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Ziprasidone 80 mg/day and 160 mg/day in the Acute Exacerbation of Schizophrenia and Schizoaffective Disorder: A 6-Week Placebo-Controlled Trial

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In this double-blind study, patients with an acute exacerbation of schizophrenia or schizoaffective disorder were randomized to receive either ziprasidone 80 mg/day (n = 106) or 160 mg/day (n = 104) or placebo (n = 92), for 6 weeks. Both doses of ziprasidone were statistically significantly more effective than placebo in improving the PANSS total, BPRS total, BPRS core items, CGI-S, and PANSS negative subscale scores ($p < .05$). Ziprasidone 160 mg/day significantly improved depressive symptoms in patients with clinically significant depression at baseline (MADRS ⩾ 14, over-all mean 23.5) ($p < .05$) as compared with placebo. The percentage of patients experiencing adverse events was similar in each treatment group, and resultant discontinuation was rare. The most frequent adverse events associated with ziprasidone were generally mild dyspepsia, nausea, dizziness, and transient somnolence. Ziprasidone was shown to have a very low liability for inducing movement disorders and weight gain. The results indicate that ziprasidone is effective and well tolerated in the treatment of the positive, negative, and depressive symptoms of an acute exacerbation of schizophrenia or schizoaffective disorder.

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Ziprasidone (5-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloroindolin-2-one hydrochloride hydrate) is a novel antipsychotic with high affinity for dopamine D_2 and D_3, serotonin $5HT_{2A}$, $5HT_{2C}$, and $5HT_{1D}$ receptors and high affinity for the $5HT_{1A}$ receptor, where it acts as a potent agonist (Seeger et al. 1995) (Table 1). Ziprasidone moderately inhibits 5HT and norepinephrine re-uptake into nerve terminals, has relatively modest affinity for histamine H_1 and adrenergic α_1 receptors, low affinity for dopamine D_1 and α_2 receptors, and negligible affinity for M_1 receptors.

In vitro functional dopamine receptor antagonism by ziprasidone has been demonstrated by concentration-dependent blockade of effects induced by a D_2 agonist, quinpirole (inhibition of forskolin-stimulated adenylate cyclase) (Seeger et al. 1995). After systemic administration, ziprasidone produced relatively modest increases in dopamine metabolites as compared with haloperidol (Seeger et al. 1995). The inhibition by ziprasidone of the firing of dorsal raphe 5HT neurons was antagonized by the selective $5HT_{1A}$ antagonist WAY-100,635, as was the elevation of extracellular levels of dopamine in the me-

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Table 1. In Vitro Receptor Binding Affinities and Neurotransmitter Re-Uptake Inhibition by Ziprasidone, Olanzapine, Risperidone, and Haloperidol (Ki in nM)[a]

Receptor	Ziprasidone	Olanzapine	Risperidone	Haloperidol
Neurotransmitter Receptor Binding				
D_1	525[a]	31[b]	430[a]	210[a]
D_2	5[a]	11[b]	4[a]	0.7[a]
D_3	7[a]	49[c]	10[a]	2[a]
D_4	32[a]	27*[b]	9[a]	3[a]
$5HT_{2A}$	0.4[a]	4[b]	0.5[a]	45[a]
$5HT_{1A}$	3[a]	>1,000[b]	210[a]	1,100[a]
$5HT_{2C}$	1[a]	11[b]	25[a]	>10,000[a]
$5HT_{1D}$	2[a]	800[b]	170[a]	>10,000[a]
α_1	11[a]	19[b]	0.7[a]	6[a]
α_2	260[a]	230[b]	0.9[a]	360[b]
H_1	50[a]	7[b]	20[a]	440[a]
Muscarinic M1	>1,000[a]	2[b]	>10,000[b]	>1,500[b]
Neurotransmitter Re-Uptake Blockade				
5HT reuptake	53[d]	>15,000[d]	1,400[d]	1,800[d]
NE reuptake	48[d]	2,000[d]	28,000[d]	5,500[d]

*Denotes IC50s.
[a]Data from Seeger TS, Seymour PA, Schmidt AW, Zorn SH, et al. *J Pharmacol Exp Ther.* 1995;275:101–113.
[b]Bymaster FP, Calligro DO, Falcone RD, et al. *Neuropsychopharmacology* 1996; 14:87–96.
[c]Schotte A, et al. *Psychopharmacology* 1996; 124:57–73.
[d]Data on file. Pfizer Inc. 1997 provided by L Lebel and S Zorn.

dial frontal cortex, establishing in vivo $5HT_{1A}$ agonist activity (Reynolds et al. 1997; Lu et al. 1997). Ziprasidone also exhibited selectivity for prefrontal cortical vs. striatal dopamine release (Lu et al. 1997).

The pharmacological properties of ziprasidone may be predictive of enhanced clinical efficacy and a favorable tolerability profile, as compared with other agents, in the treatment of schizophrenia (Seeger et al. 1995; Tandon et al. 1997) (Table 1). These properties include a high ratio of $5HT_{2A}$ to D_2 receptor affinities (Meltzer, 1995, for review; Meltzer et al. 1989, for review; Deutch et al. 1991; Matsubara et al. 1993; Stockmeier et al. 1993) stimulation of $5HT_{1A}$ receptors (Sharma and Shapiro 1996, for review; Newman-Tancredi et al. 1996; Neal-Beliveau et al. 1993). Blockade of $5HT_{1D}$ receptors and moderate affinity in blocking synaptic re-uptake of serotonin and norepinephrine distinguishes ziprasidone from conventional and other newer antipsychotics and have been associated with the therapeutic effects of antidepressant agents (Rickels and Schweizer 1993; Briley and Moret 1993). Ziprasidone's negligible affinity for muscarinic M_1 receptors (Seeger et al. 1995) contrasts with clozapine and olanzapine (Moore et al. 1993; Seeman and van Tol 1993; Bymaster et al. 1996); its relatively modest affinity for α_1 receptors contrasts with risperidone and sertindole (Seeger et al. 1995; Schotte et al. 1996); and its agonist properties at the $5HT_{1A}$ receptor are in contrast to olanzapine, quetiapine (Reynolds et al. 1997), risperidone (Seeger et al. 1995), sertindole and clozapine (Schotte et al. 1996).

In behavioral pharmacology, assays with predictive value for antipsychotic action (Niemegeers and Janssen 1979), ziprasidone antagonized d-amphetamine-induced hyperactivity and apomorphine-induced stereotypy and inhibited conditioned avoidance (Seeger et al. 1995). Ziprasidone also reversed both dopamine agonist- (apomorphine) and NMDA antagonist- (ketamine) induced prepulse inhibition deficits (Brooks and Mansbach 1997). In models considered to have predictive value for extrapyramidal side-effect liability (Niemegeers and Janssen 1979), the in vivo potency of ziprasidone in blocking a $5HT_{2A}$ agonist-(quipazine) induced head twitches and amphetamine-induced locomotor activity each occurred at substantially lower doses than those needed to produce catalepsy (Seeger et al. 1995). These data suggest that there is good separation of the therapeutic efficacy of ziprasidone vs. the propensity to produce extrapyramidal side effects (Seeger et al. 1995).

Ziprasidone was selected for clinical development, because its preclinical profile was considered predictive of antipsychotic efficacy, with modest anti-adrenergic and antihistaminergic and no anticholinergic side-effect liability. Its high ratio of $5HT_{2A}$ to D_2 antagonism, low potency to produce catalepsy, agonist effects at the $5HT_{1A}$ receptor, reversal of ketamine disruption of prepulse inhibition, preferential release of dopamine in the prefrontal cortex vs. the striatum, and blockade of synaptic re-uptake of 5HT and norepinephrine were considered favorable predictors of low liability for motor side effects and benefits in negative symptoms, cognition, and mood.

In healthy volunteers, positron emission computed tomography (PET) studies confirmed that the occupancy by ziprasidone of $5HT_2$ receptors substantially

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exceeded that of D_2 receptors (Fischman et al. 1996; Bench et al. 1993; Bench et al. 1996). In a 28-day clinical trial in which the majority of patients (84/90) had an acute exacerbation of schizophrenia or schizoaffective disorder, ziprasidone 160 mg/day reduced Brief Psychiatric Rating Scale (BPRS) total and core item scores and Clinical Global Impression of Severity (CGI-S) scores similarly to haloperidol 15 mg/day (Goff et al. 1998). In a second 28-day clinical trial, involving 139 patients with an acute exacerbation of schizophrenia or schizoaffective disorder, ziprasidone 120 mg/day was significantly more effective than placebo in improving BPRS total, BPRS anxiety–depression cluster, BPRS anergia factor scores, and CGI-S (Keck et al. 1998).

In the present article, we report the results of a large, Phase III, randomized, placebo-controlled, parallel group, fixed dose study designed to evaluate the efficacy and safety of 6 weeks of treatment with ziprasidone (80 mg/day and 160 mg/day) in patients with an acute exacerbation of schizophrenia or schizoaffective disorder.

METHODS

Subjects

Men or women aged over 18 years, with an acute exacerbation of chronic or subchronic schizophrenia (295.x3) or schizoaffective disorder (295.x4) as defined in DSM-III-R (American Psychiatric Association 1987) were eligible to enter. They were to have been hospitalized within the previous 4 weeks and been diagnosed at least 6 months before the study. The patients were required to have a total score ≥ 60 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1989) and a score of at least 4 on two or more core items in the PANSS (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) in the 24 hours before study treatment was started. In addition, the patients were required to have a score of 3 (minimally improved) or greater (worse) on the Clinical Global Impression Improvement Scale (CGI-I) (National Institutes of Mental Health 1976a) at baseline as compared with screening.

Patients were excluded if they were resistant to neuroleptic treatment (defined as failure to respond to two or more marketed antipsychotic agents given at an adequate dose for sufficient time), had been hospitalized for more than 4 weeks before screening, or had DSM-III-R-defined psychoactive substance abuse/dependence in the preceding 3 months. Also excluded were those with mental retardation, an organic mental disorder, previous brief reactive psychosis, those who had received long-acting intramuscular neuroleptic medication within 4 weeks of the first day of double-blind treatment (unless blood level was below therapeutic level), and those judged by the investigator to be at imminent risk of suicide or homicide.

Patients were required to have normal electrocardiograms (ECG, with the exception of abnormalities considered by the investigator to be clinically unimportant) and normal laboratory test results (with the exception of minor deviations considered by the investigator to be clinically unimportant). Body weight was generally at least 80% of the lower limit of normal and no greater than 160% of the upper limit of normal according to sex, height, and frame (Metropolitan Life Insurance Company 1993). Urine samples obtained during screening were required to be negative for all illicit drugs, except cannabinoids and benzodiazepines that were allowed based on the investigators' discretion. Patients were excluded if they had received any investigational drug in the 4 weeks immediately preceding the baseline visit of the study, fluoxetine within 5 weeks of the first day of double-blind treatment, or phencyclidine during the 90 days before admission. They were also excluded if they had a history of clinically significant or currently relevant illness, or if they had a history of hypersensitivity to, or malignant syndrome developing from, the administration of antipsychotic compounds.

Women were either of nonchildbearing potential, had been using an oral or injectable contraceptive for at least 1 month before entry into the study, and agreed to continuing using it or another reliable barrier method of contraception during the study. The study was approved by appropriate institutional review boards at each site. Before initiation of any study-related procedure, written informed consent was obtained from all patients who were competent to give it. In the case of patients who were not competent to give informed consent, a pre-existing legal representative consented on their behalf.

Study Design

This randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, multicenter clinical trial was carried out at 34 sites; 32 in the United States and two in Canada. Patients who met the study entry criteria entered a mandatory, single-blind placebo washout period lasting 3 to 7 days. During this washout period, any pre-existing neuroleptic or antidepressant treatment was discontinued. Sedative, anxiolytic, or hypnotic treatments (except lorazepam) were also discontinued or substituted with an appropriate dose of lorazepam. Anticholinergic and β-adrenoceptor antagonist treatment were also withdrawn by reducing the daily dose by one-third each day during the washout period. After washout, patients who still met the study entry criteria were randomized to receive orally either ziprasidone 80 mg/day (given 40 mg BID), ziprasidone 160 mg/day (given 80 mg BID), or placebo for 6 weeks. Patients randomized to receive ziprasidone 160 mg/day received 80 mg/day for the first 2 days of the study, and then received the full dose for the remainder

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of the study. Patients were to remain in hospital for the first 14 days of the study. Concomitant lorazepam (for insomnia or agitation), benztropine (for extrapyramidal symptoms), and a β-adrenoceptor antagonists (for akathisia) were allowed if required during the study but were not administered prophylactically.

Efficacy Assessments

The following efficacy variables were used to evaluate the efficacy of ziprasidone: PANSS total score (the sum of all 30 items); the PANSS negative subscale score (the sum of the seven negative items on PANSS); the CGI-severity (CGI-S) score, ranging from 1 (normal) to 7 (most severely ill) (National Institutes of Mental Health 1976b), and the CGI-I score. The BPRS (BPRSd) total score was derived from the PANSS, as was the BPRSd core items score (the sum of items P2, conceptual disorganization, P6, suspiciousness, P3, hallucinatory behavior, and G9, unusual thought content). Responder rates based on the PANSS total score (defined as a ⩾30% decrease from baseline to last observation) and the CGI-I score (defined as a score of 1, very much improved, or 2, much improved at the last observation) were also determined. The Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score (the sum of all 10 items) was also measured. Discontinuations because of insufficient clinical response and adverse events were recorded.

Efficacy variables, with the exception of MADRS, were measured at baseline (Day 0), and weekly for 6 weeks or on early termination (within 24 hours of receiving the last dose). For CGI-I, the baseline value was based on the comparison with screening, and subsequent weekly assessments were based on comparisons with baseline. The MADRS total score was assessed at baseline and at weeks 1, 2, 3, and 6, or on early termination.

Safety and Tolerability Assessments

All adverse events volunteered and observed during the study or within 6 days of the last day of treatment were recorded using the COSTART dictionary, together with their date of onset, duration, concurrent therapy, the investigator's assessment of severity, and the possible causative relationship to study drug, and whether a change in dose or withdrawal of treatment was required. All serious adverse events were recorded.

Safety assessments were performed at regular intervals or within 24 hours of early termination. Movement disorders were assessed using the 10-item Simpson–Angus Rating scale (Simpson and Angus, 1970), to measure extrapyramidal symptoms (0 = normal to 4 = most severe), the Barnes Akathisia scale (Barnes 1989) to evaluate akathisia (0 = normal to 5 = most severe), and the Abnormal Involuntary Movement Scale (AIMS) (0 = normal to 4 = most severe) (National Institutes of Mental Health 1976c) to evaluate tardive dyskinesia. The Simpson–Angus Rating scale incorporated a new item 7, head rotation, in place of the original item 7, head dropping. The Simpson–Angus Rating and Barnes Akathisia assessments were conducted at baseline and at weeks 1, 3, and 6. The AIMS was assessed at baseline and at week 6. Concomitant use of benztropine, β-adrenoceptor antagonists, and lorazepam was recorded.

Vital signs, including blood pressure (sitting and standing) and pulse rate, were measured weekly. A 12-lead ECG was done at baseline and at weeks 2 and 6. Patients were weighed at baseline and at week 6. Clinical laboratory tests, including routine hematology, serum chemistry, urinalysis with microscopic evaluation, and liver function tests, were done at baseline and at weeks 1, 3, and 6.

Serum Ziprasidone Concentrations

Venous blood samples were collected for the determination of serum ziprasidone concentrations before administration of the morning dose of study drug at weeks 1, 2, and 6 (and, in some cases, week 3). Samples were analyzed using a validated high-pressure liquid chromatography (HPLC) assay with solid phase extraction and detection by ultraviolet absorption (Janiszewski et al. 1995).

Statistical Analysis

It was estimated that approximately 100 patients per group would be required to detect a difference of five points between the placebo group and a ziprasidone treatment group in the mean change from baseline in the BPRSd total score with at least 80% power and a comparison-wise error rate of 0.05 (two-sided).

The primary statistical analysis used for all efficacy variables was an intention-to-treat (ITT) analysis with the last observation being carried forward (LOCF). All patients with a baseline assessment and at least one postbaseline assessment were included in the ITT LOCF analysis. MADRS scores were calculated for the entire ITT cohort, for the subset of patients with baseline MADRS scores ⩾14, and for patients with a primary diagnosis of schizoaffective disorder.

Mean baseline to endpoint changes were compared between the placebo group and each of the ziprasidone groups. Estimates of treatment effects were based on least-squares means derived from an analysis of covariance (ANCOVA) model, with the measured value as the dependent variable and the baseline value as the covariate, with fixed terms for the study centers and treatment. Comparisons between treatments were estimated using least-squares means from a type III sum of

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squares analysis of PROC GLM of SAS®. Confidence intervals and p-values were derived from a Student's t-test. Responder rate p-values and confidence intervals for the PANSS total score and the CGI-I score and were obtained using normal approximation to binomial, with correction for continuity.

All statistical tests performed were two-sided, and values of test statistics were considered significant if $p < .05$. No adjustments for multiple comparisons were made to significance levels.

Descriptive statistics were used to compare features of the history of illness, baseline characteristics, the incidence of adverse events and laboratory test abnormalities, discontinuations because of insufficient clinical response, and concomitant use of benztropine, β-adrenoceptor antagonists, and lorazepam among treatment groups. Serum ziprasidone concentrations were summarized as means and standard deviations, but no formal hypothesis testing was performed.

RESULTS

Clinical Characteristics

A total of 440 patients were screened. Of these, 302 (215 men and 87 women) were randomized and received at least one dose of double-blind treatment. Baseline patient characteristics and illness characteristics were generally similar across treatment groups (Table 2). Psychiatric illness history was highly variable within each group, but mean values for each attribute were generally consistent across the treatment groups (Table 2). One exception was the duration of the last psychiatric hospitalization, where the mean value in the ziprasidone 160 mg/day group was considerably greater than those in the other two groups. This was mainly attributable to two patients whose previous psychiatric hospitalizations lasted 900 and 1300 days, respectively. Almost all patients had received antipsychotic treatment in the previous 12 months.

The mean baseline PANSS total and negative subscale scores, BPRSd total and core items scores, as well as the CGI-S scores, indicate that all three treatment groups had moderately severe levels of over-all psychopathology, positive symptoms, and negative symptoms (Table 2). Furthermore, over 50% of patients in each treatment group had clinically significant depression at baseline (MADRS score ≥ 14) (Table 3).

Study Therapy

The median duration (range) of treatment was 36 (2–45), 40 (1–46), and 42 (2–46) days for patients in the placebo, ziprasidone 80 mg/day, and ziprasidone 160 mg/day groups, respectively. The percentage of patients discontinuing because of an insufficient clinical response was lower in the ziprasidone 160 mg/day (15%) and ziprasidone 80 mg/day groups (25%) than in the placebo group (35%). Although infrequent, discontinuations because of adverse events occurred more often in the ziprasidone 160 mg/day group than the other two groups in which they were similar (Table 4). No patient discontinued as a result of a laboratory test abnormality. The percentage of patients who discontinued for other reasons (protocol violation, lost to follow-up, withdrawn consent, failure to meet randomization criteria, or other unspecified reasons) was 15, 23, and 13% in the placebo, ziprasidone 80 mg/day, and ziprasidone 160 mg/day groups, respectively. The majority of patients in each the placebo (92%), ziprasidone 80 mg/day (81%), and ziprasidone 160 mg/day (87%) groups took lorazepam at some time during the study. In all three groups, the percentage of patients who required lorazepam was greatest in the first week and decreased throughout the study.

Efficacy Analysis

Both doses of ziprasidone were statistically significantly more effective than placebo in treating psychosis as measured by reduction between baseline and 6 weeks (endpoint) in all assessments of global, positive, and negative symptoms ($p < .05$) (Figure 1). The efficacy of ziprasidone was also evident when the responses to treatment were expressed as the percentage of patients classified as responders (Figure 2). The percentage of patients classified as PANSS responders was significantly greater than placebo (17.6%) in the ziprasidone 160 mg/day group (31.1%, $p < .05$) and numerically greater in ziprasidone 80 mg/day group, (28.8% $p = .09$). Similarly, the percentage of patients classified as CGI-I responders was significantly greater than placebo (26.1%) in the ziprasidone 160 mg/day group (42.7%, $p < .05$) and numerically greater in ziprasidone 80 mg/day group (32.7%, $p = .39$).

In the all patient group, ziprasidone had no significant effect on MADRS scores (Table 3). However, in patients with clinically significant depressive symptoms at baseline (baseline MADRS ≥ 14; over-all mean 23.5), ziprasidone 160 mg/day produced a statistically significant reduction in MADRS scores as compared with placebo (31.3% vs. 12.6%) ($p < .05$) (Figure 3). In the small subset of patients with schizoaffective disorder, the severity of depressive symptoms at baseline was less than in the subset with baseline MADRS ≥ 14, and ziprasidone 80 mg/day and 160 mg/day were associated with numerically, but statistically, nonsignificantly greater improvements (18.5 and 30.0%, respectively) in depressive symptoms than placebo (11.9%).

In addition to the analysis of mean baseline to endpoint changes, the time course for symptom improve-

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