New Drugs

Ziprasidone: An Atypical Antipsychotic Drug for the Treatment of Schizophrenia

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ABSTRACT

Background: Over the past decade, use of the atypical antipsychotic drugs clozapine, risperidone, olanzapine, and quetiapine has significantly changed the treatment of schizophrenia in the United States. The ability to make optimal drug choices will depend on determining whether there are clinically important differences between these drugs.

Objective: This review describes ziprasidone, the most recently introduced antipsychotic drug. Its mechanism of action, pharmacokinetics, and adverse-effect profile are discussed, and the results of clinical efficacy trials are summarized.

Methods: This review of ziprasidone is based on data from premarketing clinical efficacy and safety trials, a briefing document from the US Food and Drug Administration Psychopharmacological Drugs Advisory Committee, published studies, and abstracts presented at national and international meetings. International Pharmaceutical Abstracts and MEDLINE were searched for relevant citations, with no limitation on year.

Results: Ziprasidone has been reported to be an effective antipsychotic drug for both positive and negative symptoms of schizophrenia, and long-term use has been effective in preventing relapse. Its 5-hydroxytryptamine $(HT)_{1D}$–antagonist and $5\text{-}HT_{1A}$–agonist activity are consistent with a potential for antidepressant and anxiolytic activity beyond its antipsychotic effects. Ziprasidone has been associated with a low incidence of sedative effects, a low likelihood of extrapyramidal symptoms and postural hypotension, and no anticholinergic effect, although it may cause transient hyperprolactinemia. Unlike most atypical antipsychotic drugs, ziprasidone is not associated with weight gain, hyperlipidemia, or elevated plasma glucose levels. It is, however, more likely than other atypical

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antipsychotic drugs to increase the QTc interval (QT interval corrected for heart rate). For acute psychotic symptoms in patients with schizophrenia, schizoaffective disorder, or acute mania, ziprasidone is administered twice daily at a usual daily dose of 80 to 160 mg, whereas 40 mg/d may be an effective maintenance dose.

Conclusions: Differences in efficacy and tolerability between existing atypical antipsychotic drugs allow individualization of drug therapy for patients with schizophrenia or schizoaffective disorder. Ziprasidone differs from other atypical antipsychotic drugs in several clinically important ways, although further experience is necessary to clarify the significance of these differences.

Key words: ziprasidone, atypical antipsychotic, weight gain, QTc interval. (*Clin Ther.* 2002;24:21–37)

INTRODUCTION

The 1990s saw the introduction of 4 atypical antipsychotic drugs that significantly changed the treatment of schizophrenia and have effectively supplanted the typical antipsychotic drugs haloperidol, chlorpromazine, and fluphenazine. Clozapine was the first atypical antipsychotic drug to demonstrate superior efficacy to the typical antipsychotic drugs in treatment-resistant schizophrenia and for the negative symptoms of schizophrenia. Subsequently, risperidone, olanzapine, and quetiapine demonstrated improved safety compared with clozapine while maintaining improved efficacy and tolerability compared with the typical antipsychotic drugs. During the 1990s, the focus of interest was on the atypical antipsychotic drugs' improved efficacy and reduced likelihood of causing extrapyramidal symptoms (EPS) and tardive dyskinesia compared with the typical antipsychotic drugs. More recently, however, the focus has shifted to the characterization of clinically important differences between individual atypical antipsychotic drugs, including their relative likelihood of inducing hyperprolactinemia, elevated plasma glucose and lipid levels, weight gain, and cardiovascular effects.

It is within this context that ziprasidone became the fifth atypical antipsychotic drug to be approved for the treatment of schizophrenia and schizoaffective disorder in the United States. This review describes the drug's mechanism of action, pharmacokinetics, and adverse-effect profile, and summarizes the results of clinical efficacy trials. Relevant data were obtained from reports of premarketing clinical efficacy and safety trials, a briefing document from the US Food and Drug Administration Psychopharmacological Drugs Advisory Committee, published studies, and abstracts presented at national and international meetings. International Pharmaceutical Abstracts and MEDLINE were searched for relevant citations, with no limitation on year.

MECHANISM OF ACTION

Ziprasidone is a benzothiazolylpiperazine, unrelated to the phenothiazine and butyrophenone antipsychotic drugs. Like other atypical antipsychotic drugs, it is an antagonist of both the 5-hydroxytryptamine-2A ($5\text{-}HT_{2A}$) and dopamine-2 (D_2) receptors, with an ~8-fold greater affinity for the $5\text{-}HT_{2A}$ receptor than the D_2 receptor. These effects are consistent with antipsychotic activity and a decreased risk of

EPS. Unlike other atypical antipsychotic drugs, however, ziprasidone also has potent 5-HT_{1D}–antagonist and 5-HT_{1A}–agonist activity, and moderate inhibitory activity against 5-HT and norepinephrine reuptake.[1–3] These receptor effects are consistent with the potential for both antidepressant and anxiolytic activity. Ziprasidone binds with moderate affinity to the histamine-1 and alpha-1–adrenergic receptors, corresponding to potential sedation and orthostatic hypotension, respectively. Ziprasidone has negligible affinity for the muscarinic-1 receptor. Its receptor affinities are summarized and compared with those of the other atypical antipsychotic drugs in Table I.

PHARMACOKINETICS

Absorption and Distribution

Over a dosing range of 80 to 160 mg/d, linear increases have been observed in both the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of ziprasidone. The C_{max} occurs 6 hours after multiple oral dosing with food. The absolute bioavailability of a 20-mg dose under fed conditions is 60%. Absorption of ziprasidone is increased up to 2-fold in the presence of food. No difference in absorption has been found with low- or high-fat meals or with administration up to 2 hours after a meal. Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is >99% bound to plasma proteins, binding primarily to albumin and alpha-1–acid glycoprotein.[3,4]

Metabolism and Elimination

Ziprasidone is extensively metabolized to 4 major metabolites. Two thirds of its metabolism is via reduction by aldehyde oxidase, a non–cytochrome P450 (CYP) pathway, to a metabolite with much lower pharmacologic activity than the parent compound. One third is metabolized via a CYP3A4 pathway that produces inactive metabolites.[3,5,6] After mul-

Table I. Relative receptor affinities of atypical antipsychotic drugs, using the scale 5 = very high, 4 = high, 3 = moderate/high, 2 = moderate, 1 = low, and – = negligible.

Receptor Effects	Ziprasidone	Risperidone	Olanzapine	Quetiapine
D_2	4	4	2	1
5-HT_{2A}	5	5	4	1
5-HT_{1A}	4	1	–	1
5-HT_{1D}	4	1	1	–
Alpha-1–adrenergic	2	4	2	2
Muscarinic-1	–	–	4	2
Histaminic-1	2	2	4	4
5-HT/NE reuptake inhibition	2	–	–	1 (NE only)

D = dopamine; HT = hydroxytryptamine; NE = norepinephrine.
Adapted from the transcript of the US Food and Drug Administration Psychopharmacological Drugs Advisory Committee hearing, July 19, 2000.[3]

tiple oral dosing, ziprasidone has a mean terminal elimination half-life of 6.6 hours (range, 3.2–10.0 hours). Steady-state serum concentrations are reached within 1 to 3 days after twice-daily dosing under fed conditions.[3]

Special Populations

Neither age, sex, nor mild to moderate renal impairment has been observed to have any clinically significant influence on the pharmacokinetic behavior of ziprasidone.[4,6] In a study in patients with Child-Pugh class A or B cirrhosis, the AUC of ziprasidone was increased by 13% and 34%, respectively. The elimination half-life was 4.8 hours in the control group, compared with 7.1 hours in the patients with cirrhosis.[3,7]

DRUG INTERACTIONS

Because it is only partly dependent on CYP3A4 for its metabolism, ziprasidone is unlikely to interact with other drugs metabolized by this isozyme. Its principal metabolic pathway, aldehyde oxidase, has no known inhibitors or inducers.[3] In 11 subjects who received ziprasidone coadministered with 800 mg of cimetidine, a weak CYP3A4 inhibitor, no significant changes in ziprasidone pharmacokinetics were seen.[8] In 14 subjects who received ziprasidone coadministered with 400 mg of ketoconazole, a potent CYP3A4 inhibitor, the AUC of ziprasidone was increased by 33% and its C_{max} was increased by 34%.[9] At the maximum dose of 160 mg, serum concentrations of ziprasidone increased 39% when coadministered with 400 mg of ketoconazole, with no adverse effects or changes in electrocardiographic (ECG) parameters.[3] No other CYP-isozyme inhibitors have been reported to affect the metabolism of ziprasidone, and ziprasidone has not been reported to affect the metabolizing activity of CYP isozymes.[3,10]

Although ziprasidone is highly protein bound, warfarin and propranolol have not been shown to alter its plasma protein binding in vitro.[3] This suggests that the potential for displacement drug interactions with ziprasidone is minimal.[3] No changes in ziprasidone's pharmacokinetic parameters occurred with coadministration of cimetidine or an aluminum hydroxide–magnesium hydroxide antacid.[8] Ziprasidone had no effect on steady-state lithium levels or renal clearance of lithium,[11] and caused no change in the pharmacokinetics of an ethinyl estradiol–levonorgestrel oral contraceptive agent.[12]

CLINICAL EFFICACY TRIALS

Four short-term double-blind, placebo-controlled, fixed-dose clinical trials of ziprasidone have been conducted in hospitalized patients with an acute exacerbation of schizophrenia or schizoaffective disorder.[3,13,14] In addition, a 52-week randomized, double-blind, controlled, fixed-dose trial has been conducted in inpatients with chronic schizophrenia to assess its efficacy in treating negative symptoms and its ability to prevent acute exacerbation.[3,15] Double-blind, placebo-controlled clinical trials of ziprasidone have also been conducted in the treatment of acute mania in patients with type 1 bipolar disorder[16] and in Tourette's syndrome.[17] These trials are summarized in Table II. Head-to-head clinical trials comparing ziprasidone with other atypical antipsychotic drugs are currently under way.

Table II. Placebo-controlled clinical trials of oral ziprasidone.

Study	Duration, wk	Dose, mg/d	No. of Patients	Diagnosis
104[3]	4	Z 10	47	Inpatient, acute exacerbation of schizophrenia or schizoaffective disorder
		Z 40	55	
		Z 80	48	
		Placebo	50	
106[13]	4	Z 40	44	Inpatient, acute exacerbation of schizophrenia or schizoaffective disorder
		Z 120	47	
		Placebo	48	
114[14]	6	Z 80	106	Inpatient, acute exacerbation of schizophrenia or schizoaffective disorder
		Z 160	104	
		Placebo	92	
115[3]	4	Z 40	87	Inpatient, acute exacerbation of schizophrenia or schizoaffective disorder
		Z 120	78	
		Z 200	86	
		Hal 15	85	
		Placebo	83	
303[3,15]	52	Z 40	76	Inpatient, stable chronic schizophrenia
		Z 80	72	
		Z 160	71	
		Placebo	75	
Keck and Ice[16]	3	Z 80–160*	131	Acute mania
		Placebo	64	
Sallee et al[17]	8	Z 5–40*	16	Tourette's syndrome
		Placebo	12	

Z = ziprasidone; Hal = haloperidol.
*Flexible dosing.

Acute Therapy

Study 104

In a fixed-dose comparative clinical trial of ziprasidone 10 (n = 47), 40 (n = 55), and 80 (n = 48) mg/d,[3] no differences in efficacy were found between any treatment group and placebo (n = 50). The 10- and 40-mg doses were ineffective in these acutely symptomatic patients. Forty-four percent of the 80-mg group dropped out of the study within 2 weeks, approximately half for protocol violations or withdrawal of consent and the other half for inadequate response. Given that later clinical trials found this dose to be effec-

tive, the overall lack of efficacy in this study may be explained by the high dropout rate.

Study 106

In a comparison of fixed-dose ziprasidone 40 (n = 44) and 120 mg/d (n = 47),[13] only the 120-mg/d dose demonstrated significant efficacy compared with placebo (n = 48) ($P < 0.05$). The only concomitant medications allowed were lorazepam (for insomnia or agitation) and benztropine or beta-blockers (for EPS). Ziprasidone 120 mg/d was more effective than placebo in improving mean Brief Psychiatric Rating Scale (BPRS) total scores and Clinical Global Impression–Severity (CGI-S) scores. Mean improvements in primary efficacy variables were no different with ziprasidone 40 mg/d than with placebo. At 4 weeks, mean BPRS depression cluster scores and BPRS anergia factor scores were significantly improved with ziprasidone 120 mg/d compared with placebo (both scores, $P < 0.05$), suggesting some benefit for affective symptoms in this patient population. After 1 week of treatment, improvement was noted in all 3 treatment groups. No further improvement was seen in the placebo group after the first week, but patients receiving ziprasidone 120 mg/d improved progressively over the 4 weeks, with maximal improvement at 4 weeks.

Study 114

In a 6-week trial,[14] both ziprasidone 80 (n = 106) and 160 mg/d (n = 104) were more effective than placebo (n = 92) on the primary efficacy measures (Positive and Negative Syndrome Scale [PANSS] total, BPRS total, BPRS core items, CGI-S, and PANSS negative subscale scores). Again, the only concomitant medications allowed were lorazepam (for insomnia or agitation) and benztropine or beta-blockers (for EPS). The percentages of patients classified as PANSS responders and CGI-Improvement responders were significantly greater in the group that received ziprasidone 160 mg/d compared with placebo (both, $P < 0.001$). Significant improvement in negative symptoms was demonstrated with both doses of ziprasidone compared with placebo (80 mg/d, $P < 0.05$; 160 mg/d, $P < 0.001$).

An evaluation of depressive symptoms found that ziprasidone had no significant effect on overall Montgomery-Asberg Depression Rating Scale (MADRS) scores. In patients with more severe depressive symptoms (MADRS score >13), ziprasidone 160 mg/d significantly reduced scores compared with placebo ($P < 0.05$), suggesting that ziprasidone may reduce but not completely resolve depressive symptoms in patients with an acute exacerbation of schizophrenia or schizoaffective disorder.

Study 115

In a trial that compared fixed doses of ziprasidone 40 (n = 87), 120 (n = 78), and 200 mg/d (n = 86) and haloperidol 15 mg/d (n = 85) with placebo (n = 83)[3] all active-treatment groups demonstrated statistically significant improvement in PANSS total ($P < 0.03$), BPRS total ($P < 0.05$), BPRS core items ($P < 0.05$), and CGI-S scores ($P < 0.04$). Only ziprasidone 200 mg/d was associated with statistically significant improvement in the PANSS negative subscale score ($P < 0.012$). There was no difference in improvement in negative symptoms between ziprasidone and haloperidol, although the ability to assess the response of negative symptoms is limited in a 4-week study of this type.

Schizoaffective Disorder

Results from 115 patients with schizoaffective disorder in 2 studies[13,14] were combined to compare the efficacy of ziprasidone doses of 40, 80, 120, and 160 mg/d and placebo.[18] In this diagnostic subgroup, ziprasidone 160 mg/d was significantly more effective than placebo in improving mean BPRS total ($P < 0.01$), BPRS core items ($P < 0.01$), BPRS mania ($P < 0.001$), and CGI-S scores ($P < 0.01$). Ziprasidone 120 mg/d was significantly more effective than placebo in improving mean CGI-S scores ($P < 0.05$). Mean improvements in BPRS depression items and MADRS scores were not statistically significant compared with placebo.

Maintenance Therapy

The standard of practice for chronic schizophrenia requires maintenance drug therapy for the prevention of relapse.[19] Study 303 compared maintenance therapy with fixed doses of ziprasidone 40 (n = 76), 80 (n = 72), and 160 mg/d (n = 71) versus placebo (n = 75) over 1 year in inpatients with stable chronic schizophrenia.[15] This patient population had long-standing illness, stable overall psychopathology (reflected in relatively modest positive symptoms), but moderate to severe negative symptoms, with seriously impaired social and occupational functioning. All ziprasidone doses significantly reduced the probability of an acute exacerbation of psychotic symptoms compared with placebo (41%, 35%, 36%, and 71%, respectively). Significant improvements in PANSS total and CGI-S scores occurred at all ziprasidone doses compared with placebo (both scales, $P < 0.05$). Ziprasidone 40 and 160 mg/d were statistically superior to placebo for the treatment of negative symptoms ($P < 0.05$ and $P < 0.01$, respectively), with improvement continuing throughout the study. Ziprasidone was associated with significant improvements in Global Assessment of Functioning (GAF) scores in all dose groups (40 and 80 mg/d, $P < 0.05$; 160 mg/d, $P < 0.001$).

To more specifically evaluate the response of negative symptoms, a 28-week study in outpatients with stable schizophrenia compared flexible doses of ziprasidone 80 to 160 mg/d (n = 110) and haloperidol 5 to 15 mg/d (n = 117).[20] Whereas both groups had similar overall improvement, a response in negative symptoms occurred in 48% of patients receiving ziprasidone compared with 33% of patients receiving haloperidol.

Switching from Other Antipsychotic Drugs to Ziprasidone

Several open-label studies have evaluated the efficacy and tolerability of a switch from other antipsychotic drugs to ziprasidone. In a study in patients with a diagnosis of schizophrenia or schizoaffective disorder, those with at least a partial response to current antipsychotic drug therapy but with inadequate efficacy or tolerability were switched to ziprasidone.[21] Ninety patients were switched from olanzapine, 42 from risperidone, and 97 from typical antipsychotic drugs. Three switching strategies were compared—abrupt discontinuation of the original antipsychotic drug, 50% reduction for 1 week followed by discontinuation, and gradual tapering over 1 week. In all groups, ziprasidone was initiated at 80 mg/d for 2 days and then given at flexible open-label doses of 40 to

160 mg/d for the remainder of the 6-week study. Significant improvements were observed in negative symptoms ($P < 0.01$) and overall psychopathology ($P < 0.05$) with a switch from any of the original drugs. Ziprasidone was associated with significant improvements in positive symptoms compared with conventional antipsychotic drugs and olanzapine ($P < 0.001$) but not compared with risperidone. Abrupt switching without cross-tapering was as well tolerated as the other switching strategies, suggesting that patients can be switched to ziprasidone over a relatively short period.

Acute Mania

A randomized, double-blind study compared ziprasidone at doses ranging from 80 to 160 mg/d (n = 131) with placebo (n = 64) over 21 days in inpatients with acute mania.[16] Patients had a diagnosis of type 1 bipolar disorder, manic or mixed, with moderate to marked symptom severity. Concomitant anxiolytic agents (oral or intramuscular lorazepam up to 8 mg/d or temazepam up to 30 mg at night) were administered to 76% of patients in each group in the first 9 days of the study. At baseline, patients had high levels of manic and positive psychotic symptoms as well as a low GAF score. Based on scores on the Mania Rating Scale and its manic syndrome and behavior/ideation subscales, after 2 days of ziprasidone therapy there were significant improvements in both manic ($P < 0.05$) and behavior/ideation ($P < 0.01$) symptoms compared with placebo. These improvements persisted throughout the 21-day trial. From days 7 through 21, those receiving ziprasidone had significant improvements in CGI-S ($P < 0.01$) and PANSS positive subscale ($P < 0.001$) scores. GAF scores were also significantly improved in the ziprasidone group compared with placebo ($P < 0.01$). Discontinuation of treatment due to lack of clinical response occurred in 19% of ziprasidone and 36% of placebo recipients.

Tourette's Syndrome

Treatment of Tourette's syndrome has traditionally involved use of typical dopamine-blocking antipsychotic drugs such as haloperidol. Preliminary evidence suggests that the atypical antipsychotic drugs may be as effective as such agents, with the potential for fewer adverse effects.[17] An 8-week randomized, double-blind clinical trial compared ziprasidone 5 to 40 mg/d with placebo in 28 patients with Tourette's syndrome.[17] Ziprasidone was initiated at 5 mg/d, with titration to a maximum of 40 mg/d; the mean (±SD) daily dose in the last 4 weeks of the study was 28 ± 9.6 mg. Ziprasidone was significantly more effective than placebo in reducing global severity ($P < 0.016$) and total tic ($P < 0.008$) scores on the Yale Global Tic Severity Scale, and it significantly reduced tic frequency as determined by blind videotape tic counts ($P < 0.039$). Although the patient sample was small, results of this study support the efficacy of atypical antipsychotic drugs in the treatment of Tourette's syndrome.

ADVERSE EFFECTS

Common Adverse Effects

Table III compares the relative adverse-effect profiles of the atypical antipsychotic drugs based on the results of receptor-affinity studies and clinical trials.[22] In the

Table III. Relative adverse effects of atypical antipsychotic drugs, on a scale from 1 = low to 5 = high.

Drug	Sedation	EPS	Anticholinergic Effect	Postural Hypotension	Weight Gain	Hyperprolactinemia
Haloperidol	1	5	0–1	1	2	5
Chlorpromazine	4	2	4	5	5	5
Clozapine	4	0–1	4	5	5	0–1
Olanzapine	2	1	2	1	5	1
Quetiapine	2	0–1	1	2	3	0–1
Risperidone	1	1–2	1	3	3	3
Ziprasidone	1–2	1	0	1	0–1	1

Adapted from Stimmel GL.[22]

4- to 6-week efficacy studies in hospitalized patients with an acute exacerbation of schizophrenia or schizoaffective disorder, the most common adverse effects occurring at least twice as often as with placebo were somnolence (14%), respiratory disorder (8%), and EPS (5%).[3] Somnolence was described as mild to moderate and transient, and rarely required discontinuation of therapy. Using the Simpson-Angus and Barnes Akathisia rating scales, no significant difference in the incidence of EPS was found between ziprasidone and placebo (see following section on EPS). Over 90% of events classified as respiratory disorders were initial transient cold symptoms or upper respiratory tract infections. Adverse effects commonly seen with some antipsychotic drugs that were not observed more often with ziprasidone than placebo included orthostatic hypotension (1.3%), weight gain (0.4%), and male sexual dysfunction (0.3%).[3]

In the 1-year maintenance trial,[3] the only adverse effect that occurred significantly more often with ziprasidone than with placebo was asthenia (5.5%) ($P < 0.05$). Although not statistically different from placebo, other treatment-emergent adverse events reported with ziprasidone in this study included insomnia (35.6% ziprasidone vs 32.0% placebo), akathisia (9.6% vs 5.3%), headache (6.8% vs 5.3%), and rash (5.9% vs 1.3%).

In the acute mania study,[16] all adverse effects were reported as either mild or moderate in severity. Seven percent of ziprasidone patients and 4% of placebo recipients discontinued treatment because of adverse effects. The most common adverse effects reported with ziprasidone compared with placebo included somnolence (37% vs 13%, respectively), dizziness (22% vs 10%), headache (21% vs 19%), nausea (11% vs 10%), akathisia (11% vs 6%), agitation (9% vs 13%), and insomnia (8% vs 10%). No clinically significant changes in blood pressure, heart rate, or ECG variables were observed.

In the study in patients with Tourette's syndrome,[17] the most common adverse effect was mild sedation. Sedation was present on at least 1 visit in 69% of ziprasidone patients and 45% of placebo recipients. In the ziprasidone group, sedation scores (based on a rating scale from 0 =

absent to 3 = severe) were 1.2 at baseline and varied from 1.1 to a high of 1.8 at week 6. One case of sedation (day 35, ziprasidone 40 mg/d) and 1 case of akathisia (day 43, ziprasidone 40 mg/d) were considered to be severe. Both cases resolved with dose reduction, and the patients continued in the study. No significant differences were noted in movement disorder ratings between the ziprasidone and placebo groups, nor were there any clinically significant changes in heart rate, standing or sitting blood pressure, or ECG parameters. The mean (±SD) change in body weight at week 8 was minimal and similar between groups (+0.7 ± 1.5 kg ziprasidone vs +0.8 ± 2.3 kg placebo).

In the short-term clinical trials, 5% of the ziprasidone groups and 4% of the placebo groups developed a rash. The overall incidence of rash in the Phase II and III trials was 4.5% with ziprasidone and 3.4% with placebo. Most of these patients continued treatment, with resolution of the rash, and no other evidence of systemic illness or hypereosinophilia was reported.[3]

Ziprasidone has a pregnancy category C rating.[5] No adequate controlled studies have been conducted in pregnant women.

Extrapyramidal Symptoms

In the short-term efficacy trials, movement disorders were assessed using both the Simpson-Angus and Barnes Akathisia rating scales. There were no statistically significant differences in mean decreases from baseline to study end point on either movement disorder scale between the ziprasidone and placebo groups.[3] Further information on the occurrence of EPS can be inferred from the use of benztropine for EPS and beta-blockers for akathisia. Pooled data from the short-term, fixed-dose trials showed similar numbers of ziprasidone and placebo recipients requiring adjunctive benztropine (22% vs 18%, respectively) or propranolol (7% vs 6%). During study 115, in contrast, 51% of patients receiving haloperidol required benztropine, and 19% required a beta-blocker.[3]

The 1-year data from study 303[15] showed no difference in the occurrence of EPS between the 3 doses of ziprasidone and placebo, with scores on both the Simpson-Angus and Barnes Akathisia rating scales decreasing from baseline. Anticholinergic and beta-blocker use was lower than before the study and similar in all groups.

In an early dose-finding study,[23] 4 doses of ziprasidone were compared with haloperidol 15 mg/d for 4 weeks. At the end of the trial, 67% of patients receiving haloperidol required benztropine, compared with 30% of patients receiving ziprasidone 40 mg/d and 15% of those receiving ziprasidone 160 mg/d. The majority of patients in the 4 ziprasidone groups had either no change or a decrease in Simpson-Angus rating scale scores at the end of the study, and no between-group differences were seen in the mean change in Simpson-Angus, Barnes Akathisia, or Abnormal Involuntary Movement Scale scores from baseline.

Weight Change

Whereas EPS were the common adverse effects of most concern with the older typical antipsychotic drugs, the common adverse effect of most concern with the atypical antipsychotic drugs is weight gain. Among these agents, clozapine and olanzapine cause the greatest weight gain, followed by queti-

apine and risperidone, whereas ziprasidone is weight neutral. In 1 study,[24] mean weight gains after 10 weeks of treatment were 4.5 kg with clozapine, 4 kg with olanzapine, 2 kg with quetiapine (after 8 weeks), 2 kg with risperidone, 1 kg with haloperidol, and 0.04 kg with ziprasidone.

Although the exact numbers vary among studies, the mean weight gain with olanzapine has been reported to be 4.5 kg after 10 weeks of therapy, 7 to 8 kg after 40 weeks, and 12 kg after 1 year.[25] Within the dose range from 5 to 20 mg/d, weight gain with olanzapine has not been shown to be dose dependent; the amount of weight gain appears to increase over time and plateau at ~36 to 40 weeks. In 1 report,[26] 43% of olanzapine-treated patients had no weight change or had gained <5 kg after 2 years of treatment, 23% gained 5 to 10 kg, and 34% gained >10 kg; 7% gained >20 kg.

Fewer data are available on weight gain with risperidone and quetiapine, but both commonly cause less weight gain than olanzapine. With risperidone, weight gain reaches a plateau of 2 to 3 kg at 8 to 12 weeks. Quetiapine has been associated with a weight gain of 3 kg in short-term trials and 2 to 5.6 kg with longer-term treatment.[25]

Given the growing concern about weight gain with the atypical antipsychotic drugs, ziprasidone has been carefully evaluated for its effect on weight. In the 4 short-term trials, ziprasidone was associated with a weight increase of 0.9 kg, compared with a 0.4-kg weight loss with placebo. Weight gain, defined as ≥7% of body weight, occurred in 9.8% of the ziprasidone groups and 4% of the placebo groups.[3] In the 1-year clinical trial, the mean weight loss was 1, 2, 3, and 3 kg in the ziprasidone 40-, 80-, and 160-mg groups and the placebo group, respectively.[3] In the switching studies,[3,21] patients switched from olanzapine to ziprasidone had a mean decrease in body weight of 1.8 kg after 6 weeks, whereas patients switched from risperidone to ziprasidone had a mean decrease in body weight of 0.8 kg over the same period.

Changes in Laboratory Values

Serum Prolactin Levels

Because of its D_2-receptor antagonism, ziprasidone has the potential to increase serum prolactin levels. In men, such increases may be associated with decreased libido, erectile dysfunction, and hypospermatogenesis, whereas women may experience disturbances in the menstrual cycle, galactorrhea, vaginal dryness, and sexual dysfunction.[27] Ziprasidone increases serum prolactin levels less frequently than do haloperidol and risperidone, and the elevations appear to be transient.[21]

In the Phase II and III clinical trials, prolactin levels >22 ng/mL occurred in 4% of placebo, 20% of ziprasidone, 46% of haloperidol, and 89% of risperidone groups. In women, at least 1 serum prolactin measurement >50 ng/mL occurred in 9% of ziprasidone, 27% of haloperidol, and 77% of risperidone groups.[3] In a 4-week clinical trial,[23] serum prolactin levels did not differ from baseline during treatment with ziprasidone 4, 10, 40, or 160 mg/d, whereas they increased by a factor of 5 with haloperidol. In the clinical trial in Tourette's syndrome,[17] 5 of 14 boys treated with ziprasidone had a transient increase in prolactin levels, which returned to normal by the end of the study. In the studies of therapeutic switching,[21]

mean serum prolactin levels decreased significantly ($P < 0.05$) when therapy was switched from conventional antipsychotic drugs to ziprasidone (from 18.3 to 14.6 ng/mL) and from risperidone to ziprasidone (from 37.4 to 11.3 ng/mL).

Serum Lipid Levels

Recently, attention has also focused on the potential for increases in serum lipid levels with atypical antipsychotic drugs. In a prospective study in 25 inpatients who received 12 weeks of olanzapine treatment (mean ± SD dose, 14 ± 4.4 mg),[28] fasting triglyceride levels increased a mean of 60 mg/dL, and weight increased by 5.4 kg. There was a strong correlation between weight gain and elevations in triglyceride levels. Fasting total cholesterol levels did not increase. In another study in 14 outpatients who received olanzapine 5 to 20 mg/d,[29] hypertriglyceridemia was found in 62% of patients and hypercholesterolemia in 85% of patients after 5 months of therapy. Interestingly, lipid levels were inversely correlated with serum concentrations of *N*-desmethylolanzapine. Clozapine and quetiapine have also been associated with increases in lipid levels, whereas there is some evidence that risperidone is associated with decreases in lipid levels.[3]

Total serum cholesterol and triglyceride levels decreased in both the short- and long-term clinical trials of ziprasidone.[3] In studies of a switch from risperidone, olanzapine, or typical antipsychotic agents to ziprasidone,[21] 6 weeks of ziprasidone led to significant decreases in cholesterol ($P < 0.001$) and triglyceride levels ($P = 0.018$) in patients switched from risperidone or olanzapine, independent of changes in weight.[30] Ziprasidone use was associated with reductions in nonfasting median triglyceride and total cholesterol levels in these patients.[21]

Plasma Glucose Levels and New-Onset Diabetes Mellitus

There have also been reports of elevations in plasma glucose levels with clozapine and olanzapine, including cases of new-onset diabetes mellitus[31] and diabetic ketoacidosis.[32] In the short-term clinical trials of ziprasidone, the incidence of abnormal elevations in random glucose levels was the same in the ziprasidone and placebo groups (8%), compared with 14% in the haloperidol group. In all Phase II and III clinical trials, elevations in random glucose levels occurred in 12% of placebo, 15% of ziprasidone, 15% of risperidone, and 16% of haloperidol groups.[3] There were no cases of treatment-emergent diabetes mellitus in the 3834 patients who received ziprasidone. In the switching studies,[21] there were no changes in plasma glucose levels over a 6-week trial of ziprasidone.[30]

Cardiovascular Effects

Orthostatic Hypotension

Although the receptor-affinity data indicate an alpha-adrenergic effect, ziprasidone has been associated with orthostatic hypotension in 1.3% of patients, compared with 0.4% of placebo recipients.[3] Relative lack of orthostatic hypotension allows rapid initiation and titration of ziprasidone dosing (similar to olanzapine dosing); this is not possible with risperidone or quetiapine.

QT-Interval Effect

Early concerns about ziprasidone's potential to prolong the QT interval led to

extensive evaluation of its cardiovascular effects. Of greatest concern is the possibility of torsades de pointes, a potentially fatal ventricular arrhythmia most commonly associated with a QTc interval (QT interval corrected for heart rate) of ≥500 to 700 milliseconds. In placebo-controlled trials, the highest recommended dose of ziprasidone (160 mg/d) increased the QTc interval by ~10 milliseconds compared with placebo. In the clinical trials, 2 of 3095 ziprasidone patients and 1 of 440 placebo recipients had a QTc interval exceeding the clinically relevant threshold of 500 milliseconds. Ziprasidone was not implicated in either of the 2 cases. One patient had a history of QTc-interval prolongation; the baseline QTc interval of 489 milliseconds increased to 503 milliseconds with ziprasidone therapy. In the other case, the QTc interval was 391 milliseconds at the end of ziprasidone therapy and increased to 518 and 593 milliseconds on 2 consecutive ECGs after the patient was switched to thioridazine.[3]

Due to the seriousness of this potential event, study 054 was conducted to investigate the effect of antipsychotic drugs on the QT interval.[3] The drug regimens were ziprasidone 160 mg/d, haloperidol 15 mg/d, thioridazine 300 mg/d, risperidone 6 to 8 mg/d, olanzapine 20 mg/d, and quetiapine 750 mg/d. Study drugs were given for 21 to 29 days, and 3 separate ECGs were obtained after steady state was achieved and drug concentrations were at their maximum. Bazett's formula was used to calculate QTc-interval prolongation.

Thioridazine produced the greatest prolongation (its labeling was subsequently modified to include a warning of dose-related QTc-interval prolongation), followed in descending order by ziprasidone, quetiapine, risperidone, olanzapine, and haloperidol. The QTc interval was ~14 milliseconds greater with thioridazine than with ziprasidone, whereas with ziprasidone it was 9 to 14 milliseconds greater than with quetiapine, risperidone, olanzapine, and haloperidol. Only patients receiving thioridazine (10%) or ziprasidone (3%) had an increase in QTc interval of ≥75 milliseconds at steady state. The 95% CIs for the observed changes with ziprasidone, quetiapine, and risperidone overlapped, whereas olanzapine and haloperidol caused less QTc-interval prolongation. In no case did any of the drugs, at maximal doses and maximum plasma concentrations, increase the QTc interval to >500 milliseconds.[3,5]

In a final phase of study 054, appropriate potent metabolic inhibitors were added to each study drug to assess the potential for drug interactions to worsen prolongation of the QTc interval. The potent CYP3A4 inhibitor ketoconazole was added to ziprasidone. Compared with steady-state concentrations before addition of the appropriate metabolic inhibitor, ziprasidone levels increased by 39%, compared with increases of >50% for risperidone, olanzapine, quetiapine, and haloperidol. There was no evidence of additional QTc-interval prolongation when ketoconazole was added to ziprasidone,[3,5] which can be explained by ziprasidone's primary metabolism via the nonsaturable aldehyde oxidase pathway.

Ziprasidone should not be given with other drugs that prolong the QT interval (eg, thioridazine, pimozide, quinidine, dofetilide, sotalol, moxifloxacin, sparfloxacin), nor should it be given to patients after a recent myocardial infarction or to those with uncompensated heart fail-

ure. Caution is also advised in the presence of other factors that could potentiate QT-interval prolongation, such as hypokalemia, hypomagnesemia, and bradycardia. Baseline serum potassium and magnesium levels should be obtained before initiating ziprasidone therapy, and serum electrolyte levels must be monitored periodically in patients receiving diuretics during ziprasidone therapy.[5]

OVERDOSE

In the 10 cases of ziprasidone overdose documented in premarketing trials, all 10 patients survived without sequelae. The most common symptoms were sedation and nausea. At the highest dose ingested (3240 mg), the QTc interval was 476 milliseconds at 4.5 hours after ingestion and 472 milliseconds at 6 hours. This patient's baseline pretreatment QTc interval ranged from 454 to 458 milliseconds.[3]

In another reported case of overdose,[33] a 50-year-old man ingested 3120 mg of ziprasidone and was seen 4.5 hours later in the emergency department. He was well oriented with no evidence of delirium, was a little drowsy, and had slightly slurred speech. His blood pressure showed a transient elevation (200/95 mm Hg) and returned to normal within 90 minutes. Four ECGs were obtained per hour, showing minimal and transient QT-interval prolongation (QT/QTc, 430/490) 6 hours postingestion that subsequently returned to normal. No arrhythmias occurred during the patient's 13-hour stay.

DOSING AND ADMINISTRATION

The effective adult dose of ziprasidone ranges from 40 to 160 mg/d, given in divided doses with food. All studies thus far have employed a twice-daily dosing schedule based solely on the drug's 6.6-hour elimination half-life. Ziprasidone should always be taken with food to maximize its bioavailability.

Based on the results of the short-term efficacy trials in patients with acute exacerbation of psychosis, ziprasidone should be initiated at 40 mg BID in such patients and titrated to a total daily dose of 160 mg as needed. A daily dose of 40 mg may be effective for maintenance therapy. Because only study 115 provided evidence that a daily dose of 40 mg may be effective in some patients, the package insert recommends an initial dose of 20 mg BID.[3]

INTRAMUSCULAR ZIPRASIDONE

A parenteral atypical antipsychotic drug would be expected to offer some benefits over parenteral haloperidol and lorazepam, the drugs most commonly used in the acute setting at present. An IM formulation of ziprasidone has been developed but is not yet approved for marketing. The optimal IM dose in a psychotic patient with acute agitation appears to be 10 to 20 mg, which may be repeated after 2 to 4 hours.[2] The elimination half-life of IM ziprasidone is 3 hours.

A double-blind, fixed-dose comparison of ziprasidone 2 and 10 mg IM was conducted in 117 acutely agitated psychotic inpatients.[34] Patients were given up to 4 injections in a 24-hour period, spaced at intervals of at least 2 hours. The 10-mg dose rapidly reduced symptoms of acute agitation without excessive sedation, and 57% of patients were classified as responders after the first 10-mg dose, compared with 30% after the first 2-mg dose. One patient receiving 10 mg developed moderate akathisia. Mild to moderate nau-

sea and somnolence were reported in 8% of the 10-mg group and 2% of the 2-mg group. No postural hypotension, tachycardia, ataxia, confusion, or behavioral disinhibition was reported. There was no evidence of ECG changes, with the mean QTc interval decreasing slightly from baseline (−3.7 milliseconds with 2 mg, −1.8 milliseconds with 10 mg). Another study compared ziprasidone 2 and 20 mg IM and found the 20-mg dose to be effective in 65% of patients, with 42% of patients requiring only 1 injection of 20 mg.[35]

CONCLUSIONS

Ziprasidone differs from other atypical antipsychotic drugs in several clinically important ways, although further experience is necessary to clarify the significance of these differences. Ziprasidone shares with these other drugs the common mechanism of 5-HT_{2A} and D_2 antagonism, but it also has 5-HT_{1A}–agonist activity and inhibits both serotonin and norepinephrine reuptake. The potential clinical benefits of anxiolytic and antidepressant effects have yet to be explored. Clinical trials have established ziprasidone's efficacy in treating both positive and negative symptoms of schizophrenia, acute exacerbation of symptoms in both schizophrenia and schizoaffective disorder, and prevention of relapse with long-term use. The limited evidence to date also suggests efficacy in the treatment of acute mania in patients with type 1 bipolar disorder and of Tourette's syndrome.

With a low incidence of sedative effects on initial dosing, low likelihood of producing EPS or postural hypotension, and no anticholinergic effect, ziprasidone has an advantageous adverse-effect profile relative to typical antipsychotic drugs, although it may cause transient hyperprolactinemia. Unlike most atypical antipsychotic drugs, ziprasidone is not associated with weight gain, hyperlipidemia, or elevated plasma glucose levels. It is more likely to increase the QTc interval than other atypical antipsychotic drugs and less likely to do so than thioridazine.

The results of clinical trials suggest that 80 to 160 mg/d is the most effective dose range for acute psychotic symptoms in patients with schizophrenia, schizoaffective disorder, or acute mania. A daily dose of 40 mg can be effective for maintenance therapy. Ziprasidone should always be taken with food to maximize its bioavailability. An IM formulation has been developed for the treatment of acute agitation in psychotic patients, although it has not yet been approved for marketing.

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