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DRUG BULLETIN

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Ziprasidone Unzipped

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Introduction

Ziprasidone is an atypical antipsychotic that has been available in North America since 2001 and is currently approved for use in approximately 70 countries[1]. It was approved for use in Australia in late 2006 and was Commonwealth-subsidised for all Australian patients with approved conditions through the Pharmaceutical Benefits Scheme as of 1 April 2007[2]. Several pharmacodynamic properties of this drug offer promise for useful distinguishing features; experience and clinical trials have however not borne out all of this promise. Pfizer markets Ziprasidone in Australia, under the trade name Zeldox®[3]. It is also marketed overseas under the trade name Geodon®.

Relevant pharmacodynamics

Ziprasidone shares the core receptor activity that most other atypical antipsychotics feature – namely, dopamine D2 receptor antagonism coupled with serotonin $5HT_{2A}$ antagonism, with far greater affinity for the latter[4]. Ziprasidone is the only atypical antipsychotic that is a $5HT_{1D}$ antagonist, a $5HT_{1A}$ agonist, and inhibits both serotonin and noradrenaline reuptake. **Table 1 summarises some potentially important binding properties of ziprasidone.** Ziprasidone exhibits relatively little antagonism at histamine H_1 and cholinergic M_1 receptors, and mild antagonism at the $alpha_1$ adrenergic receptor, which explains its favourable adverse effect profile compared with many other antipsychotics[5].

Property	Theoretical effects
D_2 antagonism	Reduction in positive symptoms of schizophrenia Extrapyramidal syndrome Prolactin elevation
$5HT_{2A}$ antagonism	Reduction of extrapyramidal side effects and hyperprolactinaemia Possible improvement in negative symptoms
5HT and NA reuptake blockade	Antidepressant effect Anxiolytic effect
$5HT_{1D}$ antagonism	Antidepressant effect through increased serotonin release
$5HT_{2C}$ antagonism	Antipsychotic effect Weight gain
$5HT_{1A}$ agonism	Improved mood and cognition
H_1 antagonism	Weight gain and sedation
α_1 antagonism	Postural hypotension
M_1 antagonism	Dry mouth, blurred vision, constipation, urinary retention Mitigation of extrapyramidal syndrome

Table 1: Selected receptor binding properties of ziprasidone[4,5]

Key: D = dopamine; 5HT = 5-hydroxytryptamine (serotonin); NA = noradrenaline; H= histamine; α= alpha adrenergic; M= muscarinic (cholinergic)

Relevant pharmacokinetics

Oral bioavailability of ziprasidone is not complete and averages approximately 60% of the ingested dose when taken with food. Taking ziprasidone without food may decrease bioavailability by up to a half[3]. **Hence, ziprasidone should always be given with food**. The drug is highly plasma protein-bound, though this has not led to any significant interaction with other highly bound drugs in trials to date. Metabolism to ziprasidone's inactive metabolites is largely (approximately two-thirds) via aldehyde oxidase, with the remainder accounted for by CYP 3A4[6]. No clinically significant pharmacokinetic drug interactions have been thus far observed with ziprasidone[3]. Ziprasidone's plasma half-life is variable with dose and duration of therapy, but is generally around 6 to 10 hours, necessitating twice-daily dosing[7].

Place in therapy

The Therapeutic Goods Administration has approved ziprasidone for use in Australia for the indications of schizophrenia and related psychoses, and as monotherapy for acute manic or mixed episodes associated with bipolar I disorder. It is *not* approved for treatment-resistant schizophrenia. It has not been directly compared with clozapine and has not proven superior efficacy over the other non-clozapine atypical antipsychotics[3].

Schizophrenia and related psychoses

Ziprasidone has consistently shown superior efficacy to placebo for acute exacerbations of schizophrenia and schizoaffective disorder, and equivalence to haloperidol, olanzapine and risperidone on relevant symptom domains in the acute setting[8].

Ziprasidone has also shown superiority to placebo in long-term maintenance treatment of schizophrenia and related disorders[8]. Comparison with other atypical antipsychotics has been a little more controversial; comparative trials funded or otherwise supported by olanzapine's manufacturer, Eli Lilly, have shown olanzapine to be superior to ziprasidone in treating symptoms of schizophrenia as measured by relevant rating scales, but the clinical significance of these findings has been disputed[8,9]. Pfizer-sponsored studies of similar nature have failed to detect a difference in efficacy between the two drugs[10,11]. Phase I of the multi-centre, long-term Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found olanzapine to be the only antipsychotic that could be separated from all others in the trial (including ziprasidone) with statistical significance, and found it to be superior in terms of the trial's primary outcome measure of treatment discontinuation for any reason[12]. Ziprasidone was also studied in CATIE phase II, where patients entered this phase after discontinuation of phase I medication due to poor tolerability. It was expected that patients would remain on ziprasidone longer than the other antipsychotics due to its favourable adverse effect profile, however the time to discontinuation for any reason was significantly shorter for ziprasidone than with olanzapine or risperidone but did not differ for quetiapine[13].

Bipolar affective disorder

The evidence for efficacy of ziprasidone in bipolar affective disorder is limited to short-term studies (3- and 12-week) in a total of 850 patients, all assessing ziprasidone's efficacy in treating manic symptoms associated with bipolar I. Ziprasidone was found to be effective in reducing Mania Rating Scale and Clinical Global Impression-Severity scores when compared to placebo[3].

Does ziprasidone treat depression?

No studies have shown ziprasidone to be uniquely effective among the atypical antipsychotic drugs in treating depressive symptoms, despite ziprasidone's favourable pharmacodynamic properties. In a head-to-head comparative trial with olanzapine in patients with schizophrenia or schizoaffective disorder, ziprasidone showed a similar order of efficacy in treating depressive symptoms[14,15,16]. When depressive symptoms have been examined as a secondary outcome measure in various clinical trials, ziprasidone-treated patients have shown improvement; but again, no evidence exists to suggest that this improvement would be any less so than with other atypical antipsychotics were they used as comparators[17].

Ziprasidone has been shown to be effective as an augmenting agent with selective serotonin reuptake inhibitors in treatment-resistant depression, as have other atypical antipsychotics[18].

Safe use of ziprasidone

Among the most common adverse effects reported with ziprasidone are gastrointestinal symptoms such as nausea and dyspepsia, somnolence, dizziness, headache and rash[3]. **Table 2 summarises the relative incidence of some of the classic side effects of various antipsychotics.**

Metabolic effects

The metabolic adverse effect profile of ziprasidone warrants particular mention.

Weight gain, while it still may occur, is far less frequent with ziprasidone than with olanzapine, risperidone and quetiapine and may be less common than with amisulpride[8]. Aripiprazole and ziprasidone

	Anticholinergic effects	Sedation	Hypotension	EPSE	Prolactin Elevation	Weight gain	Relative risk of QTc Prolongation	Significant risk of diabetes	Significant risk of worsening of lipid profile
Amisulpride	0	+	+	++	++	+	High	No	No
Aripiprazole	0	++	+	+	0/+	+	Low	No	No
Clozapine	+++	+++	+++	+	0/+	+++	High	Yes	Yes
Olanzapine	++	+++	+	+	+	+++	Low	Yes	Yes
Quetiapine	+	+++	++	+	0/+	++	High	Discrepant results	Discrepant results
Risperidone	0	++	+++	++	++	++	High	Discrepant results	Discrepant results
Ziprasidone	**+**	**++**	**+**	**+**	**+**	**+**	**High**	**No**	**No**

Table 2: Selected adverse effect profiles of the atypical antipsychotics[3]
Key: 0(<2%)=absent or negligible; +(>2%)= infrequent; ++(>10%)= moderately frequent; +++(30%)= frequent

share a similar incidence of clinically relevant weight gain.

Ziprasidone also has a low propensity for causing dyslipidaemia and has shown favourable effects on triglycerides, low-density lipoprotein and total cholesterol when compared directly with olanzapine in clinical trials[8]. While the statistical and clinical significances were undetermined, ziprasidone, along with risperidone, showed decreases in cholesterol and triglyceride levels where olanzapine and quetiapine showed increases in the CATIE trial[12].

Impaired glucose tolerance and hyperinsulinaemia occurs much less frequently with ziprasidone when compared with most other atypical antipsychotics. This may put patients treated with ziprasidone at a lower risk of developing type II diabetes mellitus than patients treated with higher-risk drugs such as olanzapine or quetiapine, particularly where other risk factors are present.

Despite the unlikelihood of metabolic adverse effects occurring with ziprasidone, it is always prudent to consider baseline and periodical evaluations of body mass index, fasting glucose and fasting lipids for all patients on antipsychotic therapy[19]. As the long-term effects of ziprasidone may not be well known, there is the possibility that long-term treatment with ziprasidone, may lead to an increased probability of these effects occurring. In addition, patients with schizophrenia are at an increased risk of cardiovascular disease and death regardless of antipsychotic therapy[20].

Cardiovascular effects

The controversy surrounding ziprasidone as being an antipsychotic with a higher risk of QTc prolongation and possibly torsade de pointes needs to be understood in context[21]. While ziprasidone does appear to cause a greater degree of QTc prolongation than the other atypical antipsychotics, the average interval lengthening of 20ms in one study was significantly less than that of thioridazine, and torsade de pointes and sudden death have not been conclusively associated with ziprasidone[8]. Ziprasidone is therefore now generally considered as safe as the other atypical antipsychotics with respect to cardiac arrhythmias.

Nonetheless, ziprasidone should be used with particular caution in patients at risk of QTc prolongation and/or torsade de pointes. This includes patients taking Type IA antiarrhythmics (quinidine, disopyramide, procainamide), Type III antiarrhythmics (sotalol, amiodarone) and other QTc-prolonging drugs (eg macrolide antibiotics); patients with a congenital long QTc syndrome; and patients with or at risk of electrolyte disturbances including hypokalaemia, hypocalcaemia and hypomagnesaemia, including patients taking diuretic drugs[3]. The utility of ongoing electrocardiogram and electrolyte monitoring in patients without such risk factors is debatable, though baseline tests may be worthwhile[19].

Prescribing ziprasidone

The recommended dose of ziprasidone for schizophrenia and bipolar disorder is 40mg twice daily with food. If clinically required, the dose can be increased by increments of 20mg twice daily up to a maximum dose of 80mg twice daily. The maximum dose can be reached as early as day 3 of treatment.

There is some published information suggesting that some patients on lower doses (20-40mg twice daily)

of ziprasidone experience 'activating' effects that can present as a worsening of symptoms. It has been postulated that an increase in dose to 60mg-80mg twice daily would be beneficial to overcome this activation as a greater level of D_2 antagonism will overcome such side effects[19]. This potential problem is also cited as the reason that ziprasidone should be rapidly upwardly titrated at commencement of therapy[1].

Although open studies suggest that patients can successfully switch to ziprasidone by cross-titration, partial overlap or by having a washout period, clinical experience suggests that many patients have a good outcome by adding ziprasidone to the first antipsychotic and then reducing the dose of the first antipsychotic after 3 weeks[19,22]. However, this switch strategy is not recommended when switching from an antipsychotic known to prolong the QTc interval.

While ziprasidone is listed on the Pharmaceutical Benefits Scheme, its only listed indication is schizophrenia. Prescribers should therefore be aware that outpatients might not be able to access the medication if they have not been diagnosed with schizophrenia. A four-week supply of ziprasidone at a dose of 160mg per day would cost the patient approximately $400. Ziprasidone is available in 20mg, 40mg, 60mg and 80mg capsules in packs of 60 for oral administration.

Conclusion

Ziprasidone is an atypical antipsychotic characterised by a low incidence of metabolic adverse effects and similar efficacy to other non-clozapine atypical antipsychotics. While there has been some concern about its cardiac effects, these are unlikely to be clinically significant in most patients.

Beta-lactam Use in Patients With a History of Penicillin Allergy

A recent letter to Australian Prescriber drew attention to the issue of cross-reactivity between penicillin and cephalosporin allergies[23]. In a six-month period (December 2005 to May 2006) in western Sydney the authors noted four serious adverse reactions to cephalexin prescribed to patients with a documented history of rash with amoxicillin. Two of the four cases resulted in death.

Though anaphylaxis induced by penicillins is rare (0.01-0.05% of exposures) and even less common with cephalosporins, there is an increased risk of serious reactions to cephalosporins in patients with a history of a reaction to a penicillin. The rate of cross-reactivity is frequently cited as 5-10% and the risk of cephalosporin allergy is four-fold greater in patients with a history of penicillin allergy than in the general population[24,25,26]. Since the death rate with anaphylaxis is high (at least 10%)the risk is not insignificant[23,24,25].

Anaphylaxis is an immediate or Type I hypersensitivity reaction mediated by IgE antibodies causing mast cells to release histamine and other inflammatory compounds. An initial sensitising exposure is necessary for these IgE antibodies to be formed. Type I hypersensitivity reactions (immediate type hypersensitivity) are typified by urticaria, angioedema, bronchospasm or anaphylaxis within one hour of drug administration[23]. Hypotension, hypoxia, and serum tryptase elevation are objective measures.

Any history of a Type I hypersensitivity reaction to a beta-lactam antibiotic or other life-threatening reaction (eg Stevens-Johnson syndrome) contraindicates the use of any penicillin, cephalosporin or carbapenem in that patient[23].

Often the precise nature of the allergy (whether immediate or delayed and mild) cannot be determined. In these cases, if it is decided that a cephalosporin should be used then the first dose must be given in a monitored setting with resuscitation equipment available.

Generally, in cases where the previous reaction was mild and delayed then a cephalosporin may be used, but only with caution[27].

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