

ZIPRASIDONE — AN ATYPICAL ANTIPSYCHOTIC

By David Taylor, MSc, MRPharmS

In this article, the author reviews ziprasidone, an atypical antipsychotic currently licensed in Sweden and the United States, and its use in schizophrenia. He suggests that further trials and more clinical experience are necessary before the drug's place in therapy can be established

Ziprasidone is an atypical antipsychotic, structurally unrelated to any other antipsychotic, with an unusual combination of pharmacological actions. It is a potent antagonist at 5-HT_{2A}, D₂, 5-HT_{2C}, and 5-HT_{1D} receptors, an agonist at 5-HT_{1A} receptors and an inhibitor of 5-HT and noradrenaline reuptake. Ziprasidone has an elimination half-life of up to 10 hours and is given twice daily immediately after food. Dose changes are not required in old age, mild renal failure, or moderate hepatic failure. Ziprasidone appears to be involved in very few pharmacokinetic drug interactions; it does not inhibit to an important extent any known cytochrome enzymes.

Human efficacy studies indicate that ziprasidone is effective in the treatment of positive, negative and depressive symptoms of schizophrenia and schizoaffective disorder. It appears to be well tolerated and to cause few, if any, extrapyramidal adverse effects or symptoms relating to hyperprolactinaemia. Weight gain is uncommon.

No serious adverse events have so far been reported. Ziprasidone has not been properly compared with other atypicals or subjected to widespread clinical use. Its relative efficacy and tolerability compared with established atypicals are therefore impossible to establish at this early stage.

Intramuscular ziprasidone appears to be effective in the treatment of acute psychosis with agitation. This preparation has been suggested to be at least as effective as intramuscular haloperidol but may have a faster onset of action and does not appear to engender extrapyramidal adverse effects, hypotension, or profound sedation. Intramuscular ziprasidone has not been compared with benzodiazepine/neuroleptic combinations.

While data at present are incomplete, ziprasidone appears to offer promise as a worthwhile alternative to other typical and atypical antipsychotics. Further trials and greater clinical experience are needed to establish ziprasidone's place in therapy.

CHEMISTRY

Ziprasidone (formerly CP88,059-1) is a benzothiazolylpiperazine compound which is structurally unrelated to any available antipsychotic drug.¹ Its chemical structure is shown in Figure 1.

PHARMACOLOGY

Receptor activity — *in vitro* The importance of nuances in receptor activities with different drugs is often overstated. In fact, our knowledge of receptor effects in schizophrenia is somewhat limited. Nevertheless, *in vitro* affinities and, perhaps more importantly, *in vivo* occupancies do help predict antipsychotic activity and, with more certainty, the likelihood of a number of adverse effects. Table 1 (see p397) summarises current knowledge of the effect of various receptor activities (adapted from a comprehensive review²).

For individual antipsychotics, *in vitro* receptor activities vary slightly according to the source of animal tissue and the method and ligands used. There is agreement,¹⁻³ however, that ziprasidone has high affinity for D₂, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1D} receptors, moderate affinity for 5-HT_{1A} and H₁ receptors and very low activity at 5-HT_{2B}, 5-HT₃, 5-HT₄, and M₁ (muscarinic) receptors.

Ziprasidone is distinguished from other atypical antipsychotics by a novel *in vitro* binding profile (see below) and by markedly different activity on some neuronal functions. It is a potent agonist at 5-HT_{1A} receptors⁴ an activity which is thought to predict anxiolytic or antidepressant activity.² Ziprasidone is also an inhibitor of the neuronal reuptake of serotonin and noradrenaline (actions also predictive of antidepressant activity) with similar *in vitro* potency to amitriptyline.⁵ Also, ziprasidone has potent activity at 5-HT_{1D} receptors and so may inhibit serotonin release. This also has been

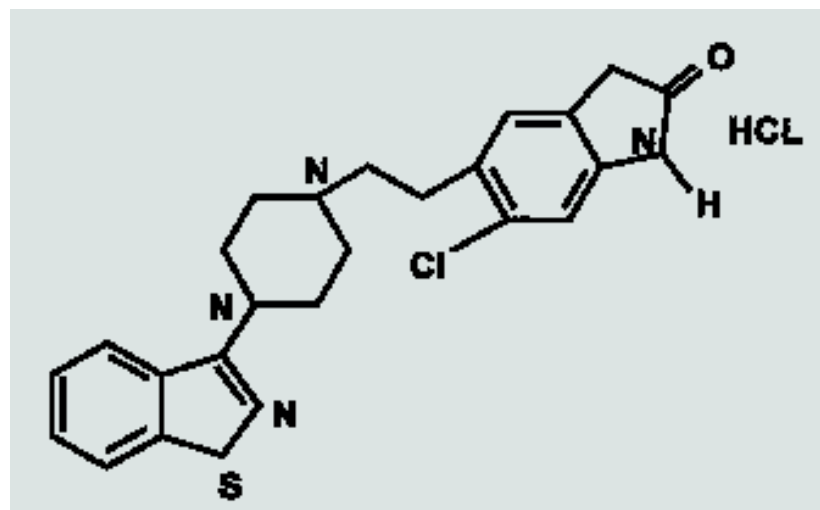


Figure 1: Ziprasidone's chemical structure is 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-chloro-1,3-dihydro-2(1H)-indole-2-one

suggested as being predictive of antidepressant activity. In addition, ziprasidone has a very high 5HT_{2A}/D₂ receptor binding ratio,³ a property which is thought to indicate a low potential for extrapyramidal symptoms. Finally, ziprasidone's effects at H₁ and 5-HT_{2C} receptors are theoretically consistent with weight gain, although this seems not to be borne out in practice (see later).

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Receptor activity — *in vivo* Measurements of *in vivo* receptor occupancy are also subject to variation according to methods and ligands used, but their values are probably more dependable predictors of therapeutic

TABLE 1: RECEPTOREFFECTSOZIPRASIDONE

Receptor activity	Clinical effect
D ₁ antagonism	Not known. May impair cognitive function if potent
D ₂ antagonism	Relief of positive symptoms. Induction of extrapyramidal symptoms. Rise in prolactin
D ₃ antagonism	Not known, but no antipsychotic effect
D ₄ antagonism	Not known, but no antipsychotic effect
D ₅ antagonism	May inhibit reproductive behaviour. No antipsychotic effect
5-HT _{1a} agonism	Possible antidepressant/anti-anxiety effects
5-HT _{2a} antagonism	Probable improvement in negative symptoms and cognitive impairment. May attenuate extrapyramidal symptoms
5-HT _{2c} antagonism	Possible anxiolytic. May attenuate rise in prolactin. Probably contributes to weight gain. Limited evidence of antipsychotic effects
5-HT ₃ antagonism	Antiemetic. Other effects not known
5-HT ₄ , 5-HT ₅ , 5-HT ₆ , 5-HT ₇ , antagonism	Not known
α ₁ antagonism	Sedation, hypotension, reflex tachycardia
α ₂ antagonism	May improve depression and negative symptoms
H ₁ antagonism	Sedation. Contributed to weight gain
H ₂ antagonism	Anticholinergic adverse effects. Limited evidence of antidepressant effects

and adverse effects. The technology for evaluating *in vivo* receptor activity is relatively new and expensive. Partly as a result, there are fewer data available pertaining to *in vivo* activity of ziprasidone but they do largely bear out *in vitro* findings.

Positron emission tomography (PET) has been used to assess human *in vivo* activity at D₂ and 5-HT₂ receptors. Using ¹¹C-raclopride as a specific D₂ receptor ligand, a single dose of 40mg ziprasidone produced 77 per cent occupancy.² Two further PET studies⁶ using ¹¹C-raclopride as a D₂ ligand and ¹⁸F-setoperone as a 5-HT₂ ligand essentially confirmed *in vitro* observations of high 5-HT₂/D₂ ratio of activity. A dose of 40mg twice daily was predicted to provide 5-HT₂ occupancies of 80 per cent to 90 per cent while at the same time affording D₂ occupancies of 45 per cent to 75 per cent. This preferential effect *in vivo* on 5-HT₂ receptors is predictive of a low incidence of extrapyramidal side effects, as are low rates of D₂ occupancy.

Another important consideration, and one which is thought to affect changes in negative symptoms, is *in vivo* activity in the prefrontal cortex. Drugs that promote dopamine release in this area are thought to improve negative symptoms. Both ziprasidone and clozapine have

been shown to promote dopamine release in rat prefrontal cortex.⁷ This seems at least partly to be mediated via 5-HT_{1a} agonism (clozapine is a partial agonist).

Animal behavioural studies

Animal behavioural studies indirectly indicate that ziprasidone affords potent *in vivo* D₂-blockade in rats (it suppresses amphetamine-induced hyperactivity and apomorphine-induced stereotypy) along with relatively more potent effects on 5-HT₂ receptors (it suppresses quiazapine-induced head twitching at lower doses).⁸ Ziprasidone, like risperidone, is much less potent in inducing catalepsy and decreasing spontaneous locomotion.¹

Taken together, these observations predict antipsychotic activity with low or minimal levels of extrapyramidal side effects.

PHARMACOKINETICS

Ziprasidone shows a plasma half-life of 3.2 to 10 hours in healthy males.^{3,9} Time to peak plasma level is quite long at around four to five hours. Steady state levels are attained after one to three days^{9,10} and peak-to-trough concentration ratio ranges from 2 to 5 in twice daily dosing.⁹ The results of a small-scale trial in elderly and young healthy volunteers¹⁰ suggest that gender and age have a clinically unimportant effect on ziprasidone pharmacokinetics.

Administration of food, however, has an important effect on ziprasidone absorption. Absorption is doubled by the presence of food providing an absolute bioavailability of around 60 per cent.^{1,3}

These observations have led to the establishment of a standard "twice daily, with food" dosing regimen in males and females of all ages.

In humans, ziprasidone is metabolised to ziprasidone sulphoxide and then to ziprasidone sulphone — reactions which appear to be catalysed by the hepatic cytochrome CYP3A4.¹¹ Other enzymes appear not to be involved in ziprasidone metabolism. Ziprasidone does not inhibit cytochromes CYP3A4¹¹ or CYP2D6^{11,12} to a clinically important extent and so pharmacokinetic interactions involving these enzymes are not expected.

Neither renal impairment¹³ nor mild to moderate hepatic impairment¹⁴ appear to have an important effect on ziprasidone pharmacokinetics. Hepatic impairment does extend plasma half-life by around two

hours,¹⁴ but renal impairment of any severity has essentially no effect on elimination half-life. This is to be expected, since only 1 per cent of a given dose of ziprasidone is excreted unchanged.

Ziprasidone metabolites appear to have little clinical activity,¹ although this needs to be confirmed in human *in vivo* studies.

INTERACTIONS

As already mentioned, ziprasidone appears not to inhibit the activity of CYP3A4 or CYP2D6. Ziprasidone is, therefore, unlikely to affect plasma levels of co-administered drugs metabolised by these enzymes. Prospective studies have also shown that ziprasidone does not affect to an important degree the pharmacokinetics of co-administered combined oral contraceptives¹⁵ or to any degree the clearance of lithium.¹⁶

Of course, another major consideration is the potential effects of co-administered drugs on the pharmacokinetic profile of ziprasidone. Inducers (eg, carbamazepine) or inhibitors (eg, norfluoxetine, nefazodone) of CYP3A4 might be expected to alter the metabolism of ziprasidone. However, the CYP3A4 inhibitor cimetidine had only a marginal effect on ziprasidone pharmacokinetics in a prospective trial (half-life increased from 3.81 to 3.93 hours [not significant]).¹⁷ This might indicate that ziprasidone has alternative routes of metabolism when CYP3A4 is inhibited. In the same trial,¹⁷ the co-administration of the antacid Maalox delayed time to peak plasma level by three hours (eight vs 11 hours). This is, in the author's view, unlikely to be a clinically important effect.

In vitro experiments¹¹ indicate that ziprasidone has little effect on the cytochromes CYP1A2, CYP2C9 or CYP2C19. If these properties are reflected in humans, interactions involving these enzymes are unlikely.

Ziprasidone is very highly (>99 per cent) protein bound and this may lead to pharmacokinetic interactions, albeit short-lived ones, with other highly bound drugs. The occurrence and importance of this type of reaction are yet to be clearly determined.

CLINICAL EFFICACY

Clinical efficacy studies in schizophrenia and schizoaffective disorder assess symptom changes using recognised, validated rating scales. Broad-based measures include the 18-item Brief Psychiatric Rating Scale (BPRS), the more comprehensive 30-item Positive and Negative Symptom Scale (PANSS), and the rudimentary but meaningful Clinical Global Impression (CGI).

Positive symptoms (hallucinations, delusions, etc) are usually evaluated using the positive symptom subscales (ie, only those items relating to positive symptoms) of the BPRS or PANSS. Negative symptoms (lack of volition, poverty of speech, etc) are better assessed using the negative subscale of the PANSS or by specific rating scales such as the Schedule for Assessment of Negative symptoms (SANS). Other scales for

efficacy assessment include the Montgomery-Asberg Depression Rating Scale (MADRS), the Quality of Life Scale (QLS) and the Global Assessment of Functioning (GAF).

Adverse effects are also systematically evaluated using validated scales. These include the Simpson-Angus Scale (SAS — acute extrapyramidal symptoms), the Barnes Akathisia Scale (BAS) and the Abnormal Involuntary Movement Scale (AIMS — tardive dyskinesia).

Schizophrenia An early dose-ranging clinical study of ziprasidone in schizophrenia and schizoaffective disorder¹⁸ (Pfizer study code number 101) suggested that ziprasidone 160mg/day was as effective as haloperidol 15mg/day as assessed using the BPRS and CGI scales. However, lower doses of ziprasidone (4mg, 10mg, 40mg/day) were shown not to be effective.

Another 28-day study¹⁹ (study 106) in a similar patient group compared two doses of ziprasidone (40mg and 120mg/day) with placebo. Only the higher dose of ziprasidone was shown to be superior (BPRS, CGI) to placebo. Differences in the treatment of negative symptoms assessed by the SANS were not significant, but ziprasidone 120mg/day did appear effective in treating depressive symptoms (evaluated using BPRS anxiety-depression cluster [a rather crude measure]).

Another trial (code 114) compared two doses of ziprasidone (80mg and 160mg/day) with placebo over six weeks.²⁰ Both doses of ziprasidone were found to be superior to placebo overall (BPRS, CGI) and in the treatment of negative symptoms (PANSS, negative subscale). Results for the higher dose of ziprasidone were numerically but not significantly superior to the lower dose. Ziprasidone was statistically superior to placebo on most measures after only seven days. Using the MADRS scale, ziprasidone 160mg/day was found to be effective in treating depressive symptoms in those patients showing clinically significant depression at baseline (cited in reference 21).

The longest ziprasidone trial completed to date is study 303, a 52-week evaluation of three doses (40mg, 80mg and 160mg/day) of ziprasidone compared with placebo in stable patients with moderate to severe negative symptoms.²² All doses of ziprasidone were superior to placebo in relapse prevention, in the treatment of negative symptoms (PANSS) from 16 weeks onwards, and in improving overall functioning (GAF) (at 52 weeks). There were no differences between active treatments.

Details of study 304 have recently become available (see Hirsh *et al.*²³). Ziprasidone (80–160mg/day) was compared with haloperidol (5–15mg/day) over 28 weeks. Few clear differences between treatments were uncovered, but there were significantly more negative symptom “responders” in the ziprasidone group (48 per cent) than in the haloperidol group. (Response was defined as a 20 per cent fall in PANSS negative sub-scale.) Both treatments were broadly effective.

Only one small study has evaluated the effect of ziprasidone on cognitive function (study 117)²⁴ — a known deficit in schizophrenia, partly improved by drugs such as clozapine. In this study, subject numbers were too small to allow drawing of meaningful conclusions.

Anxiety The pharmacology of ziprasidone is predictive of anxiolytic activity in humans. Study code 009 compared oral doses of ziprasidone 20mg, diazepam 10mg and placebo given three hours before dental surgery.²⁵ When a self-evaluation scale for anxiety was used, diazepam was shown to be superior to placebo and ziprasidone at one hour, but ziprasidone (not diazepam) was superior to placebo at three hours. Investigator ratings confirmed the rapid onset of activity with diazepam with a slower onset for ziprasidone. Diazepam was significantly more sedative than ziprasidone, but ziprasidone could not be distinguished from placebo in this respect.

Acute psychosis Ziprasidone is unusual among atypical antipsychotics in that a parenteral preparation of it has been provisionally evaluated in the treatment of acute psychosis. A simple intramuscular injection of ziprasidone mesylate has been investigated in a number of studies.

An uncontrolled pilot study in 12 patients with acute psychosis (mean BPRS around 48) evaluated IM ziprasidone (twice to four times daily) in doses of 10mg to 60mg/day over three days, followed by two days of oral ziprasidone 80 to 160mg/day (study 120).²⁶ Patients showed a reduction in symptoms, particularly hostility and excitement, while on IM therapy and maintained these improvements when switched to oral therapy.

A larger (n=132) open study²⁷ (study 306) compared IM ziprasidone (10mg initially, then 5–20mg *qds*) with IM haloperidol (2.5mg initially, then 5–10mg *qds*) given for three days followed by four days of oral therapy. Ziprasidone produced a statistically greater reduction in scores for BPRS and CGI.

IM antipsychotics are often used in the short term to control problem behaviours as much as for their antipsychotic activity. However, rating scales such as the BPRS and NOSIE are not specific measures of behavioural disturbance and are thus not ideal measures of acute response to IM antipsychotics. In addition, many rating scales are readily affected by the degree of sedation provoked by IM antipsychotics. Sedation, particularly if severe, is usually not desirable or necessary, but is essentially a by-product of the use of many drugs.

The Behavioural Activity Rating Scale (BARS)²⁸ has been developed to evaluate changes in behavioural activity. It is a seven-point scale, ranging from profound sedation (1 = “difficult or unable to rouse”) through to profound agitation (7 = “violent, requires restraint”). The aim of treatment is to reduce scores to a level of 4 (“quiet and awake [normal level of activity]”) or just below. The BARS has been carefully validated and

provides clinically meaningful information which may be more sensitive to change than other broader measures.²⁸

Three studies of IM ziprasidone have used the BARS as one part of a small battery of tests, usually including CGI scale and selected items from PANSS. In study 121, three doses of IM ziprasidone (20mg, 40mg and 80mg/day given *qds*) were compared with haloperidol 10–40mg/day given mostly twice daily over three days. Subjects were then switched to oral therapy for a further four days.²⁹ All ziprasidone regimens gave an abrupt response on BARS, whereas the response to haloperidol emerged more slowly (peak effects at two hours and four hours, respectively). There were no differences between treatments evaluated using the BPRS agitation scale over the full seven-day period and all showed a moderate effect on psychosis as a whole (BPRS total scores fell by around 6 or 7 points).

Studies 125³⁰ and 126³¹ compared high and low doses of IM ziprasidone given for one day. In study 125, ziprasidone 10mg given two-hourly up to four times daily was found to be significantly more effective (BARS, CGI, PANSS agitation item) than 2mg IM (a pseudo placebo) given in a similar regimen.³⁰ Using similar measures in study 126, ziprasidone 20mg given four-hourly up to four times a day was found to be more effective than 2mg IM. Effects of IM ziprasidone peaked at two hours (BARS score = 2 to 3) and lasted at least four hours.³¹

Data from 483 patients and healthy volunteers have been used to estimate population pharmacokinetics of intramuscular ziprasidone.³² Plasma levels obtained appear to be dose-related and affected in a linear fashion by bodyweight and body surface area. Age, gender, renal function and liver function seem not to affect to an important extent the pharmacokinetic parameters of intramuscular ziprasidone.

Population pharmacokinetics indicate that peak plasma levels are obtained within 30 minutes of injection of IM ziprasidone, with steady state being reached within one day following repeated administration.³³ Measured plasma half-life ranges from 3.8 hours on the first day of treatment to 10.4 hours on the third day, although accumulation does not occur.³³

ADVERSE EFFECTS AND TOLERABILITY

Acute extrapyramidal side effects Acute extrapyramidal side effects (Parkinsonism, dystonia and akathisia) are commonly seen with typical antipsychotics and obviously have an important effect on patient morbidity. These adverse effects are decidedly unpleasant and may also adversely contribute to negative symptom severity (by inducing so-called “secondary” negative symptoms).

Atypical antipsychotics generally do not give rise to acute extrapyramidal side effects (EPS) at clinically effective doses, although some — risperidone, for example — do cause extrapyramidal side effects at higher,

licensed doses. With ziprasidone, EPS are rarely seen. For example, study 101¹⁸ showed that the higher dose of ziprasidone (160mg/day) did not worsen EPS from baseline (SAS) and overall anticholinergic use was lower with ziprasidone (15 per cent) than with haloperidol (53 per cent). Study 106 revealed a similar low liability for EPS: only three of 47 patients receiving ziprasidone 120mg/day reported EPS (although nine received benztropine) and neither dose of ziprasidone differed significantly from placebo on measures for EPS.¹⁹ There is, however, some suggestion of a minor dose-related incidence of EPS. For example, in study 114, 6.7 per cent of patients receiving 160mg/day reported EPS, compared with 1.9 per cent on 80mg/day and 1.1 per cent with placebo (statistical analysis not given).²⁰ Nevertheless, the longest study to date of oral ziprasidone²² showed that overall patient scores on the BAS and, particularly, on the SAS demonstrated improvement over baseline for all doses of ziprasidone and could not be distinguished from placebo. Note also that in all comparator trials, EPS were significantly more common with haloperidol than with any dose of ziprasidone.

Acute EPS are also uncommon with parenteral ziprasidone. Apparently, no emergent EPS of any sort was observed in study 120.²⁶ In study 121,²⁹ EPS were less common with ziprasidone (0–4 per cent) than with haloperidol (15 per cent) and benztropine use was twice as high in the haloperidol group. Similar results were obtained in study 306²⁷: anticholinergic therapy was given to 14 per cent of those on ziprasidone and 48 per cent of those on haloperidol. Moreover, in studies 125 and 126, only one patient reported akathisia, only two “EPS” (both on 2mg IM schedule) and all doses showed improvement in EPS as evaluated by SAS and BAS.²⁸ Benztropine use was low (around 10–15% of patients) and no dose-response effect was evident.

In summary, both oral and IM ziprasidone are significantly less likely to engender EPS than is haloperidol. Symptoms of EPS are only rarely observed with any dose of ziprasidone up to 160mg/day and use of benztropine is uniformly low. All trials using SAS and BAS to evaluate EPS show mean improvement in patients receiving ziprasidone.

Tardive dyskinesia Tardive dyskinesia is a syndrome which involves abnormal involuntary movements, usually of the mouth and tongue, but occasionally involving the face, neck and trunk. These abnormal movements are sometimes seen in untreated schizophrenia, but are especially common in patients receiving typical antipsychotics, particularly those who experience acute EPS early in therapy. The accepted incidence of tardive dyskinesia is around 4–5 per cent per year in those taking typical antipsychotics.

Tardive dyskinesia is usually cosmetically undesirable rather than functionally dangerous. However, the potentially profound effects on patients' quality of life should not be underestimated, nor indeed should the

palpably stigmatising effect of this syndrome. Since atypical drugs have, by definition, a low incidence of acute EPS (a known risk factor for tardive dyskinesia), it is hoped that some or all of these drugs will give rise to a correspondingly low incidence of tardive dyskinesia. This hope has materialised with clozapine, with which tardive dyskinesia is extremely rare. With other drugs, evidence of lower rates of tardive dyskinesia are accumulating, but are by no means unequivocal.

Only the year-long study 303²² is valuable in assessing ziprasidone's influence on tardive dyskinesia. Although emergence of tardive dyskinesia was not evaluated, all doses of ziprasidone showed either small reductions in AIMS scores from baseline, or no change. Similar results were reported in the 28-week study 304.²³ This simply provides a signal that ziprasidone may be associated with low rates of tardive dyskinesia. Longer-term, placebo- and comparator-controlled studies are required.

Hyperprolactinaemia All typical antipsychotics provoke prolactin release via D₂ receptor blockade in the hypothalamus. Hyperprolactinaemia is also seen with risperidone, amisulpride and, albeit transiently, with olanzapine. Symptoms include menstrual disturbances, failure to conceive, loss of libido, impotence and breast growth. These effects undoubtedly reduce patients' quality of life.

Ziprasidone has not been associated in any study with adverse effects related to hyperprolactinaemia. In studies where prolactin levels were measured, ziprasidone either did not elevate prolactin,²² or did so minimally and transiently only at 160mg/day.¹⁸

Hypotension Symptomatic hypotension (eg, involving dizziness or postural effects) is a dose-limiting adverse effect of many antipsychotics, both typical and atypical. Some atypicals (eg, risperidone, sertindole, quetiapine) require careful dose titration, largely because of the risk of hypotensive episodes. Hypotension is usually a consequence of the blockade of α_1 -noradrenergic receptors.

Ziprasidone has only moderate activity at α_1 -receptors and hypotension is only infrequently reported. Only two transient episodes of hypotension were observed in study 101¹⁸ and none in study 106.¹⁹ Dizziness was no more common with ziprasidone than with placebo in study 106,¹⁹ but was almost twice as common with ziprasidone 160mg/day (16.3 per cent) as with placebo (8.7 per cent) in study 114,²⁰ although hypotension was not reported. Postural hypotension was apparently not observed in the year-long study of ziprasidone (study 303).²²

With IM ziprasidone, postural hypotension is also rarely observed: only two of 41 patients receiving 20mg IM up to four times daily reported postural hypotension.³¹ Dizziness is also uncommon with any dose of IM ziprasidone (<20 per cent).^{29–31} Only one study²⁶ detected any meaningful effect on blood pressure (study 120), where a me-

dian decrease of 10mmHg in sitting blood pressure was measured. This did not give rise to any cases of postural hypotension.²⁶

Weight gain Weight gain is commonly seen in patients taking typical and atypical antipsychotics. A meta-analysis³⁴ has revealed that all currently available atypical drugs cause a mean weight gain (at 10 weeks) ranging from 2.1kg (risperidone) to 4.45kg (clozapine). The mechanism for this is not known, but antagonism of central H₁ and, perhaps, 5-HT_{2c} receptors may be involved. Substantial weight gain is cosmetically undesirable in most cases and may present an important health risk in some. It is, therefore, a major contributor to patient morbidity.

Ziprasidone appears not to cause clinically important weight gain. In study 303²² all ziprasidone dose regimens and placebo produced median overall weight loss of 1–3kg. In addition, in study 304 (28 weeks) weight changes averaged +0.3kg for men and +0.8kg for women. Pooled analysis³⁴ indicates that mean weight gain with ziprasidone at 10 weeks is 0.04kg. A recent systematic review³⁵ suggested that ziprasidone has the lowest risk of inducing weight gain compared with other atypicals.

These results rather go against expectations for a drug with H₁ and 5-HT_{2c} activity, but are nevertheless compelling.

Sedation Sedation is a well-known and common adverse effect of nearly all antipsychotics. It may be considered a useful by-product of antipsychotic use in the treatment of acute distress or violent behaviour (when it is usually termed “tranquillisation”) but, in the longer term, sedation is an undesirable effect which is likely to contribute to negative symptom severity.

Oral ziprasidone is associated with low observed rates of sedation. Reports of “somnia” appear to be dose-related,³⁶ but are infrequent (eg, 19.2 per cent of patients on 160mg/day ziprasidone²⁰). Pooled data²¹ suggest that overall (n=702) 14 per cent of patients given ziprasidone experience somnolence, compared with 7 per cent of those on placebo (n=273).

IM ziprasidone appears to be more sedative, particularly at higher doses. For example, in study 126,³¹ mean BARS score for 20mg dose at two hours was between 3 (“drowsy”) and 2 (“asleep”) and 19.5 per cent of patients reported moderate “somnia”. There were no cases of profound sedation and mean BARS scores showed recovery at three and four hours.

Laboratory abnormalities Ziprasidone appears not to be firmly associated with any biochemical or haematological abnormalities.²¹ Very infrequently, changes in liver function tests^{18,19} are observed with results returning to normal on discontinuation. Many studies reported no laboratory abnormalities²² and, overall, withdrawals caused by such abnormalities were at a very low rate (0.5% of 688 patients).²¹

Changes in blood counts have not been associated with ziprasidone. No sympto-

matic laboratory abnormalities of any type have been observed.

Electrocardiogram changes Early trials of ziprasidone indicated that oral ziprasidone was not clearly associated with any clinically significant ECG changes, including clinically relevant prolongation of the cardiac QTc interval.^{19,22} Similarly, IM therapy, even at 20mg four times daily, did not produce any clinically relevant changes in QTc (no reports of QTc interval greater than 500ms or of greater than 20 per cent change).³¹ However, no study to date has assessed ECG changes at peak plasma levels of ziprasidone. Collated data indicate a mean overall change of QTc interval of 2.86ms in patients taking ziprasidone (data on file, Pfizer Ltd). Importantly, overdose with ziprasidone appears not to engender a dangerously long QTc interval,³⁷ but cardiac safety cannot be assured without reference to QTc effects at peak plasma levels of ziprasidone. These data are awaited.

Overall tolerability Ziprasidone seems to be very well tolerated. In a short-term study,²⁰ 9.6 per cent of patients on 160mg/day withdrew from therapy because of adverse effects (placebo 5.4 per cent). In the year-long study,²² discontinuations due to adverse effects were more common in the placebo group (14.7 per cent) than in any ziprasidone-treated groups (range 7.0–9.7 per cent). Pooled data from short-term placebo-controlled studies give withdrawal rates due to adverse effects as 4.1 per cent for ziprasidone and 2.1 per cent for placebo.²¹

DISCUSSION AND CONCLUSIONS

The major obstacle to preparing a meaningful review of the utility of ziprasidone is the dearth of data available in peer-reviewed, reputable scientific journals. Most of the data considered here are derived from conference posters, abstracts and reviews. Although there is no reason to believe that these data will not later prove to be scientifically robust, it is difficult to assess the quality of any research when it is presented in the brief format of a poster or abstract.

Another point to note is that it is in no one's interest for pharmaceutical manufac-

turers to embark on scientifically flawed research projects. Manufacturers are keenly aware of the need for research results to appear in peer-reviewed journals if their products are to be properly evaluated and then used in clinical practice. One should, however, bear in mind the consequences of companies suppressing the results (usually by declining to submit for publication) of any trials deemed unsuitable to their needs for whatever reason.

Notwithstanding these reservations, ziprasidone does appear to be a promising addition to the range of atypical antipsychotics available. Ziprasidone appears to be as effective as haloperidol in treating positive symptoms and is possibly more effective against negative symptoms and depressive symptoms (further studies are required in these conditions). It appears to be very well tolerated with very low rates of extrapyramidal side effects, no symptoms relating to hyperprolactinaemia, and only infrequent reports of hypotension and dizziness. Unlike some other antipsychotic drugs, ziprasidone has not been clearly associated with clinically significant ECG changes (although data are incomplete) or haematological toxicity. Ziprasidone appears only mildly sedative and is unusual among atypical drugs in having no important effect on body weight. Overall, ziprasidone appears to be extremely well tolerated in trials, as evidenced by the observation that in no study did more than 10 per cent of patients withdraw from ziprasidone because of side effects. This may be considered to have a beneficial effect on adherence to prescribed regimens, but should be set against the supposed disadvantages of the need for twice daily dosing.

Overall, however, these data are far from conclusive. More clinical trials are needed fully to determine ziprasidone's effects on negative, cognitive and depressive symptoms. Perhaps more importantly, much more widespread clinical experience is needed to establish ziprasidone's safety and tolerability, particularly in regard to ECG effects and other possible idiosyncrasies.

The availability of an IM formulation of ziprasidone should be considered something of an advance in the treatment of acute psychosis. The risks associated with drugs used

currently include sudden death (eg, typical antipsychotics), extrapyramidal side effects (haloperidol), hypotension (chlorpromazine) and profound sedation (chlorpromazine, benzodiazepines). Ziprasidone appears to engender none of these risks and seems to be rapidly acting, well tolerated and at least as effective as haloperidol. A switch to oral ziprasidone seems to provide acceptable continuity of treatment response. Ziprasidone has not yet been compared with benzodiazepine/neuroleptic combinations traditionally used in clinical practice. Moreover, as previously indicated, much more widespread use is required before safety can be assured.

How then might ziprasidone complement the currently available antipsychotics? Certainly ziprasidone may be a sensible option, among others, for patients suffering extrapyramidal side effects, hyperprolactinaemia or sedation on other typical or indeed atypical drugs. Arguably, ziprasidone might be used for patients wishing to avoid these adverse effects. It cannot yet be recommended in the treatment of negative symptoms and of depressive symptoms occurring in schizophrenia because data are less than conclusive at present. The theoretical risk of drug-induced mood elevation in schizoaffective disorder should be noted. Ziprasidone may, however, be an appropriate choice for patients who do not wish to put on weight or who have already put on weight with other antipsychotics. IM ziprasidone may, as more data emerge, become a treatment of choice in acute psychosis requiring parenteral therapy.

Ziprasidone has not been tested in refractory schizophrenia, where clozapine remains the drug of choice. Another minor concern is the need for twice daily oral dosing, which some may consider a factor in poor compliance. In addition, ziprasidone has not yet been compared with other established atypical antipsychotic drugs.

Ziprasidone is undoubtedly a promising new atypical antipsychotic. While more investigations need to be completed and more data published, ziprasidone appears at present to be a potentially valuable addition to the range of antipsychotics currently available. Its licensing in the UK is awaited.

References (p401)

INTERNATIONAL PHARMACEUTICAL STUDENTS FEDERATION

The International Pharmaceutical Students Federation was established in 1949, following an initiative by the British Pharmaceutical Students Association. It is a non-political, non-religious organisation represented in more than 45 countries. It has 33 national pharmacy student associations as full members, plus a number of local student organisations as associate members. Individual membership is available to students, new pharmacy graduates and pharmacists who have been registered for less than five years.

The focal point of IPSF activities is its annual congress. This includes general assemblies, symposia, workshops, a poster exhibition and social activities. Jointly with the International Pharmaceutical Federation, the IPSF also presents a students' day during the annual FIP congress.

IPSF projects include work on national and international educational and health issues and "village concept" schemes, in which pharmacy students work with others to improve the standard of living and health conditions in remote areas of developing countries.

A student exchange scheme gives IPSF members the opportunity to work in a branch of pharmacy in another country for a short period. The federation's publishing activities include project reports and a thrice-yearly news.

Those wishing to support IPSF through individual membership should apply to the IPSF Secretariat, International Pharmaceutical Federation, Andries Bickerweg 5, 2517 JP Den Haag, The Netherlands (tel +31 70 3 63 1925; fax +31 70 3 65 9047; e-mail ipsf@fip.nl; website www.ipsf.org).

REFERENCES

- Tandon R, Harrigan E, Zorn SH. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. *J Serotonin Res* 1997;4:159-77.
- Leysen JE, Janssen PMF, Heylen L, Gommeren W, Van Gompel P, Lesage AS, et al. Receptor interactions of new antipsychotics: relation to pharmacodynamic and clinical effects. *Int J Psychiatr Clin Pract* 1998;2:S3-S17.
- Davis R, Markham A. Ziprasidone. *CNS Drugs* 1997;8:153-9.
- Sprouse JS, Reynolds LS, Braselton JP, Rollema H, Zorn SH. Comparison of the novel antipsychotic ziprasidone with clozapine and olanzapine: inhibition of dorsal raphe cell firing and the role of 5-HT_{1A} receptor activation. *Neuropsychopharmacology* 1999;21:622-31.
- Gunn KP, Zorn SH, Heym J. Ziprasidone: preclinical profile of a new antipsychotic agent. *Schizophrenia Res* 1997;24:204.
- Miceli JJ, Gunn KP, Rubin RH, Frackowiak RSJ, Williams SA, Fischman A, et al. 5HT₂ and D₂ receptor occupancy of ziprasidone in healthy volunteers. *Schizophrenia Res* 1997;24:178.
- Lu Y, Zorn SH, Schmidt AW, Rollema H. Comparison of the novel antipsychotic ziprasidone with clozapine and olanzapine: effects on dopamine release in rat prefrontal cortex and dorsolateral striatum. *Soc Neurosci Abstr* 1997;23:1031.
- Seeger TF, Seymour PA, Schmidt AW, Zorn SH, Schulz DW, Lebel LA, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Ther* 1995;275:101-13.
- Miceli JJ, Hansen RA, Johnson AC, Wilner KD. Single and multiple dose pharmacokinetics of ziprasidone in healthy males. *Pharm Res* 1995;12(Suppl 9):S392.
- Tensfeldt TG, Wilner KD, Baris B, Smolarek TA, Turncliff RZ, Colburn WA, et al. Steady-state pharmacokinetics of ziprasidone in healthy elderly and young volunteers. *Biol Psychiatr* 1997;42:42S.
- Prakash C, Kamel A, Cui D, Whalen RD, Miceli JJ, Tweedie DJ. Ziprasidone metabolism and cytochrome P450 isoforms. *Biol Psychiatr* 1997;42:40S.
- Wilner KD, DeMattos SB, Anziano RJ, Apseloff G, Gerber N. Lack of CYP 2D6 inhibition by ziprasidone in healthy volunteers. *Biol Psychiatr* 1997;42:42S.
- Aweeka F, Horton M, Swan S, Wilner KD, Sherwood J, Anziano R. The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. *European Neuropsychopharmacology* 1997;7(Suppl 2):S214.
- Everson G, Lasseter KC, Anderson KE, Bauer LA, Wilner KD, Johnson A, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function. *Eur Neuropsychopharmacol* 1997;7(Suppl 2):S220.
- Muirhead GJ, Holt PR, Oliver S, Harness J, Anziano RJ. The effect of ziprasidone on steady-state pharmacokinetics of a combined oral contraceptive. *Eur Neuropsychopharmacol* 1996;6(Suppl 3):38.
- Wilner KD, Anziano RJ, Tensfeldt TG, Pelletier SM, Apseloff G, Gerber N. The effects of ziprasidone on steady-state lithium levels and renal clearance of lithium. *Eur Neuropsychopharmacol* 1996;6(Suppl 3):38.
- Wilner KD, Hansen RA, Folger CJ, Geoffroy P. Effects of cimetidine or Maalox on ziprasidone pharmacokinetics. *Biol Psychiatr* 1997;42:42S.
- Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1998;18:296-304.
- Keck P, Buffenstein A, Ferguson J, Feighner J, Jaffe W, Harrigan EP, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology* 1998;140:173-84.
- Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M et al. Ziprasidone 80mg/day and 160mg/day in the acute exacerbation of schizophrenia and schizo-affective disorder: a six-week placebo-controlled trial. *Neuropsychopharmacology* 1999;20:491-505.
- Keck PE Jr, Reeves KR, Harrigan EP. Ziprasidone: an overview of efficacy and tolerability in the treatment of patients with an acute exacerbation of schizophrenia or schizoaffective disorder. *Biol Psychiatr* 1997;42:42S.
- Arato M, O'Connor R, Meltzer H, Bradbury J, for the Ziprasidone Investigators' Study Group. Ziprasidone: efficacy in prevention of relapse and in the long term treatment of negative symptoms in chronic schizophrenia. *Eur Neuropsychopharmacol* 1997;7(Suppl 2):S214.
- Hirsch S, Power A, Kissling P. A 28-week comparison of flexible dose ziprasidone and haloperidol in outpatients with stable schizophrenia [abstract]. American Psychiatric Association Annual Meeting; May, 1999; Washington DC. Washington DC: American Psychiatric Association. p135. Abstract no NR254.
- Hagger C, Mitchell D, Wise AL, Schulz SC. Effects of oral ziprasidone and risperidone on cognitive functioning in patients with schizophrenia or schizoaffective disorder: preliminary data. *Eur Neuropsychopharmacol* 1997;7(Suppl 2):S219.
- Wilner KD, Anziano RJ, Johnson AC, Miceli JJ, Fricke JR, Titus CK. Anxiolytic effects of ziprasidone compared with diazepam and placebo prior to dental surgery. *Eur Neuropsychopharmacol* 1996;6(Suppl 3):117.
- Brook S, Swift R, Harrigan EP. The tolerability and efficacy of intramuscular ziprasidone. *Eur Neuropsychopharmacol* 1997;7(Suppl 2):S215.
- Brook S, Lucey JV, Gunn KP, for the Ziprasidone IM Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatr* 2000;61:933-41.
- Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. Validation of the Behavioural Activity Rating Scale (BARS): a novel measure of activity in agitated patients [abstract]. American Psychiatric Association Annual Meeting; June, 1998; Toronto, Canada. Washington DC: American Pharmaceutical Association. p194. Abstract no NR466.
- Swift RH, Harrigan EP, van Kammen DP. A comparison of intramuscular (IM) ziprasidone with IM haloperidol [abstract]. American Psychiatric Association Annual Meeting; June, 1998; Toronto, Canada. Washington DC: American Psychiatric Association. p194. Abstract no NR465.
- Reeves KR, Swift RH, Harrigan EP. Intramuscular ziprasidone 10mg and 20mg in patients with psychosis and acute agitation [abstract]. American Psychiatric Association Annual Meeting; June, 1998; Toronto, Canada. Washington DC: American Psychiatric Association. p201. Abstract no NR494.
- Reeves KR, Swift RH, Harrigan EP. A comparison of rapid-acting, intramuscular (IM) ziprasidone 2mg and 20mg in patients with psychosis and acute agitation [abstract]. American Psychiatric Association Annual Meeting; June, 1998; Toronto, Canada. Washington DC: American Psychiatric Association. p201. Abstract no NR495.
- Tensfeldt T, Miceli J, Kuye O. The population pharmacokinetics of intramuscular ziprasidone in healthy volunteers and schizophrenic patients. *Eur Neuropsychopharmacol* 1998;8(Suppl 2):S239.
- Miceli J, Preskorn S, Wilner K. Pharmacokinetics of intramuscular ziprasidone in schizophrenic patients: population pharmacokinetic modeling. *Eur Psychiatr* 1998;13:S304-S305.
- Allison DB, Mentore JL, Moonseong H. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatr* 1999;156:1686-96.
- Taylor DM, McAskill R. Atypical antipsychotics and weight gain — a systematic review. *Acta Psychiatr Scand* 2000;101:416-32.
- O'Connor R, Harrigan E, Heym J, Ko G, Chandler L. The efficacy and safety profile of a new antipsychotic, ziprasidone. *Eur Neuropsychopharmacol* 1995;5:351.
- Burton S, Heslop K, Harrison K, Barnes, M. Ziprasidone overdose [letter]. *Am J Psychiatr* 2000;157:835.