Efficacy and Tolerability of Ziprasidone Versus Risperidone in Patients With Acute Exacerbation of Schizophrenia or Schizoaffective Disorder: An 8-Week, Double-Blind, Multicenter Trial

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Background: More head-to-head comparisons of antipsychotics are needed to discern the relative efficacy and safety profiles of these compounds. Thus, we compared ziprasidone and risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder.

Method: Patients with DSM-III-R acute exacerbation of schizophrenia or schizoaffective disorder were randomly assigned to double-blind ziprasidone 40 to 80 mg b.i.d. (N = 149) or risperidone 3 to 5 mg b.i.d (N = 147) for 8 weeks. Primary efficacy measures included Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impressions-Severity of Illness scale (CGI-S) score; secondary measures included scores on the PANSS negative subscale, CGI-Improvement scale (CGI-I), and PANSS-derived Brief Psychiatric Rating Scale (BPRSd) total and core items. Safety assessments included movement disorder evaluations, laboratory tests, electrocardiography, vital signs, and body weight. Efficacy analyses employed a prospectively defined Evaluable Patients cohort. Treatment equivalence was conferred if the lower limit of the 95% confidence interval of the ziprasidone/risperidone ratio of least-squares mean change from baseline was > 0.60. Data were gathered from August 1995 to January 1997.

Results: Equivalence was demonstrated in PANSS total scores, CGI-S scores, PANSS negative subscale scores, BPRSd total and core item scores, and PANSS total and CGI-I responder rates. Both agents were well tolerated. Risperidone exhibited a significantly higher Movement Disorder Burden (MDB) score ($p < .05$) and higher incidences of prolactin elevation and clinically relevant weight gain. However, compared with current recommendations, study dosing may have been high for some risperidone-treated patients (mean dose = 7.4 mg/day) and low for some ziprasidone-treated patients (mean dose = 114.2 mg/day).

Conclusion: Both agents equally improved psychotic symptoms, and both were generally well tolerated, with ziprasidone demonstrating a lower MDB score and less effect on prolactin and weight than risperidone.

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Atypical antipsychotics, now considered first-line agents in the treatment of schizophrenia, share a low liability for movement disorders and possibly greater effectiveness in reducing negative symptoms than do conventional agents.[1,2] However, they vary with regard to receptor-binding activity[3] and tolerability profiles.[4] Head-to-head comparisons are needed both to elucidate the relative efficacy of these compounds and to compare liabilities for such adverse events as movement disorders, prolactin elevation, weight gain, and metabolic alterations.

Risperidone is a widely studied atypical antipsychotic that has been shown to improve positive, negative, and affective symptoms of psychosis.[5–8] Comparisons with haloperidol have shown a reduced risk of relapse[9] and a lower liability for movement disorders,[8,9] although dose-related extrapyramidal symptoms (EPS)[8] and serum prolactin elevations similar to those seen with haloperidol can occur.[10,11] More recent controlled trials have demonstrated comparable efficacy between risperidone and olanzapine but marked differences in side effect profiles, with weight gain more prevalent and pronounced with olanzapine and EPS, prolactin elevation, and sexual dysfunction more prevalent with risperidone.[10,12]

Ziprasidone has been shown to improve positive, negative, and affective symptoms versus placebo in patients with schizophrenia and schizoaffective disorder, while re-

ducing risk of relapse.[13–17] It has proved as effective as haloperidol in improving patients' positive symptoms and is associated with a greater negative symptom response rate.[17,18] Ziprasidone is associated with a low incidence of EPS and prolactin elevation[17] and has little effect on body weight.[13–16] In a comparison of antipsychotic-induced weight gain that employed a meta-analysis and random effects meta-regression, ziprasidone was associated with the lowest mean increase in weight of 5 atypical agents.[19] A 6-week comparative trial showed efficacy comparable to that of olanzapine but a lower incidence of weight gain and more favorable effects on lipid profile and glucose regulation for ziprasidone-treated patients.[20]

Because atypical antipsychotics do not substantially differ from one another in terms of efficacy, but rather their differences are usually seen in terms of safety and tolerability, this head-to-head comparison of active agents focused on determining the equivalence of efficacy between agents. The primary objective of the present 8-week trial was to demonstrate equivalence of efficacy of flexible-dose ziprasidone and risperidone in the treatment of patients with acute exacerbation of schizophrenia or schizoaffective disorder. The study also compared the safety and tolerability of the 2 agents.

METHOD

Subjects

Men and women aged 18 to 64 years with a *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSM-III-R) diagnosis of schizophrenia or schizoaffective disorder with acute exacerbation were eligible for study participation. Patients were required to have a Positive and Negative Syndrome Scale (PANSS) total score[21] ≥ 60 and a score of ≥ 4 on at least 2 of the core items (conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content) at baseline. Normal laboratory and electrocardiographic measurements at screening and written informed consent were also required. Exclusion criteria included DSM-III-R–defined substance abuse/dependency within the preceding 3 months (or a positive urine drug screen) or use of any of the following prior to study baseline: fluoxetine (within 5 weeks), monoamine oxidase inhibitors or moclobemide (within 2 weeks), or antidepressants or lithium (within 1 week). Patients taking concurrent antipsychotic medication at randomization were excluded. The study was conducted in accordance with the Declaration of Helsinki (1989). Data were gathered from August 1995 to January 1997.

Study Design

In this 8-week, multicenter, double-blind, randomized, parallel-group study, enrolled patients received single-blind placebo for ≥ 3 days, during which time antipsychotics, anticholinergic agents, and β-blockers were discontinued. After washout, only patients with a PANSS total score ≥ 60 and a score of ≥ 4 on 2 of the PANSS core items were randomly assigned to double-blind treatment with ziprasidone or risperidone. Patients were started with ziprasidone 40 mg b.i.d. for the first week. Ziprasidone was then adjusted at weekly intervals in increments of 20 mg b.i.d. within the range of 80 to 160 mg/day. Risperidone was titrated from 1 mg b.i.d. (day 1) to 3 mg b.i.d. (days 3 to 7) during the first week. Risperidone was then adjusted at weekly intervals in 1-mg increments to a maximum of 5 mg b.i.d. In patients experiencing adverse events, the dose could be decreased, by 1 dose interval at a time, to a minimum of 40 mg b.i.d. for ziprasidone and 3 mg b.i.d. for risperidone. The minimum interval between dose titration steps was 1 week. Study drug was taken with food in the morning and evening. These regimens were consistent with dosing recommendations at the time of study design. Subsequent clinical trial data in patients with schizophrenia have shown superior efficacy and good tolerability with ziprasidone at daily doses of 120 and 160 mg versus 80 mg.[22] Concomitant medications permitted during double-blind treatment included lorazepam, temazepam, anticholinergics, and propranolol.

Efficacy assessments. Primary efficacy variables were the PANSS and Clinical Global Impressions-Severity of Illness scale (CGI-S).[23] Secondary efficacy variables included the Clinical Global Impressions-Improvement scale (CGI-I),[23] Global Assessment of Functioning (GAF),[24] PANSS-derived Brief Psychiatric Rating Scale (BPRSd)[25] total and core items, PANSS total and negative scales, and Montgomery-Asberg Depression Rating Scale (MADRS).[26] The PANSS total and negative scales, CGI-S, and BPRSd total and core scales were administered at screening, at baseline, and on days 7, 21, 42, and 56 or at early discontinuation. The CGI-I and MADRS were administered at baseline and on days 7, 21, 42, and 56. The GAF was administered at baseline and on day 56 or at early discontinuation.

Safety assessments. All observed or reported adverse events, including illnesses with onset during the study and exacerbations of preexisting illnesses, were recorded. A 10-item Sexual Dysfunction Questionnaire derived from the UKU Side Effect Rating Scale[27] was administered at baseline and on day 56 (or at early discontinuation) to capture disturbances of sexual functioning.

Laboratory assessments performed only at screening included hepatitis battery, thyroid function, urine drug screen, and pregnancy test for women of childbearing potential. Tests performed both at screening and on days 28 and 56 (or at early discontinuation) included complete blood count with differential, hematocrit, and platelet count; urinalysis; and blood chemistries.

A physical examination, including body weight measurement, and a 12-lead electrocardiogram (ECG) were performed at screening and on day 56 (or at early discontinuation). Blood pressure and pulse rate were measured at each visit, including screening, baseline, and early discontinuation.

Abnormal movements assessments. Parkinsonism was assessed with the Simpson-Angus Rating Scale[28] and akathisia with the Barnes Akathisia Scale[29] at baseline and on days 7, 21, 42, and 56 or at early discontinuation. Abnormal involuntary movements were assessed using the Abnormal Involuntary Movement Scale (AIMS)[23] at baseline and on day 56 (or at early discontinuation). In addition, the prospectively designed Movement Disorder Burden (MDB) score was used to quantify the overall discomfort from movement disorders (dystonia, parkinsonism, tardive dyskinesias, and akathisia). All dystonic movements were recorded as adverse events, and use of concomitant therapy for movement disorders (anticholinergics or propranolol) was recorded.

Statistical Methods

For all efficacy, safety, and special variable analyses, baseline was defined as the last visit occurring during the period ending at day 1, inclusive, provided the day 1 measurement was taken prior to dosing. Day 1 was the first day of double-blind treatment.

Sample size was based on the treatment equivalence of 2 treatment groups in terms of the ziprasidone/risperidone ratio of the mean change from baseline in PANSS total score. It was estimated that 120 patients per group would provide an 80% (± 1%) chance of showing treatment equivalence. Equivalence of the 2 treatment groups was determined by the ziprasidone/risperidone ratio of the mean change from baseline to last visit. The treatments were deemed equivalent if the lower limit of the 95% confidence interval (CI) for the ratio exceeded 0.60 (based on the Fieller's theorem).[30] To examine interactions, these variables were also assessed using analysis of covariance (ANCOVA) models that included terms for country, center, treatment, baseline, center-by-treatment interaction, and country-by-treatment interaction.

Analysis groups and types of analyses. Efficacy analyses included the following groups. The Evaluable Patients population consisted of patients who received ≥ 14 days of double-blind treatment and had no major protocol violations or deviations. The All Patients (intent-to-treat [ITT]) population consisted of all randomized patients with a baseline and ≥ 1 postbaseline evaluation for any of the primary efficacy variables. The Completer population was a subset of the All Patients group who completed the 8-week study.

Last visit (last postbaseline observation) and observed cases analyses were performed. Only patients having data at the scheduled visit under consideration were included in observed cases analysis; no imputation of missing data was performed.

Background and demographic data were recorded at baseline and summarized with descriptive statistics. ANCOVA was used to adjust potential baseline imbalance in efficacy variables.

Efficacy analyses. Mean changes from baseline to last visit in mean PANSS total and CGI-S scores were the primary efficacy analyses; secondary efficacy analyses included mean changes from baseline in PANSS negative subscale score, BPRSd total score, BPRSd core items scores, MADRS total score, and GAF score. Responder rates were based on 20%, 30%, 40%, and 50% decreases from baseline in PANSS total score or a CGI-I score of 1 or 2 at last observation.

Safety analysis. Adverse events. All adverse events occurring during treatment or within 6 days after the last day of treatment were recorded (using the Coding Symbols for Thesaurus of Adverse Reaction Terms [COSTART] dictionary) according to treatment emergence, body system, preferred term, investigator assessment of severity (mild, moderate, severe), and relation to study drug. Treatment-emergent adverse events were defined as either not present at baseline but occurring after initiation of study drug or present at baseline but having greater severity after initiation of study drug.

Laboratory data, vital signs, body weight, and ECG. Laboratory tests, which assessed clinically significant abnormalities, were performed during treatment or within 6 days after the last day of treatment. Median changes in vital signs (sitting and standing blood pressures and pulse rate) and body weight from baseline to last observation (within 6 days of last day of study medication) were calculated for each group. Baseline and final mean and median values were determined from the ECGs for the following variables: QTc (Bazett's correction) and QT intervals, heart rate, PR interval, and QRS interval.

Special variables: movement disorders. Simpson-Angus, Barnes Akathisia, and AIMS scores were summarized as the percentage of patients with a change from baseline and as change from baseline by treatment group and day. No formal statistical analyses were performed. The Simpson-Angus Rating Scale and Barnes Akathisia Scale data were assessed at baseline; at weeks 1, 3, 6, and 8; and at last visit for the ITT population. AIMS score was assessed at baseline and week 8. Post hoc analyses of baseline-to-endpoint changes in Barnes Akathisia Scale, AIMS, and Simpson-Angus Scale scores used the general linear model procedure with treatment, center, and baseline as terms. Differences in least squares (LS) means were calculated, with adjustment for multiple comparisons.

The MDB score was developed and defined prospectively to quantify the overall discomfort from movement disorders experienced by patients during the study. The

Table 1. Baseline Characteristics of Patients Entering Double-Blind Treatment

Characteristic	Ziprasidone (N = 149)	Risperidone (N = 147)
Sex, N (%)		
Men	110 (74)	105 (71)
Women	39 (26)	42 (29)
Age, mean, y		
Men	34.6	33.2
Women	36.6	35.6
Primary diagnosis, N		
Schizophrenic disorder	133	127
Schizoaffective disorder	16	20
Age at onset, mean (range), y	25.2 (12–54)	24.6 (14–52)
No. of previous psychiatric inpatient hospitalizations, mean	4.7	4.7
Patients taking prestudy medications, N (%)[a]		
Antipsychotics	143 (96)	144 (98)
Antimuscarinics	76 (51)	68 (46)
PANSS total score, mean (SD)	93.8 (16.3)	97.6 (17.4)
CGI-S score, mean (SD)	4.7 (0.7)	4.9 (0.8)

[a]Within 3 months prior to the start of study drug administration.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale.

MDB score reflects the incidence, duration, and severity of movement disorder adverse events; prescribed treatment; and total number of days the patient received study treatment and is calculated using the following formula:

$$\text{MDB score (patient)} = \frac{\sum (S \times D \times C)}{\text{TTD (patient)}}$$

where S = movement disorder severity score, D = adverse event duration (in days), C = concomitant medication factor (C = 1.5 if anticholinergics or β-blockers were used for treating the movement disorder; C = 1 if no concomitant medication was used), and TTD = total number of treatment days for the patient.

Movement disorder severity was rated 1 (mild), 2 (moderate), or 3 (severe). The severity score was 0.5 when an adverse event stopped but concomitant medication for movement disorders continued to be administered. A higher score indicates a greater movement disorder burden. Mean and standard deviation values of the MDB score were calculated for each treatment group, and a p value for the comparison of mean scores was obtained by t test.

RESULTS

Patients

Two hundred ninety-six patients were randomly assigned to treatment with ziprasidone (N = 149) or risperidone (N = 147). The treatment groups were similar with regard to history of psychiatric illness and medications used within 3 months before study drug initiation (Table 1). All patients were analyzed for adverse events, and a majority were evaluated for laboratory test result abnormalities. A total of 125 ziprasidone-treated patients (83.9%) and 132 risperidone-treated patients (89.8%) were included in the Evaluable Patients population.

Dosing

Median duration of treatment for both groups in the All Patients population was 56 days. Mean total daily dose for ziprasidone-treated patients was 114.2 mg (maximum = 160 mg) and for risperidone-treated patients, 7.4 mg (maximum = 10 mg). Total prescribed daily doses by week are shown in Table 2.

Discontinuations

Approximately 37% of the ziprasidone and 29% of the risperidone groups discontinued treatment, with more patients in the ziprasidone group discontinuing because of insufficient clinical response (Table 3). Fewer ziprasidone- than risperidone-treated patients discontinued because of treatment-related adverse events; however, more patients in the ziprasidone group were discontinued within 14 days of study initiation.

Primary Efficacy Outcomes

Positive and Negative Syndrome Scale total score. Both ziprasidone-treated and risperidone-treated Evaluable Patients demonstrated a significant reduction in PANSS total mean score from baseline to last visit ($p < .001$ vs. baseline) (Table 4). The mean change ratio (ziprasidone/risperidone) was 0.95, with a lower limit of the 95% CI of 0.78, thus meeting the protocol-defined criterion for equivalence. Changes from baseline by week for the 2 groups are shown in Figure 1. Equivalence was also demonstrated for the All Patients and Completers populations.

Clinical Global Impressions-Severity of Illness scale. Mean decreases from baseline to last visit for CGI-S in the Evaluable Patients population were significant and similar for both groups ($p < .001$ vs. baseline) (Table 4). The mean change ratio was 0.87 (lower limit of 95% CI = 0.70). Changes from baseline by week for the 2 groups are shown in Figure 2. Equivalence was also demonstrated for the Completers population. Analysis of the All Patients population did not show treatment equivalence for the CGI-S as prospectively defined. The LS mean change from baseline at last observation was –0.8 (95% CI = –1.0 to –0.6) for ziprasidone and –1.1 (95% CI = –1.4 to –0.9) for risperidone. The mean change ratio was 0.73 (lower limit of 95% CI = 0.55).

Secondary Efficacy Outcomes

Significant reductions from baseline to last visit were observed for PANSS negative subscale score, BPRSd total score, BPRSd core items score, and GAF score in both the ziprasidone-treated and risperidone-treated Evaluable Patients groups (all $p < .001$ vs. baseline) (Table 4), with

Table 2. Total Prescribed Daily Dose (mg) by Week in Patients With Schizophrenia or Schizoaffective Disorder Receiving Ziprasidone or Risperidone

	Week								
Treatment	1	2	3	4	5	6	7	8	Total
Ziprasidone									
Mean	79.98	98.71	118.39	124.00	125.66	128.51	128.79	128.70	114.18
Maximum	120.00	160.00	160.00	160.00	160.00	160.00	160.00	160.00	160.00
N[a]	149	132	123	118	110	104	102	95	149
Risperidone									
Mean	5.14	6.92	7.56	7.83	8.08	8.16	8.11	8.05	7.39
Maximum	8.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
N[a]	147	139	133	129	122	115	112	107	147

[a]Number of patients who had at least 1 intended dose during the week.

Table 3. Reasons for Discontinuation, N (%)

Patient Disposition	Ziprasidone (N = 149)	Risperidone (N = 147)
Completers	94 (63.1)	104 (70.7)
Total discontinuations	55 (36.9)	43 (29.3)
Due to insufficient clinical response	22 (14.8)	12 (8.2)
Due to treatment-related adverse events	7 (4.7)	11 (7.5)
Unrelated to study drug	26 (17.4)	20 (13.6)
Discontinuations within 14 days of study initiation	26 (17.4)	14 (9.5)
Due to insufficient clinical response	7 (4.7)	4 (2.7)
Due to withdrawn consent	6 (4.0)	3 (2.0)
Due to adverse events	6 (4.0)[a]	5 (3.4)[b]
Due to other reasons	7 (4.7)	2 (1.4)

[a]Three adverse events related to treatment, 3 adverse events unrelated.
[b]Four adverse events related to treatment, 1 adverse event unrelated.

equivalence shown between treatment groups for these variables. Equivalence was also demonstrated in the All Patients and Completers populations.

Treatment equivalence was seen in the Evaluable Patients and All Patients populations for all responder rate categories (20%–50% decrease from baseline to last visit in PANSS total score). As the responder rate category increased from 30% to 50%, there was a corresponding decrease in the number of responders in both the Evaluable Patients (Figure 3) and All Patients populations.

Treatment equivalence was also shown among Evaluable Patients when responder rates were based on a CGI-I score of 1 or 2 at last visit. Fifty percent of ziprasidone- and 59.8% of risperidone-treated patients were CGI-I responders. The ziprasidone/risperidone ratio for responder rates was 0.84 (lower limit of 95% CI = 0.67). Equivalence of treatments for CGI-I was also seen in the All Patients population.

Mean (SD) improvements from baseline to last visit for MADRS total scores in Evaluable Patients were –5.2 (9.6) for ziprasidone patients (mean baseline score = 17.3) and –7.1 (9.0) for risperidone patients (mean baseline score = 18.4). Similar improvements were seen in Evaluable Patients with baseline MADRS scores ≥ 14. However, the magnitude of change was greater for these patients with higher mean baseline scores, i.e., ziprasidone, –7.7 (9.3), mean baseline = 22.5; and risperidone, –10.0 (9.1), mean baseline = 24.3.

Abnormal Movements Outcomes

Mean Simpson-Angus, Barnes Akathisia, AIMS, and MDB scores at baseline were comparable for both ziprasidone- and risperidone-treated patients in the All Patients population. Mean Simpson-Angus scores decreased 0.6 from baseline to last visit in both groups. Percentages of ziprasidone- and risperidone-treated patients with an increase (26.9% and 30.1%, respectively) or a decrease (43.0% and 45.6%, respectively) were similar at week 8 in the 2 treatment groups. Between-group LS mean changes at last observation in Simpson-Angus scores were similar and not statistically significant for ziprasidone versus risperidone (–0.57 [0.33] and –0.23 [0.33], respectively; p = .4).

Mean change in Barnes Akathisia score from baseline to last visit was –0.4 in ziprasidone-treated patients and 0.1 in risperidone-treated patients. Percentages of patients with an increase (18.3% for ziprasidone and 19.2% for risperidone) or a decrease (29.0% and 26.9%, respectively) in score were similar at week 8 in the 2 treatment groups. There was a statistically significant between-group difference in LS mean Barnes Akathisia scores at last observation between ziprasidone and risperidone (–0.28 [0.22] vs. +0.28 [0.21], respectively; p = .04).

Mean change in AIMS scores from baseline to last visit was –0.6 in the ziprasidone group and –0.2 in the risperidone group. Consistent with these data, fewer ziprasidone- than risperidone-treated patients had an increase in AIMS score at last visit (10.6% vs. 21.5%), while a greater proportion of ziprasidone-treated patients had a decrease in AIMS score (27.5% vs. 18.8%). A numerically greater LS mean between-group decrease in AIMS score was seen at last observation in the ziprasidone group versus the risperidone group (–0.25 [0.17] vs. –0.04 [0.17]; p = .3).

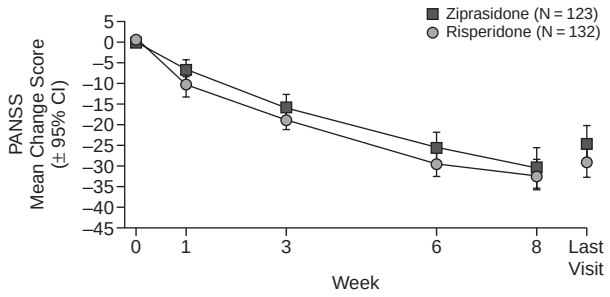
The mean MDB score was significantly higher for risperidone- than for ziprasidone-treated patients (0.35 vs. 0.20; p = .015). Fifty-four patients (36.7%) in the risperidone group experienced a movement disorder adverse event compared with 44 (29.5%) in the ziprasidone group.

Table 4. Primary and Secondary Efficacy Evaluations: Evaluable Patients

Efficacy Evaluation	Ziprasidone		Risperidone			
	Mean Baseline Score (N)	LS Mean Change, Baseline to Last Visit	Mean Baseline Score (N)	LS Mean Change, Baseline to Last Visit	Ratio[a]	Lower Limit[b]
Primary						
PANSS total	94.0 (123)	–25.8[c]	98.2 (132)	–27.3[c]	0.95	0.78
CGI-S	4.7 (124)	–1.1[c]	4.9 (132)	–1.2[c]	0.87	0.70
Secondary						
PANSS negative subscale	24.7 (123)	–6.4[c]	25.5 (132)	–6.4[c]	1.00	0.80
BPRSd total	53.2 (123)	–15.2[c]	55.6 (132)	–15.9[c]	0.95	0.79
BPRSd core[d]	15.9 (123)	–5.5[c]	16.6 (132)	–6.0[c]	0.91	0.77
GAF	37.7 (108)	16.5[c]	34.9 (111)	15.6[c]	1.06	0.81

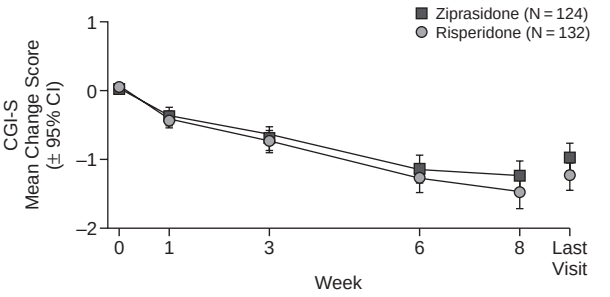
[a]Ziprasidone/risperidone ratio of the LS means at last visit.
[b]Lower limit of the 95% confidence interval of the ratio.
[c]$p < .001$ vs. baseline.
[d]Core items were conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (PANSS-derived), CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LS = least squares, PANSS = Positive and Negative Syndrome Scale.

Figure 1. Change in PANSS Total Score From Baseline by Treatment Group and Week: Evaluable Patients, Observed Cases



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. Change in CGI-S Score From Baseline by Treatment Group and Week: Evaluable Patients, Observed Cases



Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

More than a quarter (27.5%) of ziprasidone-treated patients and a third (37.4%) of risperidone-treated patients required medication for the management of movement disorders, most commonly anticholinergic drugs, which were given to 22% of ziprasidone-treated patients and 33% of risperidone-treated patients.

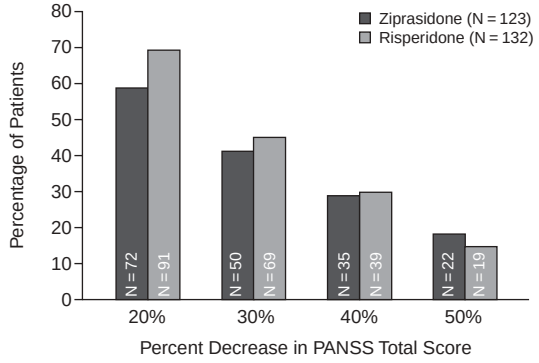
Tolerability and Safety

Adverse events. Treatment-emergent adverse events were reported in 113 (75.8%) of ziprasidone-treated patients and 122 (83.0%) of risperidone-treated patients. Those events judged by investigators to be treatment related were reported in 87 (58.4%) and 92 (62.6%) of patients in the ziprasidone and risperidone groups, respectively. Adverse events rates noted in ≥ 10% of patients were similar between groups, except for a higher rate of insomnia in the ziprasidone group and a higher rate of akathisia in the risperidone group (Table 5).

Twenty-one ziprasidone-treated and 2 risperidone-treated patients reported a total of 25 treatment-emergent serious adverse events, a great majority being exacerbations of schizophrenia. Twenty events (in 1 risperidone- and 17 ziprasidone-treated patients) were attributed by the investigators to the disease under study. Four events (all in ziprasidone patients) were attributed to other conditions (severe dystonic reaction ascribed to previous antipsychotic therapy; deep vein thrombosis; nausea, vomiting, and diarrhea ascribed to viral disease; and involvement in an altercation). One serious event (agitation in a patient taking risperidone) was attributed by the investigator to the study drug. This same patient also experienced hypochondriasis.

Clinical laboratory values. Clinically significant elevations (> 35 ng/mL for men, > 50 ng/mL for women) in serum prolactin concentration were seen more consistently in both male and female patients given risperidone than in patients given ziprasidone (Table 6). Among female patients, 76.9% of those receiving risperidone had clinically significant elevations in prolactin at ≥ 1 visit, compared with 21.9% of those receiving ziprasidone. Mean postbaseline serum prolactin concentrations were higher in risperidone-treated patients (men, 38.1 ng/mL; women, 81.7 ng/mL) than in ziprasidone-treated patients (men, 14.0 ng/mL; women, 23.2 ng/mL).

Figure 3. Responder Rates at Last Visit: 20%, 30%, 40%, or 50% Change From Baseline in PANSS Total Score, Evaluable Patients



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

No other clinically important laboratory test abnormalities or median changes in laboratory parameters were reported in either treatment group. No patient discontinued study participation because of laboratory test abnormalities.

Vital signs, body weight, and ECG. Median blood pressure, pulse rate, and body weight at baseline were comparable between treatment groups. There were no relevant changes from baseline in median values for any vital sign in either group. The incidence of a clinically important increase in body weight (≥ 7% weight gain) was 16.0% (N = 20) in risperidone-treated patients versus 8.2% (N = 10) in ziprasidone-treated patients. In contrast, 7.4% (N = 9) of ziprasidone-treated patients experienced a clinically important decrease in body weight (≥ 7% weight loss) versus 2.4% (N = 3) of risperidone-treated patients. In the risperidone group, a small increase (1.0 kg [2.2 lb]) from baseline in median body weight was observed; no change was seen in the ziprasidone group.

Several small changes in mean ECG values were observed over the course of the study but were not considered clinically important. Seven patients (4 risperidone, 3 ziprasidone) with normal baseline ECG findings exhibited abnormalities at last observation. In ziprasidone-treated patients, these included sinus bradycardia, right bundle-branch block, and intraventricular conduction block; in the risperidone group, left ventricular hypertrophy, sinus bradycardia, anterior hemiblock, and preexcitation syndrome. The mean QTc interval in 113 ziprasidone-treated patients with ECG data was 410.1 msec (range, 338–486 msec) at baseline and 409.6 msec (range, 219–491 msec) at final ECG. Mean QTc interval in 123 risperidone-treated patients was 415.0 msec (range, 173–623 msec) at baseline and 408.9 msec (range, 302–473 msec) at final ECG. No patient in either treatment group exhibited a QTc ≥ 500 msec.

Table 5. Adverse Events Reported in ≥ 10% of Patients in Either Group, N (%)

Adverse Event	Ziprasidone (N = 149)	Risperidone (N = 147)
Insomnia	37 (24.8)	18 (12.2)
Somnolence	31 (20.8)	26 (17.7)
Agitation	24 (16.1)	20 (13.6)
Headache	23 (15.4)	27 (18.4)
Akathisia	19 (12.8)	30 (20.4)
Tremor	15 (10.1)	14 (9.5)

Sexual dysfunction. Table 7 presents findings for variables from the Sexual Dysfunction Questionnaire. Values were comparable between groups for most sexual dysfunction variables.

DISCUSSION

This is the first double-blind trial to compare the efficacy and tolerability of ziprasidone and risperidone. Both drugs comparably improved measures of psychosis and global disease severity. Significant and equivalent improvements from baseline to last visit were observed among Evaluable Patients in both treatment groups for the primary efficacy variables of PANSS total score and CGI-S and the secondary variables of PANSS negative subscale score, BPRSd total and core items scores, and GAF score. Equivalence was demonstrated for PANSS total and all secondary efficacy variables (with the exception of the MADRS, for which equivalence was not calculated) in the All Patients population.

Ziprasidone and risperidone were generally well tolerated. Most of the treatment-emergent serious adverse events were seen in the ziprasidone group; however, the vast majority were attributed to the disease under study by the study investigators. Of the 2 serious events in patients treated with risperidone, 1 (severe agitation) was attributed to the study drug. Approximately 37% of ziprasidone- and 29% of risperidone-treated patients discontinued treatment, of which 4.7% and 7.5% discontinued due to treatment-related adverse events in the ziprasidone and risperidone groups, respectively. The risperidone group showed greater overall discomfort from movement disorders, as indicated by a significantly higher mean MDB score, and exhibited a higher incidence of movement disorder adverse events.

The incidence of abnormal prolactin elevation was higher among both men and women receiving risperidone than among those receiving ziprasidone. More patients treated with risperidone had clinically important increases in weight (a 1.0-kg [2.2-lb] median increase vs. no median increase with ziprasidone). Over the course of this 8-week study, 16.0% of risperidone-treated patients experienced a clinically significant weight gain of ≥ 7%, and 8.2% of ziprasidone-treated patients experienced a weight

Table 6. Incidence of Clinically Significant Increases in Serum Prolactin Concentration[a]

	Ziprasidone		Risperidone	
Patient Group	Total Patients, N	Patients With Clinically Significant Increases, N (%)	Total Patients, N	Patients With Clinically Significant Increases, N (%)
Men	92	13 (14.1)	99	58 (58.6)
Men with increase more than once	73[b]	1 (1.4)	76[b]	34 (44.7)
Women	32	7 (21.9)	39	30 (76.9)
Women with increase more than once	25[b]	0	29[b]	17 (58.6)

[a]Prolactin level > 35 ng/mL in men and > 50 ng/mL in women was considered clinically significant.
[b]Patients with ≥ 2 prolactin measurements.

Table 7. Sexual Dysfunction Questionnaire Variables in Men and Women From Both Treatment Groups

	Symptom Absent at Baseline and Present at Last Visit, N/N (%)				Symptom Increased From Baseline at Last Visit, N/N (%)			
	Ziprasidone		Risperidone		Ziprasidone		Risperidone	
Symptom	Men	Women	Men	Women	Men	Women	Men	Women
Erectile dysfunction	6/76 (8)	NA	7/73 (10)	NA	7/76 (9)	NA	7/73 (10)	NA
Ejaculatory dysfunction	2/75 (3)	NA	8/72 (11)	NA	4/75 (5)	NA	8/72 (11)	NA
Galactorrhea	0/47 (0)	0/22 (0)	0/47 (0)	1/31 (3)	0/47 (0)	0/22 (0)	0/47 (0)	2/31 (6)
Gynecomastia	0/67 (0)	0/16 (0)	0/61 (0)	0/25 (0)	0/67 (0)	0/16 (0)	0/61 (0)	0/25 (0)
Increased libido	1/75 (1)	2/20 (10)	4/73 (5)	0/30 (0)	1/75 (1)	2/20 (10)	4/73 (5)	0/30 (0)
Decreased libido	7/76 (9)	1/19 (5)	11/73 (15)	1/30 (3)	7/76 (9)	1/19 (5)	12/73 (16)	1/30 (3)
Orgastic dysfunction	3/57 (5)	0/15 (0)	6/45 (13)	0/28 (0)	3/57 (5)	0/15 (0)	6/45 (13)	0/28 (0)
Menorrhagia	NA	0/20 (0)	NA	0/29 (0)	NA	0/20 (0)	NA	0/29 (0)
Amenorrhea	NA	3/18 (17)	NA	3/29 (10)	NA	3/18 (17)	NA	3/29 (10)
Dry vagina	NA	0/23 (0)	NA	1/30 (3)	NA	0/23 (0)	NA	1/30 (3)

Abbreviation: NA = not applicable.

gain of ≥ 7% (7.4% of ziprasidone patients experienced a weight loss of ≥ 7%). These results support those of the EIRE study group, which reported a clinically significant weight gain (≥ 7%) in 30.6% of patients taking risperidone.[31]

The results of this study are consistent with data from trials comparing ziprasidone with placebo,[13–16] haloperidol,[17] or olanzapine[20] in patients with schizophrenia and schizoaffective disorder. Ziprasidone was shown to be more effective than placebo in improving patients' positive, negative, and affective symptoms[13–16]; superior to haloperidol in negative symptom response rate[18]; and equivalent to olanzapine in improving symptoms and global illness severity.[20] These trials also demonstrated that ziprasidone was well tolerated, with low incidences of EPS, clinically significant weight gain, prolactin elevation, postural hypotension, and discontinuations due to adverse events.[13–15,17,20]

Data from the present trial are also consistent with those from previous trials of risperidone,[5,7,11] which demonstrate antipsychotic efficacy and improved tolerability compared with conventional agents but liabilities for EPS, prolactin elevation, and weight gain. Risperidone has been associated with dose-related increases in EPS in other studies.[31–34] However, dosing in the current study, which was based on available data from pivotal clinical trials at study design, may have been high for some risperidone-treated (mean dose = 7.4 mg/day) and low for some ziprasidone-treated (mean dose = 114.2 mg/day) patients. Current indicated dosages for schizophrenia are 4 to 8 mg/day for risperidone[35] and up to 160 mg/day for ziprasidone.[36]

Of the atypical agents, risperidone has been associated with the greatest increases in prolactin concentration, the magnitude being comparable to that reported with typical antipsychotics.[11] We found that both men and women treated with risperidone had serum prolactin concentrations approximately 3 times greater on average than patients treated with ziprasidone. Our data also suggest that elevations in prolactin concentration are sustained with risperidone. Persistently greater elevations of serum prolactin with risperidone have also been found in comparative studies involving olanzapine.[10] Serum prolactin concentrations > 60 ng/mL commonly result in amenorrhea and can cause galactorrhea, gynecomastia, sexual dysfunction, anovulation, and osteoporosis.[35] Of note, occurrence and worsening of sexual dysfunction (particularly erectile, ejaculatory, or orgastic dysfunction, and increased or decreased libido in men), as elicited in the Sexual Dysfunction Questionnaire responses, were reported more frequently in risperidone-treated patients in our study. These findings suggest a need for direct investigations of atypical antipsychotics with regard to prolactin elevation and associated sexual dysfunction.

The ziprasidone group had a mean change from baseline of –0.5 msec in the QTc interval versus –6.1 msec in

the risperidone group. No patient in either group had a QTc interval of ≥ 500 msec while on treatment with study medication. These findings are consistent with the cardiac safety profile of ziprasidone established in safety studies and clinical trials.[36]

More ziprasidone- than risperidone-treated patients were discontinued because of insufficient clinical response. Notably, more than a third of ziprasidone discontinuations occurred in the first 2 study weeks, when protocol-defined restrictions on dosage escalation limited the daily ziprasidone dose to 40 mg b.i.d. the first week, with subsequent titration by increments of 20 mg b.i.d. at 1-week intervals. These restrictions may have contributed to the relatively greater incidence of serious adverse events in the ziprasidone group, which study investigators attributed to disease under study. Further, at the time of protocol initiation, it was predicted that ziprasidone 40 mg b.i.d. would be sufficient for a clinical response. However, a recent report from a pooled analysis of 7 trials (ranging from 4 to 8 weeks) in patients with schizophrenia showed superior efficacy with ziprasidone at daily doses of 120 mg and 160 mg versus 80 mg.[22] In addition, the analysis showed ziprasidone doses ≥ 120 mg/day were associated with lower rates of early discontinuation due to inadequate clinical response and comparable tolerability across dosages, which suggests greater beneficial effects with more rapid titration to ≥ 120 mg/day in patients with acute schizophrenia. In the present study, dosages of 80 mg b.i.d. were not reached before week 2. Additionally, the protocol-defined restriction on dosage escalation may have influenced the efficacy results in the All Patients analysis, which failed to demonstrate an a priori–defined equivalence between the groups in CGI-S score. In the study by Simpson et al.,[20] the protocol allowed dosage titration from 40 mg to 80 mg b.i.d. on day 3, where it remained for all of week 1 and could continue until study endpoint, at the investigators' discretion. The change in BPRS and CGI-S scores in that study was comparable for ziprasidone and olanzapine in the All Patients analysis, as was the percentage of treatment-related discontinuations for both drugs.

The average total daily dose of risperidone in this study (7.4 mg) was higher than that currently recommended.[37] Risperidone was flexibly dosed between 3 and 5 mg b.i.d. (at weeks 2–8); this was consistent with clinical practice at the time the study was designed and conducted. For example, a study of state hospital inpatients conducted at the time of our trial found a mean daily risperidone dose of 7.1 mg/day.[38] Subsequent analysis indicates that clinical response to risperidone plateaus at approximately 6 mg/day.[39] A consistent finding in clinical trials of risperidone was that daily doses below 10 mg were not associated with significantly more extrapyramidal symptoms than observed with placebo.[40]

In conclusion, in the present study, ziprasidone and risperidone proved efficacious in the treatment of patients with acute exacerbation of schizophrenia and schizoaffective disorder, demonstrating a priori–defined equivalence in major psychometric indices. Both agents were generally well tolerated, with ziprasidone demonstrating a lower movement disorder burden and less effect on prolactin and weight than risperidone.

Drug names: fluoxetine (Prozac and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Innopran, Inderal, and others), risperidone (Risperdal), temazepam (Restoril and others), ziprasidone (Geodon).

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