Efficacy of Olanzapine: An Overview of Pivotal Clinical Trials

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Olanzapine is a new "atypical" antipsychotic agent that belongs chemically to the thienobenzodiazepine class. Its relatively greater binding affinity for 5-HT_2 compared to D_2 receptors makes it similar to the atypical agent clozapine, a serotonin/dopamine antagonist. Four double-blind pivotal studies, which compare olanzapine to placebo and/or haloperidol, are presented. The results suggest that olanzapine is as effective as haloperidol for positive symptoms and more effective than haloperidol for the treatment of the negative symptoms of schizophrenia.

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Olanzapine is a new antipsychotic agent that belongs chemically to the thienobenzodiazepine class. The compound has high affinity for the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, D_1, D_2, D_3, D_4, muscarinic M_1–M_5, α_1-adrenergic, and histaminergic H_1 receptors. Although olanzapine is chemically and pharmacologically distinct from currently available and investigational antipsychotic agents, its pharmacologic profile of activity appears to be similar to that of the atypical agent clozapine, which has been shown to improve both positive and negative symptoms of schizophrenia. An open-label trial[1] of olanzapine demonstrated the potential efficacy and safety of this agent.

The data submitted to regulatory agencies for approval of olanzapine were from February 14, 1995. As of that date, olanzapine had been investigated in 50 studies in 22 countries, resulting in a total of 3139 persons having been exposed to at least one dose of olanzapine (data on file, Eli Lilly and Co.). In primary clinical trial database studies, 2500 patients received treatment with olanzapine. Of these, 876 received at least 6 months of treatment, and 301 received at least 1 year of treatment. The longest duration of treatment for any one patient was 3 years and 72 days. These data represent a total of more than 1100 patient-years of exposure to olanzapine (data on file, Eli Lilly and Co.). This report summarizes the acute efficacy findings of four adequate and well-controlled double-blind clinical trials for olanzapine in the treatment of schizophrenia and related disorders, then provides a more detailed examination of the three studies conducted with the intent of also demonstrating the efficacy of olanzapine in the long-term treatment of schizophrenia and related psychoses.

CORE CLINICAL TRIALS

Study 1 (HGAP): The U.S. Clinical Trial

Methods. The U.S. Clinical Trial[2] was a multicenter study conducted in the United States that involved 152 inpatients with a DSM-III-R diagnosis of schizophrenia and a Brief Psychiatric Rating Scale (items scored 0–6) ($BPRS_{0-6}$) total score ≥ 24. This randomized, double-blind placebo-controlled, parallel study compared olanzapine at doses of 1 mg/day (Olz 1.0) and 10 mg/day (Olz 10.0) with placebo. Following a 4- to 9-day lead-in period (Study Period 1) in which all patients received placebo, patients were randomly assigned to one of three treatment groups. The acute phase (Study Period 2) lasted 6 weeks. Patients who completed more than 3 weeks of double-blind therapy and were not responding to treatment could enter the open-label olanzapine phase (Study Period 3) of the trial. In addition, patients who completed the 6-week acute phase, regardless of whether they were responding to treatment, could enter Study Period 3, which was an open-label extension. Efficacy was established in the U.S. Clinical Trial using last-observation-carried-forward (LOCF) endpoint analyses of mean changes on the BPRS, Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression-Severity of Illness (CGI-S) scores. Patients completing at least 3 weeks of treatment were defined as responders if they evidenced at least a

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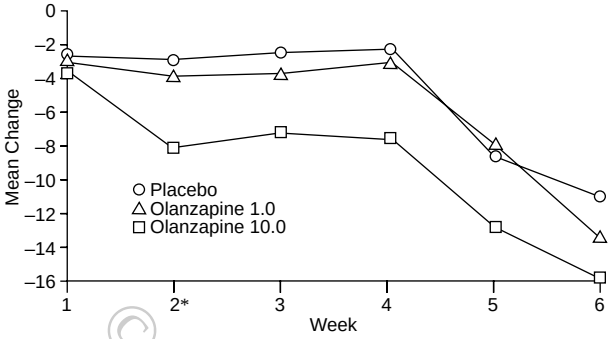
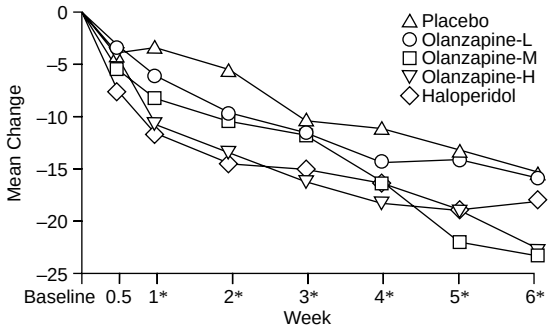
Figure 1. Weekly Change in Brief Psychiatric Rating Scale (BPRS) Total Scores (Observed Cases) in Study 1†



†From reference 2, with permission.
*Overall treatment comparison statistically significant; p ≤ .05.

Figure 2. Weekly Change in Brief Psychiatric Rating Scale (BPRS) Total Scores (Observed Cases) in Study 2†



†From reference 3, with permission.
*Overall treatment comparison statistically significant; p ≤ .05.

40% decrease in BPRS total score or an endpoint BPRS total score of 18 or lower.

Results. Treatment groups did not differ significantly with respect to patient and illness characteristics or baseline severity of illness rating score. Patients were generally in their late 30s (mean age = 38 years), white, and male. The majority were of the paranoid subtype (53.3%), had a chronic course (98.%), and experienced an acute exacerbation (65.1%). Mean $BPRS_{0–6}$ total score was approximately 38, reflecting relatively severe overall psychopathology. The mean baseline PANSS negative score was approximately 25, indicating relatively severe negative symptomatology. The acute phase results of the U.S. Clinical Trial (Figure 1) demonstrate that improvement in the endpoint (LOCF) mean BPRS total score in the Olz 10.0 treatment group was statistically significantly greater than in the placebo treatment group. Improvements in the endpoint (LOCF) mean PANSS total, positive, and negative scores in the Olz 10.0 treatment group were statistically significantly greater than in the placebo treatment group. The Olz 1.0 group did not show significant improvement over placebo for any efficacy measurement.

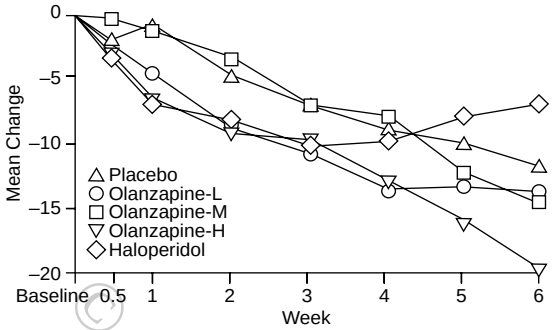
Study 2 (HGAD):
North American Clinical Trial

Methods. The North American Clinical Trial[3] was a multicenter study conducted at 22 sites in the United States and Canada that involved 335 patients with a DSM-III-R diagnosis of schizophrenia with acute exacerbation and $BPRS_{0–6} \geq 24$. This study compared olanzapine in the dosage ranges of 5.0 ± 2.5 mg/day (designated as the Olz-L treatment group), 10.0 ± 2.5 mg/day (Olz-M treatment group), and 15 ± 2.5 mg/day (Olz-H treatment group) with haloperidol in the dosage range of 15 ± 5 (Hal treatment group) and with placebo. This was a randomized, parallel, active-controlled and placebo-controlled study. After a 4- to 7-day lead-in period (Study Period 1) in which all patients received placebo, patients were randomly assigned to a treatment group. All patients received their assigned therapy for a 6-week acute phase of treatment (Study Period 2). Treatment responders could continue double-blind therapy for up to 12 months (Study Period 3). Continued responders could continue treatment beyond 1 year (Study Period 4). Patients treated with olanzapine during Study Period 4, when unblinded, were given the opportunity to receive olanzapine for an indefinite period (Study Period 5). Efficacy was assessed using LOCF endpoint analyses of the mean change in the BPRS, Scale for the Assessment of Negative Symptoms (SANS), and CGI-S scores. Response criteria were the same as those in Study 1.

Results. Treatment groups, at baseline, were similar in regard to patient and illness characteristics, with the exception of slightly higher scores for extrapyramidal symptomatology in the Hal group. Patients were generally white, male, in their mid-30s, of the paranoid subtype, and had a chronic course. Mean baseline $BPRS_{0–6}$ total score was approximately 42, while mean baseline SANS-composite score was approximately 44, indicating relatively severe overall psychopathology, and severe negative symptomatology. The patient group demonstrated a clinically severe mixed symptom profile in the context of a chronic course. Based on the acute phase results, olanzapine in the dosage range of 7.5 mg/day (Olz-M) to 17.5 mg/day (Olz-H) was shown to be an effective antipsychotic agent with respect to overall psychopathology and core positive psychotic psychopathology. BPRS total score reduction was statistically significantly greater in Olz-M and Olz-H groups compared to placebo (Figure 2). CGI and BPRS positive score reductions were also statistically significantly greater in the Olz-M and Olz-H groups compared to placebo.

Negative symptoms. Olanzapine in the dosage range of 15 ± 2.5 mg/day (Olz-H) was more effective than haloperidol 15 ± 5 mg/day (Hal) against negative symptoms, as

Figure 3. Weekly Change in Scale for the Assessment of Negative Symptoms (SANS)-Composite Scores (Observed Cases)†



†From reference 3, with permission.

Figure 4. A Model of Negative Symptom Path Analysis

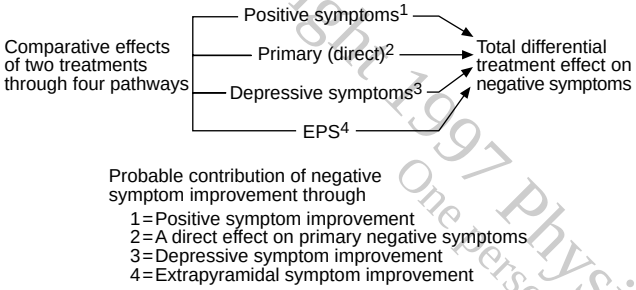
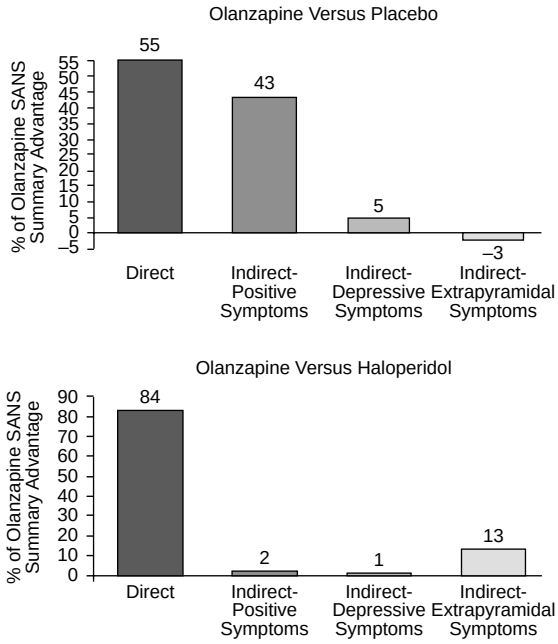


Figure 5. Direct Versus Indirect Effects on Negative Symptoms of Schizophrenia in Study 2



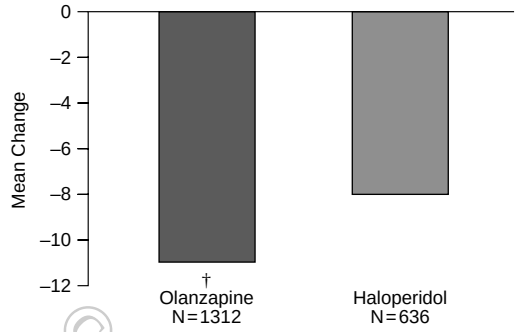
evidenced by statistically significantly greater mean decrease (LOCF) in the BPRS negative score and SANS (Figure 3). Path analysis (a method of analysis of covariance) was used to detect the primary direct effect of olanzapine on negative symptoms (Figure 4). This methodology enabled the contributions of changes in positive symptoms, affective symptoms, and EPS on observed changes on the negative symptom scale to be factored out. Figure 5 shows the results for olanzapine versus placebo; it indicates that 55% of the relative difference is accounted for by a direct therapeutic effect on negative symptoms, and this difference remained statistically significant. A statistically significant primary effect on negative symptoms, in the olanzapine versus haloperidol comparison in Study 2 is also shown in Figure 5 where 84% of the difference between treatments was accounted for by a direct effect on negative symptoms.

Study 3 (E003): Eastern Hemisphere Clinical Trial

Methods. The Eastern Hemisphere clinical trial was a multicenter study conducted in Europe, South Africa, Israel, and Australia that involved 431 inpatients with a DSM-III-R diagnosis of schizophrenia with acute exacerbation and $BPRS_{0-6} \geq 24$. The trial compared three dosage ranges of olanzapine (Olz-L, 5.0 ± 2.5 mg/day; Olz-M, 10.0 ± 2.5 mg/day; Olz-H, 15.0 ± 2.5 mg/day) with one dosage range of haloperidol (Hal, 15 ± 5 mg/day) and an extremely low dose of olanzapine (Olz 1.0, 1.0 mg/day). This was a randomized, double-blind, active-controlled and parallel study.[4] After a 4- to 7-day lead-in period (Study Period 1) in which all patients received placebo, patients were randomly assigned to one of the treatment groups. After a 6-week period of assigned therapy (Study Period 2), treatment responders, i.e., all patients who experienced at least a 40% decrease in the BPRS or whose BPRS was no higher than 18 at endpoint, could continue double-blind treatment for up to 12 months (Study Period 3). Patients who continued to respond to treatment in Study Period 3 could continue double-blind therapy beyond 1 year (Study Period 4), and those who had received olanzapine in Study Period 4 could receive open-label olanzapine for an indefinite period (Study Period 5).

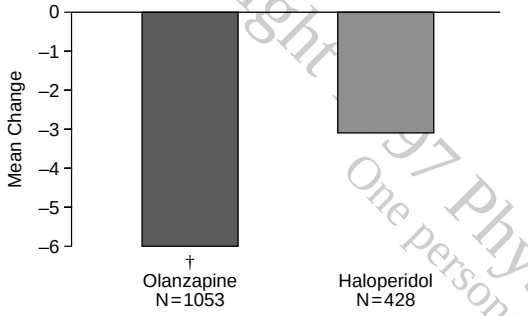
Results. Patients were comparable at baseline. No statistically significant differences were observed between the mean change in BPRS total score in the Olz-L, Olz-M, Olz-H treatment groups and the Olz 1.0 group. In addition, based on the primary efficacy analysis, no statistically significant differences were detected when comparing the efficacy of the olanzapine treatment groups with the haloperidol group. The Olz-H treatment group did show statistically significantly greater improvement than the Olz 1.0 treatment group in several secondary efficacy analyses, including the BPRS positive score, the PANSS positive score, and the CGI-Severity score.

Figure 6. Mean Change (LOCF) in BPRS Total Scores in the Acute Phase of Study 4



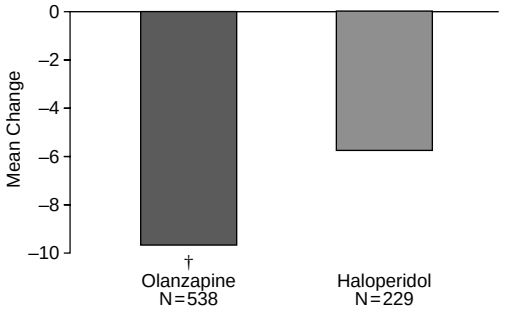
†p ≤ .050 vs haloperidol.

Figure 7. Mean Change (LOCF) in MADRS Total Scores in the Acute Phase of Study 4



†p ≤ .050 vs haloperidol.

Figure 8. Mean Change (LOCF) in MADRS Total Score in the Acute Phase of Study 4 in Significantly Depressed Patients*



*MADRS baseline scores ≥ 16.
†p ≤ .050 vs haloperidol.

Study 4 (HGAJ): International Clinical Trial

Methods. The international trial was a multicenter trial conducted in the United States, Canada, and Europe that involved 1996 inpatients or outpatients with a DSM-III-R diagnosis of schizophrenia (83.1%), schizophreniform disorder (1.9%), or schizoaffective disorder (15.0%) with either $BPRS_{0–6} \geq 18$ or intolerance to current therapy.[5] This randomized, double-blind, active-controlled, parallel study compared olanzapine in a dosage range of 5.0 to 20.0 mg/day (Olz) with haloperidol in a range of 5.0 to 20.0 mg/day (Hal).[5] After a 2- to 9-day screening phase (Study Period 1), patients were randomly assigned to either the Olz or the Hal treatment group. The randomization ratio was 2:1 olanzapine to haloperidol, meaning that approximately twice as many patients received olanzapine treatment (N = 1336) as received haloperidol treatment (N = 660). During the 6-week acute treatment phase (Study Period 2), patients received 5 mg/day of the assigned drug, with an option to increase the dose by 5 mg/day, on a weekly basis. Treatment responders, i.e., those who experienced at least 40% decrease in BPRS at endpoint, could continue double-blind treatment into Study Period 3. Patients who did not respond to treatment after more than 3 weeks in the acute phase could receive open-label olanzapine, as could those who did continue through the double-blind phase. Efficacy was assessed using LOCF endpoint analyses of mean change on the BPRS, PANSS, Montgomery-Asberg Depression Rating Scale (MADRS), and CGI-Severity scores.

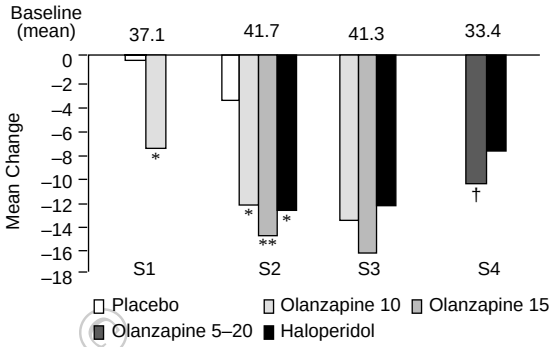
Results. Treatment groups were generally comparable with respect to patient characteristics at baseline. For the acute phase of treatment, the Olz treatment group had statistically significantly greater mean improvement in BPRS total score compared to the Hal treatment group (Figure 6). Negative symptoms were assessed through evaluation of the PANSS and BPRS negative scores, and depressive symptoms were assessed with the MADRS total score. Compared to the Hal treatment group, the Olz treatment group demonstrated statistically significant greater improvement in endpoint (LOCF) mean PANSS negative, BPRS negative, CGI-Severity, and MADRS total scores. Figure 7 shows the effect of olanzapine versus haloperidol on depressive symptomatology, as measured by the MADRS, while Figure 8 demonstrates the therapeutic effect in the more severely depressed patients. The Olz treatment group also experienced statistically significantly greater mean improvement in the MADRS in comparison to the Hal group within this subset of patients.

RESULTS: INTER-STUDY COMPARISONS

Acute Phase Efficacy Results

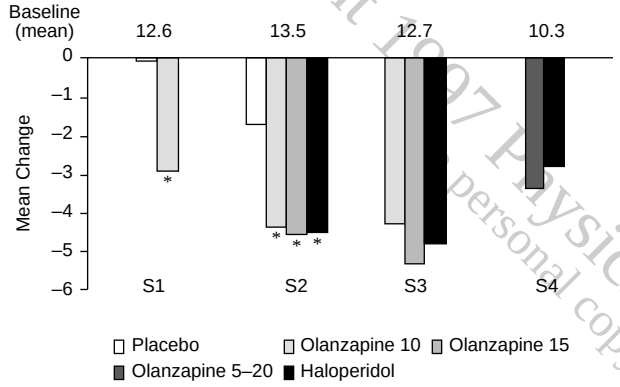
Figure 9 shows comparison of acute phase mean change (LOCF) for $BPRS_{0–6}$ total score for Studies 1 to 4. Statistically significant differences are seen in this primary efficacy assessment in groups treated with olanzapine 10 mg fixed dose vs. placebo (Study 1), 10 and 15 mg doses vs. placebo (Study 2), and olanzapine 5 mg to 20 mg vs. haloperidol (Study 4). BPRS positive subcluster scores are seen in Figure 10. Statistically significant differences are seen for olanzapine vs. placebo in Studies 1 and 2, while comparable results are found for olanzapine versus haloperidol. Negative symptomatology was as-

Figure 9. Mean Change (LOCF) in BPRS Total Scores in Acute Phases of Studies 1 to 4 (S1 to S4)



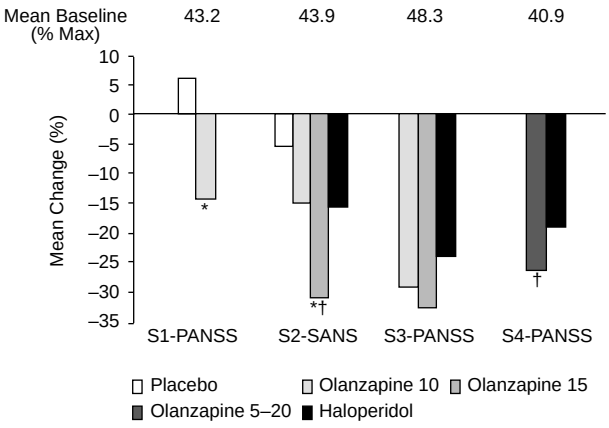
*p ≤ .050 vs placebo.
**p < .001 vs placebo.
†p ≤ .050 vs haloperidol.

Figure 10. Mean Change (LOCF) in BPRS Positive Scores in Acute Phases of Studies 1 to 4 (S1 to S4)



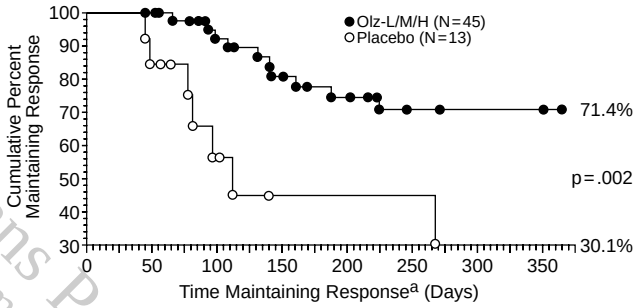
*p ≤ .050 vs placebo.

Figure 11. Mean Change (%, LOCF) in Negative Symptom Scale Scores in Acute Phases of Studies 1 to 4 (S1 to S4)[a]



[a]PANNS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms.
*p ≤ .010 vs placebo.
†p ≤ .050 vs haloperidol.

Figure 12. Time Maintaining Response to Olanzapine (Olz) or Placebo in Study 2*



*Olz-L = olanzapine 2.5–7.5 mg/d; Olz-M = olanzapine 7.5–12.5 mg/d; Olz-H = olanzapine 12.5–17.5 mg/d.
[a]Time maintaining response = time maintaining a sufficiently reduced level of psychopathology such that hospitalization is not required.

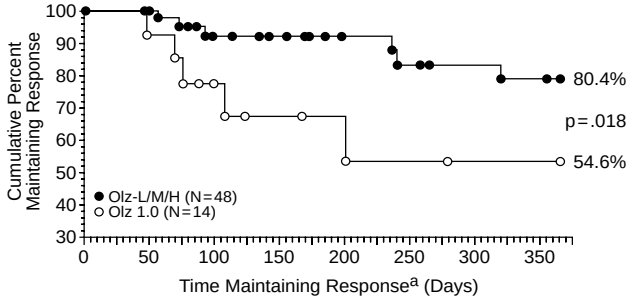
sessed through analysis of the PANSS in all studies except the North American study (Study 2), which employed the SANS. Figure 11 shows statistically significant changes, converted to percent from baseline, for the olanzapine versus placebo groups in Studies 1 and 2, and for olanzapine versus haloperidol groups in Studies 2 and 4.

Long-Term Efficacy Results

Methods. Long-term efficacy results were based on data gained from the double-blind extensions for patients who responded to acute-phase therapy in Studies 2 to 4. The long-term effectiveness of olanzapine was evaluated by analyzing prevention of relapse (defined as hospitalization for psychopathology during extension treatment). Kaplan-Meier survival analysis techniques were employed for these analyses. This form of analysis allows an estimation of outcomes over the entire period under consideration. These analyses, which consider data from patients who relapsed and those who discontinued for other reasons, were performed only on the subset of patients entering the extension phases who were definitely on outpatient status prior to entering the extension phase. Data were pooled within studies and across studies for these analyses as indicated in the figure legends (Figures 12–14).

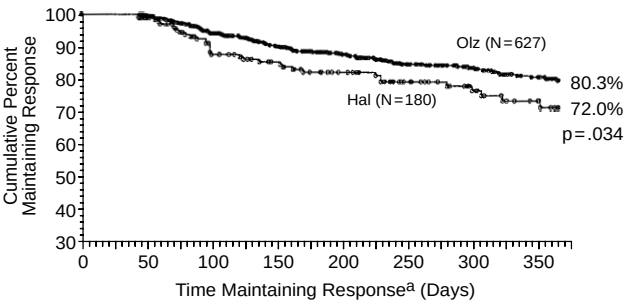
Results. Figure 12 shows an estimated 71% maintenance of response for olanzapine-treated patients in Study 2 (N = 45) compared to 30% for placebo-treated (N = 13). The difference in maintenance across the treatment period was statistically significant. In Figure 13, a similar result is seen for 48 patients in Study 3 who were responders to olanzapine, compared to patients who received olanzapine 1 mg, and again the difference was statistically significant. Pooled data from Studies 2 to 4 (olanzapine vs. haloperidol) are shown in Figure 14. A statistically significant difference in long-term maintenance of response is seen for the olanzapine-treated patients, compared to those who received haloperidol.

Figure 13. Time Maintaining Response to Olanzapine (Olz)-L/M/H or Olanzapine 1.0 in Study 3



[a]Time maintaining response = time maintaining a sufficiently reduced level of psychopathology such that hospitalization is not required.

Figure 14. Time Maintaining Response to Olanzapine (Olz) or Haloperidol (Hal) in Studies 2 to 4



[a]Time maintaining response = time maintaining a sufficiently reduced level of psychopathology such that hospitalization is not required.

DISCUSSION

The primary finding among the four pivotal, double-blind trials presented here is that olanzapine is effective in the treatment of the overall psychopathology in acute schizophrenia, as indicated by decrease in $BPRS_{0–6}$ total score. In the acute phase of each study presented, olanzapine demonstrated statistically significant or numerically superior results compared to placebo and haloperidol in regard to overall psychopathology. As would be expected from the pharmacologic profile of olanzapine, the treatment of negative symptoms, as assessed by the PANSS and the SANS, showed statistically significant improvement over haloperidol. These data were supported by path analysis, which suggested that olanzapine has a significant primary therapeutic effect on the amelioration of negative symptoms. In addition, olanzapine was associated with superior improvement in the treatment of depressive symptoms associated with acute schizophrenia, as measured by the MADRS, in comparison to haloperidol.

Long-term efficacy results,[6] based on data gained from the double-blind extensions for patients who responded to the acute phase of therapy, showed that fewer patients treated with olanzapine were estimated to experience a relapse at any given point in time, during the 1 year studied, than patients treated with placebo, very low dose olanzapine, or haloperidol.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa).

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