Superior Efficacy of Olanzapine Over Haloperidol: Analysis of Patients With Schizophrenia From a Multicenter International Trial

Juan-Carlos Gomez, M.D., and Ann Marie K. Crawford, Ph.D.

Background: Previously, a double-blind, 6-week, parallel-group trial compared the therapeutic profiles of olanzapine (5–20 mg/day; N = 1336) and haloperidol (5–20 mg/day; N = 660) in 1996 patients with DSM-III-R schizophrenia (83.1%) or schizophreniform (1.9%) or schizoaffective disorders (15.0%) and showed olanzapine to have a superior, broader spectrum of efficacy as well as a more favorable adverse event profile. The present post hoc analysis examined the efficacy of olanzapine compared with haloperidol in the schizophrenic cohort of that study and in subgroups of schizophrenic patients defined by baseline symptom profile and course of illness. ***Method:*** A total of 1658 patients were included. Patients were included in analyses of change if they had both a baseline and at least 1 postbaseline measurement (N = 1622; 1096 olanzapine-treated patients, 526 haloperidol-treated patients). An analysis of variance was used to compare treatment effects on efficacy measurements including the Brief Psychiatric Rating Scale (BPRS; scored 0–6) and the Positive and Negative Syndrome Scale (total, positive subscale, and negative subscale scores). ***Results:*** Olanzapine-treated patients exhibited statistically significantly greater improvements from baseline (last observation carried forward) on all efficacy measurements. Olanzapine-treated patients with predominantly positive, predominantly negative, or mixed symptoms had statistically significantly greater improvements in BPRS total scores compared with similar haloperidol-treated patients. Patients with primarily chronic negative symptoms and patients with chronic or subchronic courses of illness had statistically significantly greater mean improvements from baseline on the BPRS total with olanzapine compared with haloperidol. Furthermore, within the olanzapine treatment group, patients with a subchronic course of illness had greater mean improvements than patients with a chronic course of illness. ***Conclusion:*** Olanzapine was more effective than haloperidol in treating a varied spectrum of patients with schizophrenia, including patients with positive, negative, or mixed symptom profiles and either a chronic or subchronic course of illness.

(J Clin Psychiatry 2001;62[suppl 2]:6–11)

Clinical registration trials of new antipsychotic drugs generally examine efficacy and safety in large groups of broadly defined patients, which may include patients with schizophrenia or schizophreniform or schizoaffective disorder. While this practice is necessary to mimic the clinical population that may ultimately receive the drug, reports on conventional antipsychotic agents suggest that specific agents may be better suited for particular patient populations. For example, "low-potency" conventional antipsychotic agents, such as chlorpromazine or thioridazine, appear to be appropriate for agitated, floridly psychotic patients, while schizophrenic patients with predominantly negative symptoms may respond better to "high-potency" (incisive) drugs, such as haloperidol.[1] Since these potential differences have not been confirmed by controlled trials,[2,3] all commonly used conventional antipsychotic agents are regarded as equally effective in treating schizophrenia.[4] Thus, controlled clinical trials in well-defined, homogeneous groups of patients are necessary to evaluate the performance of antipsychotic agents, especially the newer agents. Additionally, it is unclear if these novel drugs are equally effective when compared with conventional drugs across different schizophrenic patient populations.

Novel antipsychotic agents (such as olanzapine, risperidone, and clozapine) have demonstrated advantages over conventional neuroleptics, especially in treating the negative symptoms of schizophrenia.[5–8] It is unclear whether this finding may correlate with greater overall efficacy of these drugs in specific patient populations having predominantly negative symptoms. In a large trial involving 1996 patients with schizophrenia or schizophreniform or schizoaffective disorders,[7] olanzapine-treated patients showed a

From Eli Lilly Spain, Alcobendas, Madrid (Dr. Gomez), and Lilly Corporate Center, Indianapolis, Ind. (Dr. Crawford), Lilly Research Laboratories, Eli Lilly and Company.

Supported by an unrestricted grant from Eli Lilly and Company.

Reprint requests to: Ann Marie K. Crawford, Ph.D., Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 2233, Indianapolis, IN 46285.

greater improvement than haloperidol-treated patients in global psychopathology (Brief Psychiatric Rating Scale [BPRS] total score) and negative symptoms (Positive and Negative Syndrome Scale [PANSS] negative subscale). The purpose of the present analysis is to explore to what extent the differences in symptomatic change with olanzapine and haloperidol (shown in such a large sample) are applicable to a homogeneous schizophrenic patient population and subgroups of schizophrenic patients defined by symptom profiles and course of illness.

METHOD

Patient Population

The details for the acute (up to 6 weeks) treatment phase of this study have been previously described.[7] The protocol was approved by the ethical review boards for each of the 174 investigational sites that participated in the study, and each patient gave either written informed or witnessed oral consent after the details of the study had been fully explained. For the present analysis, the study population consisted of patients meeting the DSM-III-R criteria for schizophrenia (N = 1658). Within the schizophrenic patient population, patients were further categorized according to symptom profile and course of illness.

A patient's symptom profile at baseline was defined as being predominantly positive, predominantly negative, mixed, or "other," according to specific PANSS criteria.[9] Patients with a predominantly positive symptom profile at baseline had a score of at least 4 on 3 or more PANSS positive subscale items (items 1–7) and a score of at least 4 on no more than 2 PANSS negative subscale items (items 8–14). Patients with a predominantly negative symptom profile at baseline had a score of at least 4 on 3 or more PANSS negative subscale items and a score of at least 4 on no more than 2 PANSS positive subscale items. Patients with a mixed symptom profile at baseline had a score of at least 4 on 3 or more PANSS positive subscale items and a score of at least 4 on 3 or more PANSS negative subscale items. Patients who did not have a positive, negative, or mixed symptom profile, or for whom baseline symptom profile was unknown, were classified as "other."[10,11] Patients were further categorized as being chronic with predominantly negative symptoms if they had a length of illness of at least 2 years (the DSM-III-R criterion for chronicity) and a negative symptom profile. Schizophrenic course of illness was categorized as being either subchronic or "other" (chronic, chronic with acute exacerbation, unspecified course, or in remission) according to DSM-III-R criteria.

Study Design

For enrollment in the study, patients must have had a minimum BPRS total score (extracted from the PANSS and scored 0–6) of 18 and/or have been intolerant to current antipsychotic therapy (excluding haloperidol). The majority of these patients (98% of the total patient population) had baseline BPRS total scores ≥ 18. After a 2- to 9-day placebo lead-in phase, qualified patients were randomly assigned to treatment with either olanzapine (5 mg/day) or haloperidol (5 mg/day) in a 2:1 ratio. After 1 week of therapy, either drug could be increased by 5 mg/week to a maximum of 20 mg/day or subsequently decreased to a minimum of 5 mg/day at the discretion of the investigator.

Assessments

Psychiatric evaluations, including the BPRS and the PANSS, were conducted weekly throughout the 6-week acute phase. Safety assessments for the total patient population have been described previously.[7]

Statistical Methods

Statistical analyses were conducted on an intent-to-treat basis. Patients were included in treatment groups to which they were randomly assigned even if they did not strictly adhere to the protocol. All total scores of rating scales were derived from the individual items; if any of the individual items were missing, the total score was treated as missing. Patients were included in analyses of change from baseline only if they had both a baseline and at least 1 postbaseline measurement.

For analyses of continuous efficacy measures, treatment effects were compared using an analysis of variance model. Both last-observation-carried-forward and observed case analyses of change from baseline used a model that included the independent terms of treatment and geographic region. Response rate was analyzed using the Pearson chi-square test.

RESULTS

Patient Demographics and Baseline Severity of Illness

Of the original patient population, 1658 patients (83.1%) were diagnosed with schizophrenia and were randomly assigned to receive either olanzapine (N = 1112) or haloperidol (N = 546). The majority of patients were men (68.3%) and white (79.7%). The mean ± SD age was 38.79 ± 11.53 years in the olanzapine treatment group and 38.27 ± 11.14 years in the haloperidol treatment group. The treatment groups were comparable at baseline with respect to gender, racial origin, age, and duration of hospitalization (Table 1). Most patients (64.1%) had been hospitalized for less than 2 months prior to entry into the study. The treatment groups were also comparable with respect to severity of illness upon entering the trial (Table 2). As a whole, the group was moderately ill, and no statistically significant treatment differences were found in any of the measures of symptomatology at baseline. With respect to baseline symptom profile, more patients had a mixed profile (39.2%) than any other type. Eighty-seven

Table 1. Baseline Characteristics for Schizophrenic Population[a]

Characteristic	Olanzapine (N = 1112)	Haloperidol (N = 546)	Total (N = 1658)
Age, y, mean ± SD	38.79 ± 11.53	38.27 ± 11.14	38.62 ± 11.41
Sex, N (%)			
Male	764 (68.7)	368 (67.4)	1132 (68.3)
Female	348 (31.3)	178 (32.6)	526 (31.7)
Racial origin, N (%)			
White	886 (79.7)	435 (79.7)	1321 (79.7)
African descent	121 (10.9)	66 (12.1)	187 (11.3)
Other	105 (9.4)	45 (8.2)	150 (9.0)
Hospitalization duration prior to study participation, N (%)[b]	(N = 1108)	(N = 535)	(N = 1643)
None	419 (37.8)	195 (36.5)	614 (37.4)
> 0 to < 2 mo	294 (26.5)	145 (27.1)	439 (26.7)
2 to < 6 mo	190 (17.2)	100 (18.7)	290 (17.7)
6 to < 12 mo	78 (7.0)	37 (6.9)	115 (7.0)
≥ 12 mo	127 (11.5)	58 (10.8)	185 (11.3)

[a]Data from Tollefson et al.[8]
[b]Hospitalization duration calculated only when both hospitalization status and duration are known.

Table 2. Mean Baseline to Endpoint Change in Efficacy Rating Scale Scores (LOCF) in Schizophrenic Population (N = 1622)[a]

	Olanzapine (N = 1096)			Haloperidol (N = 526)			
Rating Scale	Baseline Score	Mean Change	SD	Baseline Score	Mean Change	SD	p Value
BPRS							
Total	32.99	–10.80	12.76	34.05	–8.31	12.55	< .001
Positive subscale	10.39	–3.38	4.23	10.60	–2.92	3.95	.022
Negative subscale	6.78	–2.04	2.88	6.86	–1.34	2.92	< .001
PANSS							
Total	90.45	–17.53	21.65	92.32	–14.04	21.16	< .001
Positive subscale	21.33	–4.69	6.72	21.70	–3.97	6.36	.023
Negative subscale	24.44	–4.48	6.32	24.69	–3.37	6.19	< .001

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

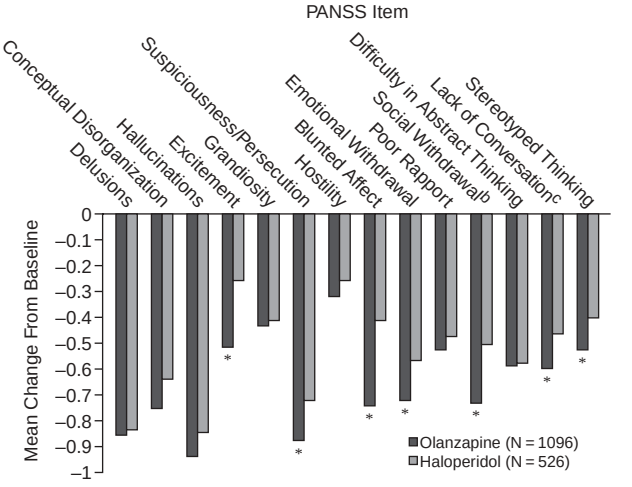
percent of the patients had either a chronic course or a chronic course with an acute exacerbation, although only 22.7% of the patients had both a negative symptom profile and a length of illness of at least 2 years.

Efficacy

Overall schizophrenic population endpoint analyses. Analysis of mean change from baseline to 6 weeks of acute therapy indicated that olanzapine-treated patients experienced statistically significantly greater improvement than haloperidol-treated patients with respect to overall, positive, and negative symptomatology, as measured by both the BPRS and the PANSS (see Table 2).

The positive and negative subscales of the PANSS were further analyzed on an individual item basis (Figure 1).

Figure 1. PANSS Results by Item[a]



[a]Abbreviation: PANSS = Positive and Negative Syndrome Scale.
[b]Passive/apathetic social withdrawal.
[c]Lack of spontaneity/flow of conversation.
*p < .05.

Olanzapine-treated patients experienced significant improvement in excitement, suspiciousness, blunted affect, emotional withdrawal, social withdrawal, lack of spontaneity/flow of conversation, and stereotyped thinking compared with haloperidol-treated patients.

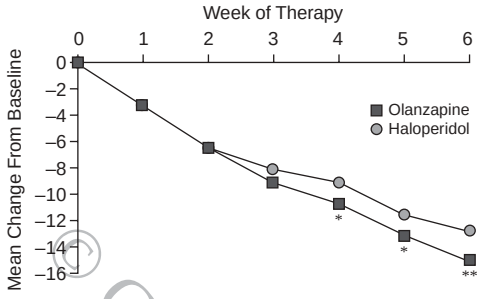
The response rate (improvement of at least 40% in baseline BPRS total score in patients who had completed at least 3 weeks of treatment and had a baseline BPRS total score greater than 18) was significantly higher with olanzapine (51.5%; p < .001) than with haloperidol (35.4%).

Weekly analyses. Figures 2 through 4 depict mean change from baseline to each visit for the BPRS total score and the PANSS positive and negative subscale scores. For olanzapine, statistically superior differences in mean change from baseline were observed in both the BPRS total scores (weeks 4–6) and the PANSS negative scores (weeks 4 and 6).

Symptom profile at baseline. In the predominantly positive, predominantly negative, and mixed symptom profile subgroups, olanzapine was statistically superior to haloperidol with respect to mean change in BPRS total score from baseline to at least 6 weeks of therapy (Table 3). This finding was corroborated in the analysis of mean change in PANSS total score. In the analysis of PANSS positive and negative subscale scores, only the olanzapine-treated patients in the predominantly negative symptom cohort showed statistical superiority to haloperidol-treated patients (positive subscale, p = .03; negative subscale, p = .002).

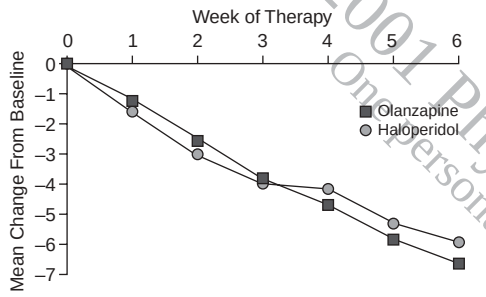
Course of illness. The majority of schizophrenic patients in this study were classified as "other" (90.0%). Of these, 0.6% were in remission. Olanzapine-treated patients

Figure 2. Mean Change in BPRS Total Score (observed case analysis)[a]



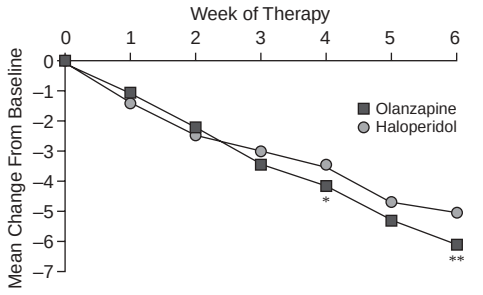
[a]Abbreviation: BPRS = Brief Psychiatric Rating Scale.
*p ≤ .05.
**p ≤ .01.

Figure 3. Mean Change in PANSS Positive Subscale Score (observed case analysis)[a]



[a]Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 4. Mean Change in PANSS Negative Subscale Score (observed case analysis)[a]



[a]Abbreviation: PANSS = Positive and Negative Syndrome Scale.
*p ≤ .05.
**p ≤ .01.

in both categories of course of illness exhibited a statistically significantly greater improvement in BPRS total score during acute therapy compared with haloperidol-treated patients (Table 4). This finding was replicated in the analysis of PANSS total score. With respect to the analysis of PANSS positive subscale score, only the olanzapine-treated patients in the subchronic cohort showed significantly superior improvement compared with haloperidol-treated patients (p = .005). In contrast, olanzapine was statistically superior to haloperidol in improving PANSS negative subscale scores in the "other" course of illness subgroup (p < .001).

Chronic schizophrenia with predominantly negative symptoms. Patients were categorized as *chronic, predominantly negative* if they had a length of illness of at least 2 years and a negative symptom profile (N = 251). Patients who were categorized as not being chronic, predominantly negative had a length of illness less than 2 years or had a non-negative symptom profile (N = 841).

Olanzapine displayed statistically significantly greater improvement (p = .007) in BPRS total, PANSS total, and PANSS negative scores compared with haloperidol in chronic, predominantly negative patients, as well as in patients not categorized as chronic, predominantly negative. In the analysis of PANSS positive subscale scores, olanzapine-treated patients not categorized as chronic, predominantly negative exhibited a significantly superior improvement compared with haloperidol-treated patients (p = .036).

DISCUSSION

In a previous large-scale clinical trial,[7] olanzapine was statistically significantly superior to haloperidol in improving global psychopathology (BPRS total score) and negative symptoms (PANSS negative subscale score) in patients with schizophrenia or schizophreniform or schizoaffective disorders. The present analysis of the schizophrenic cohort of that study yielded similar results, with olanzapine demonstrating statistical superiority over haloperidol in improving mean baseline-to-endpoint scores in global psychopathology (BPRS total score, PANSS total score) and negative symptoms (BPRS negative subscale score, PANSS negative subscale score). In addition, olanzapine was statistically significantly superior to haloperidol in improving mean baseline-to-endpoint positive symptoms, as measured by the BPRS positive subscale and the PANSS positive subscale. This finding is of particular practical and heuristic value, since it is the first report of a novel antipsychotic agent showing significant superiority in positive symptoms compared with haloperidol in a study population limited to schizophrenic patients other than those meeting specific criteria for treatment resistance. The results of the present analysis suggest a greater efficacy of olanzapine when compared with haloperidol in the treatment of overall schizophrenic symptomatology.

The magnitude of improvement observed in the present analysis is comparable with what has been previously reported. In a trial including schizophrenic patients with acute exacerbation,[5] decreases in BPRS total score were 3.1 with placebo (mean baseline score = 39.7), 15.2 with

Table 3. Mean Baseline to Endpoint Change in Brief Psychiatric Rating Scale Total Score (LOCF) by Symptom Profile at Baseline (N = 1622)[a]

	Olanzapine (N = 1096)				Haloperidol (N = 526)				
Patient Symptom Profile at Baseline	N	Baseline Score	Mean Change	SD	N	Baseline Score	Mean Change	SD	p Value
Predominantly positive[b]	197	31.80	–10.32	12.15	111	31.01	–6.77	11.33	.005
Predominantly negative[c]	270	29.77	–9.99	11.01	128	29.81	–7.16	9.93	.003
Mixed[d]	424	39.93	–13.43	14.47	207	41.47	–10.95	14.56	.029
Other[e]	205	24.03	–6.87	10.35	80	25.86	–5.48	11.18	.215

[a]Abbreviation: LOCF = last observation carried forward.
[b]Score ≥ 4 on 3 or more Positive and Negative Syndrome Scale (PANSS) positive subscale items and score ≥ 4 on no more than 2 PANSS negative subscale items.
[c]Score ≥ 4 on 3 or more PANSS negative subscale items and score ≥ 4 on no more than 2 PANSS positive subscale items.
[d]Score ≥ 4 on 3 or more PANSS positive subscale items and score ≥ 4 on 3 or more PANSS negative subscale items.
[e]Not positive, negative, or mixed, or for whom baseline symptom profile was unknown.

Table 4. Mean Baseline to Endpoint Change in BPRS Total Score (LOCF) by Course of Illness (N = 1622)[a]

	Olanzapine (N = 1096)				Haloperidol (N = 526)				
Patient Population	N	Baseline Score	Mean Change	SD	N	Baseline Score	Mean Change	SD	p Value
Course of illness									
Subchronic	105	33.64	–14.00	14.76	57	33.54	–8.79	13.34	.014
Other[b]	991	32.92	–10.46	12.49	469	34.12	–8.26	12.47	< .001
Chronic, predominantly negative									
Yes[c]	251	29.65	–9.63	10.82	115	29.99	–6.97	10.09	.007
No[d]	841	33.99	–11.15	13.27	409	35.21	–8.66	13.15	< .001
Unknown	4	33.00	–9.75	13.48	2	32.00	–15.50	13.44	.505

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.
[b]Includes chronic, chronic with acute exacerbation, unspecified, and in remission categories.
[c]≥ 2 years of chronicity and negative symptom profile.
[d]< 2 years of chronicity or non-negative symptom profile.

olanzapine (mean ± SD dose = 16.3 ± 1.6 mg/day; mean baseline score = 42.6), and 12.9 with haloperidol (mean baseline score = 41.8). Olanzapine and haloperidol arms were statistically different from placebo. In the present analysis, the mean total decrease in BPRS score was 10.8 with olanzapine (baseline score = 33.0) and 8.3 with haloperidol (baseline score = 34.1). Relative differences between olanzapine and haloperidol were similar for both trials, indicating that a potentially biased selection of subjects was not a significant contributor to olanzapine-haloperidol differences in this trial.

Total scores on the BPRS and especially on the PANSS include a large portion of general psychopathology and atypical schizophrenic symptoms.[12] The individual item analyses that we have conducted of the PANSS positive and negative subscale scores confirm that differences between olanzapine and haloperidol apply not only to associated psychopathology but to core schizophrenic symptoms as well. The difference between olanzapine and haloperidol in positive symptoms may be attributed mainly to improvements in excitement and suspiciousness, the 2 items that reflect statistically significant differences in the individual item analysis. It is arguable that differences in excitement may be related to sedation. However, treatment-emergent sedation was reported by 15.7% of olanzapine-treated patients and 13.0% of haloperidol-treated patients, a difference that was not statistically significant. Additionally, the presence of akathisia may contribute to excitement values. There was a significant difference in favor of olanzapine in treatment-emergent akathisia reported by these groups. Finally, the suspiciousness item from the PANSS can be considered a core positive symptom, representing the paranoid component of schizophrenia. Along with the statistically significant difference in score on BPRS positive subscale items (unusual thought content, hallucinatory behavior, conceptual disorganization, and suspiciousness), statistical differences in the suspiciousness item strongly suggest that, in our sample, olanzapine outperformed haloperidol in the treatment of core positive psychotic symptoms of schizophrenia.

Despite reports indicating that some conventional antipsychotic agents, usually high-potency drugs, are more effective in treating negative symptoms,[13,14] the current clinical knowledge considers all conventional antipsychotic agents to be equally effective. Our report suggests that the novel antipsychotic agent, olanzapine, may offer greater

negative symptom improvement over the conventional agent, haloperidol. The statistically significant superiority of olanzapine versus haloperidol in negative symptom improvement (on the basis of PANSS negative subscale score) is consistent with previous reports.[7,8] Furthermore, the individual item analysis shows statistically significant differences in favor of olanzapine in the core negative symptoms as measured by the PANSS, including blunted affect, emotional withdrawal, social withdrawal, and lack of spontaneity and flow of conversation. Thus, olanzapine was efficacious in treating the negative symptoms of schizophrenia.

In our study, olanzapine was superior to haloperidol across different subgroups of schizophrenic patients. Relative differences between olanzapine and haloperidol were similar, regardless of the predominance of positive symptoms, negative symptoms, or a mixture of both in the patient populations examined. The absolute difference between olanzapine and haloperidol based on the BPRS total tended to be slightly higher in patients with predominantly positive versus predominantly negative symptoms (3.55 vs. 2.83), but this difference was probably clinically insignificant. This finding is consistent with the notion that there are no symptom-specific antipsychotic agents and that olanzapine functions as a broad-spectrum antipsychotic.

Some aspects of the present analysis require further consideration. The finding that olanzapine is significantly superior to haloperidol on the BPRS positive subscale and the PANSS positive subscale should be interpreted with caution, since it is based on a post hoc analysis. The difference in positive symptom improvement between olanzapine and haloperidol for the whole sample[7] was almost statistically significant ($p = .06$). Since most patients were chronic and had received several other antipsychotic agents in the past but were still symptomatic at the beginning of the study (BPRS score ≥ 18), reduced variability could exist in that our sample may consist primarily of treatment-resistant patients. However, patients with a known history of treatment resistance, defined according to standard criteria,[15] were excluded from the trial. Thus, we believe that our sample is representative of the general schizophrenic population, who are not as exquisitely treatment responsive as most first-episode patients but should not be considered treatment resistant. The potential bias of selecting haloperidol-nonresponsive patients, as haloperidol is the most widely used antipsychotic drug, was minimized by excluding patients who had shown lack of response or intolerance to a last course of treatment with haloperidol. Finally, it is important also to note that the study design included flexible dosing, which allowed investigators to optimize the dosage of both drugs within the range of 5 to 20 mg/day.

CONCLUSION

In summary, olanzapine showed statistically significant superiority on several efficacy measures when compared with haloperidol in the large group of schizophrenic patients included in a phase 3 trial. These differences were consistent across different patient subgroups defined by symptom profile and course of illness. The results of the present analysis represent preliminary evidence supporting the notion that differences between olanzapine and a conventional antipsychotic agent, such as haloperidol, are not restricted to a specific patient subtype.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Marder S. Pharmacological treatment strategies in acute schizophrenia. Int Clin Psychopharmacol 1996;11(suppl 2):29–34
2. Bailine S, Lesser M, Krubit G, et al. Comparison of IM haloperidol and IM chlorpromazine in the treatment of acutely psychotic patients. Psychiatr Hosp 1987;18:127–129
3. Goldberg S, Frosch W, Drossman A, et al. Prediction of response to phenothiazines in schizophrenia: a crossvalidation study. Arch Gen Psychiatry 1972;26:367–373
4. American Psychiatric Association. Practice Guidelines for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997;154(suppl 4):1–63
5. Beasley CM, 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
6. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
7. 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
8. 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
9. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health Systems; 1986
10. Lindenmayer J, Kay S, Opler L. Positive and negative subtypes in acute schizophrenia. Compr Psychiatry 1984;25:455–464
11. Opler L, Kay S, Rosado V, et al. Positive and negative syndromes in chronic schizophrenic inpatients. J Nerv Ment Dis 1984;172:317–325
12. Mattes J. Risperidone: how good is the evidence for efficacy? Schizophr Bull 1997;23:155–161
13. Kane J, Mayerhoff D. Do negative symptoms respond to pharmacological treatment? Br J Psychiatry 1989;155(suppl 7):115–118
14. Meltzer H, Sommers A, Luchins D. The effects of neuroleptics and other psychotrophic drugs on negative symptoms in schizophrenia. J Clin Psychopharmacol 1986;6:329–338
15. Kane JM, Honigfeld G, Singer J, et al, and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796