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Ziprasidone (Zeldox® in Canada, Geodon® in US)

Availability:	US: Released in 2001 Canada: Released January 2008
Manufacturer:	Pfizer Pharmaceuticals
Therapeutic class:	Antipsychotic
Dosage:	80-160 mg daily
Spectrum of activity:	Most similar to Risperidone (Risperdal®)
Clinical efficacy:	No evidence that ziprasidone works better in the treatment of schizophrenia or schizoaffective disorder compared with currently available antipsychotics

Introduction

Ziprasidone is the newest second generation antipsychotic to become available in Canada. Its potential advantage over the currently available second generation agents is that it is associated with less weight gain, and fewer elevations in cholesterol, triglycerides and blood glucose.¹ Other second generation antipsychotics include risperidone, olanzapine, quetiapine and clozapine.

Pharmacology

Ziprasidone is a potent serotonin (5-HT) and dopamine (D2) receptor antagonist.² Its affinity at the 5-HT_{2A} receptor is 11-fold higher than at the D₂ site.³ (Table 1) It has moderate affinity for alpha-1 adrenergic and histamine (H₁) receptors and very low affinity for alpha-2 adrenergic and cholinergic (M₁) receptors. It moderately inhibits 5-HT and norepinephrine (NE) reuptake.

Antagonism at these receptor sites results in therapeutic effects as well as adverse effects⁴ These effects are summarized in Table 2. Low affinity at the D₂ site and higher affinity for the 5-HT_{2A} receptor than the D₂ site has been associated with fewer extrapyramidal side effects (EPS).⁵

When compared with second generation antipsychotics, ziprasidone is similar to risperidone in its affinity for the D₂, 5-HT₂, H₁, and M₁ receptor sites.^{2,3} It is an order of magnitude weaker at the alpha 1 site but an order of magnitude stronger at the 5-HT_{2C} and 5-HT_{1A} receptors. Weaker

activity at the alpha 1 receptor suggests that it would cause less orthostatic hypotension than risperidone, however, direct comparisons of adverse effects among antipsychotics based on receptor affinity does not always accurately predict a drug's effect in clinical practice.

Table 1: Comparative Receptor Affinity for Ziprasidone and Other Antipsychotic Agents - Affinity Ki (nM)

Receptor	Ziprasidone	Aripiprazole	Clozapine	Olanzapine	Risperidone	Quetiapine	Haloperidol
D2	3.1	0.34	130	20	2.2	180	1.4
5-HT2A	0.39	3.4	8.9	3.3	0.29	220	120
5-HT2C	0.72	15	17	10	10	1400	4700
5-HT1A	2.5	1.7	140	2100	210	230	3600
Alpha-1	13	57	4.0	54	1.4	15	4.7
H1	47	61	1.8	2.8	19	8.7	440
M1	5100	>10,000	1.8	4.7	2800	100	1600

References: 2 and 3

Table 2: Pharmacological Effects of Receptor Antagonism

Receptor Antagonism	Therapeutic Effects	Adverse Effects
D2	Antipsychotic effects	EPS, endocrine changes, sexual dysfunction
5-HT2	Improved negative symptoms, decreased EPS	Role in weight regulation
M1 (Muscarinic)	Antiparkinson effects	Dry mouth, blurred vision, constipation, QRS changes, memory dysfunction at higher doses
H1 (Histaminic)	Anti-emetic effects	Weight gain, sedation
Alpha-1	Improvement in negative symptoms (?)	Postural hypotension, reflex tachycardia, dizziness

Adapted from reference 4

Comparative Clinical Trials in Chronic Schizophrenia and Schizoaffective Disorder

The efficacy of ziprasidone has been compared with haloperidol⁶, olanzapine^{7,8} and amisulpride⁹ in double-blind, multicentre design in patients with schizophrenia and schizoaffective disorder.

Ziprasidone was found to be no different from haloperidol in a 24 week trial with respect to mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total and negative symptom scores or Global Assessment of Functioning (GAF) scores.⁶ Flexible dosing was used and the modal dose of ziprasidone was 80 mg/day and haloperidol was 5 mg/day. There was no difference in the numbers of patients who completed treatment in either group (45% of ziprasidone and 42% of haloperidol recipients).

Two studies comparing ziprasidone with olanzapine generally found that olanzapine had greater antipsychotic efficacy than ziprasidone. In the 28-week trial, olanzapine caused a significantly greater decrease in PANSS total score by the end of the study.⁸ The mean modal doses for olanzapine and ziprasidone were 15.3 mg/d and 116 mg/d respectively. The 24-week study⁷ found

no significant difference in the Calgary Depression Scale for Schizophrenia (CDSS) from baseline between the two agents, however, significantly more patients receiving olanzapine completed treatment than those on ziprasidone (45% vs 30%). There was no significant treatment difference in PANSS total score, however, olanzapine-treated patients had significantly greater improvement at the 24 week endpoint as compared with ziprasidone-treated patients. The trial used a fixed dosing schedule of ziprasidone 80, 120 or 160 mg/d or olanzapine 10, 15 or 20 mg/d.

Ziprasidone and amisulpride were compared in a 12-week, double-blind study in patients with predominantly negative-symptom schizophrenia.⁹ The mean daily dose for ziprasidone was 118 mg/day and 144.7 mg/day for amisulpride. Both treatment groups significantly reduced negative symptoms as defined by at least a 20% decrease from baseline on the PANSS Negative Subscale. There was no significant difference between ziprasidone and amisulpride in outcomes in negative symptoms.

Adverse Effects

The most common adverse events other than EPS that occurred in $\geq 5\%$ of patients receiving ziprasidone in short term trials were somnolence, nausea, constipation, respiratory tract infection, dizziness, dyspepsia, asthenia and diarrhea.¹⁰ Asthenia was the only non-EPS related adverse event that occurred significantly more frequently with ziprasidone than placebo in a 52 week trial.¹¹

In comparative trials^{6,9,12,13}, the most frequent treatment-emergent adverse events other than EPS or EPS-related events with ziprasidone were insomnia (16-25%), somnolence (3-21%), headache (6-15%), agitation (16%), vomiting (11%), nausea (10%), and anxiety (11%). (Table 3)

In CATIE I trials the most frequent adverse events reported with ziprasidone were insomnia, sleepiness, anticholinergic side effects, sexual dysfunction and menstrual irregularities.¹

Table 3: Adverse Effects of Ziprasidone from Comparative Trial

Adverse Event (%)	Drug				
	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Haloperidol
Insomnia	30	24	16	18	15-18
Sleepiness	24	28	31	31	6-9
Urinary hesitancy, dry mouth, constipation	20	25	24	31	n/a
Headache	6-15	18	<10	<10	11
Agitation	16	14	<10	<10	<10
Nausea, vomiting	10.5	<10	4	<10	4-6
Anxiety	11	<10	<10	<10	9
Sexual dysfunction	19	27	27	20	n/a
Galactorrhoea/ Gynaecomastia	3	4	2	2	n/a
Menstrual irregularities	14	18	12	6	n/a

References: 6, 12 and 13.
n/a: not reported.

The incidence of sexual dysfunction reported in the CATIE phase 1 and 2 with ziprasidone was up to 19% and galactorrhoea/gynaecomastia was up to 3% (incidences of galactorrhoea/gynaecomastia in patients on risperidone, olanzapine, quetiapine or perphenazine were 11-29% and 0 – 5%.^{1,14} respectively.

Menstrual irregularities occurred in 14% of ziprasidone, 12% of olanzapine, 6% of quetiapine, 18% of risperidone and 11% of perphenazine recipients.¹

Neurologic Side Effects

In short-term, placebo-controlled trials, the incidence of EPS or EPS-related adverse events with ziprasidone was 14% compared with 8% with placebo (Pfizer Inc). In a 52-week trial, the incidence of EPS with oral ziprasidone 20-80 mg/d twice daily ranged from 1-12% compared with placebo at 3-7%.¹¹

In comparative trials EPS occurred in up to 13% in ziprasidone, 23% in haloperidol, 3% in amisulpride, 20% in risperidone, and 0% in olanzapine recipients.^{6,8,9,12,13}

Based on the studies overall, EPS and EPS-related adverse effects with ziprasidone in dose ranges up to 120 mg /day are likely to occur in 12-14% of patients.

Cardiovascular effects

Ziprasidone prolongs the corrected QT (QTc) interval to a greater extent than other second generation antipsychotics.¹⁰ Clinically significant prolongation of the QTc interval is generally defined as > 500 ms.

Ziprasidone has only rarely been linked to QTc interval over 500msec (1.2% ziprasidone versus 1.6% for placebo in clinical trials.)¹⁵ No substantially different effects were noted in the Catie trial¹ on the QTc interval and torsades de pointes did not develop in any patients.

The risk of torsades de pointes and/or sudden death may increase with the use of drugs that prolong the QTc interval. The same results with respect to cardiovascular effects were found in the phase 2 Catie.¹⁴

Rare occurrences of torsade de pointes have been reported only with intramuscular ziprasidone during postmarketing surveillance.¹⁰

Orthostatic/postural hypotension or orthostatic faintness occurred in <13%.^{1,6,14} In comparison 6-13% of recipients receiving olanzapine, risperidone, quetiapine or perphenazine experienced these effects, while none of those on haloperidol did.

Refer to the section on precautions and drug interactions for clinical circumstances where ziprasidone is associated with increased risk of cardiac complications.

Potential Advantages over other Antipsychotics

In longer-term trials comparing ziprasidone with olanzapine, fewer patients reported weight increase (2-6% versus 13-20%) and appetite increase (3-4% versus 7-10%).^{7,8} Ziprasidone was also associated with fewer increases in glycosylated hemoglobin, cholesterol, and triglycerides than olanzapine, quetiapine and risperidone.¹

Pharmacokinetics

Limited data with 20 mg oral doses shows the greatest absorption (59%) immediately after eating, approximately double that of the fasting state resulting in the recommendation to take with food.¹⁶ Ziprasidone is > 99% bound to plasma proteins, mainly albumin and α 1-acid glycoprotein¹⁷ Steady state concentrations are achieved within 1-3 days with the terminal half-life being relatively short at 6.6 hours.^{16,17} Hence the recommendation for twice daily dosing. One report, however suggests a dose dependent increase in the half-life from 4.8 hours on 20 mg bid to 10 hours on increasing the dose to 60 mg bid.¹⁷ A second report suggests a decreased half-life immediately after eating. Alterations in absorption/dissolution between the fed and fasting states may explain these findings.¹⁶ Consistency in taking the medication with food is important in minimizing serum level fluctuations.

Metabolism – Ziprasidone is extensively metabolized in the liver with reduction by aldehyde oxidase accounting for two-thirds of the metabolism and CYP 3A4 the remainder.¹⁸ Most of the pharmacological activity is attributed to the parent drug. Approximately 66% of a dose is eliminated in the feces and 20% in the urine with less than 4% and 1% respectively excreted as unchanged drug.¹⁷

Drug Interactions

In animal studies the main route of metabolism by aldehyde oxidase has been reported to be inhibited by chlorpromazine, hydralazine, methadone and d-propoxyphene suggesting the potential for an interaction with these agents should they be used in conjunction with ziprasidone.¹⁶ A study by Obach¹⁹ looked at 36 inhibitors of aldehyde oxidase and found only tamoxifen, ketoconazole and ondansetron to have any significant inhibitory effect, although only chlorpromazine of the list suggested by Caley¹⁶ was examined.

Approximately one-third of ziprasidone is metabolized by the cytochrome P450 enzyme 3A4. Ketoconazole a potent 3A4 inhibitor increased ziprasidone concentrations by about 35-40%. Other known inhibitors of 3A4 include fluvoxamine, erythromycin, cimetidine, clarithromycin, protease inhibitors (e.g. indinavir, saquinavir) and azole antifungals (e.g. ketoconazole, fluconazole). Carbamazepine a 3A4 inducer decreased levels by about 35%. Cimetidine was not found to affect serum levels significantly in a study by Geoffrey²⁰ although only a single dose of ziprasidone 40 mg was tested with a single 800 mg dose of cimetidine.

These interactions are not considered significant by the manufacturer as the drug is mainly metabolized by other pathways. There were no significant interactions with 1A2, 2C9, 2C19 or 2D6 reported across the clinical dose range.²¹ The drug information resource, Lexicom²², also reports 1A2 to be a minor metabolizer of ziprasidone and for ziprasidone to be a weak inhibitor of 2D6. Smoking, an inducer of 1A2 has been reported to have no clinically significant effects on the kinetics of ziprasidone.¹⁷

Although ziprasidone is highly protein bound, the manufacturer reports no interactions with warfarin or propranolol.¹⁶ In a study by Apseloff²³, ziprasidone was not found to affect serum lithium levels

QTc Interval prolongation interactions - Drugs that are known to prolong the QT interval are contraindicated in all cases and include sotalol, quinidine, other class Ia and II antiarrhythmics, thioridazine, chlorpromazine, droperidol, pimozide moxifloxacin and mefloquine as well as any other drugs shown to cause this effect.

There is one case report of sudden cardiac arrhythmia, extrasystoles and prolonged QTc interval on a combination of quetiapine and ziprasidone. The authors attributed this to the common 3A4 metabolic pathway.²⁴

There is evidence for a plasma level related effect on QT and QTc. When cross-tapering other antipsychotics with ziprasidone it is suggested to avoid cross-tapering with drugs like pimozide or thioridazine and to keep the combined dose low.¹⁵

Precautions²⁵

Cardiac - Ziprasidone is contraindicated for use in patients with a known history of QT prolongation, recent acute myocardial infarction or uncomplicated heart failure or with use of other agents known to prolong the QT interval (see drug interactions). In one study ziprasidone was shown to prolong the QT interval by a mean of 9-14 msec more than that observed in patients on risperidone, olanzapine, quetiapine or haloperidol but 14 msec less than those on thioridazine. Although torsades de pointes was not associated with ziprasidone in premarketing studies, it cannot be ruled out that it may be associated with an increased risk of sudden death. Patients at risk for torsades de pointes include those with bradycardia, hypokalemia, hypomagnesemia, congenital prolongation of QTc and those received other drugs prolonging the QTc interval.

Geriatric dementia - As with other atypical agents, its use is not approved in geriatric patients with dementia-related psychosis due to an analyses of 17 placebo controlled studies showing a 1.6 - 1.7 increased incidence of mortality in this population.

Rash – 5% incidence requiring discontinuation in 17% of individuals

Toxicity

The few reported cases of overdose with oral ziprasidone suggest relative safety, although transient hypotension and hypertension have been noted.²⁶

Dosing and Administration²⁵

Ziprasidone hydrochloride is administered orally twice daily with food.

Schizophrenia:

Initial - 40 mg twice a day and increase to a maximum of 80 mg twice a day after a minimum of two days. The safety of doses over 100 mg twice daily has not been established.

Elderly – no dose changes recommended although the elderly have been reported to have serum concentrations that are 20% higher than younger subjects.¹⁶

Hepatic dysfunction has been reported to result in a 20-35% increase in serum levels.
Renal dysfunction has not been reported to affect levels.

Bipolar Disorder:

Acute mania and mixed episodes – 40 mg twice daily on day one. Dosage can then be increased to 60 or 80 mg twice daily on the second day of treatment. Treatment beyond three weeks in bipolar disorder has not been established.

Availability

Ziprasidone is available as an oral tablet in doses of 20, 40, 60 and 80 mg.

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