In general, atypical antipsychotics have replaced the older ‘typical’ antipsychotics such as haloperidol and chlorpromazine for treating schizophrenia, bipolar disorder, and other severe mental illness, although zuclopenthixol is still popular. Atypical antipsychotics have a lower propensity for causing Parkinson-like disorders, and have more distinct clinical profiles.

Typical antipsychotics are not selective for any of the four dopamine pathways in the brain and so can cause a range of adverse effects, particularly extrapyramidal symptoms.

Atypical antipsychotics are a heterogenous group of medicines which include amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. 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 to view the clozapine bulletin for more information).

There is a great variability of individual response with all antipsychotics; they act on a range of receptors, having distinct properties and adverse effect profiles. In general, start at a low dose and carefully titrate upwards to reduce the occurrence of adverse effects which are often dose-related. Treatment should be continued for 4 to 6 weeks before it is considered ineffective; combinations of medicines should be avoided (unless during switching) due to the increased risk of adverse effects.

Some adverse effects require careful monitoring and management, and some can be serious such as diabetes, stroke and cardiac death. Be cautious when prescribing these medicines to older adults, and people with cardiovascular risk factors such as obesity, diabetes or high cholesterol.

**MANAGE METABOLIC SYNDROME**

Metabolic syndrome includes rapid weight gain, raised plasma glucose and abnormal lipid profiles. Schizophrenia itself is associated with insulin resistance and diabetes; the risk of diabetes is increased further with antipsychotic medicines.

An increase in body weight of several kilos within 4-6 weeks of commencing therapy, along with hyperglycaemia and type 2 diabetes have occurred with people taking atypical antipsychotics. The risk is greatest with clozapine and olanzapine, but cases have also been reported with risperidone and quetiapine. The risk of metabolic syndrome appears to be lower with amisulpride, ziprasidone and aripiprazole.

Due to the associated risks of cardiovascular morbidity and mortality, everyone who is prescribed antipsychotics, should be provided with advice about diet and lifestyle interventions, monitored for the emergence of diabetes and have lipid levels checked regularly (see table).

**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 groups. If there is an increase of over 2kg in weight within the first 2 weeks, consider a change of medicine.

Metformin is used (off-label) up to 1.5g per day in divided doses, to prevent and reduce antipsychotic weight gain and to treat glucose intolerance. If a patient taking an atypical antipsychotic is also prescribed metformin, review the indication before deprescribing, even if current HbA1c is normal.

**Diabetes**

People with schizophrenia have an increased risk of diabetes. Avoid olanzapine in particular if risk factors such as obesity or a family history of diabetes are present. Monitor for symptoms of diabetes during treatment.

**Lipids**

Use atypical antipsychotic medicines with caution if the lipid profile is abnormal. Everyone taking antipsychotic medicines needs to have lipids monitored during treatment and lipid lowering medication prescribed if indicated.

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continued
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 these medicines. The risk increases significantly with higher doses and with combinations of antipsychotic medicines.

Atypical antipsychotic medicines can prolong the QT interval and lead to ventricular tachyarrhythmias. Prolongation of QT interval has been observed especially with ziprasidone and to a lesser extent with risperidone and aripiprazole. Tachycardia has been observed with risperidone, olanzapine, quetiapine and less so with ziprasidone. An increased risk of stroke has been associated with all antipsychotic medicines.

If there is evidence of pre-existing cardiovascular disease or if there are cardiovascular risk-factors, an ECG may be required prior to initiating treatment with antipsychotic medicines. Everyone with schizophrenia should have a physical health check-up each year, including a cardiovascular disease risk assessment.

Note: Clozapine has a known association with myocarditis and cardiomyopathy, and there have been case reports with other atypical antipsychotics. Symptoms of myocarditis are similar to congestive heart failure and include fever, chest pain, fatigue, shortness of breath.

Postural hypotension and hypertension

Postural hypotension can occur with medicines that cause a significant alpha adrenergic blockade, this includes risperidone, olanzapine and quetiapine. Inform older adults and their caregivers about the increased risk of postural hypotension and falls with these medicines. There have also been cases of severe hypertension leading to collapse with risperidone.

Movement disorders

‘Typical’ antipsychotics should never be prescribed to people with Parkinson’s disease; atypicals should be used very cautiously due to the potential exacerbation of symptoms. Higher doses of risperidone (>6mg/day) and amisulpride (>300mg/day) are associated with Parkinson-like adverse effects, such as tremor, muscular rigidity, acute dystonia. These symptoms usually occur gradually and are more common with older adults. Risperidone, amisulpride, aripiprazole and olanzapine may cause akathisia (including agitation and restlessness).

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 people, and in up to 3% of people taking risperidone. This is of particular concern because it may not be evident initially, may worsen on treatment withdrawal, and can be irreversible.

Sexual dysfunction

Hyperprolactinaemia has been observed with risperidone, paliperidone and amisulpride with associated sexual dysfunction, 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 medicines may be necessary. The antipsychotic medicines with the lowest risk of sexual dysfunction appear to be aripiprazole, ziprasidone and quetiapine. There have been case reports of priapism with risperidone and olanzapine.

Note: Sensitive questioning may be needed to uncover sexual side effects because people may be reluctant to volunteer this information. Discuss the possibility of sexual dysfunction to and during treatment to provide reassurance and support adherence. Treatment non-adherence is a major risk factor for relapse.

Other side effects

Anticholinergic effects such as constipation and blurred vision can occur particularly with clozapine and olanzapine. Sedation has been associated with clozapine, olanzapine and quetiapine.

Mood or behaviour changes (eg, anxiety, irritability, in extreme cases suicidal thoughts and self-harm) can occur with people taking these medicines; advise them and their caregivers to report any concerns.

Concomitant use of other centrally acting medicines has the potential to increase adverse effects such as somnolence, drowsiness and sedation. People who are obese or have a history of sleep apnoea may be more sensitive to these effects.

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 medicines. This is more common in young men taking higher doses and is often associated with hot weather and exercise. Symptoms include muscular rigidity, pyrexia, confusion, urinary incontinence, disorientation, tachycardia and sweating. If these symptoms occur, urgent
assessment at the Emergency Department is required, the medicine stopped and supportive treatment provided.2 This syndrome can last for up to 5-7 days after discontinuation.2 Please remember that like the older antipsychotics, atypicals are linked to rare cases of raised hepatic enzymes and blood dyscrasias.19 Arrange blood counts if unexplained infection or fever develops.2

**TAKE CARE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)**

In some cases antipsychotics are used to manage BPSD if non-pharmacological treatment is ineffective. **Risperdone** is the only atypical antipsychotic currently indicated for BPSD.3 Antipsychotics will not be effective for wandering, social withdrawal, shouting, pacing, touching or cognitive defects.

There is an increased risk of mortality and an increased risk of stroke in people with dementia who are prescribed antipsychotic medicines. Older people 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 medicines, and to review efficacy and the emergence of adverse effects regularly.2

**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 the prescriber needs to 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.1

**Anxiety**

The usual treatment of anxiety is initial psychological therapy and, if necessary SSRIs may be used. The efficacy of SSRIs should be assessed after 12 weeks before other medicines are considered.1

**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.1

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**MONITORING RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Blood Count</td>
<td>Initially then annually</td>
<td></td>
</tr>
<tr>
<td>Urea and Electrolytes</td>
<td>Initially then annually</td>
<td></td>
</tr>
<tr>
<td>Liver Function Test</td>
<td>Initially then annually</td>
<td>Not required for amisulpride</td>
</tr>
<tr>
<td>Lipid profile</td>
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<td>Clozapine or olanzapine, monitor every 3 months for the first year, then annually</td>
</tr>
<tr>
<td>Weight</td>
<td>Initially, regularly during first 3 months, then annually</td>
<td>Clozapine or olanzapine, monitor every 3 months for the first year, then annually</td>
</tr>
<tr>
<td>Fasting Blood Glucose</td>
<td>Initially, at 4-6 months, then annually</td>
<td>Clozapine or olanzapine, also test after one month</td>
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<tr>
<td>ECG</td>
<td>Initially if risk factors</td>
<td>Refer to individual datasheets</td>
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<tr>
<td>Blood Pressure</td>
<td>Initially and during dose titration</td>
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<tr>
<td>Prolactin</td>
<td>Initially, at 6 months, then annually if clinical concerns</td>
<td>For higher risk medicines (amisulpride, risperdone) or if clinical concerns</td>
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<tr>
<td>CVD Risk Assessment</td>
<td>Annually</td>
<td>For everyone with schizophrenia</td>
</tr>
</tbody>
</table>
REFERENCES


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