristic	Placebo (n = 68)	Olz-L (n = 65)	Olz-M (n = 64)	Olz-H (n = 69)	Hal (n = 69)	Overall p-Value
Age (mean ± SD)	35 ± 8	36 ± 10	37 ± 10	36 ± 10	36 ± 9	0.735
Sex						
Male (%)	91.2	92.3	87.5	78.3	89.9	0.089
Race						
White (%)	70.6	64.6	71.9	78.3	58.0	0.145
Black (%)	20.6	26.2	20.3	15.9	20.3	

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; SD = standard deviation.

ANOVA models; the primary inference was taken from the analysis of the original scale data unless the assumptions of the ANOVA appeared to be violated. The least-square means were used to calculate pairwise p-values. The average percentage decrease in severity of illness scores for each treatment group was calculated by averaging the percent change from baseline for each patient's scores. The maintenance dose for each patient was calculated as the dose that the patient received for the most number of days (modal dose).

Categorical data, which included demographic variables, response rates, reasons for study discontinuation, and treatment-emergent adverse events, were evaluated using Pearson's χ^2 test. For the analysis of discontinuations because of adverse events, no p-values were calculated because of the sparse data. For the categorical analysis of values for platelet count, leukocytes, and neutrophils, only patients whose baseline laboratory values were at or above the lower limit of the reference range were included in the analysis. For the categorical analysis of eosinophils, alanine transaminase (ALT), creatine phosphokinase (CPK), and prolactin values, only patients whose baseline measures were at or below the upper limit of the reference range were included in the analysis.

For all analyses, main effects were tested at a two-sided α level of 0.05 and treatment-by-investigator interactions and heterogeneity across investigators were tested at an α level of 0.10. If the overall main effect was significant, then pairwise comparisons with no correction for multiplicity were performed for olanzapine treatments versus placebo, olanzapine treatment groups versus haloperidol treatment, and haloperidol treatment versus placebo.

RESULTS

Baseline Characteristics

Treatment groups (Tables 1 to 4) did not differ on an overall basis statistically significantly with respect to any patient or illness characteristic, with the exception of the baseline Simpson-Angus score in which the halo-

Table 2. Illness Characteristics

Variable	Placebo (n = 68)	Olz-L (n = 65)	Olz-M (n = 64)	Olz-H (n = 69)	Hal (n = 69)	Overall p-Value
Subtype						
Paranoid (%)	60.3	55.4	64.1	58.0	59.4	0.978
Disorganized (%)	7.4	4.6	4.7	7.2	5.8	
Undifferentiated (%)	32.4	40.0	31.3	34.8	34.8	
Course						
Subchronic, AE (%)	10.3	6.2	7.8	8.7	8.7	0.941
Chronic, AE (%)	88.2	92.3	90.6	91.3	91.3	
Unspecified (%)	1.5	1.5	1.6	0.0	0.0	
Length of current episode (days)(mean ± SD)	81 ± 139	83 ± 159	80 ± 210	71 ± 130	140 ± 673	0.760
Number of previous episodes[a]						
<10 (%)	52.9	50.8	50.0	51.5	48.5	0.919
10–20 (%)	16.2	19.0	20.3	20.6	26.5	
≥20 (%)	30.9	39.2	29.7	27.9	25.0	
Age of psychosis onset (yr) (mean ± SD)	22 ± 6	22 ± 6	22 ± 6	23 ± 7	21 ± 5	0.754

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; AE = acute exacerbation; SD = standard deviation.

[a] Four patients had missing values and were not included in the total.

Table 3. Baseline Severity of Illness Scores

Measure	Placebo	Olz-L	Olz-M	Olz-H	Hal	*p*-Value
BPRS-total[a]	39.7 ± 10.5 (*n* = 62)	41.2 ± 11.7 (*n* = 63)	42.8 ± 10.0 (*n* = 62)	42.6 ± 10.9 (*n* = 65)	41.8 ± 11.4 (*n* = 68)	0.062
BPRS-positive [a,b]	13.0 ± 3.7 (*n* = 63)	13.1 ± 4.3 (*n* = 63)	14.0 ± 3.5 (*n* = 63)	13.8 ± 4.5 (*n* = 65)	13.1 ± 3.9 (*n* = 68)	0.165
BPRS-negative[a,c]	7.0 ± 3.9 (*n* = 65)	7.6 ± 3.8 (*n* = 64)	6.8 ± 3.8 (*n* = 63)	7.4 ± 3.7 (*n* = 65)	6.7 ± 3.5 (*n* = 68)	0.503
SANS-composite[d]	44.0 ± 19.3 (*n* = 65)	48.1 ± 17.1 (*n* = 62)	41.7 ± 18.3 (*n* = 63)	43.6 ± 18.2 (*n* = 64)	42.9 ± 16.5 (*n* = 68)	0.525
SANS-summary[e]	13.1 ± 5.5 (*n* = 65)	14.5 ± 5.1 (*n* = 64)	12.9 ± 4.8 (*n* = 63)	13.4 ± 5.1 (*n* = 65)	13.2 ± 4.6 (*n* = 68)	0.539
CGI-severity	4.9 ± 0.8 (*n* = 66)	4.9 ± 0.8 (*n* = 64)	5.1 ± 0.9 (*n* = 63)	5.0 ± 0.8 (*n* = 66)	4.9 ± 0.7 (*n* = 68)	0.276

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; SD = standard deviation.

Scores are mean ± SD.

[a] Items scored 0-6.

[b] Conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content.

[c] Emotional withdrawal, motor retardation, blunted affect.

[d] Sum of individual items.

[e] Sum of global items.

peridol treatment group was slightly higher than that of the other treatment groups. Patients were generally in their mid-30s (as opposed to younger patients in an early phase of their disease), white, and male. The majority of patients were of the paranoid subtype, and approximately 91% had a chronic course (with acute exacerbation) consistent with mean age. The mean length of current episode for the haloperidol treatment group was inflated by unusually high values for several patients. The median length of current episode was consistent across treatment groups (range, 28 to 32 days). Mean baseline BPRS-total score was approximately 42 (items scored 0 to 6), reflecting relatively severe overall psychopathology. The mean baseline SANS-composite score was approximately 44, indicating severe negative symptomatology. Thus, this overall patient group manifested a clinically severe, mixed (positive and negative) symptom profile in the context of a chronic longitudinal course.

Medication Use

Mean modal drug dosages, calculated for patients who completed at least 3 weeks of double-blind therapy were: Olz-L, 6.6 ± 1.4 mg/day; Olz-M, 11.6 ± 1.5 mg/day; Olz-H, 16.3 ± 1.6 mg/day; Hal, 16.4 ± 4.0 mg/day. There was an overall statistically significant difference in the use of benztropine calculated as average administration per day across all arms ($p < .001$) (placebo, 0.1 ± 0.4 mg/day; Olz-L, 0.1 ± 0.3 mg/day; Olz-M, 0.2 ± 0.8 mg/day; Olz-H, 0.5 ± 1.5 mg/day; Hal, 2.0 ±2.5 mg/day), and patients in all other treatment arms were administered statistically significantly less benztropine than those in the haloperidol arm ($p \leq .001$, in all cases). The percentages of patients who received one or more doses of anticholinergic at any time during double-blind acute therapy were: placebo, 11.8%; Olz-L, 10.8%; Olz-M, 21.9%; Olz-H, 27.5%; and Hal, 68.1%. There was no statistically significant differ-

Table 4. Baseline Extrapyramidal Symptom Scores

Score	Placebo	Olz-L	Olz-M	Olz-H	Hal	Overall *p*-Value
Simpson-Angus	1.7 ± 2.9 (*n* = 64)	1.9 ± 2.8 (*n* = 62)	1.5 ± 2.8 (*n* = 60)	1.7 ± 2.8 (*n* = 63)	2.3 ± 4.6 (*n* = 67)	0.002
Barnes	0.3 ± 0.6 (*n* = 64)	0.5 ± 0.8 (*n* = 63)	0.8 ± 1.1 (*n* = 63)	0.6 ± 0.9 (*n* = 65)	0.5 ± 0.8 (*n* = 68)	0.091
AIMS	2.7 ± 3.9 (*n* = 64)	2.0 ± 3.1 (*n* = 63)	3.0 ± 4.5 (*n* = 63)	2.7 ± 3.8 (*n* = 65)	2.7 ± 4.0 (*n* = 68)	0.576

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; Simpson-Angus = Simpson-Angus Total Score; Barnes = Barnes Akathisia Rating Global Score (item 4); AIMS = Abnormal Involuntary Movement Total Score (sum of items 1-7); SD = standard deviation.

Scores are mean ± SD.

ence across arms in use of lorazepam as expressed in mg/day (placebo, 1.1 ± 1.7; Olz-L, 1.5 ± 2.8; Olz-M, 1.2 ± 1.5; Olz-H, 0.9 ± 1.7; and Hal, 1.2 ± 1.8). The following percentages of patients received one or more doses of benzodiazepine at any time during double-blind acute treatment: placebo, 76.5%; Olz-L, 72.3%; Olz-M, 78.1%; Olz-H, 62.3%; and Hal, 76.8%.

Efficacy—Endpoint Analysis

Mean change from baseline (LOCF analysis) was used to compare illness severity changes for the five treatment groups (Table 5). With regard to overall symptomatology (BPRS-total score), Olz-M, Olz-H, and Hal were all statistically superior to placebo, and Olz-H was numerically superior to Hal. Also, an increasing dose-response curve was observed across the three olanzapine dose groups. The Olz-H treatment group showed a 35.7% decrease on average in overall symptomatology (BPRS-total). The results of CGI-S were consistent with the BPRS-total. For core positive psychotic symptoms (BPRS-positive), the two higher dose olanzapine-treated groups and the haloperidol-treated group were all comparable with respect to improvement, and the magnitude of improvement was statistically significantly greater when compared to placebo treatment. For negative symptoms (SANS-composite and SANS-summary), Olz-L and Olz-H were statistically superior to placebo, and Olz-H was also statistically significantly superior to Hal. These data suggest that the low and high dose ranges of olanzapine were effective against negative symptoms. Olz-H therapy resulted in decreases of 26.8% and 26.4% on average in negative symptom severity (SANS-composite and SANS-summary, respectively).

Efficacy—Weekly Analysis

Figures 1 to 3, which display the severity of the primary ratings for overall symptoms (BPRS-total), positive symptoms (BPRS-positive), and negative symptoms (SANS-composite), reflect the observed case analyses. Therefore, the last-visit data reflect analysis of completers. As shown, overall treatment differences were statistically significant beginning at week 1 for overall symptoms and positive symptoms. Improvement of positive symptoms in both the Hal and Olz-H treatment groups appears to plateau by the end of this 6-week acute phase. With respect to negative symptoms, Hal and Olz-H treatment groups show a divergent temporal pattern (Figure 3). In the Olz-H treatment group, these

Table 5. Endpoint Change in Severity of Illness Scores (last observation carried forward)

	Placebo	Olz-L	Olz-M	Olz-H	Hal	Overall *p*-Value
BPRS-total[a]	−3.1 ± 17.5 (n = 62)	−6.7 ± 13.5[3] (n = 63)	−12.6 ± 15.9[3,6] (n = 62)	−15.2 ± 16.1[3,6] (n = 65)	−12.9 ± 13.5[3,5] (n = 68)	<0.001
BPRS-positive[b]	−1.5 ± 5.7[1] (n = 63)	−2.7 ± 4.6[3] (n = 63)	−4.5 ± 5.6[3,5] (n = 63)	−4.6 ± 5.8[3,5] (n = 65)	−4.6 ± 5.0[3,4] (n = 68)	0.017
BPRS-negative[c]	−0.4 ± 3.9 (n = 65)	−1.6 ± 3.1[3,4] (n = 64)	−1.4 ± 3.6[3] (n = 63)	−3.0 ± 3.3[3,6] (n = 65)	−1.9 ± 3.8[3] (n = 68)	0.009
SANS-composite[d]	−1.9 ± 17.5 (n = 65)	−8.7 ± 14.8[3,4] (n = 62)	−6.1 ± 17.0[2] (n = 63)	−13.5 ± 17.0[3,6,7] (n = 64)	−6.6 ± 15.3[3] (n = 68)	0.018
SANS-summary[e]	−0.6 ± 4.9 (n = 65)	−2.5 ± 4.2[3,4] (n = 64)	−1.9 ± 5.2[2] (n = 63)	−4.1 ± 5.2[3,6,7] (n = 65)	−2.0 ± 4.6[3] (n = 68)	0.021
CGI-severity	−0.3 ± 1.2[1] (n = 66)	−0.4 ± 1.1[2] (n = 64)	−1.0 ± 1.2[3,5] (n = 63)	−1.0 ± 1.1[3,5] (n = 66)	−0.9 ± 1.1[3,5] (n = 68)	0.016

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; SD = standard deviation.

Scores are mean ± SD.

[a] Items scores 0–6.

[b] Conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content.

[c] Emotional withdrawal, motor retardation, blunted affect.

[d] Sum of individual items.

[e] Sum of global items.

[1] $p \leq .050$ vs baseline.

[2] $p \leq .010$ vs baseline.

[3] $p \leq .001$ vs baseline.

[4] $p \leq .050$ vs placebo.

[5] $p \leq .010$ vs placebo.

[6] $p \leq .001$ vs placebo.

[7] $p \leq .050$ vs haloperidol.

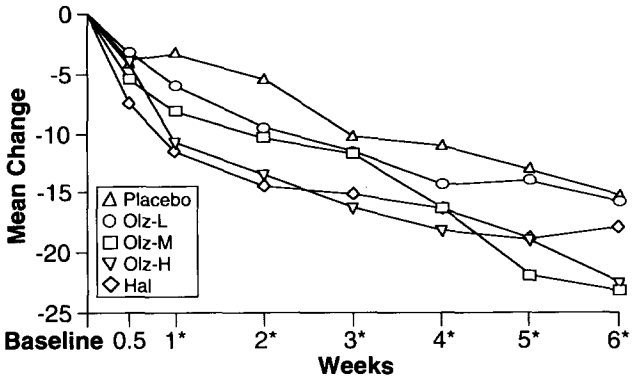

Figure 1. Weekly change in Brief Psychiatric Rating Scale (BPRS)-total scores (observed cases); $p \leq .05$.

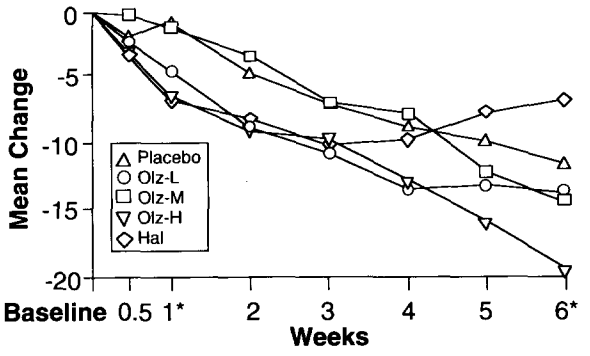

Figure 3. Weekly change in Scale for the Assessment of Negative Symptoms (SANS)-composite scores (observed cases); $p \leq .05$.

symptoms demonstrated continued improvement, but in the Hal treatment group, they worsened after demonstrating initial improvement.

Efficacy—Percentage Improvement in Severity

Olz-H was statistically significantly and/or numerically associated with a higher percentage of patients showing a given degree of improvement (Table 6), especially when considering more substantial levels of improvement (e.g., ≥80%, ≥60%). The protocol defined a responder as a patient showing a ≥40% decrease in BPRS-total score or a final BPRS-total score ≤18 in patients completing at least visit 7 (approximately 4 weeks) of double-blind therapy. The rate of response and the number of patients completing at least visit 7 were as follows: placebo, 58.8% (n = 34); Olz-L, 58.3% (n = 36); Olz-M, 64.3% (n = 42); Olz-H, 66.7% (n = 48); and Hal, 61.7% (n = 47). Because of this high placebo response rate (not unexpected in patients remaining on treatment ≥4 weeks), treatment groups did not show an overall statistically significant difference with respect to rate of response, based on this definition of responder.

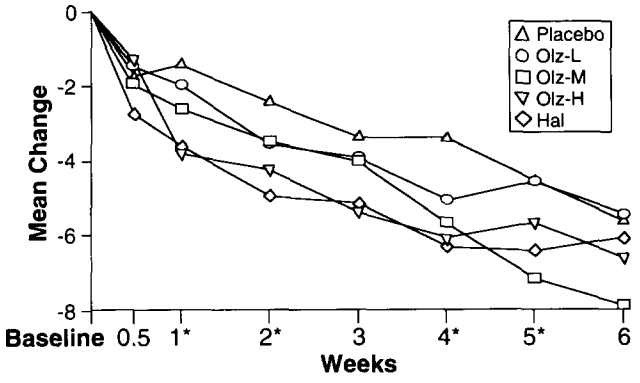

Figure 2. Weekly change in Brief Psychiatric Rating Scale (BPRS)-positive scores (observed cases); $p \leq .05$.

Patient Disposition

A greater percentage of Olz-H-treated patients completed the acute phase of the study than patients in the other treatment groups (Table 7). Overall, discontinuation for adverse events was quite low. The events that led to discontinuations in placebo-treated patients were events that may well have been manifestations of an exacerbation of psychopathology.

Safety—Adverse Events

It is notable that the most common treatment-emergent (first appeared or worsened during double-blind therapy) adverse events (somnolence, agitation, asthenia, and nervousness) (Table 8) reflect both psychomotor slowing and activation. It is possible that the activation events are more related to psychopathology than to pharmacologic effect. The potential anticholinergic events, constipation and dry mouth, showed an increasing dose-response relationship with olanzapine, but absolute rates may be less than that suggested by the affinity of olanzapine for cholinergic receptors. The incidence of acute extrapyramidal symptom-related events (dystonia, akathisia, as well as hypertonia and tremor suggestive of parkinsonism) were statistically significantly different across treatment groups, and there were no dystonic reactions with olanzapine. Weight gain reported as a treatment-emergent adverse event was not consistent with measured weight change (see Safety—Weight and Vital Signs section).

Adverse events leading to discontinuation among placebo-treated patients included agitation, akathisia, paranoid reaction, schizophrenia reaction, and suicide attempt—all probably manifestations of psychopathology. Six patients discontinued olanzapine because of

Table 6. Percentage Improvements in BPRS-Total Score[a] (last observation carried forward)

Amount of Improvement	Placebo (n = 62)	Olz-L (n = 63)	Olz-M (n = 62)	Olz-H (n = 65)	Hal (n = 68)	Overall p-Value
≥20% improvement	40.3	47.6	58.1[1]	66.2[2]	63.2[2]	0.016
≥40% improvement	33.9	33.3	43.5	47.7	47.1	0.266
≥60% improvement	14.5	11.1	27.4	29.2[1]	22.1	0.049
≥80% improvement	3.2	0.0	6.5	12.3[3]	1.5	0.008

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day.

[a] Items scored 0–6.

[1] $p \leq .050$ vs placebo.

[2] $p \leq .010$ vs placebo.

[3] $p \leq .050$ vs haloperidol.

elevated ALT values, but these patients did not manifest clinical signs of hepatic dysfunction and their ALT values decreased after they discontinued the drug. One Olz-L-treated and one Hal-treated patient were discontinued because of leukopenia. The Olz-L-treated patient who discontinued because of leukopenia had shown a marked decrease in total white blood cell count (WBC) prior to beginning the study, which continued during double-blind therapy. The decrease in WBC was primarily accounted for by a decrease in lymphocytes. The Hal-treated patient who discontinued because of leukopenia showed a decrease in WBC (primarily neutrophils) during double-blind therapy, which improved when double-blind haloperidol therapy was held for 1.5 days but recurred upon rechallenge with double-blind haloperidol for 3 days before actual discontinuation from the study.

One patient experienced a seizure during the placebo lead-in phase and was discontinued prior to receiving double-blind therapy. No seizures occurred in association with double-blind therapy.

Safety—Extrapyramidal Symptom Rating Scales

Table 9 shows that for parkinsonism (Simpson-Angus) and akathisia (Barnes), all olanzapine-treated groups improved numerically with respect to baseline, and the haloperidol-treated group worsened numerically (Barnes) and statistically significantly (Simpson-Angus) with respect to baseline. Scores on the Simpson-Angus were not consistent across study sites. Six of 22 sites, with only one or two patients in each treatment arm, had endpoint mean changes in scores that differed from the overall results, primarily improvement or less worsening in the haloperidol-treated group. All treatment groups improved slightly with respect to AIMS scores (dyskinesias), except the Olz-L-treated group.

Safety—Weight and Vital Signs

Weight gain was associated with olanzapine use, the endpoint mean increase associated with Olz-H was 3.5 ± 3.9 kg. No olanzapine treatment group demonstrated a clinically or statistically significant (compared to placebo or Hal) change in orthostatic blood pressure or heart rate changes. In fact, Olz-H resulted in a slight decrease in mean orthostatic blood pressure decrease. No mean change in vital signs within any treatment group was considered clinically significant.

Safety—Laboratory Analyses

Eosinophil count was the only hematologic parameter in which an overall statistically significant treatment

Table 7. Patient Disposition (%)

	Placebo (n = 68)	Olz-L (n = 65)	Olz-M (n = 64)	Olz-H (n = 69)	Hal (n = 69)	Overall p-Value
Completed	32.4	41.5	40.6	49.3	43.5	0.380
Discontinued						
Adverse event	10.3	7.7	1.6	5.8	8.7	0.329
Lack of efficacy	47.1	33.8	37.5	26.1	27.5	0.070
Lost to follow-up	1.5	3.1	4.7	1.4	7.2	0.315
Patient decision	2.9	10.8	10.9	10.1	10.1	0.430
Protocol variation	5.9	3.1	4.7	7.2	2.9	0.725

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day.

Table 8. Treatment-Emergent Adverse Events (percent; ≥10% in any olanzapine treatment group or statistically significant)

Event	Placebo (n = 68)	Olz-L (n = 65)	Olz-M (n = 64)	Olz-H (n = 69)	Hal (n = 69)	Overall p-Value
Somnolence	16.2	20.0	29.7	39.1[2]	34.8[1]	0.013
Agitation	23.5	16.9	29.7	26.1	30.4	0.386
Asthenia	14.7	7.7	9.4	20.3	21.7	0.081
Nervousness	19.1	16.9	14.1	20.3	27.5	0.366
Headache	22.1	20.0	14.1	18.8	24.6	0.631
Dizziness	2.9	7.7	9.4	17.4	7.2	0.051
Insomnia	22.1	21.5	25.0	17.4	20.3	0.875
Constipation	0.0	6.2[1]	7.8[1]	14.5[3]	5.8[1]	0.021
Anxiety	10.3	7.7	7.8	13.0	17.4	0.350
Dry mouth	4.4	3.1	4.7	13.0	4.3	0.094
SGPT increase	4.4	12.3	4.7	13.0	4.3	0.107
Hostility	14.7	21.5	9.4	11.6	8.7	0.178
Accidental injury	10.3	3.1	7.8	10.1	4.3	0.352
Dyspepsia	11.8	13.8	6.3	10.1	15.9	0.477
Hypertonia	4.4	3.1[6]	4.7[6]	8.7[4]	24.6[3]	<0.001
Rhinitis	4.4	4.6	12.5	8.7	10.1	0.354
Pain	13.2	9.2	14.1	7.2	13.0	0.671
Personality disorder	2.9	10.8	10.9	4.3	4.3	0.169
Nausea	8.8	0.0[1]	1.6	8.7	1.4[1]	0.015
Akathisia	1.5	4.6[4]	6.3	7.2	15.9[2]	0.017
Tremor	1.5	0.0[6]	4.7	5.8	14.5[2]	0.002
Dystonia	0.0	0.0[5]	0.0[5]	0.0[5]	13.0[2]	<0.001
Weight gain	0.0	12.3[2,4]	7.8[1]	0.0	2.9	0.001

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range, 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day.

[1] $p \leq .050$ vs placebo.
[2] $p \leq .010$ vs placebo.
[3] $p \leq .001$ vs placebo.
[4] $p \leq .050$ vs haloperidol.
[5] $p \leq .010$ vs haloperidol.
[6] $p \leq .001$ vs haloperidol.

Table 9. Endpoint Change in Extrapyramidal Symptom Scores (last observation carried forward)

Score	Placebo	Olz-L	Olz-M	Olz-H	Hal	Overall p-Value
Simpson-Angus	−0.6 ± 2.0[1] (n = 64)	−0.7 ± 2.2[2,5] (n = 62)	−0.3 ± 2.5[5] (n = 60)	−0.3 ± 2.0 (n = 63)	1.0 ± 4.0[1,4] (n = 67)	0.042
Barnes	0.2 ± 0.9 (n = 64)	−0.2 ± 0.9[3] (n = 63)	−0.3 ± 1.0[2,4,6] (n = 63)	−0.2 ± 0.9[3] (n = 65)	0.4 ± 1.0[2] (n = 68)	0.009
AIMS	−0.1 ± 2.2 (n = 64)	0.1 ± 1.9 (n = 63)	−0.8 ± 2.7[1] (n = 63)	−0.6 ± 3.9 (n = 65)	−0.2 ± 3.3 (n = 68)	0.225

Abbreviations: Olz-L = olanzapine treatment range, 2.5, 5, or 7.5 mg/day; Olz-M = olanzapine treatment range, 7.5, 10, or 12.5 mg/day; Olz-H = olanzapine treatment range , 12.5, 15, or 17.5 mg/day; Hal = haloperidol treatment range, 10, 15, or 20 mg/day; Simpson-Angus = Simpson-Angus Total Score; Barnes = Barnes Akathisia Rating Global Score (item 4); AIMS = Abnormal Involuntary Movement Total Score (sum of items 1-7); SD = standard deviation.

Scores are mean ± SD.

[1] $p \leq .050$ vs baseline.
[2] $p \leq .010$ vs baseline.
[3] $p \leq .050$ vs placebo.
[4] $p \leq .010$ vs placebo.
[5] $p \leq .050$ vs haloperidol.
[6] $p \leq .010$ vs haloperidol.

effect was observed with within-treatment changes ranging from −0.03 to 0.02 bill/L. The greatest baseline-to-endpoint changes observed were decreases in the haloperidol (statistically significant) and placebo treatment groups. The proportion of patients whose eosinophil counts were at or below the upper limit of the reference range at baseline and exceeded that limit at endpoint was not statistically significantly different across the treatment groups.

Laboratory data, both endpoint mean change and categoric increase, suggested that olanzapine is associated with increases in hepatic transaminases (ALT and aspartate transaminase [AST]) as well as gamma-glutamyl transferase (GGT) in a dose-dependent manner, at least with respect to ALT and AST. With Olz-H, the endpoint mean increase in ALT was 24.3 ± 93.5 U/L, and 9.2% of the patients with baseline ALT values at or below the upper limit of the Lilly reference range had endpoint values above the upper limit of the Lilly reference range. Discontinuations because of elevated ALT have been discussed above. These patients did not manifest clinical signs or symptoms of hepatic dysfunction, and these values decreased after discontinuation. In addition, a number of olanzapine-treated patients who experienced transaminase elevations during therapy remained on therapy, and these values returned toward normal during continued therapy.

Prolactin elevation was associated with olanzapine in a dose-dependent manner, but the increase with all doses was not statistically significantly greater than those observed with placebo (placebo, 0.1 ± 0.2 nmol/L; Olz-L, 0.1 ± 0.3 nmol/L; Olz-M, 0.2 ± 0.3 nmol/L; Olz-H, 0.2 ± 0.3 nmol/L; Hal, 0.6 ± 0.8 nmol/L). Mean increases were statistically significantly less in all olanzapine groups than in the haloperidol group ($p < .001$ in all cases). Haloperidol was associated with a greater number of endpoint categoric increases in prolactin concentrations as compared to olanzapine (placebo, 14.5%; Olz-L, 13.5%; Olz-M, 20.8%; Olz-H, 23.6%; Hal, 50.9%); no Olz-H-treated patient had an increase of greater than 0.84 nmol/L, compared to 22.2% in Hal-treated patients.

DISCUSSION

The primary finding of this study is that olanzapine demonstrated a dose-responsive ability to decrease overall psychopathology, as indicated by the decrease in BPRS-total score. Olz-H was superior to Hal with regard to improvement in negative symptoms. In addition, all olanzapine-treated groups showed decreases in acute extrapyramidal symptom severity ratings, whereas the haloperidol-treated group worsened in this regard.

The study population in this trial presented a particularly good opportunity to test olanzapine's effectiveness because these patients, with an overall mean age of approximately 36 years and with a DSM-III-R-defined chronic course (approximately 91% of the total population), were for the most part not in an early phase of their illness. These patients were also severely symptomatic in all domains at baseline. Over the treatment groups, the mean BPRS-total score, reflecting overall psychopathology, was approximately 42, which is 39% of the maximum score; the mean BPRS-positive score was approximately 13, which is 54% of the maximum score; and the mean SANS-composite score was approximately 44, which is 46% of the maximum score. Not only was the psychopathology severe, but negative symptoms were also prominent, even in the context of acute exacerbations of illness.

With regard to efficacy, the two higher dosage arms of olanzapine and haloperidol were superior to placebo. On core positive symptoms (BPRS-positive), these three treatment arms were comparable with respect to treatment effect. The numeric superiority of Olz-H compared to Hal with respect to overall psychopathology (BPRS-total) was a reflection of its superiority with respect to negative symptoms (SANS-composite and SANS-summary) and perhaps nonspecific psychopathology.

The weekly (observed cases) analyses support the clinical validity of the endpoint (LOCF) analysis, indicating a differential effect between Olz-H and Hal with respect to negative symptoms. By the end of this 6-week, double-blind, acute therapy phase, Hal-treated patients had stabilized or were showing a slight increase in positive symptoms, but were showing a more substantial increase in negative symptoms after their initial improvement. Olz-H treated patients, on the other hand, also showed a relative plateauing of improvement in positive symptoms, but were continuing to show increasing improvement in negative symptoms. The double-blind extension phase of this acute trial and/or longer trials will contribute additional comparative data regarding efficacy against negative symptoms.

When considering substantial improvement (≥60% and/or ≥80% decrease in BPRS-total score), Olz-H was superior to placebo and haloperidol. However, this finding must be considered preliminary and interpreted cautiously as it was a post-hoc finding and the study involved three olanzapine dosage ranges against one haloperidol dosage range. It is interesting that in this study of patients with a chronic disease history and marked cross-sectional severity, a substantial percentage of placebo-treated patients (33.9%) showed at least a 40% decrease. Placebo improvement declined sharply when the criterion of a decrease in BPRS-total score >40% was considered. There was also substantial deterioration with placebo (the BPRS-total score increased as much as 136%). Little deterioration (increase in BPRS-

total score) was seen with olanzapine or haloperidol; the maximum increase in BPRS-total for Olz-H and Hal was 48% and 46%, respectively.

Several factors and their potential interaction may explain the relatively high percentage of placebo-treated patients showing a decrease in BPRS-total score of 40% or more. The protocol required patients to be experiencing an acute exacerbation of symptoms in addition to having a symptom severity, based on BPRS total score, of ≥24. In spite of the majority of patients having a chronic course, these patients were required to have an acute exacerbation and therefore had unstable cross-sectional symptoms. Such symptom profiles may be more subject to improvement than more stable symptoms. Patients were required to be maintained on an inpatient ward for at least 3 weeks and were receiving considerable attention as a result of required evaluations. The effects of milieu may therefore have contributed to improvement. Finally, substantial benzodiazepine rescue was allowed (up to 10 mg/day for up to 21 days during double-blind of lorazepam). Placebo-treated patients did not receive significantly more average lorazepam per day nor did a significantly greater percentage of placebo-treated patients receive one or more doses of lorazepam. However, benzodiazepine treatment may have had a moderate effect on reducing BPRS-total scores, particularly among placebo-treated patients.

With regard to overall psychopathology, olanzapine treatment demonstrated increasing efficacy across the three fixed dosage ranges. This pattern of steady increase without reaching a plateau or a decrement, arouses interest from several perspectives. First, this pattern in treatment of overall psychopathology contrasts with that observed with risperidone, an antipsychotic agent with D_2 antagonist activity but greater $5\text{-}HT_{2A}$ antagonist activity (Chouinard et al. 1993; Marder and Meibach 1994). Risperidone efficacy results show a curvilinear pattern associated with dose, declining with both lower and higher doses. Second, the pattern observed with olanzapine in this study raises the question of the potential for increased efficacy with higher doses since no efficacy plateau was observed. As suggested by the work of Van Putten et al. (Van Putten et al. 1990), the dosage range of haloperidol included in this study may well have optimized haloperidol's efficacy. They have provided data to indicate an early advantage to a dose of 20 mg/day of haloperidol, but also suggesting that 10 mg/day of haloperidol may be the optimal overall dose. In the study reported here, the median haloperidol dose on which patients were stabilized was 15 mg/day.

The most common adverse events across all treatment groups in this study were reflective of both psychomotor slowing (somnolence, asthenia) and psychomotor activation (agitation, nervousness, insomnia, anxiety). It is possible that the psychomotor slowing events were drug-related effects, because they were dose-related with olanzapine and occurred more often with haloperidol than with placebo. Psychomotor activation events may have been more a manifestation of the schizophrenic illness and lack of therapeutic drug effect; however, slightly more agitation, nervousness, and anxiety were reported with higher doses of olanzapine and haloperidol than with placebo, suggesting some potential for a pharmacologic contribution.

Anticholinergic adverse events (constipation, dry mouth) occurred with olanzapine in a dose-dependent manner. However, given the in vivo potency of olanzapine's antagonistic affinity for muscarinic cholinergic receptors, the rates of these events were quite low. For comparison, treatment-emergent increases in dry mouth are commonly reported by an excess of 50% of patients taking tertiary amine tricyclic antidepressants in double-blind clinical trials (Stark and Hardison 1985; Beasley et al. 1993). Treatment-emergent increases in salivation were not associated with any of the olanzapine treatment groups but did occur with placebo (2.9%) and haloperidol (4.3%).

Dizziness, increasing in a dose-dependent manner, reported with olanzapine use did not appear to have been due to orthostasis. Mean changes at endpoint in the measurements of orthostatic blood pressure decrease and heart rate increase did not reveal a clinically significant orthostatic effect. More importantly, categorical occurrences of orthostasis (defined as a systolic blood pressure decrease of ≥10 mm Hg, a heart rate increase of ≥10 min^{-1}, or both) at any visit did not occur significantly more often with Olz-H than with placebo (Olz-H: blood pressure only 27.8%, heart rate only 69.4%, both 25.0%; placebo: blood pressure only 30.3%, heart rate only 57.6%, both 24.2%).

The incidence of clinical treatment-emergent acute extrapyramidal symptom events and the extrapyramidal symptom rating scores in olanzapine treatment groups were comparable to those that have been reported with clozapine (Casey 1989). Importantly, as with clozapine, no acute dystonia was observed with any dose of olanzapine (Casey 1989). Treatment-emergent parkinsonism (hypertonia and possibly tremor) occurred with Olz-H at approximately one-third the rate of Hal. Treatment-emergent akathisia occurred with Olz-H at approximately one-half the rate with Hal. On a group basis, all olanzapine doses were associated with actual decreases in both parkinsonism and akathisia severity ratings at endpoint relative to baseline, whereas haloperidol treatment resulted in increases. As would be expected in an acute study, haloperidol and effective, higher doses of olanzapine resulted in decreases in the severity ratings of dyskinetic movements (AIMS scores). However, the improvements with olanzapine were numerically greater. Further trials will be useful

in establishing the ability of olanzapine to suppress established tardive dyskinesia and whether, like clozapine, it has a decreased potential to induce tardive dyskinesia.

Laboratory analytes in this study did not yield any data to suggest an adverse hematologic effect associated with olanzapine. Additional long-term data will be important in corroborating these hematologic findings. Olanzapine was associated in a potentially dose-dependent manner with elevations in hepatic transaminases. Although greater than with haloperidol, the incidence of these elevations may approximate those observed with clozapine and other antipsychotics (Bauer and Gaertner 1983; Gaertner et al. 1989; Leppig et al. 1989; Naber et al. 1989). With a number of patients, these elevations were transient while they remained on olanzapine therapy and declined after discontinuation in the six patients discontinued for such elevation. Prolactin elevations from at or below the upper limit of the reference range at baseline to greater than the upper limit of the reference range at endpoint occurred almost twice as often with Hal as with Olz-H. More importantly, elevations observed with olanzapine were substantially smaller, when they occurred, than with haloperidol. This pattern of effect on prolactin may be comparable to that observed with clozapine (Meltzer et al. 1979; Kane et al. 1981).

In summary, these results indicate that olanzapine offers excellent overall efficacy in the acute treatment of severe acute exacerbations of chronic schizophrenia. The numeric superiority of the highest dosage range of olanzapine relative to haloperidol with respect to overall symptomatology was apparently accounted for by a selective advantage in treating negative symptoms. Olanzapine was well tolerated with no acute dystonias and few other treatment-emergent acute extrapyramidal symptoms. In fact, on the whole, olanzapine reduced parkinsonism, akathisia, and dyskinesias. No evidence of blood dyscrasias was observed. Hepatic transaminase elevations did occur in some patients but were not associated with clinical signs or symptoms of hepatic disease. The effect of olanzapine on prolactin appeared to be minimal.

These study results indicate that olanzapine fulfills several clinical criteria for consideration as an atypical antipsychotic: (1) greater efficacy in the treatment of negative symptoms of schizophrenia; (2) less acute extrapyramidal symptoms, especially dystonias; and (3) minimal prolactin elevations. Additional studies will be required to corroborate these findings. Results of the long-term extension of this trial and other studies will be important for the assessment of the influence of olanzapine on negative symptoms. A specific study will be required to evaluate the efficacy of olanzapine in the treatment of patients with schizophrenia who are nonresponsive to typical antipsychotics.

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APPENDIX

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