

# Clinical pharmacology

## Are 'atypical' antipsychotics safer than conventional antipsychotics?

Conventional antipsychotics, used for half a century to treat a range of major psychiatric conditions, are increasingly being replaced in clinical practice by so-called 'atypical' antipsychotics, which include clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. Although conventional antipsychotics (e.g. haloperidol) have proved effective in adult and paediatric populations, their use has been limited by safety concerns, such as extrapyramidal symptoms. This risk is considered higher in children than adults, and their possible adverse effects on cognition is a concern. However, the clinical use of 'atypical' antipsychotics, particularly in adolescents and children, has far exceeded the limited evidence of their efficacy and safety from randomised controlled trials.

The development of 'atypical' antipsychotics was stimulated by a landmark study in 1988 that showed clozapine to be superior in efficacy to chlorpromazine in schizophrenic patients resistant to high doses of haloperidol. Clozapine was considered atypical in having a very low risk of extrapyramidal adverse effects. This term has since been uncritically applied to any antipsychotic marketed in the last decade, despite their striking chemical, pharmacological and clinical heterogeneity. These 'atypical' agents are generally much more expensive than older antipsychotics, most of which are available in generic formulations. As a group, the 'atypical' drugs have been promoted as being broadly clinically superior, but the evidence for this is not convincing. Some comparative studies have been marred by questionable dosing equivalencies. With the exception of consistent superior efficacy and adherence to clozapine, the 'atypical' antipsychotics do not represent major gains in effectiveness when compared with appropriately dosed conventional antipsychotics.

Since efficacy appears largely equivalent between available antipsychotics, safety and tolerability become areas of particular importance for determining choice of therapy. Adverse effects would have a negative impact on patient adherence.

This review aims to guide more rational selection of antipsychotics, by focusing on the safety profiles of those available in South Africa.

### Tolerability and safety of 'atypical' antipsychotic agents

The validity of the claim that 'atypical' agents carry a lower risk of adverse effects than moderately dosed conventional antipsychotics is challenged by findings from randomised studies, which have shown similar rates of treatment discontinuation due to adverse events. The widely promoted lower risk of extrapyramidal side-effects of 'atypical' antipsychotics must be balanced against their other adverse effects (Table I).

### Neurological effects

The risk of extrapyramidal symptoms depends on the antipsychotic and dose used, and differs between the different neurological syndromes. Atypical antipsychotics are clearly associated with a lower risk of acute dystonia and late parkinsonian bradykinesia than conventional antipsychotics. Not surprisingly, differences were greater when 'atypical' agents were compared with large doses of potent conventional antipsychotics, without prophylactic anticholinergics. By contrast, clozapine and

possibly quetiapine appear to be relatively well tolerated by patients with Parkinson's disease requiring antipsychotics. However, risperidone and olanzapine are not well tolerated in this patient group, and other atypical antipsychotics have not yet been adequately studied.

The risk of tardive dyskinesia appears substantially lower with olanzapine, and to a lesser extent risperidone, than with haloperidol, which has not been compared with other 'atypical' agents. Akathisia, marked by restlessness and anxious agitation, has been associated with virtually all antipsychotic agents, including clozapine. Since neuroleptic malignant syndrome is rare, it is not clear whether the risk of this syndrome differs between antipsychotics. This potentially life-threatening cerebrototoxic delirium presents with variable degrees of fever, autonomic instability and muscle rigidity, increasing creatine kinase and causing myoglobinuria. When this syndrome is due to clozapine, delirium and fever generally predominate, without muscle rigidity or elevated creatine kinase levels.

Sedation is one of the adverse effects most commonly associated with antipsychotics, and the elderly, children and adolescents are at higher risk of this effect. This may be particularly deleterious in the paediatric population because drowsiness

Table I. Risks associated with antipsychotics available in South Africa

	'Atypical' antipsychotics					Conventional antipsychotics, by potency			
	Clozapine	Olanzapine	Risperidone	Quetiapine	Aripiprazole*	Ziprasidone*	High e.g. haloperidol	Moderate e.g. zuclopenthixol	Low e.g. chlorpromazine
Weight gain	Red	Red	Yellow	Yellow	Green	Green	Green	Yellow	Yellow
Hyperglycaemia	Red	Red	Yellow	Yellow	Green	Green	Green	Yellow	Yellow
Hyperlipidaemia	Red	Red	Yellow	Yellow	Green	Green	Green	Yellow	Yellow
Anticholinergic	Red	Yellow	Green	Green	Green	Green	Green	Yellow	Red
QT prolongation	Green	Green	Yellow	Yellow	Green	Yellow	Green	Green	Red
Hypotension	Red	Yellow	Red	Yellow	Green	Green	Green	Yellow	Red
Hyperprolactinaemia	Green	Yellow	Red	Green	Green	Yellow	Red	Red	Red
Sexual dysfunction	Yellow	Yellow	Yellow	Green	Green	Yellow	Yellow	Yellow	Red
Extrapyramidal symptoms	Green	Yellow	Yellow	Green	Yellow	Yellow	Red	Red	Yellow

\* Newer drugs with limited long-term data available currently. (Red = high risk; yellow = moderate risk; green = low to no risk)

can impair attention and learning in school. The effects on cognition of the underlying disease have not been clearly separated from possible adverse effects of antipsychotics. Sedation is common with risperidone, olanzapine, quetiapine and ziprasidone. However, this risk can be minimised by careful dose titration and is frequently transient, so generally does not lead to drug withdrawal.

Clozapine has a dose-dependent risk of epileptic seizures, with a reported risk of up to 5% at a daily dose of  $\geq 600$  mg. All 'atypical' antipsychotics are associated with EEG changes, although EEG changes are not necessarily predictive of seizure risk. The risk of epileptic seizures is generally considered less with risperidone and quetiapine.

### **Cardiovascular, metabolic and endocrine effects**

Weight gain is an important and common adverse effect of several 'atypical' and some conventional antipsychotics. The relative risk of weight gain is greatest with clozapine and olanzapine, moderate with risperidone, quetiapine and chlorpromazine and least marked with haloperidol. Weight gain has not yet been clearly associated with the newest agents, aripiprazole and ziprasidone, although case reports have been published. Although sedation and feelings of depression are the most common adverse effects reported, weight gain was found to be most distressing, and obese patients were twice as likely as non-obese patients to report skipping medication doses. While many patients experience moderate weight gain, some experience rapid and potentially massive increases that are very difficult to control. The mechanisms involved in this weight gain are complex, and include sedation and inactivity, possibly central blockade of certain histamine and serotonin receptors, as well as specific factors associated with the psychiatric disorder. Targeted interventions aimed at increasing physical activity and improving dietary habits should be used, in conjunction with careful selection of antipsychotics to limit weight gain in this vulnerable population.

Children and adolescents are at particularly high risk of weight gain and may carry this burden disproportionately, given the longer duration of their therapy and consequent cumulative effect on the risk of metabolic syndrome and cardiovascular disease, in addition to the negative impact on self-esteem. Even without antipsychotics, 17% of adolescents in South Africa are overweight or obese, affecting more girls (25%) than boys (7%); prevalence was highest (> 20% overall) in

white and Indian population groups. In an alarming study conducted in the USA, 39% of overweight children and almost 50% of severely obese children had already developed the metabolic syndrome.

Antipsychotic-induced hepatotoxicity, which may, in part, be due to weight gain, has been reported with the use of the 'atypical' antipsychotics. This manifests with elevations of liver transaminases and fatty infiltration. This effect is most often seen with risperidone, but has also been reported during olanzapine and clozapine treatment. Liver function tests are indicated in particularly obese patients, and those that experience rapid weight gain.

Hyperlipidaemia and hyperglycaemia (with resultant type 2 diabetes mellitus) have been associated with the 'atypical' antipsychotics, although their risks vary between agents. The risks of hyperlipidaemia and hyperglycaemia are associated with, but not dependent on, weight gain. The risk of these adverse effects with olanzapine is up to 3 or 4 times higher than with conventional antipsychotics, and 5 - 6 times higher than the risk associated with no antipsychotic use. The risk of hyperglycaemia and hyperlipidaemia is also increased by clozapine, possibly to a lesser extent than olanzapine. By contrast, risperidone and quetiapine have a similar risk to that of conventional antipsychotics.

As the best approach towards preventing a cardiovascular event in patients with metabolic syndrome is to attack the actual causes of the problem, namely obesity, inactivity and insulin resistance, monitoring for these is particularly important for patients on 'atypical' antipsychotics. The American Diabetes Association recommends monthly monitoring of body weight for the first 3 months and quarterly thereafter, with annual monitoring of waist circumference. Blood pressure and fasting blood glucose should be monitored at baseline, 3 months and then annually. A fasting lipid profile should be assessed at baseline, 3 months and then every 5 years. Naturally, more frequent assessment may be warranted based on personal or family history and clinical status. As children and adolescents are generally more sensitive to these adverse events than adults, more regular monitoring may be necessary for them.

New-onset diabetes during treatment with 'atypical' antipsychotics has also been associated with a less common but serious risk of acute metabolic decompensation. Among these patients, diabetic ketoacidosis has occurred as the presenting symptom of diabetes mellitus or pancreatitis; some of these cases were fatal. Diabetic ketoacidosis generally occurred

in the first 3 - 6 months of treatment with 'atypical' antipsychotics. It is difficult to predict patients at risk of pancreatitis or diabetic ketoacidosis, as there has been no clear association between higher body weight or antipsychotic-associated weight gain and diabetic ketoacidosis. Patients and clinicians should be alert for polyuria, polydipsia, mental status change or acute abdominal symptoms, in addition to regular glucose monitoring.

The risk of death and stroke associated with 'atypical' antipsychotics in the elderly is an area of particular concern. The FDA has issued a warning of a 1.6 - 1.7-fold increased risk of death reported among elderly patients taking 'atypical' antipsychotics. However, this was based on an average mortality rate over 10 weeks of 4.5% with all 'atypical' antipsychotics compared with 2.6% in those on placebo. The risk of stroke or transient cerebral ischaemia was approximately 3-fold higher following risperidone and olanzapine than after placebo. However, the attributable risk of death and stroke with conventional antipsychotics in the elderly remains unknown. A large retrospective analysis found a negligible difference in the risk of death or stroke among elderly patients taking conventional antipsychotics and those taking risperidone, olanzapine or quetiapine.

The increased risk of stroke and death could result from direct cardiovascular effects, with or without the cardiovascular risks associated with weight gain, hyperglycaemia and hyperlipidaemia described above. The risks of acute hypotensive effects are described with some conventional (such as chlorpromazine) and 'atypical' antipsychotics (such as clozapine and risperidone). However, hypertension has also been reported in patients with weight gain due to olanzapine use. Some antipsychotics are associated with prolongation of the QT interval, which is associated with torsades de pointes and sudden cardiac death, particularly when the QT interval (corrected for rate) exceeds 500 ms. A baseline electrocardiogram (ECG) is recommended before starting treatment with chlorpromazine, risperidone, olanzapine, quetiapine and ziprasidone, and should be repeated once steady-state plasma drug concentrations are reached (after 5 times the elimination half-life). As the risk of QT prolongation is not yet precisely defined for each agent, the combination of any antipsychotic with other drugs known to prolong the QT interval (see [www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm](http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm)) or reduce antipsychotic clearance (e.g. by inhibition of the cytochrome P450 enzyme system) should be avoided. Rarely,

clozapine has been associated with cardiac damage, including early myocarditis (< 20/10 000) or late cardiomyopathy (< 10/10 000). All these cardiovascular risks are further exacerbated by the physical inactivity, suboptimal dietary habits and smoking prevalent among patients requiring antipsychotics.

Moderate hyperprolactinaemia is very common with conventional antipsychotics. Among the 'atypical' agents, this effect is mostly seen with risperidone, although olanzapine has been associated, to a lesser extent, with hyperprolactinaemia and related symptoms. The mean reported prevalence of this effect with both conventional agents or risperidone is around 60% in women and 40% in men, with complication rates around 10 - 15%. Complications include amenorrhoea, galactorrhoea, gynaecomastia, infertility and erectile or ejaculatory dysfunction. Clozapine, quetiapine and aripiprazole would be preferred for patients who develop these adverse effects, or those with prolactin-dependent metastatic carcinoma of the breast.

#### Haematological abnormalities

The risk of potentially life-threatening agranulocytosis associated with clozapine has limited its use to second-line therapy, despite its greater antipsychotic efficacy. Without close monitoring of leukocyte counts, particularly during the first months of treatment, an incidence of about 1% is reported. Monitoring of white blood cell counts is thus mandatory in patients on clozapine. Agranulocytosis and granulocytopenia are seldom reported with other antipsychotics, so a blood cell count is only warranted when clinical features of leucopenia are present (e.g. recurrent infections) in patients on these agents.

#### Treating children and adolescents

Although the evidence base on the use of antipsychotics in children and adolescents is expanding, the majority of available studies are anecdotal, or short-term, open-label trials and half of the studies in this age group have been with risperidone. Most paediatric use of antipsychotics is 'off-label', as only risperidone is registered by the Medicines Control Council for use in children. As with other illnesses, children and adolescents should not be viewed as small adults, yet the pharmacokinetics of 'atypical' antipsychotics have only been studied in a small number of patients in this age group. It is not yet known whether these agents possess age-related pharmacological properties, so the rate of dosage titration in younger patients may need to be slower than in adults, in an attempt to minimise the rate and severity of adverse events. Adverse effects are likely to have a negative impact on patient adherence. Adherence rates for children tend to be lower than those for adults, and adolescents are especially at risk for poor adherence because of control issues and defensive mechanisms, such as denial and acting out. Given the lack of long-term safety studies, potential risks from prolonged use of 'atypical' antipsychotics in children and adolescents are poorly defined.

#### Conclusions

With the exception of clozapine, 'atypical' antipsychotics have not been shown to represent major gains in effectiveness. Individual antipsychotics in this class are not interchangeable; in terms of therapeutic benefits and particularly adverse effects; each agent has a unique pharmacological profile. The lower risk of adverse effects reported with the newest medications (aripiprazole and ziprasidone) may reflect the limited opportunities for data collection

at this stage, rather than better safety profiles. There are growing concerns about adverse long-term health consequences of the 'atypical' antipsychotics, notably weight gain, diabetes, hyperlipidaemia and hypertension. Children and adolescents may be particularly vulnerable to antipsychotic adverse effects, including extrapyramidal symptoms, sedation, weight gain, and prolactin elevation. Therefore, it is rational to consider both older and 'atypical' antipsychotics for clinical use, based on the individual risk profile of each patient. Regardless which antipsychotic is selected, it is important to inform patients (and their caregivers) of the relative risks and benefits, and to monitor treatment effectiveness, tolerability and adherence.

#### Recommended reading

Gardner DM, Baldessarini RJ, Warch P. 'Atypical' antipsychotic drugs: a critical overview. *Can Med Assoc J* 2005; 172(13): 1703-1710.

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## In a nutshell

- With the exception of clozapine, 'atypical' antipsychotics have not been shown to represent major gains in effectiveness.
- There are growing concerns about potential adverse long-term health consequences of the atypical antipsychotics, notably weight gain, diabetes, hyperlipidaemia and hyperprolactinaemia.
- Children and adolescents may be particularly vulnerable to antipsychotic adverse effects.
- It is rational to consider both older and 'atypical' antipsychotics for clinical use, based on the risk profile of each patient.
- Regardless which antipsychotic is selected, it is important to inform patients (and their caregivers) of the relative risks and benefits, and to monitor treatment effectiveness, tolerability and adherence.