Dosing the Antipsychotic Medication Olanzapine

Charles B. Nemeroff, M.D., Ph.D.

Olanzapine is a new antipsychotic agent with serotonin/dopamine antagonism action. Efficacy in treating overall psychopathology in acute schizophrenia as measured by the $BPRS_{0-6}$ total score was demonstrated at 10 mg/day versus placebo; at doses in a 5–20 mg/day range, olanzapine was comparable or superior to haloperidol. Superior efficacy for negative and depressive symptoms was shown in comparison to haloperidol. Olanzapine has a favorable acute and tardive extrapyramidal symptom profile relative to haloperidol and caused substantially less elevation of serum prolactin. Dose-related weight gain and asymptomatic mild transaminase elevations occurred in olanzapine-treated patients.

(J Clin Psychiatry 1997;58[suppl 10]:45–49)

© Copyright 1996 Physicians Postgraduate Press, Inc.
One personal copy may be printed

Prescribing optimal pharmacotherapy for patients with major psychiatric disorders such as schizophrenia requires balancing efficacy of the medication against possible adverse effects. Optimal dosing of the new antipsychotic drug olanzapine was studied by exploring dose-response relationships in four double-blind randomized clinical trials (Studies 1–4), some involving fixed dosages and others allowing dose titration (Table 1).

Dosing comparisons between olanzapine and haloperidol were facilitated by the fact that both medications are administered in once-daily doses and in the same dosage range.

DOSE-RESPONSE FOR EFFICACY

The efficacy of various doses of olanzapine compared to placebo and haloperidol was evaluated using a variety of measures.

- Study 1, the U.S. Clinical Trial,[1] compared a low dose (1 mg/day) of olanzapine with the therapeutic dose (10 mg/day) and placebo. This was a 6-week inpatient study (N = 152) with an open-label extension. Patients had an acute exacerbation of schizophrenia, with Brief Psychiatric Rating Scale (BPRS) total score on a 0–6 scale of ≥ 24.
- Study 2, the North American Clinical Trial,[2] compared multiple doses of olanzapine (2.5–7.5 mg/day [Olz-L], 7.5–12.5 mg/day [Olz-M], and 12.5–17.5 mg/day [Olz-H]) with placebo and haloperidol 10–20 mg/day (Hal). The mean modal dose was 6.6 mg/day for Olz-L, 11.6 mg/day for Olz-M, 16.3 mg/day for Olz-H, and 16.4 mg/day for Hal. This study was considered the most important for observation of the dose-response relationship. It was a 6-week inpatient study (N = 335) with double-blind extension up to 1 year. Patients had an acute exacerbation of schizophrenia, with BPRS total score on a 0–6 scale of ≥ 24. Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS).
- Study 3, the Eastern Hemisphere Study,[3] compared olanzapine 1 mg/day with placebo and a low, medium, and high dose as described above. Haloperidol was also used as a comparator, at 10–20 mg/day. This was a 6-week inpatient study (N = 431) with a 1-year double-blind extension. Patients had an acute exacerbation of schizophrenia, with BPRS total score on a 0–6 scale of ≥ 24. Negative symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).
- Study 4, the International Study,[4] compared olanzapine in a dosage range of 5–20 mg/day with a similar dosage range of haloperidol. Randomization entailed a 2:1 allocation for olanzapine versus haloperidol. This was a 6-week inpatient study (N = 1996) with a 1-year double-blind extension. Patients started treatment on an inpatient or outpatient basis; admitting diagnoses included acute exacerbations of schizophrenia (83.1%), schizophreniform disorder (1.9%), and schizoaffective disorder (15.0%); they were intolerant of current therapy or had BPRS total score on a 0–6 scale ≥ 18.

From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga.

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.

Reprint requests to: Charles B. Nemeroff, M.D., Ph.D., Department of Psychiatry and Behavioral Science, Emory University School of Medicine, Atlanta, GA 30322.

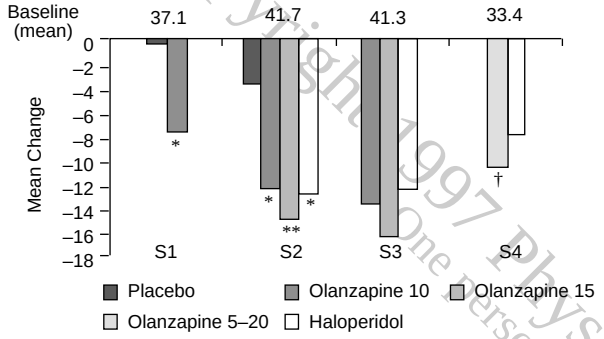
Table 1. Drugs and Dosages for Double-Blind, 6-Week Clinical Trials of Olanzapine Therapy for Schizophrenia Disorders*

	Study 1 (N = 152)	Study 2 (N = 335)	Study 3 (N = 431)	Study 4 (N = 1996)
Setting	Inpatient	Inpatient	Inpatient	Inpatient or outpatient
$BPRS_{0-6}$[a] score at entry	≥ 24	≥ 24	≥ 24	≥ 18 or intolerant of current therapy
Drug and dosage	Placebo	Placebo	Olz 1 mg/d	Olanzapine 5 to 20 mg/d
	Olz 1 mg/d	Olz-L	Olz-L	Haloperidol 5 to 20 mg/d
	Olz 10 mg/d	Olz-M	Olz-M	
		Olz-H	Olz-H	
		Hal	Hal	

*Data on file, Eli Lilly and Company. Only patients with schizophrenia were included in Studies 1, 2, and 3; patients in Study 4 could have a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
[a]$BPRS_{0-6}$ = Brief Psychiatric Rating Scale score with items rated 0 to 6; Olz = olanzapine; Olz-L = 2.5 to 7.5 mg/day; Olz-M = 7.5 to 12.5 mg/day; Olz-H = 12.5 to 17.5 mg/day; Hal = haloperidol 10 to 20 mg/day.

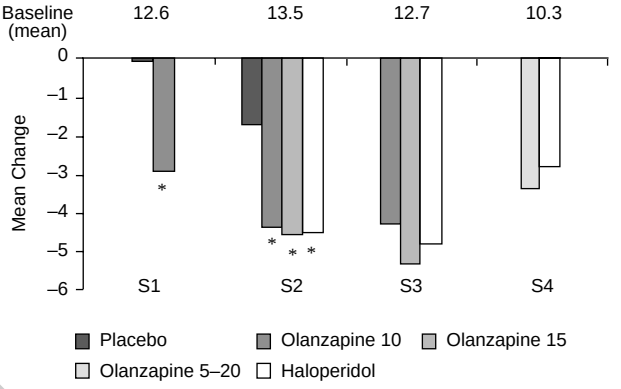
© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

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



[a]LOCF = last observation carried forward; BPRS = Brief Psychiatric Rating Scale; S1, S2, and S3 = inpatients with schizophrenia; S4 = inpatients and outpatients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.
*p ≤ .050 vs placebo; **p < .001 vs placebo; †p ≤ .050 vs haloperidol.

Figure 2. Mean Change (LOCF) in BPRS Positive Scores in Acute Phases of Studies 1 to 4 (S1 to S4)



*p ≤ .050 vs placebo.

Negative symptoms were assessed with the PANSS, and depressive symptoms were assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS).

Relief of Symptoms

In Study 1, olanzapine 10 mg/day was significantly superior to placebo in improving overall symptoms of psychopathology and for both positive and negative symptoms.

In Study 2, relief of symptoms was evaluated using total scores on the BPRS, and significantly better improvement in symptoms of schizophrenia occurred in patients receiving olanzapine at dosages of 10 or 15 mg/day, or haloperidol, compared to those receiving placebo (Figure 1).

Scores on the positive symptoms subscale of the BPRS showed similar results: the 10- and 15-mg/day dosages of olanzapine and dosages of haloperidol (mean dosage = 16.4 mg/day) were significantly more efficacious than placebo (Figure 2).

Negative symptoms of patj ùts in S tudy 2 were evaluated using the SANS. The results of this analysis revealed the 15-mg/day dosage of olanzapine to be superior to haloperidol and placebo and numerically better than the 10-mg/day dosage of olanzapine (Figure 3).

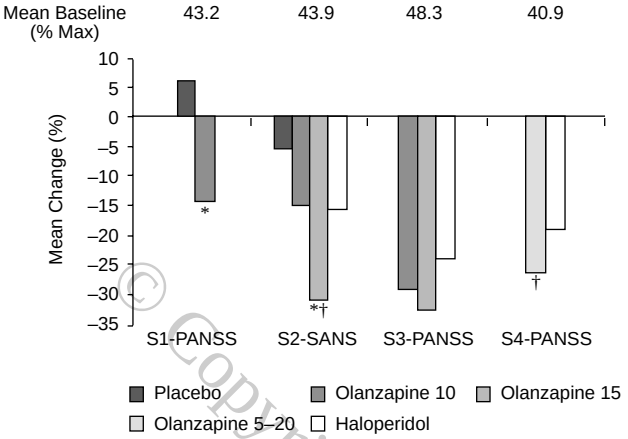
In Study 3, the 15-mg/day dose of olanzapine again showed the greatest reduction in BPRS total and positive scores (Figures 1 and 2) and for negative symptoms (Figure 3); however, this was not statistically significantly different than the 10 mg/day dose.

In Study 4, olanzapine)˚›wÆ dosage = 13.2 mg/day) was significantly more effective than haloperidol (mean dosage = 11.8 mg/day) in improving scores on the BPRS (total and negative scales); PANSS, negative scores; Clinical Global Impressions (CGI, severity); MADRS; and the Heinrichs-Carpenter Quality of Life Scale.

Response to Medication

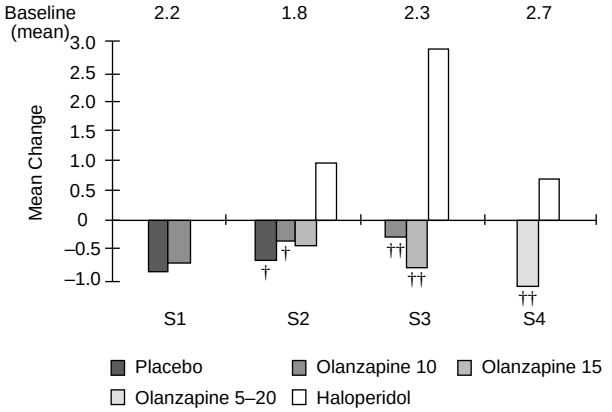
Another measure of drug efficacy is the proportion of patients who respond to the medication, using a predetermined definition of response. In the four seminal clinical trials, response was defined as a 40% or greater decrease in $BPRS_{0-6}$ scores from baseline or, for patients in Studies 1, 2, and 3, a $BPRS_{0-6}$ score of 18 or less at the endpoint of the trial. All patients were included in the response calculation for Study 3;

Figure 3. Mean Change (%, LOCF) in Negative Symptom Scale Scores in Acute Phases of Studies 1 to 4 (S1 to S4)[a]



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

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



†p ≤ .050 vs haloperidol; ††p ≤ .001 vs haloperidol.

Table 2. Dosages of Olanzapine and Haloperidol in Study 4, Acute Phase*

Drug Dose	Olanzapine	Haloperidol
5 mg/day	23.2%	28.6%
10 mg/day	22.2%	29.7%
15 mg/day	21.0%	18.3%
20 mg/day	33.5%	23.3%
Mean	13.2 mg/day	11.8 mg/day

*Data on file, Eli Lilly and Company.

for the other three studies, response was evaluated only for patients who completed more than 3 weeks of the trial.

Using these criteria, the rate of response to the 10-mg/day dosage of olanzapine was significantly greater than the rate of response to placebo in Study 1. Moreover, the response to olanzapine was significantly greater than the response to haloperidol in Study 4, in which either medication could be given over the dosage range of 5 to 20 mg/day.

When the duration of response (time maintaining symptoms at a low enough level that hospitalization was not required) was evaluated in Study 2, the high dosage (mean = 16.3 mg/day) of olanzapine was associated with the lowest rate of relapse.

Somewhat different, however again nonsignificant, treatment differences in dose-response results were obtained when the results of Studies 2 and 3 were combined. In this case, the highest cumulative percentage of patients maintaining response were those receiving the lowest dosage of olanzapine.

Comparison of Olanzapine and Haloperidol Dosages

In Study 4, clinicians could adjust the dosage of medication (olanzapine or haloperidol, randomly assigned in double-blind fashion) from 5 to 20 mg/day. During the 6-week acute phase of this trial, the proportions of patients receiving 5 mg, 10 mg, 15 mg, or 20 mg per day of either medication were similar, as were the mean dosages for the two medications (Table 2). However, olanzapine-treated patients exhibited significantly more improvement when compared to haloperidol-treated patients as assessed by BPRS total scores, BPRS negative scores, PANSS negative scores, CGI (severity) scores, MADRS scores, and Heinrichs-Carpenter Quality of Life Scale scores.

When patients in Study 4 entered the double-blind extension phase of this trial, 441 (63%) of the 697 patients remained on the same dosage of olanzapine or haloperidol they had been receiving in the acute phase, and 200 (29%) had an increase in mean modal dose. In this phase of the study, olanzapine showed significantly better maintenance of acute treatment effects, with a significantly lower rate of relapse and need for hospitalization when compared to haloperidol.

DOSE-RESPONSE FOR ADVERSE EFFECTS

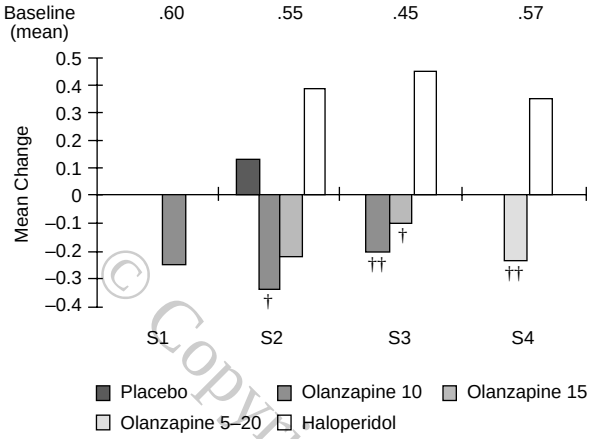
Increasing dosages of haloperidol have been associated with increased risk of adverse effects that frequently lead to discontinuation of therapy, and subsequently increased morbidity. The emergence of adverse effects and other events that might limit therapy were evaluated during the four pivotal clinical trials of olanzapine and placebo or haloperidol.

Extrapyramidal Side Effects

The frequency of extrapyramidal side effects (Figure 4) and akathisia (Figure 5) was comparable to placebo and lower for olanzapine compared to haloperidol. In fact, patients receiving haloperidol in each study experienced a

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

Figure 5. 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 ≤ .010 vs haloperidol; ††p ≤ .001 vs haloperidol.

mean increase in EPS, whereas those receiving olanzapine at any dosage experienced a mean decrease in EPS. The differences were particularly notable for the 10- and 15-mg/day dosages of olanzapine. This low potential for olanzapine to cause EPS was predicted from the results of in vivo preclinical studies in which very high doses of olanzapine were required to elicit responses in a rat model predictive of extrapyramidal side effects.[5]

Tardive Dyskinesia

The incidence of treatment-emergent tardive dyskinesia was studied in the double-blind extension phases of Studies 2, 3, and 4. On each of three measures used (any postbaseline assessment, final Abnormal Involuntary Movement Scale [AIMS] assessment, or final two AIMS assessments), olanzapine at any dosage was significantly less likely to cause tardive dyskinesia compared to haloperidol.

Other Adverse Events

"Somnolence" was reported as an adverse event among patients receiving the 15-mg/day, but not the 10-mg/day, dose of olanzapine.

There was a dose-related increase in body weight among patients receiving olanzapine (Figure 6). The weight increase was greatest for patients who had a starting dose of 15 mg and/or were underweight (as indicated by body mass index) at the start of the study.

A proportion of the men receiving active medication in Study 2 showed a transient treatment-emergent, dose-dependent increase in prolactin. However, the increases for men receiving olanzapine remained within normal laboratory values for prolactin, whereas increases for men receiving haloperidol were in the abnormal range and were

Figure 6. Mean Change in Weight During Studies 1–4

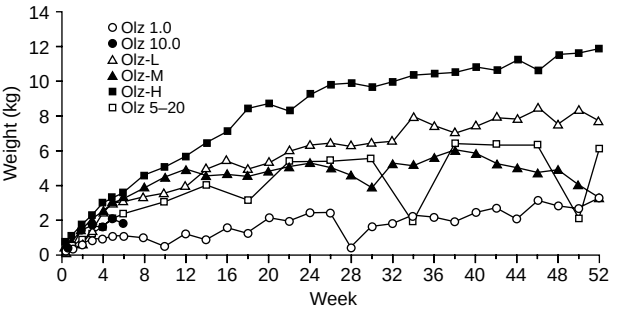
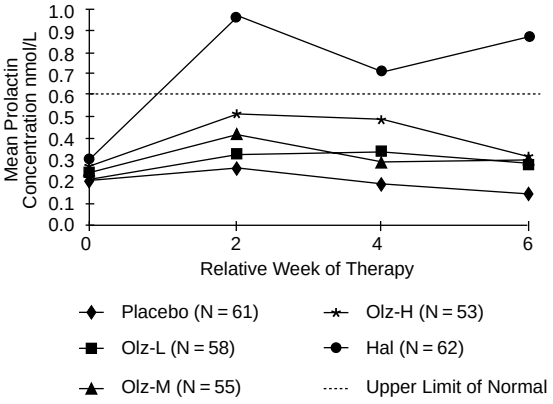


Figure 7. Mean Prolactin Concentration in Males (OC) in Study 2



significantly greater than for any dosage of olanzapine (Figure 7). These results confirm the predictions based on preclinical pharmacology that olanzapine would have a minimal effect on plasma prolactin concentrations compared to haloperidol.

Transient elevations in liver enzymes were occasionally noted, but they were transient, not dose-dependent, and not associated with any symptoms.

DOSING OLANZAPINE

Overall, the clinical trials showed that 10 mg/day of olanzapine is a therapeutic dose and that adjustments in dosage are not necessary for most patients. There was a trend for the 15-mg/day dosage to have greater efficacy than the 10-mg/day dosage in relieving the negative symptoms of schizophrenia, but this will clearly require further study.

Olanzapine is convenient to dose because the medication can be taken once a day, without regard to meals. It also has low potential for drug-drug interactions, so that other medications can be used concomitantly with olanzapine.

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

Dose-dependent adverse effects that may occur with olanzapine therapy include weight gain, which tends to be greater for those who are underweight and least for those who are overweight at the start of treatment, and transient elevations, within the normal range, of prolactin levels. Sedating effects of olanzapine may be more noticeable at higher dosages, an effect that may be clinically helpful in acutely psychotic patients.

No clear dose dependency was identified for other adverse effects of olanzapine, which has significantly less tendency compared with haloperidol to cause extrapyramidal symptoms, akathisia, and tardive dyskinesia.

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

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

REFERENCES

1. Beasley CM, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind fixed-dose olanzapine trial. Psychopharmacology 1996;124:159–167
2. Beasley CM Jr, Tollefson GD, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
3. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute-phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol. In press
4. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
5. Moore NA, Tye NC, Axton MS, et al. The behavioral pharmacology of olanzapine, a novel “atypical” antipsychotic agent. J Pharmacol Exp Ther 1992;262:545–551