National PBM Drug Monograph
Ziprasidone (Geodon®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Introduction: Ziprasidone (Geodon®) is the newest member of the atypical antipsychotic class, joining clozapine, risperidone, olanzapine, and quetiapine. It was FDA approved on February 5, 2001 for the treatment of schizophrenia.

Dosage Form(s): 20mg, 40mg, 60mg, and 80mg capsule supplied in bottles of 60.

Manufacturer: Pfizer

Approved indications: Treatment of schizophrenia

Clinical Efficacy:
Most of the efficacy of neuroleptics agents can be attributed to D_2 receptor blockade within limbic system. This results in improvement of positive symptoms. Neuroleptics also bind the D_2 receptors in the nigrostriatal pathway, which explains why parkinsonism and other extrapyramidal (EPS) side effects occur. Agents that bind to 5-HT_{2A} receptor (creating a low D_2 to high 5-HT_{2A} receptor antagonism) can offset the potential for developing EPS. Extrapyramidal side effects can also be mitigated if an agent possesses muscarinic receptor activity. Unfortunately, muscarinic receptor antagonism is also responsible for the well-known adverse effects such as blurred vision, dry mouth, sinus tachycardia, constipation, urinary retention, etc.

Neuroleptics may also block alpha-1, alpha-2 adrenoreceptors, and histamine-1 receptors, which contributes to the side effect profile. Blocking alpha-1 receptors can cause postural hypotension, dizziness, and reflex tachycardia. Alpha-2 receptor blockade can antagonize the antihypertensive effects of clonidine, methyldopa, or guanabenz. Histamine-1 receptor blockade can cause sedation, which may or may not be a desired effect, and weight gain.

Table 1. Relative Receptor Blockade

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Haloperidol
D_2	High	High	Moderate	Low	Low	High
$5HT_{2A}$	High	High	Moderate	Low	Moderate	Low
α_1-adrenergic	Moderate	Moderate	Low	Moderate	Moderate	Low
α_2-adrenergic	Low	High	Low	Moderate	High	Low
Muscarinic-1	Negligible	Negligible	High	Negligible	High	Negligible
Histaminic-1	Moderate	Moderate	High		High	Low

Ziprasidone may possess moderate antidepressant effects because it also is a $5HT_{1A}$ receptor agonist and an inhibitor of norepinephrine and serotonin reuptake.

The efficacy of ziprasidone has been established for the treatment of schizophrenia in four controlled trials comparing it to placebo and/or haloperidol for acute treatment and a 52-week study evaluating long-term treatment. These studies generally excluded patients with significant medical disorders or other psychiatric disorders (unless specified). There is a 6-week clinical trial comparing ziprasidone to olanzapine and has been presented as a poster, and an 8-week clinical trial comparing ziprasidone to risperidone (data undergoing analysis by Pfizer).

The Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale (BPRS) are commonly used in schizophrenia trials as a means of measuring the severity of illness and response to treatment. The PANSS is comprised of 7 positive items, 7 negative items, and 16 general psychopathology items with the sum of all 3 sections as the overall score. The BPRS evaluates four clusters of symptoms: thought disturbance, anxious depression, withdrawal-retardation, and hostility-suspiciousness. A decrease

in the PANSS or BPRS score indicates improvement. To evaluate negative symptoms, the sub score for the 7 negative items from PANSS scale or the Scale for Assessment of Negative Symptoms (SANS) are used.

All 4 acute treatment studies were intent-to-treat last observation carried forward analysis (LOCF). Results are presented as the treatment effect which is defined as the adjusted mean change from baseline for the active treatment group mean minus the adjusted mean change from baseline for the placebo group.

Table 2. Short-term trials

Clinical Trial	Inclusion	Dose	Treatment effects (95% CI)
104[4] RDB, fixed dose Ziprasidone vs. placebo N=200 4 weeks	DSM III-R chronic or subchronic schizophrenia or schizoaffective disorder	Ziprasidone 10mg daily 40mg daily 80mg daily	
Keck 1998[1] RDB, fixed dose multicenter Ziprasidone vs. placebo N=139 4 weeks	DSM III-R Acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder 18-64 years old hospitalized within previous 3weeks of study duration of illness ≥ 1 year BPRS ≥ 37 Score of ≥ 4 on at least 2 core BPRS items	4-7 day washout Ziprasidone 40mg 120mg	40mg BPRS – 1.102 (- 6.0, 3.8) BPRS core – 0.356 (-2.097, 1.366) CGI-S – 0.254 (-0.651, 0.144) SANS –6.2 120mg BPRS –5.812 (-10.76, -0.86)* BPRS core – 1.682 (-34.28, 0.064) CGI-S –0.421 (-0.82, -0.022)* SANS –5.0 Discontinuations %- total/LOE/AE Placebo- 50%/25%/0% 40mg- 36%/25%/2% 120mg- 49%/17%/9%
Daniel 1999[2] (study 114) RDB, fixed dose multicenter Ziprasidone vs. placebo N=302 6 weeks	>18 y/o DSM-III-R acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder Hospitalized within previous 4 weeks of study Duration of illness ≥ 6 months PANSS ≥ 60 and ≥ 4 on 2 or more core items in the PANSS CGI-I ≥ 3 between screening and baseline	3-7 day washout Ziprasidone 80mg 160mg	80mg PANSS –6.661 (-13.25, -0.065)* BPRS –3.875 (-7.701, -0.049)* BPRS core –1.345 (-2.625, -0.065)* CGI-s –0.314 (-0.596, -0.031)* 160mg PANSS –12.45 (-19.048, -5.855)* BPRS –7.152 (-10.97, -3.33)* BPRS core –2.466 (-3.746, -1.186)* CGI-s –0.60 (-0.884, -0.316)*
115[4] RDB, fixed dose Ziprasidone vs. haloperidol vs. placebo N=419 6 weeks		Ziprasidone 40mg 120mg 200mg haloperidol 15mg	40mg PANSS –6.774 (-12.93, -0.618)* BPRS –3.588 (-7.163, -0.013)* BPRS core –1.396 (-2.682, -0.110)* CGI-s –0.33 (-0.628, -0.033)* 120mg PANSS –8.232 (-14.59, -1.873)* BPRS –4.39 (-8.09, -0.69)* BPRS core –1.351 (-2.678, -0.024)* CGI-s –0.331 (-0.638, 0.024)* 200mg PANSS –8.009 (-14.279, -1.739)* BPRS –4.242 (-7.884, -0.599)* BPRS core –1.736 (-3.042, -0.43)* CGI-s –0.427 (-0.728, -0.125)* Haloperidol 15mg PANSS –13.841 (-20.075, -7.607)* BPRS -7.215 (-10.835, -3.594)* BPRS core -3.159 (-4.46, -1.857)* CGI-s –0.745 (-1.045, -0.445)*

<table>
<tr>
<td>Simpson[5]
RDB
Ziprasidone vs. olanzapine
N=269
6 weeks</td>
<td>18-55 y/o
DSM-IV chronic or subchronic schizophrenia or schizoaffective disorder
Persistent psychotic sxs for the week prior to hospital
Clinical need for hospitalization
At screening and at baseline: a score ≥ 4 on the CGI-S and at on at least one of the following, delusions, conceptual disorganization, hallucinatory behavior</td>
<td>Ziprasidone 40mg BID on days 1, 2; 80mg BID on days 3-7; flexible dosing of 40, 60, or 80mg BID dosing thereafter (mean dose 130mg)

Olanzapine 5mg QD days 1, 2; 10mg QD days 3-7; flexible dosing 0f 1, 10, or 15mg QD thereafter (mean dose 11mg)</td>
<td>
<table>
<tr><th></th><th>Ziprasidone</th><th>Olanzapine</th></tr>
<tr><td>Dropouts
2° AE
2° tx failure</td><td>48.5%
2.2%
8.8%</td><td>36.8%
1.5%
8.3%</td></tr>
<tr><td>BPRS</td><td colspan="2">-2.36, 3.18</td></tr>
<tr><td>CGI-S</td><td colspan="2">-0.27, 0.29</td></tr>
<tr><td>PANSS total
PANSS neg.
PANSS pos</td><td colspan="2">-4.44, 5.21
-1.48, 1.25
-1.14, 1.87</td></tr>
<tr><td>% of pts. with 20%/30%/40% ↓ in CDSS</td><td>65/60/53</td><td>61/53/49</td></tr>
</table>
Difference between ziprasidone and olanzapine [95% CI]
</td>
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*significant vs. placebo

Long-term study

This was a 1-year, double-blind, placebo-controlled multicenter study that evaluated time to relapse as the primary endpoint. [4] Relapse was defined as a score of ≥ 6 in either the CGI-improvement score or item P7 (hostility) or P8 (uncooperativeness) on the PANSS scale for at least 2 successive days. The patients enrolled (n=294) were hospitalized and had significant negative symptomotology. After their current antipsychotic was stopped, patients were randomized to receive ziprasidone 40mg, 80mg, 160mg, or placebo.

The Kaplan-Meier product-limit method was used for determining the cumulative probability for relapse. At week 28, the probability of relapse was 0.32-0.34 for all 3 ziprasidone doses and 0.55 for placebo. At week 52, the probability of relapse for ziprasidone was 0.35-0.41 and 0.71 for placebo. Other efficacy variables such as the PANSS and CGI-severity scores continued to show improvement in the ziprasidone group.

Efficacy in treating negative symptoms

Two of the short-term studies and the one long-term study evaluated ziprasidone's effect on negative symptoms using the PANSS negative subscale. [4] Both ziprasidone 80mg and 160mg daily were significantly superior to placebo in reducing the PANSS negative score. In the second study, ziprasidone 200mg and haloperidol 15mg daily were statistically superior to placebo, with the 120mg dose only showing a trend for superiority (p=0.069). A statistical comparison between ziprasidone and haloperidol was not given, although numerically, haloperidol lowered PANSS negative scores more than ziprasidone.

In a short-term trial, it is difficult to say whether improvement in negative symptomatology is the result of improvement in positive symptoms or truly an independent effect of the drug.

As mentioned earlier, EPS, co-existent depression, and untreated positive symptoms can cause negative symptoms. The long-term trial tried to control for these factors by enrolling patients who had predominantly negative symptoms (PANSS negative score ≥ 21) with relatively stable positive symptoms. Also, depressive scores at baseline were low and EPS in the ziprasidone and placebo groups were similar. All 3 doses of ziprasidone were significantly superior to placebo in reducing the PANSS negative score.

Table 3.

	Mean baseline PANSS negative score	Results (95% CI)
Study 114 6 weeks	24.8	80mg -2.030 (-3.786, -0.274)* 160mg -3.094 (-4.849, -1.339)*
Study 115 6 weeks	22.9	40mg -1.439 (-3.361, 0.383) 120mg -1.745 (-3.6.30, 0.139) 200mg -2.201 (-4.048, -0.355)* haloperidol 15mg -2.533 (-4.384, -0.681)*
Study 303 1 year	27.8	40mg -3.444 (-5.192, -1.697)* 80mg -2.272 (-4.030, -0.513)* 160mg -3.967 (-5.717, -2.216)*

*significant versus placebo
Data from the Advisory Committee Briefing Document

In the ziprasidone versus olanzapine trial, change in the PANSS negative subscale was not significant between groups. Baseline values were not provided.

Treatment- refractory patients
A schizophrenic patient who does not respond to at least two adequate trials of conventional antipsychotics is usually classified as a treatment-refractory patient and occurs in approximately 30-40% of patients. There are no published trials evaluating ziprasidone in treatment-refractory patients at this time.

Adverse Events:
Prolonged QT-interval
Prolonged QT interval is the adverse event that is of greatest concern. In 1998, the FDA issued a "non-approvable" letter for ziprasidone and asked that the sponsor conduct a study with respect to QT effects. A QTc $\geq$ 500mmsec is associated with an increased risk of developing torsades de pointes. In the Phase 2/3 studies, 2/3095 (0.06%) of the patients had a QTc $\geq$ 500mmsec. In the study described below, no patient had a QTc $\geq$ 500mmsec.

This open-label, parallel group trial (study 054) evaluated patients with schizophrenia in order to assess the effect of oral ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QT interval. EKGs were obtained during the expected peak serum concentration for each drug.[4] The patient's existing antipsychotic medication was tapered over a period of 7 days, followed by a washout period lasting 5 days. Baseline EKGs were obtained during the last 3 days of the washout period. Patients were randomized to receive one of the six study drugs. Dosing was initiated at the usual starting doses and was titrated to the highest dose recommended in the product package insert. EKGs were measured in triplicate on 3 separate days while at steady state conditions. This study went one step further and evaluated what the effect on EKG would be in the presence of a metabolic inhibitor. A CYP450 metabolic inhibitor specific to each drug was given for 5-7 days and EKGs were obtained on the last 3 days of treatment. Since ziprasidone is metabolized via the CYP3A4 pathway, ketoconazole a potent 3A4 inhibitor was co-administered at a dose of 200mg bid.

Table 4. Mean QTc Δ from baseline (msec) and % Δ

	Mean baseline (msec) (95% CI)	Steady state **No inhibitor**	Steady state **Inhibitor present**
Ziprasidone	402.1 (393.4, 410.8)	20.3 (14.2, 26.4) % Δ 5.2 (3.6, 6.8)	20 (13.7, 26.2) % Δ 5.1 (3.5, 6.8)
Risperidone	396.3 (389.6, 403)	9.1 (1.9-16.2) % Δ 2.4 (0.5, 4.2)	3.2 (-4.7, 11.1) % Δ 0.9 (-1.2, 2.9)
Olanzapine	397.9 (389.7, 406.1)	6.8 (0.8, 12.7) % Δ 1.8 (0.2, 3.3)	5.3 (-0.1, 10.7) % Δ 1.4 (0, 2.8)
Quetiapine	398 (390.9, 405.1)	14.5 (9.5, 19.5) % Δ 3.7 (2.4, 5.0)	19.7 (14.3, 25) % Δ 5.0 (3.6, 6.3)
Thioridazine	395.9 (388.5, 403.3)	35.6 (30.5, 40.7) % Δ 9.1 (7.7, 10.4)	28 (21.6, 34.5) % Δ 7.2 (5.5, 8.9)
Haloperidol	394.7 (386.1, 403.4)	8.9 (-2.0, 11.3) % Δ 1.2 (0.5, 2.9)	8.9 (1.9, 15.9) % Δ 2.4 (0.6, 4.2)

Data from the Advisory Committee Briefing Document

Changes in QTc interval occurred in the following rank order from greatest to least:
Thioridazine > ziprasidone > quetiapine > risperidone > olanzapine > haloperidol.
Interestingly, the co-administration of ziprasidone and ketoconazole did not lead to any further prolongation of the QTc despite a 39% increase in serum concentration (M9 by 55%, M10 by 8%).

How does ziprasidone compare with sertindole, an antipsychotic agent that never made it to market because of concerns with QTc prolongation? At its recommended dose of 24mg/day, sertindole caused a mean QTc increase of 21-30 msec whereas ziprasidone caused a mean QTc increase of < 10 msec at the highest

recommended dose of 160mg/day. QTc values ≥ 500 msec were reported in 7-8% of patients taking sertindole at the recommended dose.

The following are risk factors for prolonged QT-interval: hypokalemia, hypomagnesemia, bradycardia, concomitant drugs known to prolong QT-interval, recent MI, uncompensated heart failure, arrhymias, and congenital long QT syndrome.

According to the manufacturer, there have been no reports of Torsades de Pointes during post-marketing experience with ziprasidone.

Extrapyramidal symptoms and tardive dyskinesia[4]

The Simpson-Angus scale and the Barnes Akathisia scale are commonly used to assess and quantify EPS. Table 5 shows the mean change in score from baseline to endpoint from the short-term trials. There was no statistical difference in mean scores between ziprasidone and placebo. Benztropine was used in 22.4%, 18.3%, and 50.6% of patients on ziprasidone, placebo, and haloperidol respectively. In the long-term trial, the Simpson-Angus score decreased by 2.0 to 2.6 (range for all 3 ziprasidone doses) and by 1.7 for placebo.

Tardive dyskinesia (involuntary movements of the face, eyes, tongue, limbs) is generally irreversible and occurs with cumulative neuroleptic exposure. The advantage atypicals have over the conventional agents is the lower likelihood for developing tardive dyskinesia. The Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS) is commonly used to evaluate severity and frequency of tardive dyskinesia. There are several reports of the atypicals both causing and as well as treating tardive dyskinesia. Though not expected to be different from the other atypicals, it is too early to tell what the risk of developing tardive dyskinesia is with ziprasidone

Table 5. Mean change in score for short-term trials (SD)

	Ziprasidone (n=686)	Haloperidol (n=83)	Placebo (n=264)
Simpson-Angus	-0.33 (2.51)	1.12 (3.81)	-0.34 (2.69)
Barnes Akathisia	-0.02 (0.88)	0.31 (1.2)	-0.11 (0.92)

Data from the Advisory Committee Briefing Document

Weight gain

Patients with schizophrenia are at a greater risk for developing cardiovascular disease than the general population. This may in part, be explained by the high incidence of smoking, sedentary lifestyle, and unhealthy diet among individuals with schizophrenia as well as the reluctance of the medical community to treat co-morbid medical conditions in mentally ill patients. Excessive weight is also contributes to the risk of developing cardiovascular disease and diabetes, therefore it becomes important to evaluate the potential for weight gain with these agents.

Table 6. Weight gain during short-term trials

	Ziprasidone/ placebo	Risperidone/ placebo	Olanzapine/ placebo	Quetiapine/ placebo
Mean wt. change	↑ 0.9kg/ ↓ 0.4kg		↑ 2.8kg/ ↓ 0.4kg	↑ 2.3kg/↑ 0.1kg
% pts. gaining ≥ 7% of baseline wt.	9.8/4.0	18/9	23/6	29.3/2.7

Data from the Advisory Committee Briefing Document

In the 6-week head-to-head trial of ziprasidone and olanzapine, there was a median decrease in weight of 0.7kg with ziprasidone and a median increase of 7.2kg with olanzapine.[5,6]

In 3 separate ongoing studies, weight was evaluated in patients switched to ziprasidone from conventional agents, olanzapine, or risperidone.[4] Data at 6 weeks showed that patients switched from conventional antipsychotics to ziprasidone gained a mean of 0.17kg (p=0.49). Patients switched from olanzapine or risperidone to ziprasidone lost a mean of 1.79kg (p<0.001) and 0.83kg (p=0.05) respectively.

Weight changes from completed or on-going active comparator trials of at least 6 months duration are presented in table 7. Patients receiving risperidone gained more weight than those receiving ziprasidone or haloperidol. It can also be seen from the table that patients who were underweight at baseline gained more weight than did patients who were overweight at the outset. [4]

Table 7. Weight gain during trials of ≥ 6 months duration

	Ziprasidone		Haloperidol		Risperidone	
	Mean wt. Change (kg)	% gaining ≥ 7%	Mean wt. Change (kg)	% gaining ≥ 7%	Mean wt. Change (kg)	% gaining ≥ 7%
BMI < 23	1.4	20.7	2.1	25.6	4.4	40.9
BMI 23-27	0	12.6	-0.5	11.5	2.6	33.3
BMI >27	-1.3	10.9	-0.8	8.8	0.3	17.9
All patients	0.23	21.8	1.02	14.4	3.04	36.3

Data from the Advisory Committee Briefing Document

Serum Lipids

Given the risk of cardiovascular disease in this population of patients, the effect atypicals have on serum lipids is important. There are three 6-week open label studies where patients were switched from their previous therapy with an atypical or typical agent to ziprasidone. [4] Patients must have been on their previous therapy for at least 3 months and had either a partial response or intolerable adverse effect to this therapy. Lipid samples were obtained at random times. Total cholesterol and triglycerides decreased by a median value of 7mg/dl and 4mg/dl respectively in patients switching from a typical agent to ziprasdone. In patients switching from olanzapine to ziprasidone, total cholesterol and triglycerides decreased by a median value of 17mg/dl and 53mg/dl respectively. When switching from risperidone to ziprasidone total cholesterol and triglycerides decreased by 9mg/dl and 24mg/dl respectively.

In another switch study, 37 outpatients taking olanzapine, risperidone, or a typical agent were changed to ziprasidone. Patients were started on ziprasidone 40mg BID on day 1 and were taken off their previous drug by day 7. After day 7, the ziprasidone dose could be adjusted up to 80mg BID. The average dose was 62.16mg BID. Baseline cholesterol and triglycerides (obtained randomly) were 210.65 ± 51.74 and 262.68 ± 193.49mg/dl respectively. After 6 weeks, cholesterol decreased to 183.06 ± 47.47 and triglycerides decreased to 176.30 ± 101mg/dl.[7]

In the EKG study presented earlier (study 054), lipids were also assessed. Keep in mind that patients received treatment ranging from 14 to 24 days. Lipid values were obtained under fasting conditions. In general, it appears that ziprasidone has a favorable lipid profile. [4]

Table 8. Lipid changes during short-term administration (study 054)

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioriazine	Haloperidol
Total cholesterol	-7.5%	-1.6%	+2.1%	+2.4%	+13.7%	-11.5%
LDL	-8.5%	+6.5%	+1.1%	-0.3%	+18.6%	-10.5%
HDL	0	-4.9%	-4.6%	-8.6%	+3%	-6%
Triglycerides	-28%	-6.7%	+31%	+18.3%	+7.9%	-18%

Median % change from baseline
Data from the Advisory Committee Briefing Document

Changes in lipids were assessed in the head-to-head ziprasidone and olanzapine trial using fasting values. Total cholesterol remained unchanged in the ziprasidone group and increased by 16mg/dl in the olanzapine group from a baseline of approximately 185mg/dl. LDL decreased by 3mg/dl with ziprasidone (baseline 114 mg/dl) and increased by 10mg/dl with olanzapine (baseline 108mg/dl). There was an insignificant increase in HDL in both groups. Fasting triglycerides decreased by 3mg/dl and increased by 28mg/dl in the ziprasidone and olanzapine groups respectively from a baseline of around 123mg/dl. [6]

Cholesterol and triglycerides were evaluated in long-term active-comparator trials or ongoing open label trials in those patients having baseline and on treatment values. [4] Lipid samples were drawn at random times at week 28, 40, and 52. When looking at the data as last observation carried forward, cholesterol

decreased by 10mg/dl, 6mg/dl, and 2mg/dl for ziprasidone, haloperidol, and risperidone respectively. Similarly, triglycerides decreased by 7mg/dl, 13mg/dl, and 7.5mg/dl for the 3 drugs respectively.

Diabetes
Clozapine and olanzapine have been associated with the development of hyperglycemia and treatment emergent diabetes.

In the short-term clinical trials, the incidence of random glucose values >1.2 x ULN was 8% in both the ziprasidone group and the placebo group, and 14% in the haloperidol group. The overall incidence of random glucose values >1.2 x ULN from Phase 2/3 clinical trials was 14.9%, 12.2%, 16.3%, and 14.9% with ziprasidone, placebo, haloperidol, and risperidone respectively. There have been no cases of treatment emergent diabetes with ziprasidone. [4]

In the head-to-head ziprasidone and olanzapine trial, fasting insulin and insulin resistance (as measured by HOMA-IR) increased significantly from baseline with olanzapine and increased insignificantly with ziprasidone. However, the difference between groups did not reach significance. There was no change from baseline in fasting glucose in either group. [6]

Prolactin
Blockade of D2 receptor in the hypothalamus can result in increased prolactin secretion. Increased prolactin can lead to breast swelling, tenderness, and discharge as well as menstrual cycle irregularity and sexual dysfunction.

In the 1-year trial, prolactin > 22ng/ml (> 1.1 x ULN) was seen in 17.3% of the ziprasidone patients versus 4.3% in the placebo group. Table 8 shows the prolactin results when all trials were combined.

Table 9. All trials combined

	Ziprasidone	Placebo	Haloperidol	Risperidone
Prolactin > 22ng/ml	20%	4%	46%	89%
Mean prolactin levels	9.7ng/ml (males), 18.2ng/ml (females)	7.6ng/ml (males), 8.6ng/ml (females)	17.1ng/ml (males), 40.1ng/ml (females)	34 ng/ml (males), 89.2ng/ml (females)
Prolactin > 35ng/ml (males)	6.6%	1.7%	11.3%	50.6%
Prolactin > 50ng/ml (females)	8.5%	0%	27.3%	77.1%

Data from the Advisory Committee Briefing Document

It seems that this is a transient effect for most patients. Approximately 2/3 of these patients had repeated prolactin measurements. The percentage of patients whose repeat measurements remained elevated were 1.7% males and 3.5% of the females on ziprasidone, none in the placebo group, 4% males and 21.1% females in the haloperidol group, and 32% of males and 73.1% of females on risperidone. By way of comparison, in a side-by-side analysis by David et al., prolactin levels were increased by a mean of 1-4ng/ml for olanzapine (5-20mg/d), 17ng/ml for haloperidol (5-20mg/d), and 45-80ng/ml for risperidone (4-10mg/d). [3] Review of quetiapine studies also showed a very low propensity for prolactin elevation.

Drug Interactions:
Ziprasidone does not appear to interfere with CYP450 enzymes. The IC_{50}s for CYP1A2, CYP2C9, and CYP2C19 were greater than 100µM and the Ki values for CYP2D6 and CYP3A4 were 11µM and 64µM respectively. The maximal serum concentration of unbound ziprasidone at its highest dosage of 160mg is approximately 0.5nM and is therefore, unlikely to interfere with the metabolic activity of these enzymes. Furthermore, the metabolism of dextromethorphan (a CYP2D6 substrate) and ethinyl estradiol (a CYP3A4 substrate) was not altered when co-administered with ziprasidone. [4]

Although quetiapine, risperidone, and olanzapine are metabolized by the cytochrome P450 isoenzymes, these agents like ziprasidone, are not significant inhibitors or inducers of CYP450.

Other drugs can interfere with the metabolism of ziprasidone. Concomitant administration of ziprasidone and carbamazepine resulted in a 35% decrease in ziprasidone area under the curve (AUC). When co-administered with ketoconazole, AUC of ziprasidone increased by 35-40%. [4]

CYP2D6 has a polymorphic distribution which genetically predisposes individuals to being slow or fast metabolizers of drugs that are substrates. This is significant for risperidone, since CYP2D6 is the significant metabolic pathway.

As can be seen from Table 10, olanzapine has many routes of metabolism. Therefore, inhibition of one pathway by another agent may not lead to a significant drug interaction. Risperidone and quetiapine, having only one route of metabolism, may be more susceptible to drug interactions involving the CYP2D6 or CYP3A isoenzyme respectively. A knowledge of the effect other drugs have on the CYP isoenzymes can help predict potential drug interactions. All atypical agents still carry the risk of drug interactions with other agents through mechanisms other than CYP450 (eg. use with other drug causing sedation).

Although ziprasidone is highly bound to plasma proteins, drug interactions involving protein displacement were not seen when warfarin or propranolol was co-administered. [4]

Table 10. Enzymes involved in the metabolism of the atypical agents

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine
CYP 1A2	+		++		++
CYP 2C9					+/-
CYP 2C19			+/-		+/-
CYP 2D6		++	+		+/-
CYP 3A4	++			++	++
OTHER	Aldehyde oxidase ++		FMO ++ Glucuronidation ++		CYP2E1 FMO

++=major pathway +=minor pathway +/- =possible pathway FMO=flavin-containing monooxygenase

Although formalized studies have not been conducted, ziprasidone should not be administered with other drugs known to prolong the QT interval.

Cost:

From a drug acquisition stand point only, risperidone, quetiapine, and ziprasidone are similarly priced and olanzapine the most costly. There are no cost-effectiveness studies with ziprasidone at this time. Please refer to the PBM website for most recent cost information.

Table 11. Cost of the atypical agents at commonly used dosages

Drug	Price/unit	Price/month
Risperidone		
2mg bid	$2.60	$156
3mg bid	$3.02	$181.20
Olanzapine		
10mg	$5.22	$156.60
15mg	$7.82	$234.60
20mg	$11.20	$336.00
Quetiapine		
200mg bid	$2.23*	$133.80
300mg bid	$3.20*	$192.24
Ziprasidone		
40mg bid	$2.43 (all strengths)	$145.96
60mg bid		$145.96

*These prices reflect a 10% discount off FSS price for market share of <20%; with higher market share, further discounts will be given off FSS price.

Dosage and administration:
The usual starting for ziprasidone is 20mg taken twice daily with food. The maximum dose is 80mg taken twice daily. It can take several weeks before a response is noted. The Expert Concensus Guidelines and the American Psychiatric Association guidelines recommend waiting at least 3 weeks before determining if a response has occurred, unless the patient is having intolerable side effects.

The pharmacokinetics of ziprasidone has been studied in patients with renal impairment, hepatic impairment, and in the elderly. Renal impairment does not significantly alter ziprasidone pharmacokinetics. Hepatic impairment (Child-Pugh Class A and B) increased AUC_{0-12} by 13% and 34% respectively. Elderly patients have approximately a 20% higher serum concentration of ziprasidone than do younger patients. These changes in drug distribution seen in patients with hepatic impairment and in the elderly does not generally warrant a dosage adjustment; however, as always, caution should be exercised.

Ziprasidone should not be administered with other drugs known to prolong the QT interval. Ziprasidone is contraindicated in patients with known history of QT prolongation, recent myocardial infarction, or in uncompensated heart failure. Certain conditions such as bradycardia, hypokalemia or hypomagnesemia may increase the risk of torsades de pointes when used with drugs known to prolong the QT interval. Therefore, if these conditions exist, ziprasidone should not be used.

Conclusion:
Ziprasidone compares favorably with risperidone, olanzapine, and quetiapine. At this time, it can only be said that improvement in negative symptomotology is better than placebo, but no better than haloperidol. Like the other atypicals, the incidence of EPS and TD is low when compared to the conventional agents. Its side effect profile on prolactin is probably similar to olanzapine and quetiapine, has the most favorable weight gain and lipid profile, and the least favorable effect on QT-interval. Until more is known about its safety in patients with risk factors for prolonged QT, it would be best to avoid ziprasidone in these patients

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