The Effects of Olanzapine on the 5 Dimensions of Schizophrenia Derived by Factor Analysis: Combined Results of the North American and International Trials

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Background: The choice of drug to treat a patient with schizophrenia is one of the most critical clinical decisions. Controversy exists on the differential efficacy of olanzapine.

Data Sources and Study Selection: Raw data from all 4 registrational double-blind, random-assignment studies of olanzapine compared with placebo or haloperidol were obtained from Eli Lilly and Company for this meta-analysis.

Method: Analysis of covariance of the intent-to-treat last-observation-carried-forward endpoint scores was used to assess efficacy on Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS) total scores and the 5 factors derived by factor analysis (negative symptoms, positive symptoms, disorganized thoughts, impulsivity/hostility, and anxiety/depression).

Results: Olanzapine produced a statistically significantly greater reduction in schizophrenic symptoms than haloperidol ($p < .05$) on total scores on the BPRS and PANSS on each of the 5 factors as well as on almost all items. Olanzapine induced a response at a rate equal to that induced by haloperidol in the first few weeks, but by the end of the study produced a greater percentage of responders. Compared with haloperidol, olanzapine produced a somewhat greater response on symptoms responsive to haloperidol, but a markedly better response on symptoms unresponsive to haloperidol. This difference favoring olanzapine occurred to an equal degree in all subgroups examined. The incidence of parkinsonism or akathisia following olanzapine treatment was extremely low and not statistically distinguishable from placebo.

Conclusion: Olanzapine produced a greater improvement than haloperidol particularly by benefiting a much larger number of items or factors. Extrapyramidal side effects and akathisia during olanzapine treatment were statistically indistinguishable from effects seen with placebo.

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The choice of drug to treat a patient with schizophrenia is one of the most critical clinical decisions. The efficacy of olanzapine for the treatment of schizophrenia in comparison with that of typical neuroleptics constitutes important data for these considerations. There are marked differences of clinical opinion on the relative efficacy of olanzapine and the typical neuroleptics. Some state that olanzapine is no more efficacious than typical neuroleptics.[1–3] The National Schizophrenia Guideline Development Group (of the United Kingdom) has stated that "there is no clear evidence that atypical antipsychotics are more effective or are better tolerated than conventional antipsychotics."[4(p1371)] Other guidelines by panels place atypicals as first-line treatment (in part because of a side effect advantage), although typicals are still recommended as first-line drugs for certain indications.[5–8] Guidelines of the American Psychiatric Association[9] and of the National Institute of Mental Health (NIMH) Schizophrenia Patient Outcomes Research Team[10] recommend both typical and atypical antipsychotics as first-line treatment. Most importantly, guidelines often equivocate, and recommending all antipsychotic drugs is not necessarily helpful. We performed a meta-analysis using the raw data of the 4 registrational trials[11–14] to see if there is evidence for a definite data-based statement on the efficacy of olanzapine over that of typical neuroleptics.

We explore 2 basic questions for comparing the atypicals to typical neuroleptics: (1) How effective are the atypicals in most schizophrenia patients (what Remington and Kapur[15] call the size question)? (2) How effective are they in subpopulations, particularly in patients unresponsive to typical neuroleptics (what Remington and Kapur call the refractory question)?

It is difficult to demonstrate with consistency a statistically significant difference among drugs using the rela-

tively small patient populations studied in most trials.[16] This analysis parallels our previous meta-analysis of the North American registrational trials of risperidone.[17] A difference that is significant in one study but just misses significance in another can become unequivocally significant when combined in a meta-analysis. Conversely, differences significant in one study when linked to a nonsignificant difference in the opposite direction in other studies can become clearly nonsignificant, making failure to replicate clearly manifest. The increase in sample size may clarify the marked differences of opinion in the literature.

We generalize the size question to explore whether there are differences in clinical response with typicals and atypicals on a variety of schizophrenic symptom clusters. It is also important to characterize the qualitative nature of symptom change produced by these drugs. The positive symptom and negative symptom subscales were arbitrarily defined by the authors of the Positive and Negative Syndrome Scale (PANSS)[18] and only approximately describe the clustering of symptoms that has emerged through factor analytic studies of the PANSS. Three other factors emerged in factor analytic studies of the PANSS: disorganized thoughts, impulsivity/hostility, and anxiety/depression. Furthermore, the factor structure of the PANSS explains only 50% of the variance, and the report of the pivotal studies has not presented the effects of olanzapine and haloperidol on the individual items. We propose to quantitatively investigate the qualitative nature of the symptom change induced by olanzapine in comparison with haloperidol. This is important because the atypicals could help alleviate some of those symptoms not benefited by typical neuroleptic agents.

We would generalize the refractory concept to any drug difference between subgroups. One aspect of the refractory question that has been incompletely explored is whether olanzapine produces a better effect in certain subgroups and an equal effect in other patients. For example, does olanzapine produce a superior effect in schizophrenia patients with depression and a lackluster effect in schizophrenia patients without depression? Given that olanzapine may be somewhat more efficacious than haloperidol, does this superiority occur only in certain subgroups or does it occur as a general effect in all patients? Studies[19] have explored whether olanzapine is superior to haloperidol in a given subgroup. We feel the more interesting question is whether olanzapine is comparatively efficacious to haloperidol in those patients who are or are not members of a given subgroup. In statistical terms, we explore the interaction between treatment and the presence or absence of a given subgroup. This allows us to examine whether olanzapine is equally efficacious as haloperidol in those with and without membership in the subgroup, or whether olanzapine produces a superior effect in a given subgroup but a lackluster effect in those who are not members of that subgroup. This question has not been addressed previously.

It is important to distinguish the size effect from the subgroup (refractory) effect. For example, compared with typicals, an atypical could produce a greater benefit on a depression item in essentially all patients (the size effect), and/or the atypical could produce a much greater overall beneficial effect on the total PANSS or Brief Psychiatric Rating Scale (BPRS)[20] score in the group with high depression at baseline in comparison with a less impressive overall improvement in those patients with low baseline depression scores.

We also pool the data from these 4 studies to ascertain whether or not olanzapine produces measurable and dose-related extrapyramidal side effects (EPS) or akathisia as 2 side effects of interest.

METHOD

We performed a meta-analysis on raw data obtained from Eli Lilly and Company on 4 randomized, double-blind, multicenter registrational trials[11–14] comparing olanzapine, placebo, and haloperidol. The details of each individual study are briefly summarized below. In the current analysis, 3 comparisons were made based on data from the BPRS or the PANSS: (1) placebo versus haloperidol, (2) placebo versus olanzapine, and (3) haloperidol versus olanzapine. The doses of each drug and the number of subjects included in each comparison are summarized in Tables 1A and 1B. It is critical to have the appropriate control in each comparison. We carried out analysis for only those studies in which both the experimental drug and the control drug were compared in the same study. The placebo versus haloperidol comparison was investigated in Study 1 only, whereas the placebo versus olanzapine comparison was investigated in Studies 1 and 2. Studies 1, 3, and 4 were used in analyses comparing haloperidol versus olanzapine using the BPRS. When only the PANSS measure was used in the haloperidol versus olanzapine comparison, Studies 3 and 4 were used. It is important to note that different sets of studies were combined in the analysis of olanzapine versus placebo, olanzapine versus haloperidol, or haloperidol versus placebo, as specified in Table 1B, and therefore slightly different absolute scores were obtained in each set of comparison.

This analysis was carried out independently and without direct or indirect funding from olanzapine's manufacturer, Eli Lilly and Company.

Study Population

The study population included men and women between the ages of 18 and 65 years who were diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder based on DSM-III-R criteria. A minimum score on the BPRS of 18 (1 study) or 24 (3 studies) was used as the threshold for inclusion into the 4 clinical trials. Patients were excluded from participation for the follow-

Table 1A. Data Sets Included in Meta-Analysis[a]

Study	Treatment Groups	Description of Study	Patients, N		
			Placebo	Haloperidol	Olanzapine
1[11]	Olanzapine, haloperidol, placebo	18-item BPRS; mean olanzapine dose ranges, 5, 10, 15 mg/d for L, M, H, respectively; haloperidol dose range, 10–20 mg/d	68	69	69 (H), 64 (M), 65 (L)
2[12]	Olanzapine, placebo	30-item PANSS; fixed olanzapine dose at 10 mg/d or 1 mg/d	50	...	50 (10 mg), 52 (1 mg)
3[13]	Olanzapine, haloperidol	30-item PANSS; mean fixed olanzapine dose ranges, 5, 10, 15 mg/d for L, M, H, respectively, as well as fixed 1-mg/d dose haloperidol dose range, 10–20 mg/d	...	81	89 (H), 86 (M), 87 (L), 88 (1 mg)
4[14]	Olanzapine, haloperidol	30-item PANSS; haloperidol and olanzapine flexible dose range, 5–20 mg/d	...	659	1337

Table 1B. Analyses

Comparison	Measures	Study/Studies Used	Patients, N		
			Placebo	Haloperidol	Olanzapine[b]
Haloperidol vs placebo	BPRS[c]	1	68	69	...
Olanzapine vs placebo	BPRS[c]	1 and 2	118	...	183
Olanzapine vs haloperidol	BPRS[c]	1, 3, and 4	...	809	1645
Olanzapine vs haloperidol (PANSS only)	PANSS	3 and 4	...	740	1512

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, H = high-dose group, L = low-dose group, M = medium-dose group, PANSS = Positive and Negative Syndrome Scale.
[b]All olanzapine comparisons used 5-mg (low), 10-mg (medium), or 15-mg (high) doses unless specified otherwise.
[c]BPRS or Extracted BPRS (from PANSS).

ing conditions: diagnosis of an organic mental disorder (DSM-III-R) or a substance-use disorder within 3 months of study entry; serious suicidal risk; serious, unstable medical illness; Parkinson's disease; myasthenia gravis; illness contraindicating use of anticholinergic medication; history of a seizure disorder; history of leukopenia without a known etiology; or significantly elevated liver function test results, active hepatitis B, or jaundice. Patients were instructed not to take oral neuroleptics 2 days, or depot neuroleptics 2 weeks, before study entry. Each institutional review board approved the study protocol, and all patients gave written informed consent prior to study initiation.

Study 1. This clinical trial[11] compared the efficacy of olanzapine, haloperidol, and placebo in treating schizophrenic patients at 22 study sites in Canada and the United States. Patients were required to have a BPRS-Anchored[21] score of at least 24 to be entered into this trial. After discontinuing their current treatment regimen, the patients entered a single-blind placebo lead-in for 4 to 7 days. If their BPRS total scores remained above 24 or decreased ≤ 25%, the patients entered the double-blind phase of the study. A total of 335 patients (294 men and 41 women) diagnosed with an acute exacerbation of schizophrenia were randomly assigned to 1 of 5 treatment arms: olanzapine, 5 ± 2.5 mg/day; olanzapine, 10 ± 2.5 mg/day; olanzapine, 15 ± 2.5 mg/day; haloperidol, 15 ± 5.0 mg/day; and placebo. All patients receiving olanzapine or haloperidol started at the middle dose, and the dose was then adjusted up or down as clinically indicated. Patients could receive lorazepam (maximum of 10 mg/day) during lead-in and during the first 3 weeks of the double-blind therapy. Benztropine mesylate (maximum of 10 mg/day) was allowed during the study.

Study 2. This clinical trial[12] was conducted at 12 investigative sites in the United States and compared olanzapine with placebo in the treatment of schizophrenia. To be included in this trial, patients had to have a minimum BPRS total score of 24 (extracted from the PANSS), and a score of at least 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[22] A total of 152 patients (110 men and 42 women) were randomly assigned fixed doses of olanzapine, either 1 or 10 mg/day, or placebo. This study was similar to Study 1 for lead-in and entrance into the double-blind phase as well as for lorazepam and benztropine mesylate use.

Study 3. This clinical trial[13] compared the efficacy of olanzapine and haloperidol in the treatment of patients diagnosed with an acute exacerbation of schizophrenia. Four hundred thirty-one patients (275 men and 156 women) were enrolled at 50 sites in Europe, South Africa, Israel, and Australia. The inclusion criteria and design of the lead-in and double-blind phases were identical to those of Study 1, except that a 1-mg olanzapine dose was used instead of placebo. Patients enrolled in this study were allowed benzodiazepines (maximum of 10 mg/day lorazepam equivalents) during lead-in and the first 3 study weeks. If a benzodiazepine was used chronically for at least 60 days prior to study start, then it could be used for the 6-week period. Patients could also take biperiden at a maximum of 6 mg/day for the entire study. Drug dosing was essentially the same as in Study 1 except for the additional olanzapine treatment group at 1 mg/day (fixed) and the fact that there was no placebo arm.

Study 4. This clinical trial[14] was a second international study that compared treatment efficacies of olanzapine

and haloperidol. This trial was conducted at 174 sites in North America and throughout Europe and included patients diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder. A BPRS score of at least 18 (extracted from the PANSS) or an intolerance to current antipsychotic therapy (excluding haloperidol) qualified patients to be enrolled into this trial. The single-blind lead-in phase lasted 2 to 9 days, and entrance into the double-blind phase was similar to that in the other studies. A total of 1996 patients (1296 men and 700 women) were randomly assigned to 5 mg/day of either olanzapine or haloperidol, with the flexibility of increasing the dose up to a maximum of 20 mg/day, but no lower than 5 mg/day.

Data Analysis

Treatment groups. The mean flexible dose used in Study 4 was 13.2 mg/day. In the 2 fixed-dose studies (Studies 1 and 3), the mean dose of the medium dose range was 11.5 mg/day, which is close to 13.2 mg/day. Therefore, it seemed reasonable to pool this medium-dose group with the flexible-dose and the high-dose groups to have an approximation of average effective doses. The low 5-mg dose range was clearly below the effective dose range. Patients with low doses of olanzapine were analyzed separately in the dose-response comparisons. Analysis was conducted on the intent-to-treat sample using the last-observation-carried-forward method. We also analyzed the intent-to-treat BPRS or PANSS total score observed data on those patients with complete data at each timepoint.

BPRS and PANSS. The BPRS items were common to all studies. In Study 1, only the BPRS scale was used. In Studies 2, 3, and 4, the PANSS and the BPRS extracted from the PANSS were used. We use the term *BPRS* to refer to both the BPRS in Study 1 and the extracted BPRS in Studies 2, 3, and 4. The assessments for BPRS or PANSS scores (BPRS for Study 1) occurred at the beginning (screening) and end of the single-blind placebo lead-in (baseline) and at the end of each of the 6 weeks during the double-blind portion. Studies 1 and 3 had an additional assessment at the midpoint of week 1.

Rate of improvement. We calculated the percentage of patients who achieved greater than or equal to the conventional 20% improvement on the BPRS at each evaluation and plotted the cumulative percent improvement over time comparing olanzapine with placebo, and haloperidol with olanzapine. Pearson chi-square analysis was employed to analyze the 2 × 2 tables (improvement vs. treatment group).

BPRS and PANSS factors. A factor analysis of the BPRS and PANSS was conducted at each timepoint. Based on this analysis and the previous literature,[17] we derived scores on each factor. A value of 1 was assigned for each item in a factor except for BPRS items 4 and 6 or PANSS items 14, 26, and 29, which loaded equally on 2 factors and were therefore assigned a value of 0.5 on each of the 2 factors. An analysis of covariance (ANCOVA) with baseline as covariate was used to compare the effects of placebo, haloperidol, and olanzapine on the 5 factors of the 5-factor model of schizophrenia.

Deterioration on placebo treatment and during the washout period. Do all aspects of the psychopathology relapse at the same rate or do some aspects relapse first? The data of all patients were used to examine the degree of deterioration during the washout period using paired t tests of data at the screening and baseline evaluations. Selecting only the placebo patients, we used paired t tests to compare the degree of deterioration in the 5 factors as well as the individual items. This comparison addresses the question of whether certain dimensions of schizophrenia deteriorate when the patient stops taking medication.

BPRS items responsive and nonresponsive to haloperidol. To provide a more detailed comparison of difference in the spectrum of treatment efficacy following olanzapine and haloperidol, we explored 2 questions: (1) Did olanzapine benefit a greater variety of symptoms than haloperidol by improving those symptoms that did not respond to haloperidol? and (2) Did olanzapine produce a greater degree of improvement on symptoms that did respond to haloperidol? The 18 items of the BPRS were divided into 2 subscales using an alpha level of .10: (1) haloperidol-responsive: items in which haloperidol was superior to placebo ($p < .10$), and (2) haloperidol nonresponsive: items in which haloperidol was not different from placebo ($p \geq .10$). The haloperidol-responsive subscale included BPRS items 3, 4, 5, 9, 10, 11, 12, 14, 15, 17, and 18. The haloperidol-nonresponsive subscale, in which haloperidol failed to produce any significant improvement, included BPRS items 1, 2, 6, 7, 8, 13, and 16. Each summed score was divided by the number of items in the scale. Recall that the sole study that compared haloperidol with placebo used only the BPRS. The classification is a clustering based on drug response to complement the clustering based on factor analysis.

Dose-response relationships. Two of the studies used a low, medium, and high flexible dosing range of olanzapine (5, 10, and 15 [± 2.5] mg/day). The mean olanzapine doses administered were 6.7, 11.5, and 16.4 mg/day. We examined the data to see whether there was an association between olanzapine dose and improvement. We graphically estimated the dose of olanzapine that produced an improvement equal to that produced by haloperidol by plotting the improvement of haloperidol on the y-axis of the dose-response curve and dropping a line down and reading the dose of olanzapine from the x-axis.

Effect of dose of comparator. Two of the studies comparing haloperidol with olanzapine (Studies 1 and 3) used a relatively high dose of haloperidol comparator (about 17 mg/day), whereas one study used a relatively low dose of

11.8 mg/day. We therefore examined whether dose of comparator had any systematic effect on differential efficacy.

Subtype analysis. We wished to determine whether a certain subgroup of schizophrenia patients might be particularly responsive to olanzapine and not to haloperidol or vice versa. Is one drug specifically indicated for a subtype? Patients were dichotomized for the presence or absence of distinct factors and other classificatory variables, such as gender. For example, patients were classified according to the initial presence of high scores on each of the 5 factors: negative symptoms, positive symptoms, disorganized thoughts, impulsivity/hostility, and anxiety/depression. Since the older a patient is, the longer he or she has been at risk for relapse, consequently the frequency of admissions per unit time was calculated (as opposed to just number of admissions) to determine if patients with more admissions per year responded differently to olanzapine than to haloperidol. While some variables did predict a poor response to either drug (e.g., early-onset patients had a poor drug response), we focused on whether a certain subtype did particularly well with olanzapine and particularly poorly with haloperidol or vice versa. In other words, we tested for an interaction between each diagnostic subtype (presence or absence of that subtype) versus drug with a 2-way ANCOVA.

Effect of dropout due to adverse reactions or EPS. Since olanzapine is better tolerated and causes markedly fewer EPS than haloperidol, we examined in several ways the effect of dropout in general, due to adverse effects, or due specifically to EPS. We performed a 2-way ANCOVA of treatment (olanzapine/haloperidol) versus dropouts for adverse effects (yes/no). The test of interaction between treatment and dropout due to adverse effects is done to determine whether dropping out due to adverse effects could bias the efficacy results. It is also possible that patients who discontinued early in the trial due to adverse effects could have a greater bias, and therefore we did a 3 × 2 analysis of variance of treatment versus dropout time (dropout weeks 1–3, dropout weeks 4–6, or completing). Two similar analyses (2 × 2 and 2 × 3) exploring the same question for dropout due to EPS were examined.

Measurement of EPS and akathisia. To provide continuous variables, the Simpson-Angus Scale[23] measured EPS and the Barnes Akathisia Rating Scale[24] measured akathisia. These measurements were taken immediately before and at the end of each week during double-blind therapy. We used the maximal score on treatment with drug or placebo as our measure, with baseline as covariate.

Typically, doctors make a diagnosis of the drug-induced disease of pseudoparkinsonism, or akathisia, which is either present or absent. The following methodology was used to quantify the presence or absence of the diagnosis of EPS or akathisia. Some placebo patients had moderately high scores on the Simpson-Angus Scale and received a clinical diagnosis of having EPS, or were treated with antiparkinsonian drugs. The reasons for this are obscure. To provide positive evidence that a drug causes EPS, we feel it is necessary to show that the new drug produces a statistically reliable increase in EPS over that which occurs with placebo. Evaluation of EPS has a limitation because it is considered unethical to withhold antiparkinsonian drugs. Therefore, the measured EPS occur in spite of antiparkinsonian drugs. To truly evaluate EPS, one must take into account (1) the measured EPS by the Simpson-Angus Scale, (2) the diagnosis of EPS (parkinsonism) as a reported side effect, and (3) the use of antiparkinsonian drugs. The Simpson-Angus score at endpoint adjusted for baseline was separated into 3 categories: no EPS, borderline EPS, and definite EPS based on cutoff points derived from a comparison of haloperidol and placebo scores and assigned scores of 0, 1, and 2, respectively. The report of parkinsonian side effects was assigned a score of 1. A score of 1 was added to the score of patients who continued on antiparkinsonian drugs, and a score of 2 was added to patients who changed from no antiparkinsonian drug to antiparkinsonian drug, a sign that the clinician felt EPS were present. A score of 1 was subtracted from those patients for whom an antiparkinsonian drug was discontinued, as this is a sign that the clinician felt that they did not have EPS. A higher proportion of patients with scores of 0, 1, or 2 received placebo and a higher proportion of patients with scores of 3, 4, 5, 6, etc., received haloperidol. Scores of 0 to 2 were assigned to the "no EPS" category and scores of 3 or more were assigned to the "EPS present" category.

We also examined the incidence of what Barnes calls "true akathisia," based on the Barnes criterion of an akathisia score greater than 3 on a 5-point total global akathisia scale and a score of 3 or more on item 2, the subjective report of akathisia by the patient.[25] We used this definition to contrast the incidence of akathisia between olanzapine and placebo, between haloperidol and placebo, etc.

Effect of EPS on differential outcome. We next evaluated whether haloperidol and olanzapine patients who had EPS responded particularly poorly to haloperidol in comparison with those patients receiving olanzapine. In general, patients who have EPS tend to have a less positive therapeutic response than those who do not have EPS regardless of medication or placebo. We wished to find out whether this effect was exaggerated with one antipsychotic and minimized with another. Thus, we did a 2-way ANCOVA with treatment (haloperidol vs. olanzapine) as one factor and the presence or absence of EPS as another factor with a focus on the interaction effect.

RESULTS

Demographics

The majority of the patients were Caucasian (79.2%) and male (67.8%). Black individuals (African and African American) made up 12.4% of the patient population,

Table 2. Mean Adjusted Change Scores on the Total and 5 Factors for the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) Following Treatment in Each Comparison[a]

	Placebo vs Haloperidol				Placebo vs Olanzapine				Haloperidol vs Olanzapine			
Total score/Factor	PLA	HAL	F[b]	p Value	PLA	OLZ	F[c]	p Value	HAL	OLZ	F[d]	p Value
Total score												
BPRS	3.35	12.86	11.91	.001	2.06	11.95	28.21	2×10^{-7}	8.59	11.67	31.58	2×10^{-8}
PANSS	...	...	...	...	–3.67	12.25	13.33	4×10^{-4}	13.61	18.71	29.07	8×10^{-8}
Negative symptoms												
BPRS	0.43	1.90	5.48	.021	0.37	1.98	17.17	5×10^{-5}	1.35	2.13	48.26	5×10^{-12}
PANSS	...	...	...	...	–0.89	2.83	7.73	.007	3.07	4.75	42.86	7×10^{-11}
Positive symptoms												
BPRS	1.91	4.67	8.48	.004	1.21	4.01	18.58	2×10^{-5}	3.20	3.73	8.26	.004
PANSS	...	...	...	...	–0.57	3.83	11.35	.001	4.33	5.31	12.00	5×10^{-4}
Disorganized thoughts												
BPRS	0.23	1.43	5.88	.017	0.09	1.73	24.34	1×10^{-6}	1.05	1.52	27.24	2×10^{-7}
PANSS	...	...	...	...	–1.18	2.92	11.33	.001	3.14	4.04	13.68	2×10^{-5}
Impulsivity/hostility												
BPRS	–0.63	1.53	12.02	.001	–0.74	1.04	17.52	4×10^{-5}	0.75	1.02	4.38	.037
PANSS	...	...	...	...	–1.43	0.84	7.22	.009	0.88	1.30	6.03	.014
Anxiety/depression												
BPRS	1.58	3.17	4.33	.039	1.31	3.08	12.29	5×10^{-4}	2.24	3.26	39.43	4×10^{-10}
PANSS	...	...	...	...	0.62	1.61	1.78	.185	2.19	3.31	41.41	2×10^{-10}

[a]Abbreviations: HAL = haloperidol, OLZ = olanzapine, PLA = placebo.
[b]For placebo vs. haloperidol, F evaluated at df = 1,130.
[c]For placebo vs. olanzapine: BPRS, df = 1,288; PANSS, df = 1,95.
[d]For haloperidol vs. olanzapine: BPRS, df = 1,2387; PANSS, df = 1,2191.

whereas the remaining 8.4% consisted primarily of Asian and Hispanic patients. The mean ± SD age of the patients was 37.8 ± 11.0 years with a range of 18 to 65 years. The primary schizophrenic subtypes, as diagnosed by DSM-III-R, were paranoid (51.9%) and undifferentiated (23.7%). A chronic course of schizophrenia was diagnosed for 75.7% of the patients. The mean age at onset of psychotic symptoms was 23.6 ± 7.3 years. The number of patients with < 10, 10 to 49, ≥ 50, and an unknown number of previous episodes were 1946, 633, 286, and 49, respectively. The mean length of the current episode was 789.4 ± 1641.9 days. The 6-week treatment period was completed by 55.7% of the patients, including 27.1% of the placebo group, 47.2% of the haloperidol group, and 60.9% of the olanzapine group.

Study Effects

The degree of improvement with olanzapine was consistently greater than that with haloperidol in each study (Studies 1, 3, and 4) as evaluated by a 2-way ANCOVA with study as the second factor. This analysis failed to find any significant study interactions with treatment for total BPRS and its 5 factors (F = 0.2, 0.0, 0.6, 0.4, 0.6, 0.8; df = 2; p = NS for all). For the 2 studies using the PANSS (Studies 3 and 4), the study-by-drug interaction was also nonsignificant (F < 0.5 for all 6 comparisons).

Effect of Olanzapine Versus Placebo

Olanzapine was significantly superior to placebo in reducing total scores on the BPRS and PANSS and reducing scores on 4 of the 5 factors (Table 2). The exception was the anxiety/depression factor score in which a significant difference was observed for BPRS score ($p = 5 \times 10^{-4}$), but a trend was observed for the PANSS (p = .19). In comparison with placebo, olanzapine significantly reduced the score on 25 of the 30 PANSS items, with strong trends on 3 of the remaining items (Table 3).

Rate of Improvement

The time course of improvement is plotted in Figure 1, which shows the cumulative percentage of patients reaching responder status at each timepoint. Olanzapine produced significantly more improvement (p = .02) than placebo by week 2, with continued improvement during each subsequent week through endpoint. Olanzapine and haloperidol had a similar improvement rate in the first week, but by week 2 olanzapine produced more improvement than haloperidol, although the improvement was not statistically significant (p = .06). By week 3, olanzapine produced significantly greater improvement than haloperidol (p = .001), and by week 6 the difference was significant to $p = 1 \times 10^{-7}$. (Table 2 shows the endpoint improvement among placebo, haloperidol, and olanzapine treatment groups.)

Effect of Olanzapine Versus Haloperidol

Our primary interest was elucidating the efficacy of olanzapine in comparison with haloperidol. Olanzapine was superior to haloperidol in reducing PANSS and BPRS total scores and all 5 factor scores (Table 2). The most marked differences observed between olanzapine and haloperidol were seen for negative symptoms, disorganized thoughts, and anxiety/depression factors. On the individual items, olanzapine was (1) superior to haloperidol on all 7 items of the negative symptoms factor; (2) superior to halo-

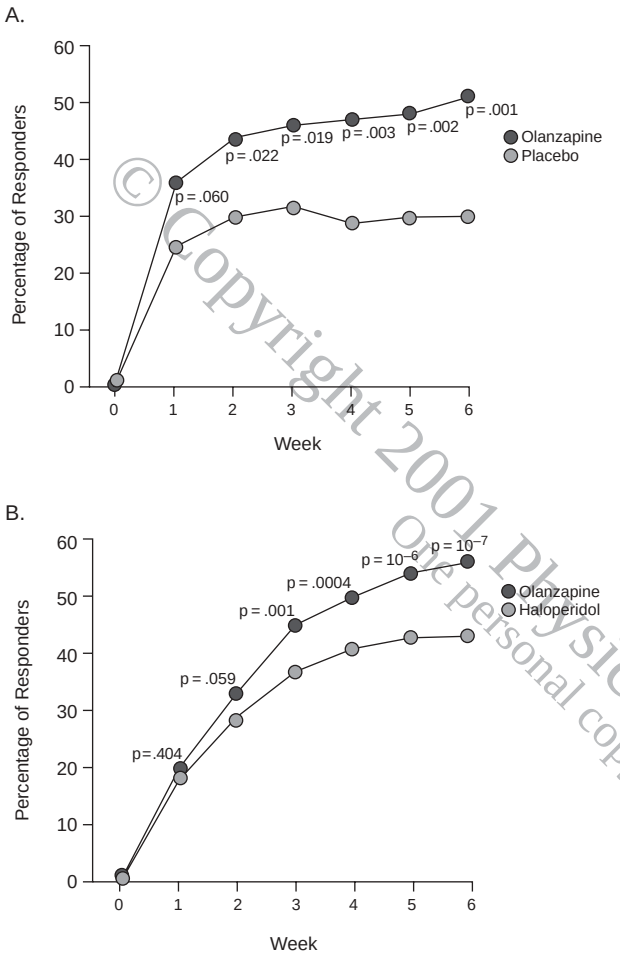
Table 3. Effect of Placebo or Drug Treatment on Scores for Individual Items of the BPRS and PANSS[a]

			PLA vs HAL[b] Mean Score				PLA vs OLZ[c] Mean Score				HAL vs OLZ[d] Mean Score			
Item Description	BPRS	PANSS	PLA	HAL	t	p Value	PLA	OLZ	t	p Value	HAL	OLZ	t	p Value
Negative symptoms														
Emotional withdrawal	3	N2	3.75	2.85	–3.29	.001	3.69	3.08	–3.60	4×10^{-4}	3.15	2.95	–4.07	5×10^{-5}
Motor retardation	13	G7	2.43	2.19	–1.05	.296	2.48	1.93	–3.87	1×10^{-4}	2.24	1.93	–7.32	3×10^{-13}
Blunted affect	16	N1	3.29	2.92	–1.48	.140	3.44	3.02	–2.55	.0112	3.13	2.85	–6.04	2×10^{-9}
Poor rapport	…	N3	…	…	…	…	3.22	2.56	–2.52	.0135	2.67	2.50	–3.55	4×10^{-4}
Passive/apathetic social withdrawal	…	N4	…	…	…	…	3.93	3.65	–0.99	.3260	3.29	3.03	–5.13	3×10^{-7}
Lack of spontaneity and flow of conversation	…	N6	…	…	…	…	3.58	2.91	–2.60	.0108	2.88	2.65	–4.74	2×10^{-6}
Active social avoidance	…	G16	…	…	…	…	3.82	3.10	–2.69	.0085	3.03	2.84	–3.88	1×10^{-4}
Positive symptoms														
Conceptual disorganization	4	P2	3.78	3.05	–2.84	.005	3.86	3.15	–4.02	7×10^{-5}	2.94	2.79	–2.89	.004
Grandiosity	8	P5	2.42	2.35	–0.32	.751	2.44	2.30	–0.91	.3666	1.94	1.83	–2.42	.015
Suspiciousness/ persecution	11	P6	3.79	3.21	–1.97	.051	3.98	3.35	–3.17	.0017	2.91	2.78	–2.19	.028
Hallucinatory behavior	12	P3	4.02	2.89	–3.76	3×10^{-4}	4.06	3.04	–5.16	5×10^{-7}	2.65	2.52	–2.32	.021
Unusual thought content	15	G9	4.01	3.47	–1.94	.054	4.26	3.80	–2.42	.0162	3.20	3.09	–1.86	.064
Delusions	…	P1	…	…	…	…	4.73	3.92	–2.84	.0055	3.24	3.11	–2.24	.025
Stereotyped thinking	…	N7	…	…	…	…	3.74	3.26	–2.03	.0454	2.99	2.79	–3.91	9×10^{-5}
Lack of judgment and insight	…	G12	…	…	…	…	4.16	3.41	–2.99	.0036	3.17	3.13	–0.77	.439
Preoccupation	…	G15	…	…	…	…	4.27	3.61	–2.45	.0162	2.93	2.75	–3.37	8×10^{-4}
Disorganized thoughts														
Tension	6	G4	3.27	2.96	–1.30	.195	3.18	2.69	–3.02	.0028	2.78	2.43	–6.45	2×10^{-7}
Mannerisms and posturing	7	G5	2.86	2.49	–1.50	.137	2.78	2.21	–3.90	1×10^{-4}	2.21	2.02	–4.71	1×10^{-10}
Disorientation	18	G10	1.88	1.50	–2.38	.019	2.01	1.52	–4.05	7×10^{-5}	1.41	1.37	–1.16	.246
Difficulty in abstract thinking	…	N5	…	…	…	…	4.32	3.88	–1.75	.0826	3.19	3.11	–1.49	.136
Poor attention	…	G11	…	…	…	…	3.34	2.82	–1.86	.0667	2.52	2.39	–2.63	.0085
Disturbance of volition	…	G13	…	…	…	…	3.03	2.36	–2.92	.0044	2.68	2.52	–3.33	9×10^{-4}
Impulsivity/hostility														
Hostility	10	P7	2.96	2.30	–2.41	.017	2.89	2.36	–2.86	.0046	1.97	1.96	–0.29	.773
Uncooperativeness	14	G8	2.95	2.25	–2.42	.017	2.78	2.21	–2.97	.0032	1.91	1.88	–0.66	.509
Excitement	17	P4	2.65	2.09	–2.81	.006	2.68	2.19	–3.25	.0013	2.29	2.06	–4.34	2×10^{-5}
Poor impulse control	…	G14	…	…	…	…	2.87	2.20	–2.46	.0158	2.13	2.03	–1.99	.047
Anxiety/depression														
Somatic concern	1	G1	2.94	2.87	–0.31	.757	2.89	2.39	–3.23	.0014	2.56	2.28	–5.44	2×10^{-9}
Anxiety	2	G2	3.72	3.42	–1.23	.219	3.51	3.13	–2.23	.0265	2.93	2.62	–5.62	6×10^{-8}
Guilt feelings	5	G3	2.19	1.67	–2.35	.020	2.10	1.87	–1.55	.1227	1.84	1.77	–1.62	.105
Depression	9	G6	2.81	2.37	–1.66	.099	2.79	2.42	–2.22	.0271	2.44	2.21	–4.34	1×10^{-5}

[a]Abbreviations: HAL = haloperidol, OLZ = olanzapine, PLA = placebo. Shading indicates significant differences between PLA and HAL groups ($p < .10$), and between PLA and OLZ, and HAL and OLZ groups ($p < .05$): light gray highlights significant differences between groups on items found in the BPRS or extracted from PANSS, while dark gray highlights significant differences between groups on those items found only in the PANSS.
[b]Placebo vs. haloperidol: BPRS items: PLA (N = 68), HAL (N = 69).
[c]Placebo vs. olanzapine: BPRS items: PLA (N = 111), OLZ (N = 177); PANSS-only items: PLA (N = 50), OLZ (N = 50).
[d]Haloperidol vs. olanzapine: BPRS items: HAL (N = 782), OLZ (N = 1608); PANSS-only items: HAL (N = 740), OLZ (N = 1512).

peridol on 7 of the 9 positive symptoms, with one of the remaining just missing significance ($p = .06$); (3) superior on 4 of the 6 disorganized thoughts items; (4) superior on the excitement and poor impulse control items of the impulsivity/hostility factor; and (5) superior on 3 of the 4 anxiety/depression items (see Table 3). Note that many of the differences are massively statistically significant. Haloperidol was superior to placebo by 9.5 BPRS points. Olanzapine was superior to haloperidol by 6.2 PANSS points or 3.5 BPRS points. An average item multiplied by 30 (PANSS) or 18 (BPRS) in each scale translates roughly into a change in total scores. The observed-case ANCOVA analysis, of just those patients who completed each assessment, found olanzapine to be significantly superior to haloperidol on the BPRS total score by week 3 ($F = 5.8$, $df = 1,2103$; $p = .02$) and at weeks 4 ($F = 17.6$, $df = 1,2005$; $p = .0003$), 5 ($F = 16.3$, $df = 1,1657$; $p = 10^{-4}$), and 6 ($F = 21.7$, $df = 1,1453$; $p = 10^{-5}$).

Figure 1. Percentage of Patients Who Showed at Least 20% Improvement in Brief Psychiatric Rating Scale Total Score Per Week Comparing (A) Olanzapine With Placebo and (B) Olanzapine With Haloperidol



Deterioration on Placebo Treatment and During the Washout Period

Patients became more symptomatic during the placebo lead-in washout period from screening to baseline evaluation. On the PANSS total score, patients deteriorated a mean of 0.66 points ($t = 6.48$, $df = 2902$, $p = 10^{-10}$). Examination of the individual PANSS items showed significant deterioration in 17 of the 30 items. As the sample size was large at this point (N = 2903 [extracted BPRS] or N = 2568 [PANSS]), the deterioration was highly significant. For example, the "unusual thought content" and "lack of judgment and insight" items showed deterioration of 0.05 PANSS point, but this is significant to p = .001. Significant deterioration during washout was also observed on all 5 PANSS factors ($p < .004$).

It is clinically important to elucidate what dimensions of schizophrenia deteriorate when the patient stops taking medication. A relatively large sample size of 114 (or 49 for PANSS only) patients on placebo treatment provided a test case. We evaluated deterioration from screening to endpoint. The BPRS impulsivity/hostility factor showed the most deterioration (1.8 points) from screening to endpoint (paired t test, $t = 4.8$, $df = 113$, $p = 10^{-5}$). Deterioration from screening to endpoint on all 4 items of the impulsivity/hostility factor was significant (poor impulse control, $t = 2.2$, $df = 48$, $p = .03$; hostility, $t = 3.0$, $df = 113$, $p = .003$; uncooperativeness, $t = 5.4$, $df = 113$, $p = 10^{-6}$; and excitement, $t = 2.0$, $df = 113$, $p = .05$). Other individual items that deteriorated included lack of judgment ($p = .03$), preoccupation ($p = .005$), poor rapport ($p = .009$), lack of spontaneity ($p = .01$), active social avoidance ($p = .009$), grandiosity ($p = .03$), stereotyped thinking ($p = .02$), and mannerisms and posturing ($p = .03$).

Effect of Olanzapine on Haloperidol-Responsive and Haloperidol-Nonresponsive BPRS Items

Olanzapine was statistically superior to haloperidol on reducing scores for 6 of the 11 BPRS items classified as haloperidol-responsive and for all 7 BPRS items classified as haloperidol-nonresponsive.

The mean improvement with olanzapine versus placebo and haloperidol on the responsive and nonresponsive items is shown in Figure 2. Interestingly, olanzapine was superior to haloperidol on the haloperidol-responsive scale by week 5; and, at endpoint, olanzapine improved the score by 0.62 points compared with 0.50 points for haloperidol ($F = 12.4$, $df = 1,2387$; $p = .0004$). Importantly, olanzapine produced a much greater improvement than haloperidol on the haloperidol-nonresponsive scale (see Figure 2). Significance was attained by week 1; and, by endpoint, the difference was massively significant in favor of olanzapine ($F = 74$, $df = 1,2387$; $p = 10^{-17}$). Olanzapine-treated patients improved a mean of 0.68 points per item on the nonresponsive items, whereas haloperidol-treated patients improved 0.42 points per item. The improvement with olanzapine was more than 50% greater than that with haloperidol. Since the unit is points per item, one would have to multiply by 18 or 30, respectively, to convert to a measure comparable to change on the BPRS or PANSS total score.

Dose-Response Relationships

We tested the difference between the 1-mg/day dose of olanzapine and placebo on the PANSS total, items, factors, and haloperidol-responsive and nonresponsive items and found no significant differences. Two studies randomly assigned patients to 3 dose ranges with initial doses of 5, 10, and 15 mg/day. The doses could be adjusted up or down by 2.5 mg/day. The mean doses actually administered were 6.7, 11.5, and 16.4 mg/day. We found the dose response relationship to be linear over these 3 doses (Figure 3). By definition, the dose-response curve (log dose vs. response)

Figure 2. Overall Improvement in Brief Psychiatric Rating Scale Change Score Per Week Comparing Olanzapine With Placebo (A and C) and Olanzapine With Haloperidol (B and D) for Haloperidol-Nonresponsive (A and B) and Haloperidol-Responsive Items (C and D)

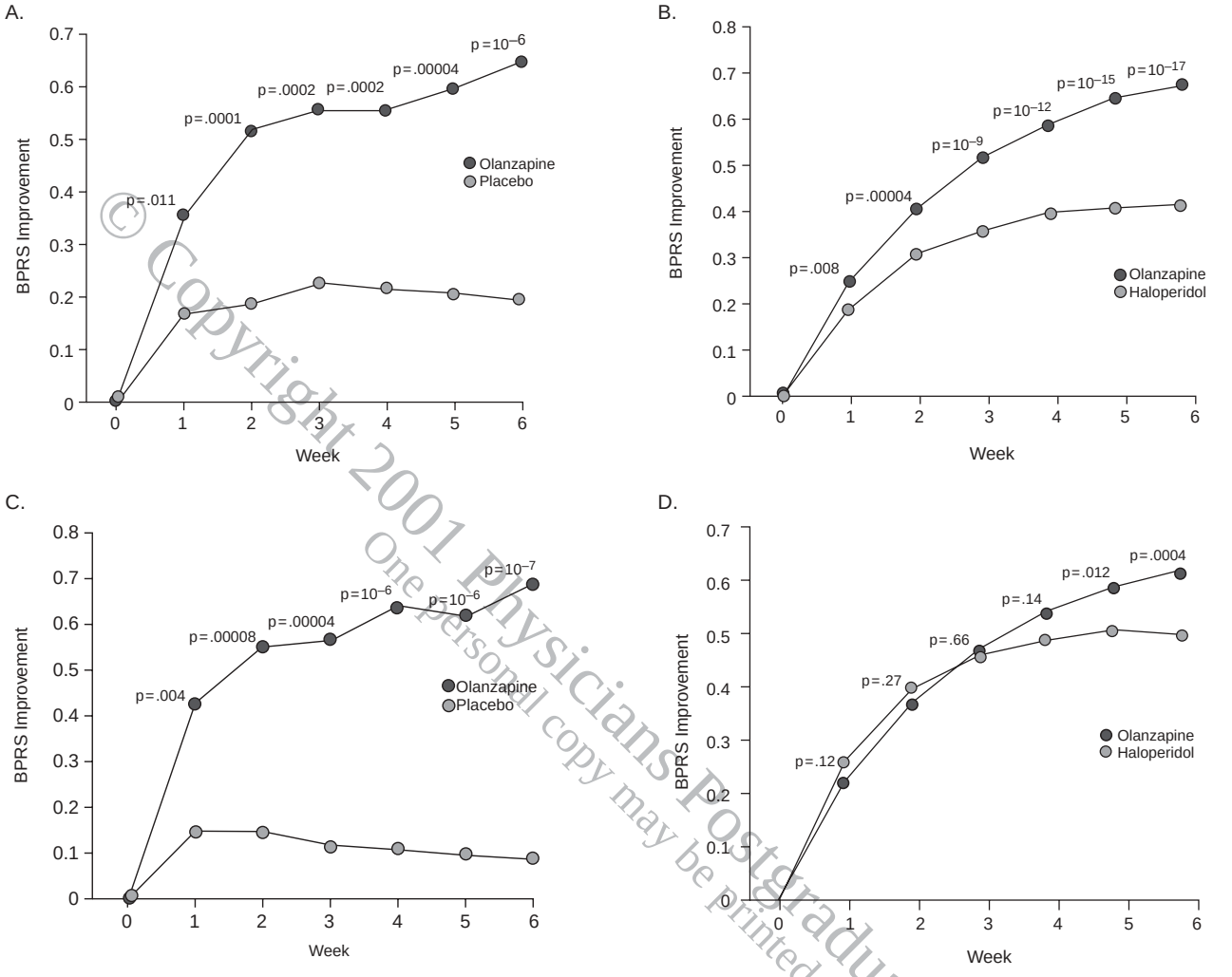
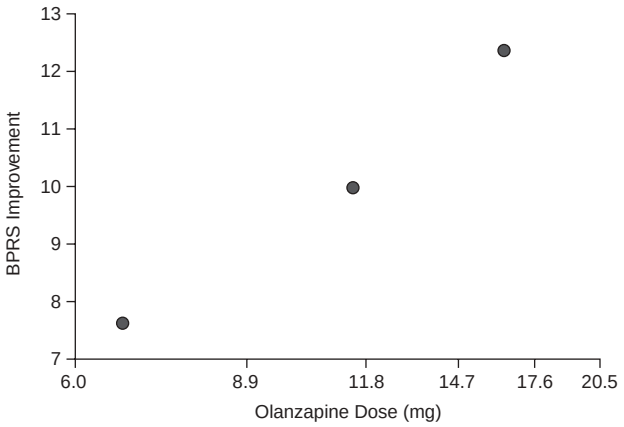
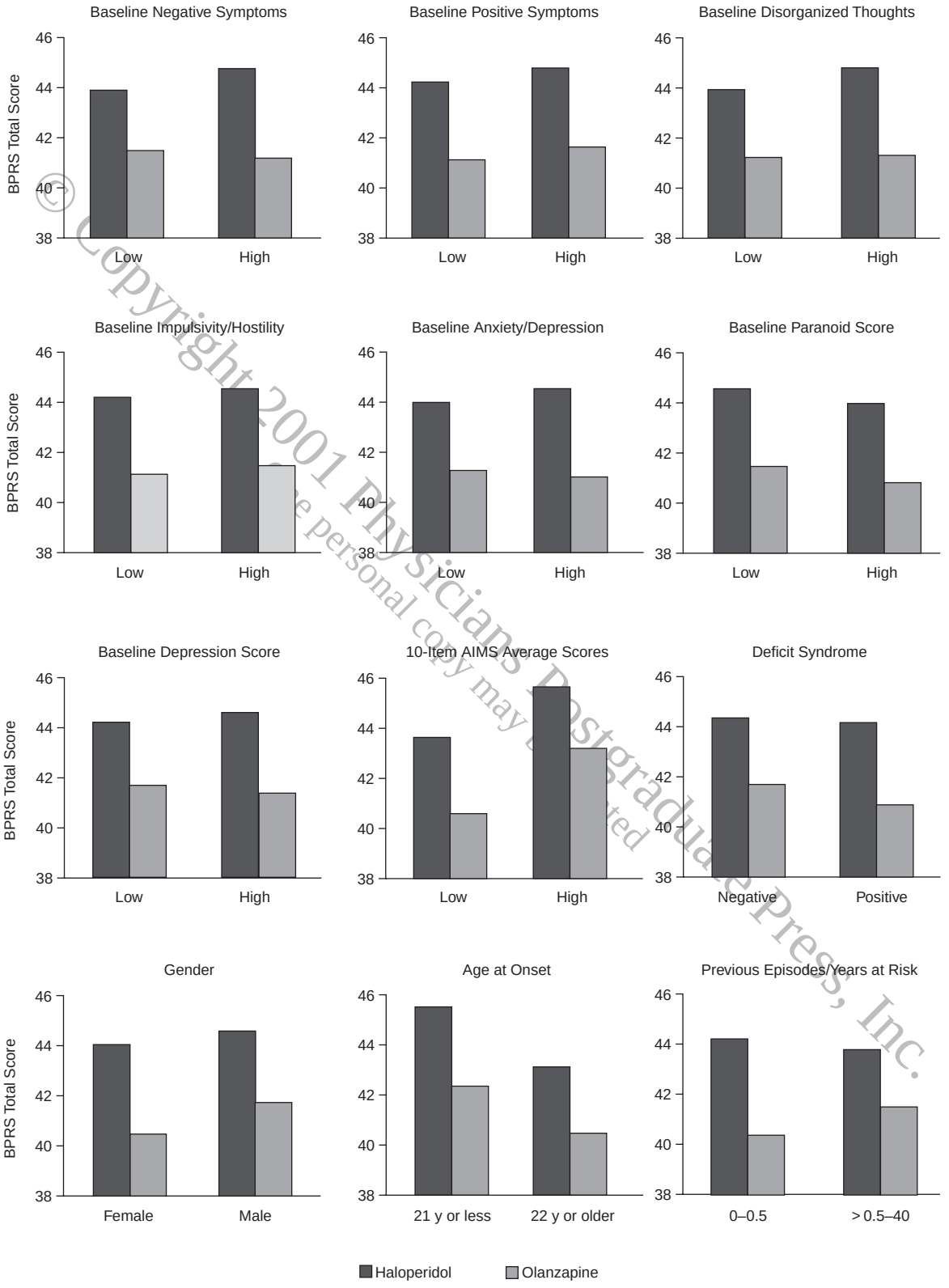


Figure 3. Relationship Between Dose of Olanzapine and Overall Improvement in Brief Psychiatric Rating Scale Total Score



should be linear over most of the range of the curve but flatten out at the top (such that an equal increment in dose should produce progressively less response). The increment in improvement between the 6.7- and 11.5-mg/day doses was 2.34 PANSS points, and the increment from 11.5 to 16.4 mg/day was 2.35 PANSS points. There was no indication that the curve was flattening out. We found the PANSS total score dose response to be linear (p = .008) on testing with polynomial contrast. Each of the 5 factors had linear dose-response curves with p values (for linear term) as follows: negative symptoms, p = .02; positive symptoms, p = .05; disorganized thoughts, p = .02; impulsivity/hostility, p = .01; and anxiety/depression, p = .07. In all cases, the quadratic term was essentially zero and clearly nonsignificant. We estimate that the dose of olanzapine that produces equal efficacy to haloperidol is approximately 10 mg/day.

Figure 4. Olanzapine or Haloperidol Versus Subtypes on Overall Improvement in Brief Psychiatric Rating Scale (BPRS) Total Score[a]



[a]Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

Effect of Dose of Comparator

We tested whether too high a dose of haloperidol comparator might decrease the comparative efficacy differences from olanzapine. This was not the case. There was no significant difference between high and low dose of haloperidol comparator and olanzapine-haloperidol differences on the PANSS total score or on any of the 5 factors (F = 1.4, 1.1, 2.3, 0.2, 0.5, and 1.7 for the total and 5 factor scores respectively; df = 1,2385; p = NS for all).

Subtype Analysis

We explored whether any subtype responded particularly better or worse to olanzapine as compared to haloperidol. A significant interaction on ANCOVA would indicate that the subgroups respond differently to olanzapine and haloperidol. Figure 4 shows results of 2-way ANCOVA with various subtypes. Olanzapine was 3 BPRS points superior to haloperidol to an equal degree in both males and females (Figure 4, bottom left panel). The interaction was essentially zero. In Figure 4 (row 3, middle panel), we present results of patients with low or high tardive dyskinesia (TD) (i.e., low versus high Abnormal Involuntary Movement Scale 10-item mean scores). Those with high TD had a less favorable outcome, i.e., there was a direct effect of the TD variable, but there was no significant interaction, in that olanzapine was superior to haloperidol in both patients without and with TD. Early-onset illness showed less improvement, with higher endpoint scores in both drug groups. Olanzapine produced better and proportionately equally better improvement in both early- and late-onset patients. Similarly, olanzapine was equally superior to haloperidol in patients with high versus low initial factor scores for all 5 factors. We also evaluated the presence or absence of paranoia symptoms and deficit state and failed to find a significant interaction.

No significant between-treatment differences in responses, including PANSS total and the 5 PANSS factor scores, were noted among patients with frequent or infrequent hospitalizations, adjusted for years at risk. There were no interactions between hospitalization frequency and PANSS total score or any of the 5 factors, i.e., olanzapine was superior to haloperidol to the same degree in both groups.

Olanzapine was superior to haloperidol to an equal degree among the paranoid and nonparanoid types of schizophrenia patients. There were no significant effects of paranoid/nonparanoid status on the degree of olanzapine or haloperidol response (i.e., interaction of drug group and the suspiciousness/persecution item for total BPRS and the 5 factors was not significant: F = 0.0, 0.4, 0.3, 0.0, 0.0, and 0.0, respectively; df = 1,2385).

Olanzapine produced almost a quarter point (0.23) greater improvement on the PANSS depression item than haloperidol (see Table 3). We tested the hypothesis that the overall greater improvement with olanzapine occurred entirely or primarily in those schizophrenia patients having a depressive component. The hypothesis that olanzapine was more effective only in depressed schizophrenia patients was rejected because olanzapine was superior to haloperidol to an equal degree on the BPRS total and all 5 factors in patients with or without depression (depression defined as a score of ≥ 3 on the PANSS depression item at baseline). A 2-way ANCOVA found no significant differential effect, i.e., there were no significant interactions of drug by depression (F = 0.4, 0.4, 0.2, 0.6, 1.0, and 1.1, respectively; df = 1,2385) on improvements in the total or 5 factor scores.

Effect of Dropout Due to Adverse Reactions or EPS

The interaction term, which tests whether dropping out due to adverse effects could alter the differential efficacy of olanzapine versus haloperidol, was not significant. There was no significant interaction of treatment and dropout status due to adverse effects on PANSS total score (F = 0.3, df = 1,2332; p = .6). A 2 × 3 ANCOVA of treatment versus dropout time (dropout weeks 1–3, dropout weeks 4–6, or completing) also showed no interaction between treatment and early discontinuation on the total score (F = 0.1, df = 2,2330; p = .9). Two similar analyses (2 × 2 and 2 × 3) exploring the same question for dropout due to EPS also found no significant interaction on total score (F = 2.7, df = 1,2332; p = .1; F = 1.1, df = 2,2331; p = .3, respectively).

Olanzapine Effect on EPS and Akathisia

Figure 5 depicts the comparison of placebo versus haloperidol, placebo versus olanzapine, and haloperidol versus olanzapine in the continuous measurement of EPS (Simpson-Angus Scale) and akathisia (Barnes Akathisia Scale). Haloperidol produced a statistically significant increase ($p = 10^{-6}$) on the Simpson-Angus Scale compared with placebo. Approximately 65% of patients receiving haloperidol experienced EPS by our operational definition, in contrast to only 7% of patients receiving placebo ($\chi^2 = 47$, df = 1, $p = 10^{-11}$). There was a high degree of statistical separation between olanzapine and haloperidol ($p = 10^{-56}$) on the Simpson-Angus Scale (see Figure 5). Forty-seven percent of patients receiving haloperidol experienced EPS compared with 13% receiving olanzapine ($\chi^2 = 339$, df = 1, $p = 10^{-75}$). In contrast, the severity of EPS on the Simpson-Angus Scale (see Figure 5) associated with olanzapine was not significantly different from that associated with placebo (p = .25). Fifteen percent of patients receiving olanzapine and 8.5% receiving placebo were evaluated as having EPS ($\chi^2 = 2.4$, df = 1, p = .12). When both variables were combined in a logistic regression, there was no significant difference between olanzapine and placebo. There was no evidence of a dose-response relationship (Figure 6) in the 3 fixed-dose ranges of olanzapine (mean daily doses = 6.7, 11.5, and 16.4 mg)

Figure 5. Mean ± SEM Maximum Score on the Simpson-Angus Scale and Barnes Akathisia Scale Observed in Placebo (PLA), Haloperidol (HAL), and Olanzapine (OLZ) Treatment Groups Per Comparison

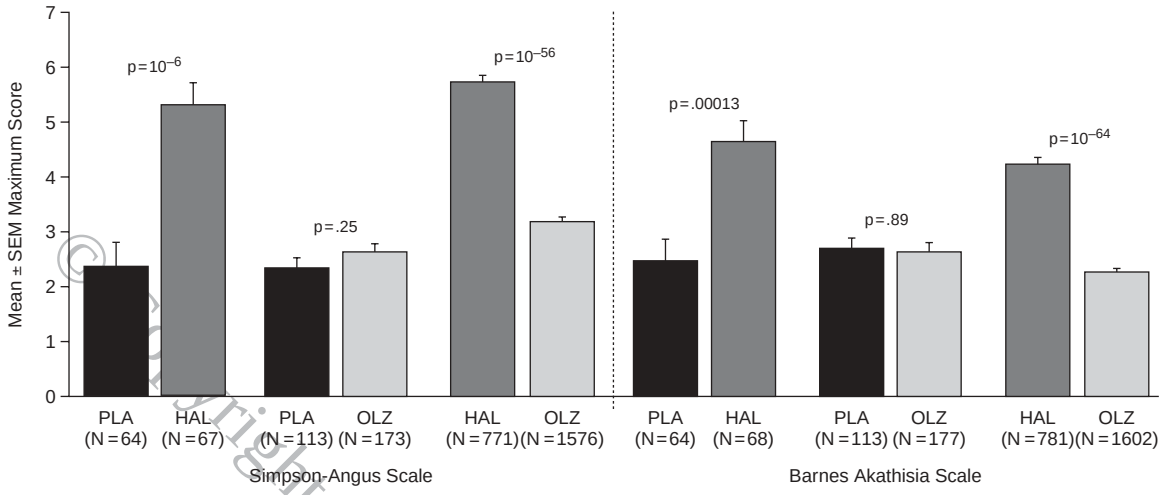
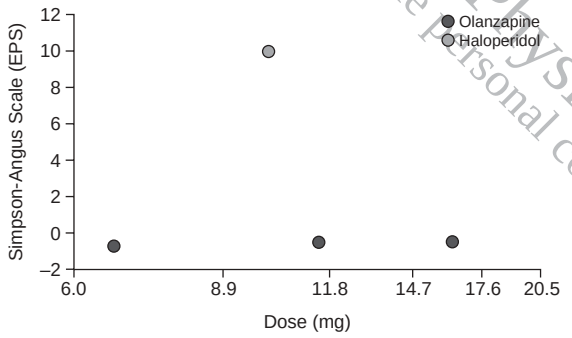
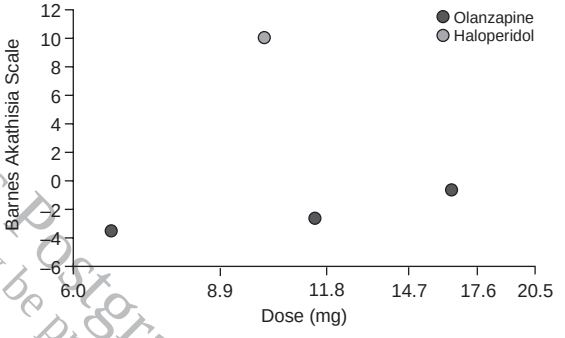


Figure 6. Relationship Between Dose of Olanzapine and Equivalent Haloperidol Dose on the Simpson-Angus Scale[a]



[a]Abbreviation: EPS = extrapyramidal side effects.

Figure 7. Relationship Between Dose of Olanzapine and Equivalent Haloperidol Dose on the Barnes Akathisia Scale



following olanzapine treatment in the Simpson-Angus maximum score ($F = 0.07$, $df = 2,436$; $p = .9$). EPS were observed in 11%, 13%, and 16% for the 3 doses of olanzapine, respectively, a difference that was nonsignificant ($\chi^2 = 1.4$, $df = 2$, $p = .48$). We also examined dose response by comparing placebo, a grouping of the 1-mg doses used in Study 2 and Study 3, and a grouping of the 10- to 11-mg doses. The Simpson-Angus score was essentially the same in the 2 olanzapine groupings ($F = 0.7$, $df = 1,264$; $p = .5$). A total of 6.5% of patients receiving the 1-mg dose had EPS, and 4.4% of those receiving 10 to 11 mg of olanzapine had EPS, a difference that was not significant and was opposite in direction of that expected ($\chi^2 = 0.5$, $df = 1$, $p = .50$).

A significant increase in akathisia was observed in 44% of patients treated with haloperidol in comparison with 12.5% of patients treated with placebo ($\chi^2 = 14.6$, $df = 1$, $p = .0001$). In contrast, only 16.9% of olanzapine-treated patients showed akathisia compared with 15% of those treated with placebo ($\chi^2 = 0.06$, $df = 1$, $p = .81$), a difference that was clearly not statistically significant in almost 300 patients. There was a substantial difference between olanzapine and haloperidol ($p = 10^{-64}$) on the Barnes Akathisia Scale (see Figure 5). Thirty-six percent of haloperidol-treated patients experienced akathisia, in contrast to 12% treated with olanzapine ($\chi^2 = 188$, $df = 1$, $p = 10^{-42}$). Also evaluated was whether there was a dose-response relationship among the 3 fixed-dose ranges of olanzapine (mean daily doses = 6.7, 11.5, and 16.4 mg) for the Barnes total score (Figure 7). The linear dose-response slope was significant to the $p = .04$ level. The incidence of akathisia was 9%, 14%, and 15% for the 3 dose ranges respectively ($\chi^2 = 2.7$, $df = 2$, $p = .3$). The Barnes total score for those patients randomly assigned to receive approximately 1 mg/day and the score for those assigned to receive 10 to 11 mg/day was essentially equal ($F = 0.5$, $df = 1,437$; $p = .5$), and the incidence of akathisia was 6% and 10.5%, respectively ($\chi^2 = 1.3$, $df = 1$, $p = .3$).

Effect of EPS on Differential Outcome

We examined whether olanzapine-treated patients with EPS had a much better outcome than haloperidol-treated patients with EPS. There was no significant interaction for the BPRS total score or any of the 5 factors (negative symptoms, positive symptoms, disorganized thoughts, impulsivity/hostility, anxiety/depression), or the haloperidol-responsive or -nonresponsive items: F = 2.8, 0.4, 3.2, 1.4, 0.9, 2.4, 3.5, and 1.1, respectively (df = 1,2386; p = NS for all 8 interactions). We also tested whether there was an interaction between the presence of akathisia and the relative improvement with olanzapine or haloperidol. While those patients who had akathisia experienced somewhat less improvement than those without the side effect, this direct effect was essentially the same for both drugs. The F values for the interaction effect for the total score and the 5 factors and the haloperidol-responsive and -nonresponsive items were as follows: F = 0.00, 0.04, 0.13, 0.04, 0.02, 0.12, 0.28, 0.73 (df = 1,2379; p = NS for all interactions). We found no evidence that akathisia had a greater effect at lessening improvement of either drug at the expense of the other.

DISCUSSION

Our reanalysis of the 4 Lilly registrational studies shows that olanzapine produced a greater reduction in schizophrenic symptoms than haloperidol. This was evidenced by the lower BPRS and PANSS total scores, as well as scores on each of the 5 factors (negative symptoms, positive symptoms, disorganized thoughts, hostility/impulsivity, and anxiety/depression). Olanzapine induced a response at an equal rate as haloperidol in the first few weeks, but produced a significantly greater number of responders from week 3 until the end of study. The importance of this is not so much that this difference is very large but rather that olanzapine produces no less rapid response than haloperidol.

The original positive and negative subscales of the PANSS were arbitrarily assigned by its authors based on the general conceptualization at the time the PANSS was developed. Subsequently, many factor analyses agree that the PANSS contains 5 factors. Each factor analysis differs slightly from others on 1 or 2 items, but there is remarkable agreement on the composition of the 5-factor structure. The original positive and negative symptom subscales are only roughly consistent with what we now know. We feel that it is important to characterize the qualitative nature of the improvement produced by olanzapine and contrast this to haloperidol, our prototypical typical neuroleptic. The old clusters are somewhat imprecise and miss 3 dimensions. In our factor analysis of this data set, 5 of the 7 original negative symptom items loaded on the negative symptoms factor, but 1 negative symptom item loaded with the positive symptoms factor while the other item loaded with the disorganized thoughts factor. Five of the 7 arbitrarily defined positive symptom items loaded on the positive symptoms factor, but the remaining 2 items (hostility and excitement) loaded on the hostility/impulsivity factor. As mentioned previously, factor-analytic–derived factors explain only 50% of the variance; therefore, characterization of the drug difference in each of the 30 items will more precisely define the qualitative nature of these changes, an analysis not previously performed. In addition, we attempted a pharmacologically derived characterization of the drug effects. Since haloperidol and olanzapine share the common property of blocking dopamine receptors, we can identify the haloperidol-sensitive items and characterize the patients by a drug-induced haloperidol-sensitive measure. We could also derive a scale of all the other items for a haloperidol-nonresponsive measure. In short, we pooled these data sets for maximum power to identify the qualitative nature of the haloperidol and olanzapine changes with the aim of more fully understanding the clinical implications of the difference between olanzapine and haloperidol as our prototypical conventional neuroleptic.

Olanzapine produced a slight but statistically significant improvement over haloperidol on the positive symptoms factor and on 7 of 9 positive symptom items. Since olanzapine, as well as haloperidol, is a D_2 blocker, the similar improvement on positive symptoms would be expected. Olanzapine is statistically significantly superior to haloperidol on 23 of the 30 PANSS items, with trends for 3 more items. Haloperidol fails to be superior on any item. The olanzapine superiority is not explainable by a strong effect on just a few items. These olanzapine-haloperidol differences were highly significant for all 7 items in the negative symptoms factor, 4 of 6 in the disorganized thoughts factor, and 3 of 4 in the anxiety/depression factor. Olanzapine showed statistically greater improvement than haloperidol on the haloperidol-responsive items, which comprised BPRS items that improved with haloperidol. Moreover, olanzapine was substantially superior to haloperidol on the haloperidol-nonresponsive items.

The overall difference between the 2 drugs is in large part because olanzapine benefits many symptoms that are not benefited by haloperidol, i.e., olanzapine produces a wider range of symptom reduction. The haloperidol-nonresponsive items account for 71% of the difference between olanzapine and haloperidol. The amount of improvement with olanzapine was about 50% greater than that with haloperidol alone. This would be consistent with the production of an additional clinical effect by an additional ingredient or ingredients in its pharmacology. The greater improvement on a broader range of items has implication for rehabilitation and social functions. We also feel it should alter the way we think about response from mere positive symptom reduction to a full social and vocational recovery. It is important to remember that the term

response actually refers to partial response. Algorithms for treatment of patients generally end once a patient is characterized as a responder. (The nonresponders are switched to a different drug; nonresponders to the second drug are switched to a third drug and so on.) Research is focused on treating these nonresponders. A consequence of this conceptualization is that too little attention is placed on the qualitative effect of the drug on responders. It is a mistake to characterize partial improvement as a full remission of the disorder. We emphasize that the fact that more symptoms are helped by olanzapine may have consequences for social adjustment and full rehabilitation.

Conley et al.[26] reported an academic investigation of olanzapine versus a typical neuroleptic. Although the study found that olanzapine produces a significantly greater effect on anxiety/depression, it found only a nonsignificant superiority for olanzapine on positive symptoms, the anergia factor, and the Scale for the Assessment of Negative Symptoms. These trends were significant to approximately the .25 level, and the effect sizes were very similar to the effect sizes observed in the present meta-analysis. Had Conley et al. used a sample size 3 times greater, they would have also found olanzapine statistically significantly superior to the typical comparator. The results in the present meta-analysis are very similar in magnitude and pattern to the results in the study by Conley et al. The study by Conley et al. was particularly well done and one of the few clinical trials not performed by the pharmaceutical industry.

The fact that some atypicals are more efficacious than typicals implies a distinction between equivalent doses and optimal doses. We plotted the olanzapine efficacy dose-response curve, which appears linear over the 3 mean doses of 6.7, 11.5, and 16.4 mg. The approximate dose equivalence of haloperidol is about 10 mg of olanzapine. However, higher doses (the pooled 11.5-mg and 16.4-mg and the 13.2-mg flexible dose) are empirically more effective than haloperidol. It is possible that even higher doses of olanzapine could be more effective. We do not know the optimal olanzapine dose, but it is probably higher than 15 mg.

We generalize Remington and Kapur's[15] refractory question conceptually to the subgroup question. Is olanzapine superior to typicals only in a subgroup, e.g., principally in depressed schizophrenics? We agree with Remington and Kapur,[15] who suggest that it is important to test the refractory patients in prospective studies. The definitions of subgroups should be based on lifetime diagnosis or biologically defined variables (i.e., ventricle size), and not just clusters of present symptoms. Since we find olanzapine superior to haloperidol, is its better efficacy a result of a good effect in just one subgroup or is it due to a modest effect in most patients? Do the extra ingredients in its pharmacology benefit patients with schizophrenia across the board or just a particular subgroup (or subgroups)? Olanzapine produced an equally superior treatment response in patients regardless of how often they were hospitalized (a possible measure of neuroleptic resistance); whether they were diagnosed with paranoid, nonparanoid, or deficit schizophrenia; whether they displayed clear signs of depression; and whether they had more severe positive symptoms or more severe negative symptoms (or thought disorder or impulsivity/hostility). The degree of olanzapine's extra benefit over haloperidol is about the same in all subgroups and represents an effect applicable to the great majority of patients and not restricted to a given subgroup.

We found no statistical evidence that olanzapine treatment was associated with an increase in EPS or akathisia over placebo, nor were these side effects consistently dose-related. The one relationship that was just barely significant was that of the Barnes Akathisia Scale for low, medium, and high doses, but it was below baseline. This should be viewed in the context of a 1-mg dose producing slightly more akathisia than the 10-mg dose. The fact that considerably more EPS and akathisia were documented with haloperidol than with placebo proves that the measures used here had some sensitivity. The incidence of these 2 side effects with olanzapine is about the same as with placebo, even in the larger sample size with meta-analysis. We caution against saying these side effects do not occur with olanzapine because they could occur at a low enough level that they are indistinguishable from that observed with placebo. Studies on olanzapine in parkinsonian patients would be more sensitive in detecting a parkinsonian effect, as would studies of high doses of olanzapine. The cause of EPS and akathisia observed with placebo in both these studies and many other studies is not well understood. This finding suggests that the EPS observed in our study were not due to medications received during the study. Since antiparkinsonian drugs have toxicity, the clinician should be mindful of unnecessary use of antiparkinsonian drugs in patients on olanzapine monotherapy. We found no evidence that EPS explained the greater improvement with olanzapine.

Geddes et al.[4] suggest that too high a dose of haloperidol might decrease the efficacy of haloperidol. Since 2 of the 3 studies here used high-dose haloperidol, we tested the effect of high- versus low-dose haloperidol on olanzapine and haloperidol efficacy. In these studies, dose of haloperidol had no effect on the improvement due to olanzapine or haloperidol.

The distinction between schizophrenic symptoms and drug side effect is clinically important. A path analysis of patients from Study 2 showed that the low incidence of EPS following olanzapine treatment was only a minor contributor to alleviating negative symptoms,[27] suggesting that improvement was attributable to olanzapine treatment. We note that it is problematic to attribute cause from correlational data. Based on our analyses and this

path analysis, we failed to find evidence that the small amount of EPS with olanzapine altered efficacy. We advise caution in ascribing cause or lack of cause to correlational analysis, including our own. We found no influence of dropout due to EPS or due to any adverse reaction on differential efficacy. Long-term effectiveness research might be more sensitive to detecting differences, as side effects can lead to poor compliance, increase cost, and otherwise complicate treatment.

It is pertinent to consider efficacy in a historical perspective. In the late 1950s and early 1960s, various pharmaceutical companies touted their drugs as having certain advantages in particular schizophrenic subtypes. A systematic review of the literature at that time (1969) by Klein and Davis[28] indicated that (1) all antipsychotics were equal in overall efficacy and (2) there was no systematic difference between responses by subtypes to different agents. Our first conclusion is no longer true, as several atypicals, including olanzapine, are clearly more effective than typical neuroleptics. The second conclusion continues to be true in that this difference favoring olanzapine occurs to an equal degree in all subgroups examined. However, the development of the atypical drugs again raises these questions, and the data presented in this article indicate that there are striking differences between the atypical and typical antipsychotics. Olanzapine was shown to be statistically superior to haloperidol not only in the improvement of negative symptoms, but also in the improvement of positive symptoms and in the treatment of hostility, disorganized thoughts, and anxiety/depression. About 70% of the difference can be attributed to symptoms not benefited by typicals. This difference favoring olanzapine occurs to an equal degree in all subgroups examined. In addition, while EPS are clearly evident in patients treated with haloperidol, the apparent incidence of parkinsonism or akathisia following olanzapine treatment was extremely low and not statistically distinguishable from placebo.

It is important that the clinician appreciate that choice of drug should be based on a much wider set of data than the acute registrational studies. Since olanzapine is better tolerated than typical neuroleptics, side effects in a real-world setting could lead to noncompliance and relapse. Effectiveness research is needed to elucidate such differences in a wider context. The broader spectrum of olanzapine efficacy might have important implications for social and vocational adjustment as well. By the same token, side effects not examined in this article, such as weight gain, vulnerability to diabetes, and hyperlipidemia, are also important. The clinician should weigh such factors in the context of their importance. Quantitative measures of efficacy, quality of improvement, and EPS are relevant but only a few of many factors to consider.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Tamminga CA. "New" rather than "atypical." Psychopharmacology (Berl) 2000;148:20–21
2. Mattes JA. Olanzapine on trial. Am J Psychiatry 1998;155:153
3. Mattes JA. Risperidone: how good is the evidence for efficacy? Schizophr Bull 1997;23:155–161
4. Geddes J, Freemantle N, Harrison P, et al, for the National Schizophrenia Guideline Development Group. Atypical antipsychotics in the treatment of schizophrenia: a systematic overview and meta-regression analysis. BMJ 2000;321:1371–1376
5. Pearsall R, Glick ID, Pickar D, et al. A new algorithm for treating schizophrenia. Psychopharmacol Bull 1998;34:349–353
6. Miller AL, Chiles JA, Chiles JK, et al. The Texas Medication Algorithms Project (TMAP) schizophrenia algorithms. J Clin Psychiatry 1999;60: 649–657
7. Osser DN, Zarate CA Jr. Consultant for the pharmacotherapy of schizophrenia. Psychiatr Ann 1999;29:252–267
8. Expert Consensus Guideline Series: Treatment of Schizophrenia 1999. J Clin Psychiatry 1999;60(suppl 11):1–80
9. American Psychiatric Association. The Practice Guidelines for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997;154 (suppl 4):1–63
10. Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998;24:1–10
11. Beasley CM Jr, Tollefson G, 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
12. Beasley CM Jr, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996:124;159–167
13. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
14. 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
15. Remington G, Kapur S. Atypical antipsychotics: are some more atypical than others? Psychopharmacology (Berl) 2000;148:3–15
16. Dawkins K, Lieberman JA, Lebowitz BD, et al. Antipsychotics: past and future. National Institute of Mental Health Division of Services and Intervention Research Workshop, July 14, 1998. Schizophr Bull 1999;25: 395–405
17. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American Trials. J Clin Psychiatry 1997;58:538–546
18. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
19. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 1999;156:990–999
20. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
21. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. Psychopharmacol Bull 1988;24:112–117
22. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Bethesda, Md: National Institute of Mental Health; 1976
23. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
24. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
25. Berardi D, Giannelli A, Barnes TR. Clinical correlates of akathisia in acute psychiatric inpatients. Int Clin Psychopharmacol 2000;15:215–219
26. Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry 1998;155:914–920
27. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997;154:466–474
28. Klein DF, Davis JM. Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore, Md: Williams & Wilkins; 1969