

## ATYPICAL ANTIPSYCHOTICS - SAFE PRESCRIBING - BETTER, BUT NOT PERFECT

- ▶ BE AWARE OF METABOLIC SYNDROME; IT IS THE MOST IMPORTANT CLINICAL PROBLEM
- ▶ MONITOR FOR ADVERSE EFFECTS AND MANAGE EARLY
- ▶ UNDERSTAND THAT THERE ARE SOME POTENTIALLY SERIOUS ADVERSE EFFECTS
- ▶ TAKE CARE WITH PATIENTS AT RISK OF DEMENTIA

Atypical antipsychotics have mostly replaced the older 'typical' antipsychotics such as haloperidol and chlorpromazine for treating schizophrenia, bipolar disorder, and other severe mental illnesses. Atypical antipsychotics have a lower propensity for causing Parkinson-like disorders, which were common with older agents,<sup>1</sup> they are more effective when treating the negative symptoms of schizophrenia, and have better patient acceptability.<sup>2</sup>

Atypical antipsychotics are a heterogeneous group of medicines which include **risperidone** (Risperdal<sup>®</sup>), **olanzapine** (Zyprexa<sup>®</sup>), **quetiapine** (Quetapel<sup>®</sup>, Seroquel<sup>®</sup>), **amisulpride** (Solian<sup>®</sup>), **aripiprazole** (Abilify<sup>®</sup>) and **ziprasidone** (Zeldox<sup>®</sup>). **Clozapine** is also an atypical antipsychotic which has a specific adverse reaction profile and higher risks associated with its use (visit [www.saferx.co.nz](http://www.saferx.co.nz) to view the clozapine bulletin for more information).

There is a great variability in individual patient response with all antipsychotics; they act on a range of receptors, having distinct properties and side effect profiles. In general, start at a low dose and carefully titrate upwards to reduce the occurrence of adverse effects,<sup>3</sup> which are often dose-related. Treatment should be continued for 4 to 6 weeks before it is considered ineffective; combinations of agents should be avoided (unless during switching) due to an increased risk of adverse events.<sup>4</sup> Some adverse effects require careful monitoring and management, and some can be serious such as diabetes, stroke and sudden cardiac death.<sup>5</sup> Be cautious when prescribing these medicines to elderly people, and those with cardiovascular risk factors such as obesity, diabetes or high cholesterol.<sup>3</sup>

### BE AWARE OF METABOLIC SYNDROME; IT IS THE MOST IMPORTANT CLINICAL PROBLEM

Metabolic syndrome is characterised by a combination of symptoms that may include abdominal obesity, raised plasma glucose, abnormal lipid profiles, and hypertension. Schizophrenia itself is associated with insulin resistance and diabetes; the risk of diabetes is increased further in those who take antipsychotic medicines.<sup>4</sup>

An increase in body weight of several kilos within 4-6 weeks of commencing therapy along with hyperglycaemia and type 2 diabetes has been observed in some patients taking atypical antipsychotics. The risk is greatest with **clozapine** and **olanzapine**, but cases have also been reported with **risperidone** and **quetiapine**. The risk of developing metabolic syndrome appears to be lower with **amisulpride**, **ziprasidone** and **aripiprazole**.<sup>6,7</sup>

Due to the associated risks of cardiovascular morbidity and mortality, all patients prescribed antipsychotics, regardless of risk factors, should be given advice on diet and lifestyle interventions, monitored for the emergence of diabetes,<sup>8</sup> and have lipid levels checked.

### MONITOR FOR ADVERSE EFFECTS AND MANAGE EARLY

#### Cardiovascular effects

Current users of typical or atypical antipsychotics have an increased risk of sudden cardiac death compared with non-users, and former-users of such medicines. The risk increases significantly with an increasing dose,<sup>5</sup> and combinations of antipsychotic medicines.<sup>4</sup> Atypical antipsychotic medicines can prolong the QT interval and lead to ventricular tachyarrhythmias. Prolongation of QT interval has been observed mostly with **ziprasidone** and to a lesser extent with **risperidone**<sup>9</sup> and **aripiprazole**.<sup>4</sup> Tachycardia has been observed with **risperidone**, **olanzapine**, **quetiapine** and less so with **ziprasidone**.<sup>9</sup>

An increased risk of stroke has been associated with all antipsychotic medicines.

If patients have pre-existing cardiovascular disease or cardiovascular risk-factors, an ECG may be required prior to initiating treatment with antipsychotic medications.<sup>4</sup> All patients with schizophrenia should have a physical health check-up, including a cardiovascular disease risk assessment performed on an annual basis.<sup>4</sup>

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## ▶ ATYPICAL ANTIPSYCHOTICS

2

### Postural hypotension and hypertension

Postural hypotension can occur, especially when initiating or up-titrating the doses of medicines that can cause a significant alpha adrenergic blockade, eg **risperidone**, **olanzapine** and **quetiapine**. Ensure that older patients and their caregivers are informed of the increased risk of falls. There have also been cases of severe hypertension leading to collapse following **risperidone** use.<sup>10</sup>

### Movement disorders

'Typical' antipsychotics should never be used in patients with Parkinson's disease; atypical agents should be used very cautiously due to the potential exacerbation of symptoms.<sup>4</sup> Higher doses of **risperidone** (>6mg/day) and **amisulpride** (>300mg/day) are associated with Parkinson-like adverse effects, eg tremor, muscular rigidity and acute dystonia. These symptoms usually occur gradually and are more common in older patients.<sup>4</sup> **Risperidone**, **amisulpride** and **olanzapine** may cause akathisia (including agitation and restlessness).<sup>11</sup>

Although new-onset tardive dyskinesia is less likely to occur with atypical, compared with typical antipsychotics, it has been estimated to occur in 1-2% of patients, and in up to 3% of patients taking **risperidone**. This is of particular concern because it may not be evident initially, may worsen on treatment withdrawal,<sup>3</sup> and can be irreversible.<sup>4</sup>

### Other adverse effects

Anticholinergic effects such as dry mouth, constipation and blurred vision can occur particularly with **clozapine** and **olanzapine**. Sedation has been especially associated with **clozapine**, **olanzapine** and **quetiapine**.<sup>3</sup>

Hyperprolactinaemia has been observed with **risperidone** and **amisulpride** with associated sexual dysfunction, amenorrhoea, gynaecomastia and osteoporosis in at-risk populations. Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medicines. **Risperidone**, in particular is associated with this; dose reduction or switching medication may be necessary.<sup>4</sup> The antipsychotic drugs with the lowest risk of sexual dysfunction are **aripiprazole**, **ziprasidone** and **quetiapine**. There have been case reports of priapism with **risperidone** and **olanzapine**.<sup>12,13</sup>

**Note:** Sensitive questioning may be needed to uncover sexual side effects as patients may be reluctant to volunteer this information.

## UNDERSTAND THAT THERE ARE SOME POTENTIALLY SERIOUS ADVERSE EFFECTS

### Neuroleptic Malignant Syndrome (NMS)

NMS is a rare but potentially fatal adverse effect of all antipsychotic medications. This is more common in young male patients taking higher doses and is often associated with hot weather and exercise. It is also more likely to occur with **risperidone**. Symptoms include muscular rigidity, pyrexia, confusion, disorientation, tachycardia and increased sweating. Patients with these symptoms require urgent assessment, cessation of antipsychotics, and supportive treatment.<sup>11</sup>

Please remember that like the older antipsychotics, atypicals are also associated with raised hepatic enzymes and blood dyscrasias.<sup>14</sup> Arrange blood counts if unexplained infection or fever develops.<sup>4</sup>

### Weight gain

**Olanzapine**, in particular is associated with weight gain. Long-term studies over 48 weeks have demonstrated a mean weight gain of 5.6kg. Teenagers are more likely to gain weight than other patient groups. If there is a weight gain of over 2kg within the first 2 weeks, consider a change of agent.<sup>3</sup>

### Diabetes

People with schizophrenia have an increased risk of diabetes. Avoid **olanzapine** in particular if there are risk factors such as obesity or a family history of diabetes. Monitor for symptoms of diabetes during treatment.<sup>3</sup>

### Lipids

If the patient has a pre-existing abnormal lipid profile, use atypical antipsychotic medications with caution. Monitor lipids during treatment in all patients.<sup>3</sup>

## TAKE CARE WITH PATIENTS AT RISK OF DEMENTIA.

In some cases, where non-pharmacological treatment is ineffective, antipsychotics are used to manage Behavioural and Psychological Symptoms of Dementia (BPSD). **Risperidone** is the only atypical antipsychotic officially indicated for BPSD.<sup>3</sup> Antipsychotics will not be effective for wandering, social withdrawal, shouting, pacing, touching, or cognitive defects.

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## ATYPICAL ANTIPSYCHOTICS

3

There is an increased risk of mortality and an increased risk of stroke in elderly patients with dementia who are prescribed antipsychotic medication. Older patients are also more susceptible to postural hypotension, hyperthermia in hot weather and hypothermia in cold weather. It is advisable when initiating treatment to use half the adult dose, or less depending on comorbidity and other medications, and to review efficacy and the emergence of adverse effects regularly.<sup>4</sup>

### Off-label prescribing

Atypical antipsychotics are frequently prescribed for anxiety, and have also been used for sedation and post traumatic stress disorder. These indications are 'off-label' so prescribers must discuss the decision to prescribe with the patient (and their family), obtain consent, and document this in the patient's notes. Be aware that there is still limited documented evidence to support off-label use.<sup>3</sup>

### Anxiety

The usual treatment of anxiety is initial psychological therapy and SSRIs may be used if necessary. The efficacy of SSRIs should be assessed after 12 weeks before other agents are considered.<sup>3</sup>

### Post traumatic stress disorder (PTSD)

Psychological therapies, social support, and if necessary antidepressants (usually SSRIs) are recommended first-line. There is a lack of evidence to support antipsychotics for this condition.<sup>3</sup>

### Insomnia

Sleep hygiene techniques should be explored prior to the use of any pharmacological treatments (see the 'Hypnotics' bulletin on [www.saferx.co.nz](http://www.saferx.co.nz) for more information). If necessary, zopiclone and short-acting benzodiazepines should be used, rather than antipsychotics or SSRIs.<sup>3</sup>

## MONITORING RECOMMENDATIONS<sup>4</sup>

Parameter	Frequency	Comments
Full Blood Count	Initially, then annually	
Urea and Electrolytes	Initially, then annually	
Liver Function Test	Initially, then annually	Not required for amsulpride
Lipid Profile	Initially, at 3 months, and annually	
Weight	Initially, regularly during first 3 months, then annually	If taking clozapine or olanzapine, monitor every 3 months for the rest of the first year
Fasting Blood Glucose	Initially, at 4-6 months, then annually	If taking clozapine or olanzapine, also test after the first month
ECG	Initially (if risk factors present)	Refer to individual datasheets
Blood Pressure	Initially, and during dose titration	Not mandatory for amisulpride and aripiprazole
Prolactin	Initially, at 6 months, then annually	Check sooner if indicated by clinical presentation
CVD Risk Assessment	Annually	For all patients with schizophrenia

## ATYPICAL ANTIPSYCHOTICS

4

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For further information on other high-risk medicines visit our website at: [www.saferx.co.nz](http://www.saferx.co.nz)

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