

Tolerability of Ziprasidone: An Expanding Perspective

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Although atypical antipsychotic agents have improved the management of patients with schizophrenia, their utility has been hindered by some limitations, including significant weight gain, glucose metabolism disturbances, and increases in total and low-density lipoprotein cholesterol and triglyceride levels. In addition to its low liability for movement disorders and its favorable tolerability record in short- and long-term clinical trials, ziprasidone is associated with a favorable metabolic safety profile (in terms of its effect on plasma lipid and glucose levels) and a negligible effect on weight. The limited effect of ziprasidone on the corrected QT interval (QTc) has also been well characterized, and experience to date has not demonstrated any increased risk of clinical events attributable to QTc prolongation. This review of pharmacokinetic and clinical trials of ziprasidone versus placebo and active comparators focuses on the safety and tolerability of both the intramuscular and oral formulations.

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The introduction of atypical antipsychotic agents, which are at least as effective as older conventional agents but with less liability for extrapyramidal symptoms (EPS),¹ has considerably improved the management of patients with schizophrenia. However, the utility of some atypical agents is limited by tolerability problems other than movement disorders. Olanzapine, clozapine, and, to a lesser extent, risperidone have been associated with clinically important weight gain.² More recently, increased risk of glucose metabolism disturbance has been reported in patients treated with olanzapine, clozapine, or risperidone,³ and elevated risk of new-onset diabetes has been reported in patients receiving olanzapine.⁴ The association between olanzapine and hyperglycemia (including ketosis or metabolic acidosis) or diabetes has been supported by data on the time of onset of these complications and the withdrawal of drug and rechallenge.⁵ Olanzapine has also been associated with significant increases in cholesterol⁶ and triglyceride levels.⁷ Overweight, diabetes, and elevated cholesterol levels are well-recognized risk factors for cardiovascular disease.⁸

Another limitation of atypical antipsychotics has been the lack of an intramuscular (IM) formulation. Consequently, clinicians continue to rely on IM formulations of

conventional agents when agitation or other manifestations of acute psychosis preclude oral administration of atypical antipsychotics. Thus, there is a need for effective, well-tolerated atypical antipsychotics for the short- and long-term management of schizophrenia.

Ziprasidone, currently the only atypical antipsychotic agent available in both IM and oral formulations, has been shown to rapidly and substantially reduce symptoms of acute agitation in patients with psychosis and to be effective in reducing overall psychopathology in the long-term treatment of stable outpatients with schizophrenia while maintaining a favorable tolerability profile. The tolerability profiles of IM and oral ziprasidone are reviewed here.

OVERALL TOLERABILITY

Short- and long-term clinical trial data show that IM and oral formulations of ziprasidone are generally well tolerated. As with other atypical antipsychotics, ziprasidone is associated with a low risk of movement disorders compared with conventional agents and has exhibited an incidence of EPS comparable to placebo over 1 year. Ziprasidone also is associated with a favorable metabolic safety profile (i.e., minimal effects on plasma lipid and glucose levels) and a weight-neutral profile that distinguish it from other atypical agents. The modest prolongation of the corrected QT interval (QTc) associated with ziprasidone has been well characterized, and clinical events attributable to QTc prolongation have not been observed.

Oral Ziprasidone

Oral ziprasidone in daily doses ranging from 40 to 160 mg has been generally well tolerated in short-term^{9–11}

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Table 1. Incidence of Treatment-Emergent Adverse Events ($\geq 5\%$ and more frequent on ziprasidone than on placebo) in Short-Term, Fixed-Dose, Placebo-Controlled Trials^a

Adverse Event	Ziprasidone (N = 702)	Placebo (N = 273)
Somnolence	14.4*	6.6
Nausea	9.5	7.0
Constipation	9.3	8.4
Akathisia	8.4	7.0
Dyspepsia	8.1	7.0
Dizziness	7.8	5.9
Respiratory disorder	7.7*	3.3

^aData from Pfizer Inc.¹¹ Values represent the percentage of patients who experienced the adverse event. The mean duration of treatment was 28.4 days for ziprasidone and 24.6 days for placebo.

* $p < .05$ vs. placebo.

and long-term^{11,12} clinical trials in patients with schizophrenia or schizoaffective disorder, with an overall incidence of adverse events similar to that of placebo.^{9,10,12}

Short-term studies. Adverse events occurring more frequently with ziprasidone versus placebo in short-term studies ($\geq 5\%$ of patients) include somnolence, gastrointestinal effects, akathisia, dizziness, and respiratory disorders, with differences being statistically significant ($p < .05$) for somnolence and respiratory disorders (Table 1).¹¹ The discontinuation rate for treatment-emergent adverse events in short-term studies was 4.1% (29/702) for ziprasidone-treated patients and 2.2% (6/273) for placebo-treated patients.¹¹

Long-term studies. In a 28-week trial comparing ziprasidone with haloperidol in 301 randomized outpatients with stable schizophrenia, Hirsch and colleagues¹³ reported treatment-emergent adverse events in 77% of ziprasidone- and 85% of haloperidol-treated patients; all adverse events were considered generally mild or moderate in severity. The most common adverse events reported in both study groups included insomnia and somnolence. Twice as many haloperidol-treated patients (16%) as ziprasidone-treated patients (8%) discontinued therapy because of adverse events.

In the 1-year, placebo-controlled maintenance trial of ziprasidone in 278 evaluable patients with chronic schizophrenia by Arató and colleagues,¹² the frequency of individual adverse events was generally similar between evaluable ziprasidone- and placebo-treated patients. A smaller proportion of ziprasidone-treated patients than placebo-treated patients discontinued therapy because of adverse events (8.7% and 14.7%, respectively).^{11,12}

Common adverse events: oral ziprasidone versus haloperidol, olanzapine, or risperidone. Comparative trials of oral ziprasidone versus oral haloperidol, olanzapine, or risperidone in patients with schizophrenia or schizoaffective disorder show that insomnia, somnolence, akathisia, and headache are among the most common treatment-emergent adverse events for these agents. Table 2 lists several of the most common treatment-

emergent adverse events occurring in $\geq 5\%$ of randomized patients in a 28-week study versus haloperidol,¹³ a 6-week study versus olanzapine,¹⁴ and an 8-week study versus risperidone.¹⁵

IM Ziprasidone and Sequential IM/Oral Treatment

Intramuscular ziprasidone in doses of 2 mg (control dose) to 20 mg administered up to 4 times daily was generally well tolerated in 3 fixed-dose and 2 flexible-dose studies in a total of 921 patients with acute psychosis.¹⁶ The most common adverse events associated with IM ziprasidone 10 or 20 mg (up to 3 days) in these 5 studies were headache, nausea, dizziness, insomnia, anxiety, and injection site pain, with most treatment-emergent adverse events in all studies being of mild-to-moderate intensity. Figure 1 shows all-cause treatment-emergent adverse events (incidence $\geq 5\%$) from the 6-week, flexible-dose, rater-blinded study of sequential IM/oral ziprasidone and haloperidol in agitated patients with schizophrenia or schizoaffective disorder (N = 567).^{16,17} The percentage of patients discontinuing therapy because of treatment-emergent adverse events in all 5 studies ranged from 1.1% to 6.1% in the ziprasidone groups.¹⁶

Three of the above studies—the two 7-day, open-label, randomized studies (1 fixed-dose and 1 flexible-dose)¹⁸ and the 6-week, rater-blinded, flexible-dose study—evaluated the tolerability and efficacy of ziprasidone (N = 725) and haloperidol (N = 280) during the transition from IM to oral therapy.^{17,18} In the two 7-day trials, fewer ziprasidone- than haloperidol-treated patients discontinued therapy for any reason (3.7% and 7.5%, respectively), whereas discontinuations because of adverse events were comparable in the 2 groups (1.5% and 0.7% for ziprasidone and haloperidol, respectively).¹⁸ During the first 2 weeks of the 6-week trial, rates of discontinuation because of adverse events were 4.2% with ziprasidone and 9.6% with haloperidol.¹⁸ Rates of discontinuation from lack of efficacy were low in both groups (3.5% and 1.5% for ziprasidone and haloperidol, respectively).

MOVEMENT DISORDERS

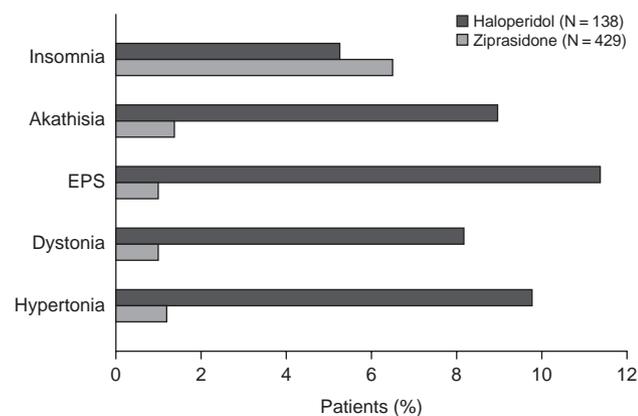
Oral Ziprasidone: Placebo-Controlled Studies

In short-term trials, the incidences of movement disorders, as assessed by the Simpson-Angus Scale (SAS) and the Barnes Akathisia Scale (BAS), have not differed significantly between oral ziprasidone and placebo.¹¹ Similar to the results in short-term placebo-controlled trials, in the 1-year maintenance trial by Arató and colleagues,¹² scores on the various movement disorder scales (SAS, BAS, and Abnormal Involuntary Movement Scale [AIMS]) were comparable between ziprasidone- and placebo-treated groups (intent-to-treat [ITT] population, last observation carried forward [LOCF]) in 294 randomized patients with schizophrenia.

Table 2. Most Common Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of All Randomized Patients in 3 Trials^a

Adverse Event	28-Week Study ¹³		6-Week Study ¹⁴		8-Week Study ¹⁵			
	Ziprasidone (N = 148)	Haloperidol (N = 153)	Adverse Event	Ziprasidone (N = 136)	Olanzapine (N = 133)	Adverse Event	Ziprasidone (N = 149)	Risperidone (N = 147)
Insomnia	16	18	Somnolence	16.9	15.0	Insomnia	24.8	12.2
Somnolence	14	9	EPS	9.6	4.5	Somnolence	20.8	17.7
Akathisia	5	16	Dizziness	7.4	6.0	Agitation	16.1	13.6
Tremor	6	10	Akathisia	6.6	3.0	Headache	15.4	18.4
Headache	6	11	Nausea	6.6	2.3	Akathisia	12.8	20.4
Vomiting	11	6	Weight gain	0.7	6.0	Tremor	10.1	9.5

^aData from Hirsch et al.,¹³ Simpson et al.,¹⁴ and Addington et al.¹⁵
Abbreviation: EPS = extrapyramidal symptoms.

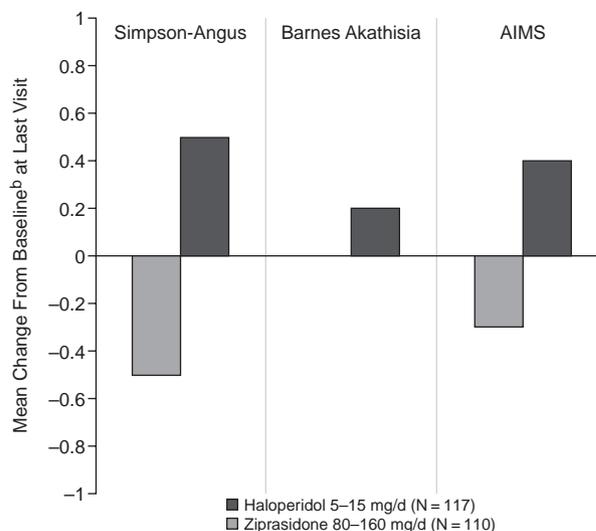
Figure 1. Treatment-Emergent Adverse Events With an Incidence $\geq 5\%$ (all causes): Ziprasidone Versus Haloperidol^a

^aReproduced with permission from Zimbroff et al.¹⁶
Abbreviation: EPS = extrapyramidal symptoms.

Oral Ziprasidone: Comparative Studies

Ziprasidone versus olanzapine 6-month continuation study. Ziprasidone 40 to 80 mg b.i.d. was compared with olanzapine 5 to 15 mg q.d. in a 6-week, double-blind, multicenter trial in 269 inpatients with acute schizophrenia or schizoaffective disorder.^{14,19} At week 6, patients in both the ziprasidone and olanzapine groups achieved substantial reductions in Extrapyramidal Symptoms Rating Scale (ESRS) total scores (-0.6 and -0.8 , respectively), as well as reductions in BAS and AIMS improvement scores; however, these reductions were not statistically significant. Improvements in movement disorder measures continued throughout the 6-month continuation study, with continued decreases in mean BAS total, AIMS total, and AIMS global severity scores for both drugs.²⁰

Ziprasidone versus haloperidol 28-week study. In the 28-week outpatient trial by Hirsch and colleagues,¹³ which compared oral ziprasidone and haloperidol in outpatients with stable schizophrenia, the emergence of any movement disorder was reported in more patients in the haloperidol group (41%) than in the ziprasidone group (15%), as was the discontinuation of treatment because of movement disorders (7% and 1% for haloperidol and zipra-

Figure 2. Changes in Movement Disorder Severity Rating Scales in a 28-Week Comparison Trial of Ziprasidone Versus Haloperidol (all patients LOCF)^a

^aReproduced with permission from Hirsch et al.¹³

^bMean baseline scores on the Simpson-Angus Scale were ziprasidone = 3.5, haloperidol = 3.2; on the Barnes Akathisia Scale, for both drugs were 0.5; and on the AIMS were ziprasidone = 1.2, haloperidol = 1.0.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, LOCF = last observation carried forward.

done groups, respectively). These between-group differences were also reflected in score changes on the movement disorder assessment scales (Figure 2).¹³

Ziprasidone versus risperidone 52-week continuation study. In a 52-week continuation trial by Addington and colleagues,²¹ oral ziprasidone was associated with a lower incidence of movement disorders than was risperidone. Findings were based on the Movement Disorder Burden Score (MDBS), which quantifies overall discomfort from treatment-emergent dystonia, parkinsonism, tardive dyskinesia, and akathisia. At the core-study endpoint (8 weeks), MDBS scores were significantly lower for all patients receiving ziprasidone (0.20 [N = 149]) than for those receiving risperidone (0.35 [N = 147]; $p < .05$ vs. ziprasidone). Ziprasidone patients continued to show more

favorable results on MDDBS at the 52-week endpoint (0.27 vs. 0.39), but the results were not statistically significant. The percentage of patients who reported movement disorders as adverse events and the percentage of days with movement disorders were also lower in patients receiving ziprasidone than in patients receiving risperidone at both the core study and continuation study endpoints, but this difference was not statistically significant.

Six-week, open-label switch trials. Three 6-week, open-label switch trials (from olanzapine [N = 104], risperidone [N = 58], or typical antipsychotic agents [N = 108] to oral flexible-dose ziprasidone [40–160 mg/day]) showed significantly improved mean SAS scores in patients switched from conventional agents (mean change = 52%; $p < .01$) or risperidone (mean change = 44%; $p < .01$); however, no significant mean change in SAS scores occurred in patients switched from olanzapine (mean change = 5.2%; $p = .74$).²²

IM Ziprasidone and Sequential IM/Oral Treatment

In the retrospective analysis of the 5 IM or sequential IM/oral dosing trials mentioned above,¹⁶ IM ziprasidone displayed a favorable safety profile and was well tolerated at doses up to 80 mg/day, with all IM and oral doses tested showing a low movement disorder liability.

IM ziprasidone. Two 24-hour studies were included in the 5-trial analysis. One compared 10-mg doses of IM ziprasidone (up to 4 injections daily) with subtherapeutic 2-mg (control) doses in 117 patients with agitation and psychosis²³; the other trial, very similar in design, compared 2- and 20-mg doses in 79 similar patients.²⁴ No patients experienced dystonia, akinesia, hypertonia, oculogyric crisis, dyskinesia, tremor, twitching, or cogwheel rigidity.^{23,24} Mild EPS was reported in 2 patients receiving IM ziprasidone 2 mg and moderate akathisia was reported in 1 patient receiving IM ziprasidone 10 mg.

IM ziprasidone versus IM haloperidol. In a comparison of fixed-dose IM ziprasidone and flexible-dose IM haloperidol in 306 patients with psychotic disorder, a lower incidence of treatment-related EPS, dystonia, and akathisia was associated with ziprasidone than with haloperidol.^{16,25} The ziprasidone groups clearly had lower rates of movement disorders compared with the haloperidol group, as evidenced by SAS and BAS scores.¹⁶ Mean changes from baseline to endpoint in SAS scores for patients receiving IM ziprasidone 5, 10, and 20 mg q.i.d. were -0.45, -0.11, and -0.18, respectively, compared with 0.15 for patients given IM haloperidol. Similar results were seen for the BAS parameter, with scores ranging from -0.09 to 0.02 for the ziprasidone groups and 0.19 for the haloperidol group.

Sequential IM/oral ziprasidone versus sequential IM/oral haloperidol. Intramuscular ziprasidone demonstrated a lower incidence of movement disorders compared with IM haloperidol in a 7-day, open-label, randomized, multicenter study in 132 patients with acute agitation asso-

ciated with a psychotic disorder.²⁶ The ziprasidone group (N = 90) received an initial IM dose of 10 mg followed by IM doses of 5 to 20 mg up to 4 times daily for 3 days, followed by oral ziprasidone (80–200 mg/day) to day 7. The haloperidol group (N = 42) received IM haloperidol 2.5 to 10 mg up to 4 times daily for 3 days, followed by oral haloperidol (10–80 mg/day) to day 7. The respective incidences of various movement disorders after 3 days of IM treatment with ziprasidone or haloperidol were as follows: EPS, 0.0% and 21.4%; hypertonia, 0.0% and 7.1%; dystonia, 1.1% and 7.1%; tremor, 1.1% and 2.4%; and akathisia, 2.2% and 0%. Also, mean changes from baseline in SAS and BAS scores favored ziprasidone over haloperidol. Ziprasidone produced small mean decreases in SAS and BAS scores at the end of IM treatment (-0.61 and -0.03, respectively) and at study endpoint (-1.09 and -0.10, respectively). Conversely, haloperidol produced mean increases in these parameters at IM treatment endpoint (SAS, 3.80; BAS, 0.34) and study endpoint (SAS, 6.0; BAS, 0.80).

A 6-week, rater-blinded trial comparing sequential IM/oral ziprasidone with IM/oral haloperidol in 567 inpatients with acute exacerbation of schizophrenia or schizoaffective disorder rated movement disorder severity using ESRS and BAS.¹⁷ At both the IM treatment phase (1 to 3 days) and study endpoints, there were significant ($p < .001$) differences favoring ziprasidone in mean changes from baseline in ESRS (Parkinson's, dystonia, and dyskinesia) and BAS total scores.

WEIGHT GAIN AND METABOLIC EFFECTS

Ziprasidone has been shown to have a negligible effect on body weight in several short-term and long-term clinical trials.

Oral Ziprasidone: Weight Change in Placebo-Controlled Trials

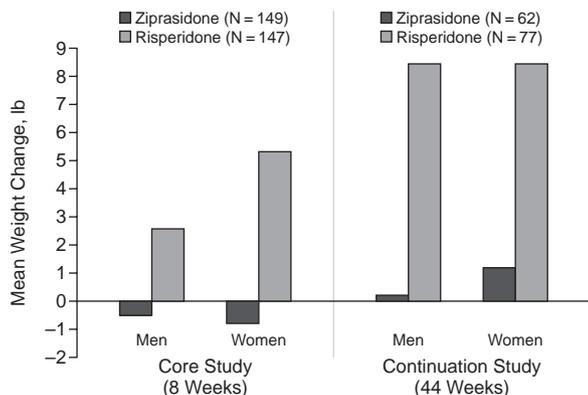
In studies lasting 4 to 6 weeks in a total of 702 patients, ziprasidone was associated with weight gain in 0.4% of patients and weight loss in an equal percentage of patients.²⁷ In comparisons with placebo, ziprasidone was associated with similar median weight gains of 0.5 to 1 kg (1.1 to 2.2 lb).²⁷

The 1-year, placebo-controlled maintenance trial by Arató and colleagues¹² showed oral ziprasidone was associated with a small mean reduction in body weight—i.e., a 3.6- and 2.7-, 3.2-, and 2.9-kg mean reduction from baseline in the placebo and ziprasidone 40-, 80-, and 160-mg/day groups, respectively.

Oral Ziprasidone: Weight Change in Comparative Studies

Ziprasidone versus olanzapine 6-week core and 6-month continuation studies. In a 6-week trial that compared oral ziprasidone (up to 80 mg b.i.d.; N = 136) or olan-

Figure 3. Mean Weight Increase in an 8-Week Trial of Ziprasidone and Risperidone and a 44-Week Continuation Study (all patients)^a



^aReproduced with permission from Addington et al.²¹

ziprasidone (up to 15 mg q.d.; N = 133) in inpatients with acute exacerbation of schizophrenia or schizoaffective disorder, olanzapine-treated patients experienced a 3.2-kg (7.2-lb) increase in weight compared with a 0.54-kg (1.2-lb) increase in ziprasidone-treated patients ($p < .0001$).¹⁹

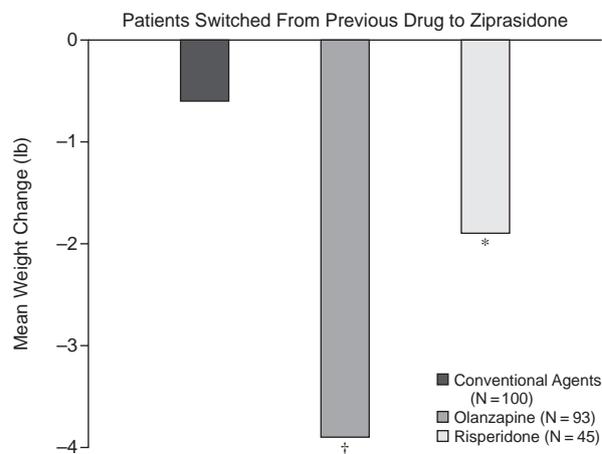
Patients who successfully completed this 6-week trial were entered into a 6-month continuation study (N = 133) and continued on the same dosage of medication based on investigator clinical assessment.²⁰ Patients treated with olanzapine had a 4.7-kg (10.4-lb) increase in weight from baseline of the 6-week core study versus a statistically significant 1.3-kg (2.9-lb) decrease in weight in ziprasidone-treated patients ($p < .001$). Body mass index also increased with olanzapine (1.251) and significantly decreased with ziprasidone (-0.686 ; $p = .001$).

Ziprasidone versus haloperidol 28-week study. The 28-week study of flexible-dose ziprasidone (80–160 mg/day) and haloperidol (5–15 mg/day) by Hirsch and colleagues¹³ found small and similar mean changes in weight from baseline to endpoint (+ 0.31 kg [0.68 lb] for ziprasidone and + 0.22 kg [0.48 lb] for haloperidol).

Ziprasidone versus risperidone 52-week continuation study. The 1-year, double-blind comparison with risperidone by Addington and colleagues²¹ demonstrated no weight gain in patients given ziprasidone 40 to 80 mg b.i.d. in the 8-week core study and minimal weight gain in ziprasidone-treated patients in the 44-week continuation study (Figure 3). In contrast, patients given risperidone 3, 4, or 5 mg b.i.d. experienced weight gain (ranging from 1.4–4.0 kg [\sim 3–9 lb]) in both study phases.

Six-week, open-label switch studies. In the three 6-week, open-label switch trials mentioned above,^{22,28} there were significant reductions in mean body weight in patients switched to ziprasidone from olanzapine (-1.8 kg [-3.9 lb]; $p < .0001$) or risperidone (-0.9 kg [-1.9 lb];

Figure 4. Weight Changes in Patients Switched to Ziprasidone From Conventional Antipsychotics, Olanzapine, or Risperidone in Three 6-Week, Open-Label Studies^a



^aReproduced with permission from Romano et al.²⁸

* $p < .05$ vs. risperidone.

† $p < .0001$ vs. olanzapine.

$p < .05$), and a modest trend toward a decrease in weight in those switched from conventional antipsychotics (-0.3 kg [-0.6 lb]; $p = \text{NS}$) (Figure 4).

Oral Ziprasidone: Lipid Profiles

Ziprasidone has been shown to have a neutral or favorable effect on patients' serum lipid profile in placebo-controlled, active-comparator, and open-label switch studies.

Short-term phase 2/3 studies. In 4 short-term (4–6 weeks), fixed-dose, placebo-controlled trials ziprasidone and placebo produced small median decreases in total cholesterol and triglyceride levels.¹¹

Comparative studies: ziprasidone versus 5 antipsychotics. In an open-label, parallel-group, short-term trial (14–25 days' treatment) in 164 inpatients with psychosis, the overall effect on the fasting lipid profile was favorable for ziprasidone compared with that for risperidone, olanzapine, quetiapine, thioridazine, and haloperidol treatments, as demonstrated by marked median decreases from baseline in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels (Table 3).¹¹

Comparative studies: ziprasidone versus olanzapine 6-week core and 6-month continuation studies. In the comparative 6-month continuation study versus olanzapine mentioned above,^{19,20} ziprasidone was associated with slight decreases from baseline in fasting total cholesterol, LDL cholesterol, or triglyceride levels at the 6-week endpoint¹⁹ and with no significant changes in fasting total or LDL cholesterol levels at 6 months.²⁰ In contrast, fasting total cholesterol level in the olanzapine-treated group increased by a median 20 mg/dL at 6 weeks ($p < .0001$ vs.

Table 3. Change From Baseline in Fasting Lipid Values With 6 Antipsychotic Agents Given for 14 to 25 Days^a

Lipids (mg/dL)	Ziprasidone (N = 33–34)	Risperidone (N = 25–28)	Olanzapine (N = 26–27)	Quetiapine (N = 28–29)	Thioridazine (N = 29–31)	Haloperidol (N = 29)
Total cholesterol						
Median change	-14.5‡	-3.0	4.0	5.0	21.0‡	-22.0‡
Median % change	-7.5‡	-1.6	2.1	2.4	13.7‡	-11.5‡
LDL cholesterol						
Median change	-11.0	9.0	1.5	-0.5	20.0‡	-14.0‡
Median % change	-8.5	6.5	1.1	-0.3	18.6‡	-10.5‡
HDL cholesterol						
Median change	0.0	-2.0	-2.0	-3.0	1.5	-3.0†
Median % change	0.0	-4.9	-4.6	-8.6	3.0	-6.0*
Triglycerides						
Median change	-37.0‡	-17.0	43.0‡	25.0‡	9.0	-18.0†
Median % change	-28.0‡	-6.7	31.0‡	18.3‡	7.9	-18.0†
Total cholesterol/HDL ratio						
Median change	-0.33†	0.31	0.28	0.48†	0.41†	-0.22*
Median % change	-7.5†	5.9*	5.4*	10.8†	12.4‡	-7.0*

^aData from Pfizer Inc.¹¹ Not every patient underwent measurements of each lipid fraction or triglycerides. Wilcoxon signed rank test on change from baseline values versus 0 and percent change from baseline values versus 0: *p < .05, †p < .01, ‡p < .001. Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

baseline; p < .0005 vs. ziprasidone)¹⁹ and by 13 mg/dL at 6 months (p < .05 vs. core-study baseline; p = NS vs. ziprasidone).²⁰ Similarly, fasting triglyceride levels increased by a median 26 mg/dL at 6 weeks in olanzapine-treated patients (p < .0005 vs. baseline; p < .005 vs. ziprasidone).¹⁹ Levels of fasting LDL cholesterol increased in the olanzapine group by a median 13 mg/dL at 6 weeks (p < .0001 vs. baseline; p < .0005 vs. ziprasidone) and a median 17 mg/dL at 6 months (p < .05 vs. baseline).^{19,20}

Six-week, open-label switch studies. In the short-term, open-label switch trials, statistically significant reductions in median nonfasting total cholesterol and triglyceride levels were observed in patients switched to ziprasidone from olanzapine (-17 mg/dL and -50 mg/dL, respectively; p < .0001 for each) or from risperidone (-11.5 mg/dL [p = .001] and -29 mg/dL [p < .01], respectively).^{22,28}

Oral Ziprasidone: Glucose Metabolism

Ziprasidone has a neutral effect on glucose metabolism and insulin resistance, as indicated by pooled data from trials in the ziprasidone phase 2/3 clinical program¹¹ and data from the continuation study versus olanzapine.^{19,20}

Pooled data from phase 2/3 clinical studies. In the phase 2/3 pooled analysis, there were no cases of treatment-emergent diabetes mellitus in 3834 patients receiving ziprasidone, 1 case (0.1%) in 686 patients receiving haloperidol and 2 cases (0.6%) in 322 patients receiving risperidone.¹¹ The overall incidence of clinically significant elevations (> 1.2× the upper limit of normal) in random plasma glucose levels in patients in short-term trials was similar across treatment groups.¹¹

Comparative studies: ziprasidone versus olanzapine 6-month continuation study. In the 6-month continuation study versus olanzapine,^{19,20} ziprasidone was not associated with significant increases from baseline in fasting plasma insulin or fasting plasma glucose levels at either

the 6-week or 6-month endpoint. Moreover, ziprasidone was not associated with significantly increased insulin resistance at 6 weeks (measured by the homeostasis model assessment of insulin resistance index statistic).¹⁹ In the olanzapine group, however, median fasting insulin levels had increased significantly from baseline at 6 weeks (3.3 μU/mL; p < .0001)¹⁹ and at 6 months (2.0 μU/mL; p < .01)²⁰; median fasting glucose levels had increased at 6 months (5 mg/dL; p = .05 vs. baseline)²⁰ and median fasting insulin resistance had increased at 6 weeks (p < .0001 vs. baseline).¹⁹

CARDIAC PROFILE

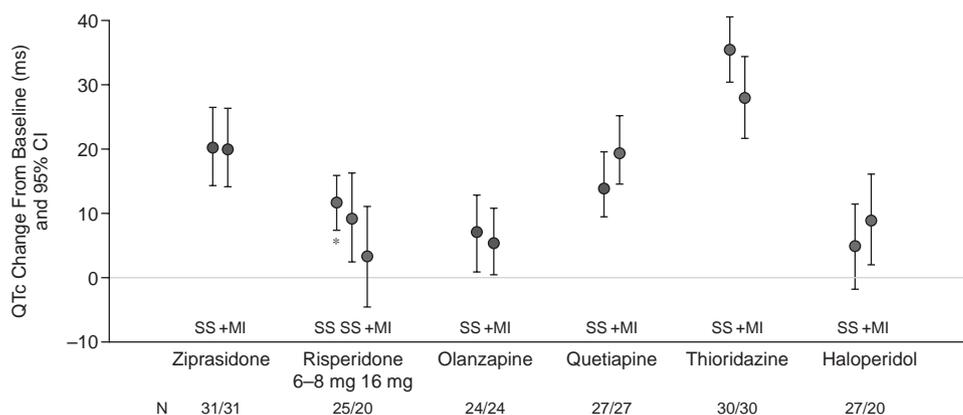
Oral Ziprasidone

A number of antipsychotic agents have been shown to prolong the QTc, either at usual doses (e.g., thioridazine, chlorpromazine, haloperidol, pimozide) or in overdose (e.g., risperidone and quetiapine).²⁹ The changes in QTc associated with ziprasidone have been well characterized in an extensive analysis of phase 2 and phase 3 clinical trials involving 4571 patients receiving up to 200 mg/day.^{11,30}

Placebo-controlled trials. In short-term, placebo-controlled trials, the incidence of postural hypotension was 1% in patients who were treated with oral ziprasidone versus 0% in those receiving placebo.³¹ Tachycardia occurred in 2% of the ziprasidone group and in 1% of the placebo group. In short-term, fixed-dose IM trials, 20-mg ziprasidone had a 5% rate of postural hypotension and a 2% rate of bradycardia.³¹

In the 1-year placebo-controlled study by Arató and colleagues,¹² no postural hypotension was reported and the incidence of tachycardia was ≤ 3% in the ziprasidone and placebo groups. There were no significant electrocardiographic (ECG) abnormalities with ziprasidone treatment, and QTc changes were similar between ziprasidone

Figure 5. Mean Changes, With 95% CI, in QTc (Bazett Correction) With Ziprasidone and Other Antipsychotics in Absence or Presence of Metabolic Inhibitors^a



^aReproduced with permission from Pfizer Inc.¹¹

*Represents 6–8 mg.

Abbreviations: CI = confidence interval, +MI = with metabolic inhibitor, N = number of patients (completers) included in period 3/period 4 analyses, SS = steady state.

and placebo patients, with no patient experiencing a QTc ≥ 500 ms.

Pooled data from phase 2/3 clinical studies. Pooled data from short-term trials in hospitalized patients on fixed doses of ziprasidone (≤ 200 mg/day) revealed a mean QTc prolongation of 5.9 to 9.7 ms (Bazett correction).³⁰ A QTc ≥ 500 ms (considered the clinically relevant threshold for increased risk of arrhythmia) was observed in 0.06% (2/3095) of ziprasidone recipients compared with 0.23% (1/440) of placebo recipients. Prolongation > 60 ms occurred in 2.6% and 1.2% of tracings from ziprasidone- and placebo-treated patients, respectively.³⁰ Interestingly, the QTc prior to treatment with ziprasidone does not appear to predict observed changes in the QTc during treatment (data on file; Pfizer Inc, New York, N.Y.). Of note, in 1733 patient-years of study, ziprasidone was not associated with an excess of syncope or sudden death compared with placebo or comparator antipsychotics, and there were no reports of torsade de pointes.³⁰

Effect on QTc: ziprasidone versus conventional and atypical antipsychotics. In a study specifically designed to assess the effect on QTc prolongation, ziprasidone was compared with thioridazine, quetiapine, olanzapine, risperidone, and haloperidol in 164 patients.³⁰ ECGs were performed at times of peak plasma drug concentrations, when the effect on QTc was predicted to be maximal. The mean change in QTc (Bazett correction) was 20.3 ms in ziprasidone recipients (N = 31), 11.6 ms in risperidone recipients (N = 20), 6.8 ms in olanzapine recipients (N = 24), 14.5 ms in quetiapine recipients (N = 27), 35.6 ms in thioridazine recipients (N = 30), and 4.7 ms in haloperidol recipients (N = 20) (Figure 5).¹¹ Coadministration of a metabolic inhibitor (ketoconazole) did not increase the mean change in QTc for ziprasidone despite an

increase in plasma concentrations of ziprasidone and its main metabolites (Figure 5).¹¹ No patient in the study had a QTc ≥ 500 ms, either with or without coadministration of a metabolic inhibitor.³⁰

High-dose ziprasidone and QTc. A recent study examined the QTc effects of oral ziprasidone and haloperidol at 3 steady-state dosage levels in patients with schizophrenia or schizoaffective disorder.³² Twenty-nine patients were assigned to treatment with escalating dosages of ziprasidone (40, 160, and 320 mg/day) and 30 patients to escalating dosages of haloperidol (2.5, 15, and 30 mg/day) over 16 days. Mean changes from baseline in QTc in ziprasidone patients were +4.5 ms, +19.5 ms, and +22.5 ms for the 40-mg/day, 160-mg/day, and 320-mg/day dosages, respectively. Corresponding QTc changes for haloperidol patients were -1.2 ms, +6.6 ms, and +7.2 ms for the 2.5-mg/day, 15-mg/day, and 30-mg/day dosages, respectively. There was a marginal increase of 3 ms in mean QTc at twice the recommended ziprasidone dosage (320 mg/day) relative to the change at 160 mg/day. No patient experienced a QTc ≥ 450 ms or an increase from baseline ≥ 75 ms.

IM Ziprasidone

Phase 2/3 studies. In fixed- and flexible-dose phase 2/3 clinical trials QTc data were derived from ECGs recorded randomly relative to IM dosing. For IM doses ≥ 5 mg, mean change in QTc was 0.1 ms, with no relation observed between QTc change and ziprasidone doses of 2 to 20 mg in fixed-dose trials.³³

In the IM ziprasidone clinical program, a total of 2136 ziprasidone serum samples were collected from 425 individuals administered IM doses while participating in 9 clinical trials.³³ The highest ziprasidone concentrations

were seen within the first 2 hours postdose, as evidenced by 1362 serum samples collected within 6 hours of receiving ≥ 5 mg IM ziprasidone. Data from 86 samples from ziprasidone-treated patients and 24 samples from haloperidol-treated patients revealed similar QTc changes within 6 hours of IM dosing. Mean change in QTc measured within the first 2 hours of IM dosing was 3.4 ms (95% CI = -1.9 to 8.6) for 51 patients receiving ziprasidone ≥ 5 mg and 5.6 ms (95% CI = -5.2 to 16.4) for 13 patients receiving haloperidol.

The ziprasidone concentrations seen in the IM clinical trial program lie within the range of those observed in the oral program. QTc changes directly observed near the time of maximum serum concentration (C_{max}) post-IM dosing suggest that the pharmacodynamic QTc profile for IM ziprasidone does not differ meaningfully from that of the oral drug.³³

Effect on QTc: IM ziprasidone versus IM haloperidol.

The effects of IM ziprasidone versus IM haloperidol on QTc have been characterized in a single-blind, randomized trial in which 58 patients received 2 injections of ziprasidone (20 mg followed by 30 mg) or haloperidol (7.5 mg then 10 mg), administered 4 hours apart.³⁴ Mean QTc increase was 4.6 ms for ziprasidone and 6.0 ms for haloperidol after injection 1, and 12.8 ms for ziprasidone and 14.7 ms for haloperidol after injection 2. No subject had a QTc ≥ 500 ms.

Cardiac monitoring. The current data regarding ziprasidone-associated changes in QTc do not support routine pretreatment cardiac monitoring.²⁹ Caution is warranted, however, in certain at-risk populations. For example, ziprasidone should be avoided in patients with a known history of QT interval prolongation, recent acute myocardial infarction, uncompensated heart failure, or arrhythmia, and in patients receiving other agents known to prolong the QTc. Baseline serum potassium and magnesium measurements should be taken in patients at risk for significant electrolyte disturbances (especially hypokalemia); low levels of potassium and/or magnesium should be repleted before proceeding with ziprasidone treatment.³¹

SPECIAL POPULATIONS

Hepatic Impairment

Ziprasidone is eliminated mainly via the hepatic route; thus, hepatic impairment would be expected to increase the area under the curve (AUC) of ziprasidone. In an open-label multicenter study, 30 subjects with normal hepatic function or chronic stable hepatic impairment received oral ziprasidone 20 mg b.i.d. for 4 days and a single 20-mg dose on day 5.³⁵ Blood samples from 26 evaluable patients, collected on days 1 and 5, showed no statistically significant differences in C_{max} or time to maximum serum concentration between the 2 groups. The mean AUC from zero to 12 hours (AUC_{0-12h}) increased by 26% in the cirrhotic group

at day 5 compared with the control group ($p = .0422$). Although this difference just reached statistical significance, it was not considered clinically significant. The investigators concluded that mild-to-moderate hepatic impairment does not have a clinically significant effect on the pharmacokinetics or tolerability of ziprasidone.

Renal Impairment

An open-label multicenter study in 39 patients with varying degrees of renal impairment found no statistically significant differences in the mean pharmacokinetic parameters of ziprasidone between patients with normal renal function and those with moderate or severe (requiring hemodialysis) impairment.³⁶ The AUC_{0-12h} and C_{max} in patients with mild renal impairment were significantly greater than in the other groups (increases of 46%–67% for AUC_{0-12h} and of 32%–72% for mean C_{max} [$p \leq .02$ for both]), but there was considerable overlap in values for these parameters between the groups. Therefore, these pharmacokinetic differences were not considered clinically significant.

Age and Gender Effects

An 8-day pharmacokinetic study of oral ziprasidone (40 mg/day b.i.d. for 7 days and 20 mg on day 8) in 8 men and 11 women aged 18 to 45 years and in 8 elderly men and 8 elderly women aged ≥ 65 years found similar values for pharmacokinetic parameters in all groups except elderly women.³⁷ The higher AUC_{0-12h} and C_{max} values observed in this group were primarily because of 2 elderly women with outlying (very high) values. The investigators found no reasons for these outlying values and concluded that age and gender do not significantly influence the pharmacokinetics of ziprasidone.

Drug-Drug Interactions

Ziprasidone is extensively metabolized via 2 enzymes, with $< 5\%$ of the administered dose excreted as unchanged drug.³⁸ Reduction of ziprasidone by aldehyde oxidase accounts for approximately two thirds of ziprasidone metabolism, while oxidation by cytochrome P450 3A4 accounts for the rest. Aldehyde oxidase has no known clinically relevant inhibitors or inducers.³⁸ Furthermore, data from in vitro studies of the effects of ziprasidone on various CYP isoforms indicate that, at clinically relevant doses, the drug is not likely to induce or inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.³⁹ It is unlikely, therefore, that ziprasidone would be associated with clinically relevant pharmacokinetic interactions with other agents metabolized by these isoforms. Ziprasidone has exhibited no effects in vivo on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium; however, in vivo studies show that the AUC of ziprasidone is decreased about 35% by concomitant carbamazepine and is increased 35% to 40% by concomitant ketoconazole.

zole.³¹ Cimetidine or antacid has no effect on ziprasidone pharmacokinetics.³¹

Race

No pharmacokinetic studies of ziprasidone have specifically evaluated the effects of race; however, population pharmacokinetic evaluation has not shown any clinically significant race-related differences in the pharmacokinetics of ziprasidone.

Smoking

In vitro studies of human liver enzymes show that ziprasidone is not a substrate for CYP1A2; thus, smoking should not affect the pharmacokinetics of ziprasidone. Moreover, population pharmacokinetic evaluation has not shown significant pharmacokinetic differences between smokers and nonsmokers.

DISCUSSION

Ziprasidone, in its IM and oral formulations, has been generally well tolerated in both short- and long-term clinical trials. The adverse events most commonly associated with ziprasidone in clinical trials include somnolence, insomnia, gastrointestinal disturbances, akathisia, dizziness, and headache, with events generally being of mild-to-moderate intensity. Like other atypical antipsychotics, ziprasidone is associated with a low risk for EPS compared with conventional agents. Ziprasidone has a favorable metabolic safety profile (in terms of plasma lipid and glucose effects) and negligible effects on body weight.

Ziprasidone's favorable effects on the lipid profile distinguish it from other atypical agents (e.g., olanzapine and risperidone) that can elevate cholesterol and triglyceride levels.^{6,7,28} The relation between increased LDL cholesterol and triglyceride levels and cardiovascular disease is well established, as are the beneficial effects of lowering these lipid levels and increasing high-density lipoprotein cholesterol levels.⁸ Ziprasidone's observed minimal effects on total and LDL cholesterol and triglyceride levels may be a consideration for patients with schizophrenia who have other cardiovascular risk factors.

Ziprasidone has a weight-neutral profile that contrasts sharply with the observed effects of other atypical antipsychotic agents, including olanzapine, risperidone, and clozapine.² The clinical implications of this contrast are considerable, given the potential impact of antipsychotic-induced weight gain on compliance with antipsychotic therapy and long-term medical outcomes.² Weight gain and increases in body mass index are clearly associated with increased mortality and morbidity from several conditions, including cardiovascular disease, type 2 diabetes, several types of cancer, gallbladder disease, osteoarthritis, and respiratory problems.⁴⁰ Antipsychotic-induced weight gain is among the side effects most likely to have a nega-

tive impact on compliance with antipsychotic medication, thus increasing the risk for relapse.⁴¹ In the switch studies reviewed above, weight gain was the side effect cited most frequently as the reason for switching from either olanzapine or risperidone to ziprasidone.¹¹

Changes associated with ziprasidone on QTc have been well characterized, and clinical events attributable to QTc prolongation have not been observed. It is important to consider the observed effects of ziprasidone on the QTc in the wider context of a multiplicity of important influences on cardiovascular health, such as weight gain, dyslipidemia, and diabetes mellitus. As noted, use of ziprasidone should be avoided in patients with cardiovascular deficiencies, such as a known history of QT interval prolongation, low serum potassium and/or magnesium levels, recent acute myocardial infarction, uncompensated heart failure, or arrhythmia and in patients receiving other agents known to prolong the QTc.³¹ The risk-benefit analysis differs with the individual patient, but for many of our patients, ziprasidone's tolerability and safety profile make it a welcome option.

Drug names: carbamazepine (Tegretol, Carbatrol, and others), chlorpromazine (Thorazine, Sonazine, and others), cimetidine (Tagamet and others), clozapine (Clozaril and others), haloperidol (Haldol and others), ketoconazole (Nizoral), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Tandon R. Safety and tolerability: how do newer generation "atypical" antipsychotics compare? *Psychiatr Q* 2002;73:297-311
2. Allison DB, Mentore JL, Moonseong H, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686-1696
3. Hedenmalm K, Hagg S, Stahl M, et al. Glucose intolerance with atypical antipsychotics. *Drug Saf* 2002;25:1107-1116
4. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243-247
5. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy* 2002;22:841-852
6. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry* 2003;160:290-296
7. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry* 2002;63:856-865
8. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421
9. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week, placebo-controlled trial. *Psychopharmacology (Berl)* 1998;140:173-184
10. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology* 1999;20:491-505
11. Pfizer Inc. FDA Psychopharmacological Drugs Advisory Committee. Briefing document for Zeldox® capsules (ziprasidone HCl). New York,

- NY: Pfizer Inc; July 2000
12. Arató M, O'Connor R, Meltzer HY, et al. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol* 2002;17:207–215
 13. Hirsch SR, Kissling W, Bäuml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *J Clin Psychiatry* 2002;63:516–523
 14. Simpson G, Romano SJ, Horne RL, et al. Ziprasidone vs olanzapine in schizophrenia: results of a double-blind trial [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
 15. Addington D, Benattia I, Pantelis C, et al. Ziprasidone vs risperidone in schizophrenia: efficacy and safety in an 8-week trial. Presented at the 42nd annual meeting of the New Clinical Drug Evaluation Unit; June 10–13, 2003; Boca Raton, Fla
 16. Zimbroff DL, Brook S, Benattia I. Safety and tolerability of IM ziprasidone: review of clinical trial data [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
 17. Brook S, Walden J, Benattia I. Ziprasidone vs haloperidol for IM/oral therapy of acute schizophrenia [poster]. Presented at the 11th Congress of the Association of European Psychiatrists; May 4–8, 2002; Stockholm, Sweden
 18. Daniel D, Brook S, Benattia I. Transition from oral to IM ziprasidone: clinical efficacy and safety data. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–22, 2002; Philadelphia, Pa
 19. Glick ID, Romano SJ, Simpson G, et al. Insulin resistance in olanzapine- and ziprasidone-treated patients: results of a double-blind, controlled 6-week trial [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
 20. Simpson GM, Weiden PJ, Pigott T, et al. Ziprasidone versus olanzapine in schizophrenia: 6-month blinded continuation study [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–22, 2002; Philadelphia, Pa
 21. Addington D, Pantelis C, Dineen M, et al. Ziprasidone vs risperidone in schizophrenia: 52 weeks' comparative data [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
 22. Weiden PJ, Daniel DG, Simpson G, et al. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol* 2003;23:595–600
 23. Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 2001;62:12–18; Correction Mar 2009
 24. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology (Berl)* 2001;155:128–134
 25. Swift RH, Harrigan EP, van Kammen DP. A comparison of fixed-dose intramuscular (IM) ziprasidone with flexible-dose IM haloperidol. Presented at the 151st annual meeting of the American Psychiatric Association; May 30–June 4, 1998; Toronto, Ontario, Canada
 26. Brook S, Lucey JV, Gunn KP, for the Ziprasidone I.M. Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000;61:933–941
 27. Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics. *CNS Drugs* 2001;15:537–551
 28. Romano SJ, Cutler N, Weiden PJ, et al. Ziprasidone's effects on weight and lipids in patients with schizophrenia [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
 29. Taylor D. Ziprasidone in the management of schizophrenia: the QT interval issue in context. *CNS Drugs* 2003;17:423–430
 30. Romano SJ. Cardiovascular safety profile of ziprasidone: review of clinical development data [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
 31. Geodon® (ziprasidone) [package insert]. New York, NY: Pfizer Inc; June 2002
 32. Miceli JJ, Shioyitz T, Swift RH, et al. High-dose ziprasidone is associated with marginal additional QTc increase [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
 33. Pfizer Inc. FDA Psychopharmacological Drugs Advisory Committee. Briefing document for ziprasidone mesylate for intramuscular injection. New York, NY: Pfizer Inc; Feb 2001
 34. Miceli JJ, Anziano RJ, Swift RH, et al. IM ziprasidone and IM haloperidol have comparable effects on QTc at C_{max} [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
 35. Everson G, Lasseter KC, Anderson KE, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function. *Br J Clin Pharmacol* 2000;49(suppl 1):21S–26S
 36. Aweeka F, Jaysekara D, Horton M, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. *Br J Clin Pharmacol* 2000;49(suppl 1):27S–33S
 37. Wilner KD, Tensfeldt TG, Baris B, et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. *Br J Clin Pharmacol* 2000;49(suppl 1):15S–20S
 38. Beedham C, Miceli JJ, Obach RS. Ziprasidone metabolism, aldehyde oxidase, and clinical implications. *J Clin Psychopharmacol* 2003;23:229–232
 39. Prakash C, Kamel A, Cui D, et al. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. *Br J Clin Pharmacol* 2000;49(suppl 1):35S–42S
 40. National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report; September 1998. NIH Publication 98-4083. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/obg_dlns.pdf. Accessed May 25, 2003
 41. Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry* 2002;63:1121–1128