A 28-Week Comparison of Ziprasidone and Haloperidol in Outpatients With Stable Schizophrenia

Steven R. Hirsch, M.D.; Werner Kissling, M.D.; Josef Bäuml, M.D.; Aidan Power, M.B., M.R.C.Psych.; and Rory O'Connor, M.D.

Background: Ziprasidone is a novel antipsychotic with a unique pharmacologic profile. This study compared ziprasidone with the conventional antipsychotic haloperidol in outpatients with stable schizophrenia.

Method: Three hundred one outpatients with stable chronic or subchronic schizophrenia (DSM-III-R) were randomized and participated in this double-blind, multicenter, parallel-group clinical study comparing flexible-dose oral ziprasidone, 80–160 mg/day (N = 148), with haloperidol, 5–15 mg/day (N = 153), over 28 weeks. Patients were assessed using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale, the Montgomery-Asberg Depression Rating Scale, the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale.

Results: Modal doses at endpoint were 80 mg/day for ziprasidone and 5 mg/day for haloperidol. Improvements in all mean efficacy variables with both ziprasidone and haloperidol were observed. Significantly more patients were categorized as negative symptom responders (≥ 20% reduction in PANSS negative subscale score) in the ziprasidone group (48%) compared with the haloperidol group (33%) ($p < .05$). Ziprasidone had clear advantages over haloperidol in all evaluations of movement disorders. Changes in body weight were negligible with both treatments. No pattern of laboratory or cardiovascular changes was observed.

Conclusion: Ziprasidone and haloperidol were both effective in reducing overall psychopathology; ziprasidone demonstrated effective treatment of negative symptoms and was better tolerated than haloperidol. Ziprasidone appears to offer an effective alternative to haloperidol in the long-term treatment of stable outpatients with schizophrenia.

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Received July 18, 2001; accepted Oct. 18, 2001. *From the Department of Psychiatry, Imperial College School of Medicine, London, United Kingdom (Prof. Hirsch); the Department of Psychiatry, Technische University, Munich, Germany (Drs. Kissling and Bäuml); the Central Research Division, Pfizer Ltd, Sandwich, Kent, United Kingdom (Dr. Power); and Pfizer Inc, New York, N.Y. (Dr. O'Connor).*

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Corresponding author and reprints: Rory O'Connor, M.D., Pfizer Pharmaceutical Group, Pfizer Inc, 235 E. 42nd St., New York, NY 10017 (e-mail: oconnr1@pfizer.com).

The introduction of novel antipsychotics is revolutionizing the treatment of schizophrenia and other psychotic disorders. The novel antipsychotics have a reduced liability for inducing extrapyramidal side effects and, possibly, tardive dyskinesia. Additionally, it has been proposed that novel antipsychotics may offer improved outcome in core negative symptoms,[1,2] affective symptoms,[3] and cognitive functioning.[4,5]

Like most newer antipsychotics, ziprasidone has a high serotonin-2/dopamine-2 ($5\text{-HT}_2/\text{D}_2$) receptor binding ratio.[6,7] Additionally, ziprasidone is a potent agonist of the 5-HT_{1A} receptor, a potent antagonist at 5-HT_{2C} and 5-HT_{2D} receptors, and a moderate inhibitor of 5-HT and norepinephrine reuptake[6,8]—features that confer a unique pharmacologic profile. Furthermore, ziprasidone exhibits modest α_1 affinity, negligible anticholinergic activity, and only modest antihistaminic activity.[6]

Ziprasidone has demonstrated efficacy in the treatment of schizophrenia and schizoaffective disorder in short-term trials involving acutely ill inpatients[9–11] and in a 1-year, placebo-controlled, randomized, double-blind study of chronically ill stable schizophrenic inpatients.[12] Results from these studies indicate that ziprasidone is effective in controlling positive symptoms, significantly improves negative symptoms, and is well tolerated.

Given the potential importance of the novel antipsychotics in the longer term management of schizophrenia

and other psychotic disorders, there are few published reports in which novel agents are compared with conventional neuroleptics in well-designed, long-term, prospective studies involving stable patients. In order to evaluate thoroughly the benefits of novel agents, such comparisons are essential, particularly as evidence from short-term acute studies cannot be extrapolated to the long-term management of stable outpatients. Here we report the results of a 28-week, prospective, randomized, double-blind, flexible-dose comparison of ziprasidone with the conventional neuroleptic haloperidol in the treatment of chronic stable schizophrenia.

METHOD

Patient Selection

Outpatients aged 18–64 years with a primary diagnosis of chronic or subchronic schizophrenia (DSM-III-R) who required antipsychotic maintenance treatment were entered into the study. Written informed consent was obtained from all patients at screening, after procedures and possible adverse effects were fully explained. Patients underwent a 3- to 14-day run-in period between screening and baseline to allow for evaluation and review of laboratory results. This period also allowed for the mandatory 2-week washout of previous depot medication, where applicable. Patients with a score of ≥ 10 on the negative subscale of the Positive and Negative Syndrome Scale (PANSS)[13] and a score of > 30 on the Global Assessment of Functioning scale (GAF; DSM-III-R)[14] at both screening and baseline were randomized. Patients were not allowed to enter if they were experiencing an acute exacerbation, had been hospitalized for psychosis during the 12 weeks before screening, or had a score of ≥ 5 (moderate/severe) on PANSS item P7 (hostility) or G8 (uncooperativeness). Patients who deteriorated notably between baseline and screening, reaching a Clinical Global Impressions-Improvement (CGI-I) scale score[15] of ≥ 6 (much worse), were also excluded.

Patients were excluded if they had a history of substance abuse or dependence (DSM-III-R) in the preceding 3 months. Urine samples were required to be negative for all illicit drugs, although patients positive for cannabinoids could enter at the discretion of the investigator. Patients were also excluded if they were at significant risk of suicide or homicide, or had a history of any of the following: allergy to any neuroleptic, neuroleptic malignant syndrome, or known resistance to conventional drugs during acute exacerbation, defined as failure to experience therapeutic response to marketed antipsychotics at least twice in the previous 2 years. Patients were not allowed to enter if they had taken part in a ziprasidone trial or had received an investigational drug within 4 weeks, fluoxetine within 5 weeks, monoamine oxidase inhibitors within 2 weeks, or antidepressants or lithium within 1 week of the first day of study therapy. Exclusion criteria also included relevant medical illness, epilepsy, neurologic disorders, human immunodeficiency virus seropositivity, serological evidence of hepatitis infection, or clinically significant electrocardiogram (ECG) or laboratory abnormalities. Women who either were unable to conceive or were reliably using contraception and were not pregnant or breast-feeding were allowed to enter the study.

Study Design and Treatment Schedule

This was a multicenter, double-blind, flexible-dose, parallel-group clinical trial comparing ziprasidone (80–160 mg/day) and haloperidol (5–15 mg/day). The study was conducted according to the Declaration of Helsinki (revised Hong Kong 1989) and received local Ethics Review Committee approval. A total of 52 centers recruited patients. Random treatment assignment, using the envelope method, was conducted according to a computer-generated, pseudo-random code, and patients received study drug the morning after discontinuation of existing antipsychotic therapy. Patients randomly assigned to ziprasidone received 40 mg/day on the first 2 days and 80 mg/day on day 3. According to clinical response, the ziprasidone dose could be increased to 120 mg/day during the second week of treatment and then to the maximum recommended daily dose of 160 mg/day during the third week of treatment. Patients randomly assigned to receive haloperidol received a starting dose of 5 mg/day, which could be increased to 10 mg/day during the second week of treatment and to 15 mg/day during the third week of treatment. If a patient experienced side effects, the dose could be decreased to a minimum of 80 mg/day of ziprasidone and 5 mg/day of haloperidol. Both drugs were taken in the morning and evening immediately after food intake. Concomitant lorazepam for agitation (up to 1 mg/day) and temazepam for insomnia (up to 20 mg/night) were permitted during the study. Anticholinergics and propranolol were gradually withdrawn by 25% per week during the first 4 weeks of the study, but were reinstated at any time during the study if necessary.

Assessments

All efficacy and safety assessments were made at scheduled visits or upon early discontinuation from the study. The PANSS was rated at screening, baseline, and weeks 3, 6, 16, and 28. The Montgomery-Asberg Depression Rating Scale (MADRS)[16] and the Clinical Global Impressions-Severity of Illness scale (CGI-S)[15] were rated at baseline and weeks 3, 6, 16, and 28. The Quality of Life Scale (QLS)[17] was rated at baseline and week 28.

All observed or reported adverse events were recorded along with details of severity and classified using COSTART.[18] The Barnes Akathisia Scale[19] and the Simpson-Angus Scale[20] were rated at baseline and weeks

Table 1. Baseline Patient Characteristics and Psychopathology and Prestudy Medication Use[a]

Characteristic	Ziprasidone (N = 148)	Haloperidol (N = 153)
Men, N (%)	92 (62)	105 (69)
Age, mean (range), y	39.2 (18–64)	39.4 (18–64)
Weight, mean (range), kg		
Men	80.2 (53–125)	78.7 (38–116)
Women	69.1 (46–101)	69.7 (44–102)
Chronic schizophrenia, N (%)[b]	138 (93)	142 (93)
Smoker, N (%)	96 (65)	93 (61)
Mean time since first episode, mo (range)	148.6 (4–464)	153.0 (9–504)
Occasions previously hospitalized for psychiatric care, mean (SD)	4.1 (4.5)	3.9 (4.1)
Duration of most recent hospitalization, mean (SD), mo	2.7 (11.1)	3.8 (9.7)
PANSS total score, mean (SD)	72.9 (17.1)	74.4 (16.1)
Baseline anticholinergics, N (%)	55 (37)	60 (39)
Medication taken in the 3 mo before the study, N (%)		
Oral antipsychotic	121 (82)	125 (82)
Depot antipsychotic	7 (5)	12 (8)
Anticholinergics	65 (44)	77 (50)
β-Blockers	1 (1)	1 (1)

[a]Abbreviation: PANSS = Positive and Negative Syndrome Scale.
[b]The remainder had subchronic schizophrenia.

6, 16, and 28. The Abnormal Involuntary Movement Scale (AIMS)[15] was rated at baseline and week 28. Laboratory tests were done at weeks 4 and 12 and an ECG at weeks 12 and 28. The ECGs were centrally read and the corrected QT interval (QTc) was calculated using Bazett's formula.

Data Analysis

The PANSS negative subscale scores (sum of items P1–P7) were derived from the PANSS for the evaluation of negative symptoms. The Brief Psychiatric Rating Scale (BPRSd) core items score (the sum of items P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness], and G9 [unusual thought content]) was derived from the PANSS to evaluate psychotic symptoms.

Patients who completed at least 14 days of therapy were considered evaluable and were included in the analysis of efficacy and outcome if they had at least 1 postbaseline assessment and were not protocol violators. The primary efficacy variables were the PANSS total, PANSS negative subscale, and GAF scale scores. Mean changes from baseline in all efficacy variables, the GAF, and the QLS total and subscale scores, were compared between treatment groups at each assessment with the last observation carried forward (LOCF). The percentage of patients classed as negative symptom responders, defined as those with at least a 20% reduction in the PANSS negative subscale score from baseline, was also compared between groups in the LOCF analysis of evaluable patients. A 20% reduction in negative symptoms was prospectively chosen as the criterion for negative symptom response as this was considered most likely to represent an observable and clinically relevant change and detect differences between treatment groups. In addition, the percentage of patients who achieved remission by the end of the 6-month treatment period was also determined to evaluate what benefit patients who stayed on treatment for the duration of the study derived. This was defined as having a PANSS total score (across 30 items) of < 60 after completing 28 weeks of study therapy. Treatment effects were estimated based on least squares means derived from an analysis of covariance (ANCOVA) model. No interaction terms were included in the final ANCOVA model as none was statistically significant. All statistical tests were 2-sided with significance at the 5% level. All patients were included in the safety and tolerability analyses. Mean changes from baseline in movement disorder assessment scales in all patients who had a postbaseline assessment were compared between groups. There was no formal statistical analysis of safety or tolerability comparisons.

RESULTS

Patients and Treatment

Of the 363 patients screened, 301 were randomized and received at least 1 dose of ziprasidone (N = 148) or haloperidol (N = 153). Baseline patient characteristics, overall psychopathology, and use of medication before the study were similar in both groups (Table 1). In the 3 months before the study, 26% of patients in the ziprasidone group and 25% in the haloperidol group had been treated with haloperidol. The median duration of treatment was 113 days in the ziprasidone group and 139 days in the haloperidol group. In total, 66 (45%) patients in the ziprasidone group and 64 (42%) in the haloperidol group completed the 28 weeks of study therapy.

Similar numbers of patients in each group, 38 (26%) and 36 (24%) in the ziprasidone and haloperidol groups, respectively, were not considered evaluable for efficacy due to a major protocol violation (8 and 11 patients), lack of a valid postbaseline efficacy assessment (3 and 5 patients), or not completing 14 days of study therapy (27 and 20 patients). Among evaluable patients, the rate of discontinuation due to insufficient clinical response was the same in the ziprasidone (N = 20/110, 18%) and haloperidol (N = 21/117, 18%) groups.

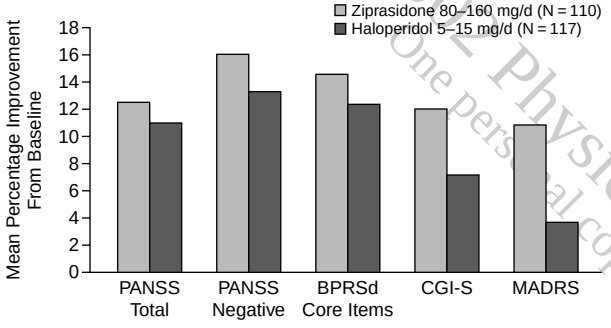
The modal doses of ziprasidone and haloperidol throughout the study were 80 mg/day and 5 mg/day, respectively. The mean doses for patients treated during week 6 were ziprasidone 109.5 mg/day and haloperidol 8.6 mg/day. In those treated during the last week of the study (week 28), the mean ziprasidone and haloperidol doses were 116.5 mg/day and 8.6 mg/day, respectively. The percentage of patients receiving lorazepam at any time during the study was similar in the ziprasidone (26%) and haloperidol (25%) groups.

Table 2. Mean ± SD Baseline and Endpoint (week 28) Psychopathology Scale Scores (evaluable patients, LOCF)[a]

	Ziprasidone (N = 110)		Haloperidol (N = 117)	
Scale	Baseline	Week 28	Baseline	Week 28
PANSS total	73.5 ± 17.4	64.4 ± 22.0	73.7 ± 15.9	65.6 ± 18.8
PANSS negative subscale	22.6 ± 6.4	19 ± 7.5	22.6 ± 5.2	19.6 ± 6.0
BPRSd core items	9.6 ± 3.7	8.1 ± 4.0	9.7 ± 3.6	8.4 ± 3.7
CGI-S	4.2 ± 0.8	3.7 ± 1.2	4.2 ± 0.7	3.8 ± 1.1
MADRS	15.0 ± 8.3	13.4 ± 9.3	14.1 ± 7.9	13.5 ± 7.9
GAF	53.0 ± 10.5	56.2 ± 16.2	53.6 ± 9.2	56.1 ± 13.7

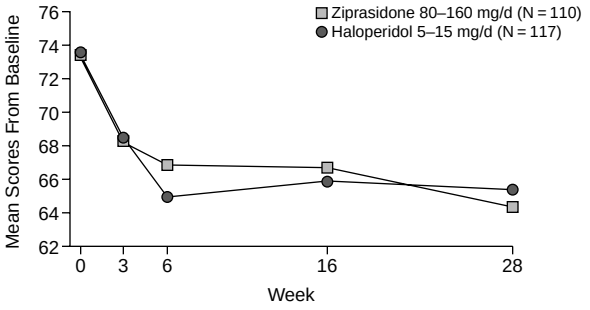
[a]Abbreviations: BPRSd = Brief Psychiatric Rating Scale derived from the PANSS, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Figure 1. Mean Percentage Improvement in Efficacy Variables From Baseline at Week 28[a]



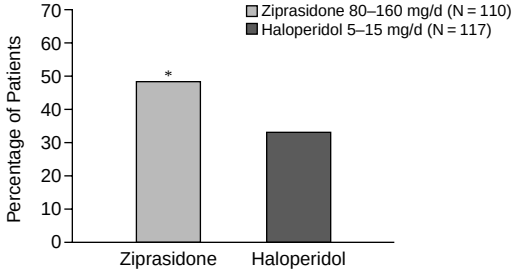
[a]Abbreviations: BPRSd = Brief Psychiatric Rating Scale derived from the PANSS, CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale. Evaluable patients, last observation carried forward.

Figure 2. Mean Positive and Negative Syndrome Scale Total Scores[a]



[a]Evaluable patients, last observation carried forward.

Figure 3. Percentage of Patients Who Were Negative Symptom Responders[a] at Endpoint[b]



[a]Evaluable patients, last observation carried forward.
[b]≥ 20% improvement in the PANSS Negative Subscale score between baseline and endpoint.
*p < .05 vs. haloperidol.

Effectiveness

Overall symptomatology improved in both groups from baseline as measured by the PANSS total, BPRSd core items, and MADRS (Table 2 and Figure 1). Mean PANSS total scores decreased in both treatment groups over the first 6 weeks of the study with further improvement observed up to endpoint, at which time the mean PANSS total scores were approximately 65 in each treatment group (Figure 2). The percentage of patients classified as negative symptom responders (≥ 20% decrease in the PANSS negative subscale score) was significantly greater in the ziprasidone group (48%) than in the haloperidol group (33%) ($p < .05$) (Figure 3). The proportion of patients in remission (PANSS < 60) at 28 weeks was 62% (41/66) in the ziprasidone group and 55% (35/64) in the haloperidol group, a difference that was not statistically significant.

Mean endpoint scores on the QLS subscales—instrumental role, intrapsychic foundations, and common objects and activities—were similar in both groups. In the ziprasidone group, the mean QLS interpersonal relations subscale score improved by 14% (from 19.8 to 22.6), and in the haloperidol group it improved by 4% (from 20.9 to 21.8), a difference that did not reach statistical significance.

Safety and Tolerability

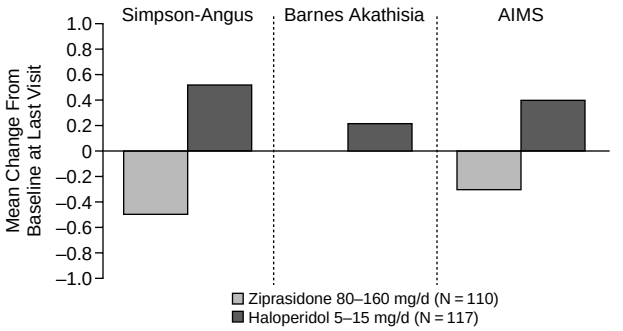
Treatment-emergent adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group (Table 3) and were generally of mild or moderate severity. Twice as many patients discontinued haloperidol (16%) as ziprasidone (8%) due to any treatment-related adverse events. The most frequently reported treatment-emergent adverse events in both treatment groups included insomnia and somnolence, which were rarely rated as severe. These adverse events rarely resulted in discontinuation (3 patients with insomnia, 1 with drowsiness, and 1 with hypersomnia). In the ziprasidone group, nausea was reported in 10% of patients and vomiting in 11%, but no case was severe and only 2 patients discontinued.

Table 3. Adverse Events Summary and Those Occurring in ≥ 5% of Patients in Either Treatment Group

Adverse Event Summary and Occurrences	Ziprasidone (N = 148) N	Ziprasidone (N = 148) %	Haloperidol (N = 153) N	Haloperidol (N = 153) %
Event summary				
Adverse events	114	77	130	85
Discontinuation due to adverse events	12	8	24	16
Patients with movement disorders[a]	22	15	62	41
Discontinuations with movement disorders	1	1	10	7
Events occurring in ≥ 5% of patients in any group				
Insomnia	24	16	27	18
Somnolence	20	14	13	9
Akathisia	7	5	25	16
Hypertonia	3	2	11	7
Tremor	9	6	15	10
Extrapyramidal syndrome	2	1	7	5
Headache	9	6	16	11
Asthenia	12	8	8	5
Vomiting	16	11	9	6
Nausea	15	10	6	4
Dry mouth	4	3	8	5
Dizziness	6	4	10	7
Psychosis	8	5	4	3
Hallucinations	9	6	12	8
Anxiety	11	7	11	7
Agitation	11	7	10	7
Depression	9	6	11	7

[a]Listed as adverse events occurring at the time of discontinuation. Movement disorders included dystonia, akathisia, extrapyramidal symptoms, hypertonia, oculogyric crisis, dyskinesia, tremor, twitching, hypokinesia, tardive dyskinesia, and cogwheel rigidity.

Figure 4. Mean Change From Baseline at Week 28 in Parkinsonism, Akathisia, and Tardive Dyskinesia Assessments[a]



[a]Abbreviation: AIMS = Abnormal Involuntary Movement Scale. All patients, last observation carried forward. Mean baseline scores on the Simpson-Angus Scale were ziprasidone = 3.5, haloperidol = 3.2; on the Barnes Akathisia Scale for both ziprasidone and haloperidol were 0.5; and on the AIMS were ziprasidone = 1.2, haloperidol = 1.0.

The percentage of patients in whom the emergence of any movement disorder was reported was markedly greater in the haloperidol group (41%) than in the ziprasidone group (15%) (Table 3). The percentage of patients who discontinued with movement disorders was also notably higher in the haloperidol group than the ziprasidone group. Among individual adverse events, akathisia was reported in the haloperidol group (16%) more frequently than in the ziprasidone group (5%). Treatment-emergent tardive dyskinesia was reported as an adverse event in 2 patients in the haloperidol group. No treatment-emergent tardive dyskinesia was reported in the ziprasidone group. Mean Simpson-Angus, Barnes Akathisia, and AIMS scores increased between baseline and endpoint in the haloperidol group (Figure 4). By contrast, mean Simpson-Angus and AIMS scores decreased in the ziprasidone group, and there was no change in the mean Barnes Akathisia score. A greater proportion of patients received anticholinergics in the haloperidol group than in the ziprasidone group at some time during the study (50% versus 40%, respectively). Similarly, among those who completed the study, a greater proportion of patients was taking anticholinergics at 28 weeks in the haloperidol group (25%) than in the ziprasidone group (15%). The use of β-blockers was low in both groups throughout the study (2% in the ziprasidone group and 3% in the haloperidol group).

Mean changes in body weight from baseline to endpoint were small and similar in the ziprasidone (+0.31 kg) and haloperidol (+0.22 kg) groups. The mean change in men was +0.1 kg and +0.2 kg in the ziprasidone and haloperidol groups, respectively. For women, the corresponding mean changes were +0.7 and +0.3 kg.

Monitoring pulse rate and blood pressure revealed no clinically relevant treatment effects. Mild postural hypotension was reported in 1 ziprasidone-treated patient. There were no clinically relevant ECG changes. The mean baseline and endpoint QT intervals were 355.2 and 356.9 ms in the ziprasidone group and 343.4 and 348.2 ms in the haloperidol group. The mean baseline and endpoint QTc values were 397.9 and 404.2 ms in the ziprasidone group and 388.9 and 387.1 ms in the haloperidol group. No patient had a QTc interval greater than 500 ms at any point. Abnormal laboratory values were reported in 38% of patients in the ziprasidone group compared with 34% in the haloperidol group, but few discontinued (2 from the ziprasidone group and 1 from the haloperidol group). There was no pattern of clinically significant changes in liver function or hematologic abnormalities in either group.

Serious adverse events attributed to study medication by the investigator were reported in 3 patients. One patient treated with ziprasidone and 1 patient treated with haloperidol were hospitalized for exacerbation of schizophrenia, and another treated with haloperidol was hospitalized due to oculogyric crisis.

DISCUSSION

The results of this study indicate that ziprasidone offers comparable efficacy to haloperidol in the long-term

treatment of outpatients with schizophrenia but has superior tolerability and potential advantages in the treatment of negative symptoms. Patients studied had moderate levels of psychopathology, were community based, and were not treatment resistant. This sample is thus representative of large numbers of patients with schizophrenia, who have stable but chronic levels of symptomatology.

Completion rates were similar in both groups and consistent with discontinuation rates from a similar study of antipsychotics in chronic schizophrenia.[21] Discontinuation rates among evaluable patients due to lack of efficacy were similar in both groups (18%).

The modal dose in each group was stable over the course of the study and consistent with expected maintenance doses for each agent (80 mg/day for ziprasidone and 5 mg/day for haloperidol). The improvement in the PANSS total score during ziprasidone treatment was similar to the improvement observed in those treated with haloperidol; most of the improvement occurred in the first 6 weeks, with more gradual improvement occurring thereafter until endpoint. This pattern of response is consistent with the observations of others[21–23] who have studied novel antipsychotic maintenance treatment in clinical trials. The endpoint mean PANSS total scores, as well as CGI ratings, were similar in both treatment groups and the proportion in remission was 62% and 55% in the ziprasidone and haloperidol groups, respectively. The remission rate was determined in patients who completed the study, rather than in the intent-to-treat population. The main purpose of the endpoint remission rate determination was to establish what benefits patients who remained on therapy for the duration derived, i.e., an analysis not confounded by tolerability differences or the dropout rate.

In the analysis of the PANSS negative symptom subscale, approximately half the patients treated with ziprasidone were classified as negative symptom responders (≥ 20% improvement) compared with one third of those treated with haloperidol, a statistically significant difference ($p < .05$). A 20% reduction in the PANSS negative subscale score was considered a minimum reduction potentially associated with clinically observable improvement in chronic, stable patients. The potential contribution of extrapyramidal symptoms to the observed difference between treatment groups in the proportions of negative symptoms was not controlled for in this study, and, therefore, we are unable to delineate if the difference was due to improvement in primary or negative symptoms. However, path analysis demonstrated a significant unexplained variance in the improvement in the PANSS negative subscale associated with ziprasidone, 40–160 mg/day, in a double-blind, placebo-controlled, 1-year study of chronically ill, stable inpatients, an effect that was apparent from 6 months onward.[24] The authors postulated that the significant unexplained variance suggested a direct effect of ziprasidone on primary negative symptoms. Evidence of the efficacy of ziprasidone in the treatment of negative symptoms from 2 well-designed long-term trials is encouraging.

Improvements in depressive symptoms, as measured by the MADRS, were seen in patients receiving ziprasidone, although this did not reach statistical significance in comparison with haloperidol. Patients entering the study had modest levels of depression, suggesting that a comparative study of ziprasidone in patients with higher baseline levels of depression is warranted, particularly as significant reductions in depressive symptoms have been observed in short-term trials of ziprasidone in acutely ill patients with schizophrenia and schizoaffective disorder.[10,11]

The improvement in the interpersonal relations subscale scores of the QLS seen in patients receiving ziprasidone was of similar magnitude to that observed in patients receiving olanzapine, 10 mg/day, compared with haloperidol in a similarly designed study.[25] The possibility of additional benefits on quality of life of novel agents over conventional antipsychotics is also an area for further prospective study, particularly if linked with outcome, function, and economic consequences.

The favorable tolerability profile of ziprasidone observed in this study was consistent with that in previous short- and long-term studies.[9–12,26] A higher rate of discontinuation due to adverse events, particularly movement disorders, and an almost 3-fold higher incidence of movement disorders with haloperidol compared with ziprasidone were expected based on the pharmacologic differences between these agents. Ratings of parkinsonism, akathisia, and tardive dyskinesia provided further evidence of an important tolerability advantage of ziprasidone over haloperidol in this regard that was supported by the lower use of anticholinergic agents observed in patients receiving ziprasidone.

A higher frequency of nausea and vomiting was observed with ziprasidone (10% and 11%, respectively) compared with haloperidol (4% and 6%, respectively), though these events were generally rated as mild and rarely resulted in discontinuation. Neither ziprasidone nor haloperidol was associated with excessive sedation, sexual dysfunction, seizures, clinically relevant ECG changes, pulse rate or blood pressure changes, or hematologic or hepatic toxicity, confirming the favorable safety and tolerability profile observed in a previously conducted 1-year prospective, double-blind, placebo-controlled study of ziprasidone.[12]

Of increasing interest in the evaluation of the tolerability of novel antipsychotics, particularly with longer term treatment, is weight gain. Patients treated with either ziprasidone or haloperidol showed negligible changes in body weight. The apparent weight-neutral effect of ziprasidone may distinguish it from olanzapine, risperidone, quetiapine, and clozapine, all of which have been associated with greater weight gain than ziprasidone.[27] The

slight change of 0.31 kg in patients who received ziprasidone for a median treatment duration of 113 days is in contrast with the reports of weight gain associated with olanzapine and risperidone.[28–30] Olanzapine has been associated with a mean 5.4-kg increase observed over median treatment duration of 238 days,[31] and risperidone with a mean increase of 2.3 kg in a 6-month study.[30]

Primary efficacy analysis reported in this article was undertaken in evaluable patients rather than the intent-to-treat sample. This excluded those who did not complete at least 14 days of treatment, and, therefore, excluded the confound of the transient effects of treatment change before being stabilized on study therapy. As the study was designed to examine relapse prevention in stable patients rather than continuation treatment after amelioration of acute illness, analysis of evaluable patients was considered to be most appropriate.

It is relevant to the evaluation of the findings of this study that patients were relatively well controlled on their prestudy antipsychotic medication, reducing the scope for symptomatic improvement as compared with studies in acutely ill patients. Comparison of symptomatic change with that seen in studies of different design in different samples should thus be undertaken with caution. This design does, however, afford the opportunity to evaluate a representative group of patients with schizophrenia, giving a sample that is generalizable to the general schizophrenia population. In this regard, the use of response and remission criteria in addition to mean changes provides a clinically meaningful approach to presenting the data. The overall discontinuation rate, which was over 50% in both groups, may at first appear high. However, fewer than 20% of evaluable patients discontinued due to lack of efficacy in either group, and we believe that this rate of discontinuation is not unusual for a double-blind, long-term clinical trial.

Collectively, the observations from this long-term, double-blind, flexible-dose comparison of ziprasidone with haloperidol in the treatment of patients with chronic, stable schizophrenia indicate that ziprasidone is an effective antipsychotic that may have advantages over haloperidol in both tolerability, particularly with extrapyramidal side effects, and the treatment of negative symptoms. Comparative studies of ziprasidone and other novel antipsychotics will help elucidate differential therapeutic effects of these agents both in important clinical dimensions, such as depressive and negative symptoms, and in tolerability profiles.

Drug names: clozapine (Clozaril and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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