Antipsychotic therapy in clinical practice

Oral therapy and monitoring

Depot antipsychotic therapy

Antipsychotic-induced cardiac arrhythmia

Pharmacological management of acute arousal
Key points for using antipsychotic therapy in clinical best practice

1. An oral atypical antipsychotic drug should be considered as first-line treatment for individuals with newly diagnosed schizophrenia. Doses should remain at the lower end of the dosage recommendations.

2. Choice of medication should be made on the basis of prior individual drug response, patient acceptance, individual side-effect profile and cost-effectiveness, other medications being prescribed and patient co-morbidities.

3. The lowest-effective dose should always be prescribed initially, with subsequent titration according to clinical response and monitoring of effectiveness of dose and ongoing need for therapy.

4. The dosage of a typical or an atypical antipsychotic medication should be within the manufacturer’s recommended range. Reasons for dosage outside of this range should be justified and documented.

5. Treatment trial should be at least 4-8 weeks before changing antipsychotic medication.

6. ‘Rapid neuroleptisation’ should not be used. Rapid loading doses should be used with extreme caution.

7. Antipsychotic medications, atypical or conventional, should not be prescribed concurrently, except for short periods to cover changeover.

8. Routine blood and clinical monitoring should occur as recommended in these guidelines.

9. Treatment should be continued for at least 12 months, then if the disease has remitted fully, may be ceased gradually over at least 1-2 months.

10. Depot formulations should be considered only where there is strong evidence for non-adherence.

11. Prophylactic use of anticholinergic agents should be determined on an individual basis and re-assessment made at 3-monthly intervals.

12. A trial of clozapine should be offered to patients with schizophrenia who are unresponsive to at least two adequate trials of antipsychotic medications.

NOTE:
See pages 8 to 12 of these guidelines for treatment algorithm and information on drug doses, costs and suggested monitoring.

The above standards may be used in the evaluation of clinical practice.
Potential complications associated with the treatment

- **Agitation**
  Consider adding a short-term oral benzodiazepine eg clonazepam 1-2mg (non-PBS for this indication) or diazepam 5-20mg or lorazepam 2.5mg (non-PBS).

- **Arousal**
  Consider adding a short-term oral benzodiazepine eg clonazepam 0.5-2mg, diazepam 5-20mg or lorazepam 1-2.5mg. If clinical situation justifies, use intramuscular clonazepam 2mg or midazolam 5-10mg. If unsuccessful use zuclopenthixol acetate (Clopixol-Acuphase®), except where patient is antipsychotic naïve.

- **Insomnia**
  Consider adding a short-term oral benzodiazepine eg temazepam 10-20mg.

- **Acute dystonic reaction**
  Consider adding an anticholinergic agent eg benztropine 2mg intramuscularly or intravenously, up to a maximum of 6mg in 24 hours.

- **Disinhibition**
  Disinhibition occasionally occurs up to 2-3 days after commencing benzodiazepine therapy. If so, consider other therapeutic options eg lower dose of atypical antipsychotic.

- **Akathisia**
  Reduce dose of antipsychotic if possible. If still present, add propranolol 10mg twice daily or clonidine 50-100 micrograms twice daily or a benzodiazepine.

- **Neuroleptic malignant syndrome**
  After this syndrome has occurred and been treated consider an alternative atypical antipsychotic or clozapine.

- **Tardive dyskinesia**
  Consider long-term risks of tardive dyskinesia associated with ongoing prophylaxis. Consider changing to an atypical antipsychotic or clozapine.

- **Persistent negative symptoms**
  Consider changing to an alternative atypical antipsychotic or clozapine. Exclude depression. If appropriate, treat depression with an SSRI. (see WAPDC Antidepressant Guidelines).

- **Intervening persistent depression**
  Add antidepressant (see WAPDC Antidepressant Guidelines).

- **Continual non–adherence**
Elderly patients and the use of antipsychotic drugs

CAUTION: Effective therapy with psychotropic medications is normally achieved with lower doses in the elderly compared to younger adults. Impaired renal or hepatic function also warrants use of lower doses. In addition to the use of smaller doses, the response of elderly patients should be careful monitored.

- Cardiovascular/stroke risk factors should be checked at baseline and during therapy.
- Benzodiazepines may cause respiratory depression. Respiratory function should be monitored.
- Benzodiazepine use may increase the risk of confusion and falls in the elderly.
- Shorter acting benzodiazepines are preferred eg. lorazepam for oral use.
- Benzodiazepines and drugs with anticholinergic activity may potentiate arousal in the elderly and exacerbate prostatic hypertrophy and glaucoma.
- Haloperidol-induced extrapyramidal side effects may be treated as they arise with benztropine 500 micrograms either orally or intramuscularly.
- Always use pharmacological interventions in conjunction with appropriate nursing care eg “one to one” specials.
- Exclude physical causes for agitation eg full bladder, head injury.
- Consider the potential for postural hypotension and the risk of falls when using antipsychotic drugs.

Drugs which may cause additive anticholinergic effects:

- benztropine, benzhexol, orphenadrine
- antispasmodics
- sedating antihistamines
- H₂ receptor antagonists
- clozapine
- carbamazepine
- phenothiazines, especially thioridazine
- tricyclic antidepressants
**Therapeutic algorithm** for the use of oral antipsychotic drugs in the treatment of schizophrenia and related disorders

1. **Exclude Organic Cause**
2. **Review Medication History**
3. **Increase Dose**
   - If not already at maximum dose, continue for further 2-4 weeks

4. **Considering Atypical Antipsychotic #**
   - Consider commencing treatment with an atypical antipsychotic or switching to an alternative atypical antipsychotic agent.
   - For choice of agent and dose, see Tables 1 and 2 opposite.

5. **Poor or Partial Response**
   - After 2-4 weeks
   - **Increase Dose**
     - If not already at maximum dose, continue for further 2-4 weeks
     - **Effective & Tolerated**

6. **Poor or Partial Response, or Unacceptable Side-Effects**
   - **Consider Alternative Atypical Antipsychotic**
     - **Effective & Tolerated**

7. **Poor or Partial Response**
   - After 2-4 weeks
   - **Increase Dose**
     - If not already at maximum dose, continue for 2-4 weeks.
     - **Effective & Tolerated**

8. **Poor or Partial Response, or Unacceptable Side-Effects**
   - **Consider Clozapine**
     - **Good Response**
     - **Continue Therapy**

9. **Poor or Partial Response**
   - After 2-4 weeks
   - **Increase Dose**
     - If not already at maximum dose, continue for 2-4 weeks.
     - **Effective & Tolerated**

10. **Poor or Partial Response, or Unacceptable Side-Effects**
    - **Consider Clozapine**
      - **Good Response**
      - **Continue Therapy**

---

* Atypical antipsychotic drugs, excluding clozapine
Selection of an atypical antipsychotic medication

Selection of an atypical antipsychotic medication for a particular patient should be determined with consideration for potential to control psychiatric symptoms, patient comorbidities, drug side-effects, potential for interaction with other medications and cost.

**TABLE 1: Relative frequency of common side-effects for atypical antipsychotics at usual adult therapeutic doses**

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Sedation</th>
<th>Postural hypotension</th>
<th>Anti-cholinergic</th>
<th>Extra-pyramidal</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++ *</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++ (initially)</td>
<td>++ (initially)</td>
<td>0</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++ (initially)</td>
<td>+++ (initially)</td>
<td>0</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Approximate frequencies of adverse effects: 0 (<2%) = negligible or absent; + (>2%) = infrequent; ++ (>10%) = moderately frequent; +++ (>30%) = frequent.

* rarely a problem at usual therapeutic doses
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**TABLE 2: Dose and cost comparison information for atypical antipsychotics**

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Adult Dose (Range of Doses Per Day)</th>
<th>Maximum Dose (Recommended Dose Per Day)</th>
<th>Elderly Dose (Range Per Day) (If applicable)</th>
<th>Cost ($) (Range of Doses Per Day)</th>
<th>Cost ($) (Modal Dose Per Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>400-800mg</td>
<td>1200mg</td>
<td>insufficient information</td>
<td>3.60 - 7.21</td>
<td>3.60 (400mg)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-30mg</td>
<td>30mg</td>
<td>generally lower doses</td>
<td>4.43 - 9.28</td>
<td>9.28 (30mg)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>200-600mg</td>
<td>900mg</td>
<td>generally lower doses</td>
<td>2.57 – 7.70</td>
<td>6.45 (500mg)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-20mg</td>
<td>30mg</td>
<td>start with 2.5 – 5mg</td>
<td>3.01 –12.14</td>
<td>12.14 (20mg)</td>
</tr>
<tr>
<td>Quetiapine*</td>
<td>400 – 800mg</td>
<td>800mg</td>
<td>generally lower doses</td>
<td>5.36 – 10.72</td>
<td>10.72 (800mg)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2 – 6mg</td>
<td>not &gt; 8mg</td>
<td>0.5 – 4mg</td>
<td>1.94 – 5.76</td>
<td>2.88 (3mg)</td>
</tr>
</tbody>
</table>

* a) 400-800mg quetiapine is the recommended adult dose for psychosis but it is often used off-label at lower doses for sedation.
  b) in clinical practice, maximum doses of up to 1200mg quetiapine have been used.

Cost comparisons based on hospital prices.
Usual daily cost based on nearest deliverable dose unit.
Suggested monitoring associated with atypical antipsychotic therapy

NOTE: Some of the following suggestions are based on considered opinion for what may constitute best-practice when monitoring patients during atypical antipsychotic therapy. Evidence supporting these suggestions is currently incomplete. Clinicians should be cognisant of potential risks, the value and regularity of monitoring in each case, and the availability of services required for monitoring.

TABLE 3: Suggested monitoring for all atypical antipsychotics

<table>
<thead>
<tr>
<th>AT BASELINE</th>
<th>DURING FOLLOW-UP OR ON TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>A baseline ECG is recommended for all patients at the commencement of antipsychotic drug treatment. Additional ECG monitoring is required depending on risk factors. For indications and recommended ECG monitoring, see Arrhythmia section of these Guidelines.</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>There is an increased incidence of diabetes mellitus in schizophrenia, although there is uncertainty regarding causality and risk. Monitor fasting blood glucose when commencing or changing antipsychotic medication and then 3 - 6 monthly. For patients diagnosed with diabetes, glycosylated haemoglobin (HbA1c) should be measured every 3 - 6 months to monitor glycaemic control.</td>
</tr>
<tr>
<td>Full blood count (FBC)</td>
<td>Neutropenia uncommonly occurs in patients treated with antipsychotic medication. A full blood count conducted 3-6 monthly may be best practice. If the neutrophil count is &lt; 1.5 x 10^9/L treatment should be stopped and haematologist advice sought.</td>
</tr>
<tr>
<td>Blood pressure (BP)</td>
<td>Monitor frequently during dose titration.</td>
</tr>
<tr>
<td>Urea &amp; electrolytes (U&amp;Es)</td>
<td>Monitor 6 monthly if risk factors for arrhythmia are present. Electrolyte monitoring should include assays for Ca^{+2} and Mg^{+2}</td>
</tr>
<tr>
<td>Liver Function (LFTs)</td>
<td>Monitor LFTs in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. Consider specialist advice if clinically significant changes in liver function occur.</td>
</tr>
<tr>
<td>Weight/ Body Mass Index (BMI)</td>
<td>Check every visit or every 3 months. Review treatment if BMI &gt; 30 kg/m²</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>Review treatment if waist/hip ratio is &gt; 1.0 in males; or &gt; 0.8 in females; check every visit or every 3 months.</td>
</tr>
</tbody>
</table>

Seek urgent specialist advice if Neuroleptic Malignant Syndrome is suspected. Neuroleptic Malignant Syndrome can develop at any time during treatment.

Additional monitoring is suggested for amisulpride, olanzapine, quetiapine, risperidone and clozapine, on the following page.
**Additional monitoring** suggested for atypical antipsychotic therapy

**For amisulpride, olanzapine and risperidone:**
Monitor plasma prolactin level. If high, seek specialist advice.

**For quetiapine:**
Changes in thyroid function may occur in patients taking quetiapine. These changes are usually not clinically significant, but a thyroid function test at baseline and at one month may be advisable. If abnormal, follow-up with specialist advice and additional thyroid function tests, as required.

**For clozapine:**
Prior to commencing clozapine the prescriber, pharmacist and patient MUST register with the relevant clozapine monitoring system. The monitoring listed in Table 4A & 4B should then be commenced.

### TABLE 4A: Obligatory monitoring for clozapine

<table>
<thead>
<tr>
<th>AT BASELINE</th>
<th>DURING FOLLOW-UP OR ON TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>Measure FBC weekly for 18 weeks, monthly thereafter, with increased monitoring when required. (see clozapine protocol) Stop clozapine if neutrophils $&lt; 1.5 \times 10^9$/L; or total leucocytes $&lt; 3.0 \times 10^9$/L; or eosinophils $&gt; 3.0 \times 10^9$/L</td>
</tr>
</tbody>
</table>

### TABLE 4B: Additional monitoring for clozapine

**NOTE:** Data collected predominantly in Australia has suggested that in patients treated with clozapine there is a small increased incidence of myocarditis early in treatment, and of cardiomyopathy within the first six-months of treatment. The following monitoring is based on manufacturer recommendations.

<table>
<thead>
<tr>
<th>AT BASELINE</th>
<th>DURING FOLLOW-UP OR ON TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram (ECG)</td>
<td>Perform an ECG at 14 days and then as needed. Stop clozapine if ECG shows significant changes.</td>
</tr>
<tr>
<td>Troponin I</td>
<td>Measure Troponin I level at 7 days, 14 days and then as needed. Perform an echo-cardiogram at 6 months. Seek advice from a cardiologist if evidence of cardiomyopathy, heart failure or myocarditis occurs. Perform electro-encephalogram (EEG) if myoclonus or seizures occur. Consider use of sodium valproate if EEG shows epileptiform changes.</td>
</tr>
</tbody>
</table>
Monitoring glucose metabolism

All patients taking antipsychotic medication should be screened for diabetic risk.

Ideally, fasting or random blood glucose levels should be assessed monthly for six months after initiating or changing antipsychotic therapy, then 3 to 6 monthly.

In patients diagnosed with diabetes, glycosylated haemoglobin (HbA1c) should be measured every 3-6 months to monitor glycaemic control. Note – glycosylated haemoglobin is not used to diagnose diabetes.

Antipsychotic drug treatment should be reviewed if the fasting blood glucose is > 7.0 mmol/L and the glycosylated haemoglobin >7%.

Risk factors

Risk factors for diabetes in patients taking antipsychotic medications are,

- older age
- family history of diabetes
- cardiovascular disease or presence of other cardiovascular risk factors
- personal history of gestational diabetes or polycystic ovarian syndrome
- ethnic predisposition
- lack of exercise
- poor diet
- obesity

Depot Antipsychotic Therapy
**Depot** antipsychotic medication use

**When to use a depot**

- The use of a depot or long acting injectable (LAI) formulation of an antipsychotic drug is a therapeutic option for patients demonstrating significant adverse consequences resulting from significant non-compliance with oral antipsychotic treatment.

- Atypical antipsychotics are generally recommended in clinical practice where available because of their improved side-effect profile. This recommendation also extends to depot antipsychotic drugs (eg LAI risperidone). However, there is no evidence that atypical antipsychotics are more effective than conventional antipsychotics in treating psychosis.

- Where a patient is clinically stable on a conventional depot, continuation of treatment is normally recommended. In this situation, the decision to continue conventional depot treatment should take into account the potential risks of tardive dyskinesia and long-term side effects against potential clinical gains. The patient should be informed of the potential risks and benefits.

- Patients currently treated with a conventional depot may switch to LAI risperidone where there are unacceptable adverse effects. Recommendations for switching in the Product Information should be followed (see opposite).

**Practical issues**

- A trial of oral risperidone is recommended to assess tolerance before LAI risperidone is considered - except in exceptional clinical circumstances.

- Risperdal Consta® requires cold chain supply and storage and may cause practical difficulties that should be fully considered before prescribing in rural and remote areas.

- Steady state is not reached for depot preparations for 6-8 weeks. Doses should be adjusted only after an adequate period of assessment (at least 4 weeks).

- Oral adjunctive antipsychotics may be used to manage acute presentations including the period waiting for steady state. Note that LAI risperidone takes 3-4 weeks for the first injection to produce therapeutic plasma levels and oral cover may be required for 6-8 weeks.

**Patient monitoring**

- It is recommended that patients be regularly asked to provide feedback on a full range of potential adverse effects.
Switching from conventional depot antipsychotic to long acting injectable (LAI) risperidone (Risperdal Consta®)

Practice guidelines

• For patients who have never taken oral risperidone administer a test dose of 1-2 mg/day for two consecutive days to rule out idiosyncratic hypersensitivity to risperidone.

• The starting dose of LAI risperidone is determined by a patient’s prior antipsychotic history. (see Table 5 below)

TABLE 5: Guidelines for switching from oral risperidone to LAI risperidone

<table>
<thead>
<tr>
<th>Dose of oral risperidone mg/day</th>
<th>Dose of intramuscular LAI risperidone mg/fortnight</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 mg</td>
<td>25mg</td>
</tr>
<tr>
<td>Between 2 and 4 mg</td>
<td>25 to 37.5 mg</td>
</tr>
<tr>
<td>&gt; 4 mg</td>
<td>37.5 to 50 mg</td>
</tr>
</tbody>
</table>

• Patients who have demonstrated a clear need for high doses of an antipsychotic or who are at risk of relapse may be initiated on 37.5 or 50mg.

• A minimum of 3 weeks’ antipsychotic supplementation is required after the first injection of LAI risperidone until the main release phase of risperidone begins.

• Steady state plasma levels following injection of LAI risperidone are typically achieved after four consecutive injections (after initiation or dose increase).

• Some patients may require additional antipsychotic supplementation for longer – the dose should be adjusted according to clinical response.

• Symptom improvement is possible after 1 month, though further improvement is seen over 3-6 months and continues in the long-term.
Switching from conventional depot antipsychotic to long acting injectable (LAI) risperidone (Risperdal Consta®)  

Switching options

Option 1  
Replace next scheduled conventional intramuscular depot dose with the first intramuscular dose of LAI risperidone.

Continue fortnightly intramuscular injections of LAI risperidone.

Option 2  
If antipsychotic supplementation is required in addition to the residual effects of the typical depot, the following regimen has been used in a post-marketing observational study:

• Give the first LAI risperidone injection 1 week after the last conventional depot injection is administered.

• Continue fortnightly intramuscular injections of LAI risperidone.

If practical, for switching Options 1 and 2 above, provide oral antipsychotic supplementation for a minimum of 3 weeks after the first injection of LAI risperidone until the main release phase of risperidone begins. Some patients may require additional antipsychotic cover for longer than 3 weeks.

For further information, see the Risperdal Consta® Product Information
Antipsychotic-Induced Cardiac Arrhythmia
Risk of antipsychotic-induced fatal arrhythmia

When using antipsychotic medications, there is a low overall risk of QT interval prolongation that may predispose to cardiac arrhythmia and Torsade de Pointes, with potential to progress to ventricular fibrillation. Nevertheless, deaths attributed to these causes have occurred in association with the use of antipsychotic medications. The degree of risk for each patient varies depending on patient factors, such as underlying pathologies, the antipsychotic medication and dose used, and concurrent use of other medication.

Prolongation of the QT interval is an important marker of increased risk of arrhythmia. Because the QT interval varies with heart rate, it is “corrected” for heart rate and is then expressed as the QTc. The generally accepted normal range for the QTc is 350-450ms in females and 350-430ms in males.

To minimise risk

- Screen patients for relevant clinical risk factors (see Table 6 below)
- Prescribe the lowest effective dose of a single atypical antipsychotic medication
- Monitor closely for clinical symptoms

### TABLE 6: Clinical risk factors

<table>
<thead>
<tr>
<th>MAJOR</th>
<th>Structural Heart Disease: including ischaemic heart disease, heart failure, and LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Congenital long QTc syndromes</td>
</tr>
<tr>
<td></td>
<td>Family history of sudden cardiac death at a young age</td>
</tr>
<tr>
<td></td>
<td>Prior QTc prolongation or Torsade de Pointes</td>
</tr>
<tr>
<td></td>
<td>Elderly - risk increases with increasing age (&gt;65 years)</td>
</tr>
<tr>
<td></td>
<td>Electrolyte imbalance, notably hypokalaemia, hypomagnesaemia &amp; hypocalcaemia</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Female gender</td>
</tr>
<tr>
<td></td>
<td>Alcohol and substance abuse</td>
</tr>
<tr>
<td></td>
<td>Renal or hepatic disease, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders, stress &amp; severe agitation</td>
</tr>
<tr>
<td></td>
<td>Polypharmacy – concomitant use of other medications</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics – risk increases in relation to dose</td>
</tr>
</tbody>
</table>
Signs of arrhythmia

- Medical practitioners and patients should monitor for signs of arrhythmia such as:

  SHORTNESS OF BREATH • DIZZINESS • LOSS OF CONSCIOUSNESS • PALPITATIONS

- Investigations, including ECG and serum electrolytes (including Mg\textsuperscript{++} and Ca\textsuperscript{++}) plus a review of medications are recommended when patients on antipsychotic medications present with these symptoms.

Indications for electrocardiogram (ECG)

- a baseline ECG is recommended for all patients at the commencement of antipsychotic drug treatment, or if this is not possible, within 1 week of commencement.

- ECG monitoring is recommended at 1-2 weeks after starting an antipsychotic drug and at least 6 monthly intervals where -
  - major or multiple risk factors exist, or
  - the drugs are high-risk (see Table 7 on page 20), or
  - drugs are to be used at high dose or in combination.

- additional monitoring is recommended following –
  - the introduction of a high-risk drug, or
  - a change in the drug or dose.

- ECG should be reviewed by a cardiologist or other practitioner competent and experienced in the interpretation of ECGs. (An automated ECG may not provide accurate assessment particularly where QT is prolonged. Referral to a cardiologist is recommended whenever an abnormality is detected).

Clinical response should continue to be monitored throughout therapy.

Review of antipsychotic therapy, including cessation of medication and referral to a cardiologist should be considered if the ECG shows any of the following features:

- QTc interval > 500 milliseconds
- QTc prolongation > 60 milliseconds over baseline
- Other ECG abnormalities e.g. unusual T waves, bradycardia

For specialist advice, ECG printouts may be referred by fax to a tertiary hospital Cardiovascular Medicine Unit. Contact details are:

<table>
<thead>
<tr>
<th></th>
<th>SCGH</th>
<th>RPH</th>
<th>Fremantle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone</td>
<td>(08) 9346 2677</td>
<td>(08) 9224 2284</td>
<td>(08) 9431 2448</td>
</tr>
<tr>
<td>Fax</td>
<td>(08) 9346 2920</td>
<td>(08) 9224 2067</td>
<td>(08) 9431 2172</td>
</tr>
</tbody>
</table>
**Arrhythmia risks** associated with antipsychotic medications

Risks and benefits of antipsychotic therapy must be assessed and explained to the patient in each case, with informed consent given by the patient when the clinical circumstances allow.

Medication selection should be based on clinical factors, followed by consideration of the risk factors associated with single or multiple drug therapy.

**TABLE 7: Pharmacological risk factors**

<table>
<thead>
<tr>
<th></th>
<th>HIGH</th>
<th>MEDIUM</th>
<th>LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorpromazine</td>
<td>- oral - use with caution;</td>
<td>amisulpride</td>
<td>aripiprazole</td>
</tr>
<tr>
<td></td>
<td>- parenteral - not recommended for use</td>
<td></td>
<td>olanzapine</td>
</tr>
<tr>
<td>droperidol</td>
<td>- not recommended for use</td>
<td>clozapine (cardiac monitoring required according to treatment protocol)</td>
<td>thioxanthenes</td>
</tr>
<tr>
<td>haloperidol</td>
<td>- use with caution</td>
<td>quetiapine</td>
<td>trifluoperazine</td>
</tr>
<tr>
<td>(parenteral</td>
<td>- high dose - not recommended for use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and high dose</td>
<td>- not recommended for use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pimozide</td>
<td>- not recommended for use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(use with QTc</td>
<td>prolonging drugs is contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thioridazine</td>
<td>- not recommended for use</td>
<td>(note restrictions on limiting thioridazine use)</td>
<td></td>
</tr>
<tr>
<td>(use with QTc</td>
<td>prolonging drugs is contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strong evidence of increased clinical risk.</td>
<td>Potential risk. Avoid use for patients with</td>
<td>Little or no evidence of increased clinical risk.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>identified risk factors.</td>
<td></td>
</tr>
</tbody>
</table>

**Polyprescribing and risk of cardiac arrhythmia**

Concomitant use of other medications with antipsychotic therapy may increase the risk of fatal arrhythmia by:

- Exacerbating the QTc prolongation. For a complete and up-to-date listing of drugs that prolong the QTc interval see www.torsades.org
- Causing an electrolyte imbalance.
- Introducing another medication that inhibits CYP450 metabolism of the antipsychotic drug, leading to higher plasma concentrations of the antipsychotic medication.
- Ceasing a medication that induces CYP450 metabolism of the antipsychotic drug, leading to higher plasma concentrations of the antipsychotic medication.

**NOTE:** The following Tables 8-11 are not comprehensive and serve as a guide only.

**TABLE 8: Some medications that may prolong the QTc interval and/or induce Torsades de Pointes**

For a more complete and up-to-date listing see www.torsades.org

<table>
<thead>
<tr>
<th><strong>Antipsychotics</strong></th>
<th>chlorpromazine, clozapine, droperidol, haloperidol, pimozide, quetiapine, risperidone, thioridazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>venlafaxine</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td>amiodarone, disopyramide, flecainide, procainamide, quinidine, sotalol</td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td>azithromycin, clarithromycin, erythromycin, foscarnet, gatifloxacin, moxifloxacin, pentamidine, voriconazole</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>amantadine, chloroquine, dexamphetamine, dolasetron, lithium, methylphenidate, methadone, tacrolimus, vardenafil</td>
</tr>
</tbody>
</table>

**TABLE 9: Some medications that may change electrolyte balance**

| **Antihypertensives** (including diuretics, beta-2 antagonists) | cisplatin, corticosteroids, laxatives |
**Polyprescribing** and risk of cardiac arrhythmia

### TABLE 10: Some medications that may inhibit CYP450 metabolism, resulting in increased antipsychotic plasma concentrations

See [http://medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm) for a more complete list.

<table>
<thead>
<tr>
<th>CYP 1A2</th>
<th>Amiodarone, cimetidine, ciprofloxacin, fluvoxamine, interferon, paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4, 5, 7</td>
<td>Amiodarone, chloramphenicol, cimetidine, clarithromycin, delavirdine, erythromycin, fluconazole, fluvoxamine, indinavir, lpraconazole, ketoconazole, nefinavir, norfloxacin, ritonavir, grapefruit juice</td>
</tr>
<tr>
<td>CYP 2D6</td>
<td>Amiodarone, celecoxib, chlorpheniramine, cimetidine, clomipramine, es/citalopram, fluoxetine, methadone, moclobemide, paroxetine, quinidine, ranitidine, rironavir, sertraline</td>
</tr>
</tbody>
</table>

### TABLE 11: Some medications that may induce CYP450 metabolism resulting in reduced antipsychotic plasma concentrations

See [http://medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm) for a more complete list.

<table>
<thead>
<tr>
<th>CYP 1A2</th>
<th>Insulin, omeprazole, broccoli, brussel sprouts, smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4, 5, 7</td>
<td>Barbiturates, carbamazepine, glucocorticoids, phenytoin, pioglitazone, rifabutin, rifampicin, ritonavir, St John’s wort</td>
</tr>
<tr>
<td>CYP 2D6</td>
<td>Dexamethasone, rifampicin</td>
</tr>
</tbody>
</table>

**NOTE:** When prescribing a medication to a patient receiving antipsychotic therapy, clinicians should ensure the patient receives and is directed to read a relevant Consumer Medicine Information sheet (CMI). Their attention should be drawn to the side-effect and drug interaction information in the CMI, particularly cardiac side-effects.
Pharmacological Management of Acute Arousal
Pharmacological management of acute arousal

Sedation is the aim of pharmacological management of acute arousal. Sedation should usually be titrated up to the desired level but not greater than the point of rousable sleep. Benzodiazepines achieve this most effectively with minimal side-effects. On occasions it may be necessary to use a combination of agents. Treat neuroleptic naïve patients with caution using recommended drug doses in the lower range. Avoid using antipsychotic drugs in first episode patients.

TABLE 12: Mild - Moderately Aroused: Oral Therapy

<table>
<thead>
<tr>
<th>MILDLY AROUSED</th>
<th>MILDLY AROUSED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing, still willing to talk reasonably.</td>
<td>Agitated, becoming more vocal, unreasonable or hostile.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORAL THERAPY</th>
<th>Repeat dose (if required)</th>
<th>Max daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diazepam 5 to 10 mg</td>
<td>every 60 minutes</td>
<td>120 mg/24 hrs</td>
</tr>
<tr>
<td>OR lorazepam 1 to 2.5 mg</td>
<td>every 60 minutes</td>
<td>10 mg/24 hrs</td>
</tr>
<tr>
<td>OR clonazepam 500 micrograms to 2 mg</td>
<td>every 60 minutes</td>
<td>6 mg/24 hrs</td>
</tr>
</tbody>
</table>

If ineffective, consider Options 2A or 2B or 3

| Option 2A | chlorpromazine 50 to 200 mg either alone or in combination with oral Option 1 above | every 2 to 4 hours | 600 mg/24 hrs |
| Option 2B | haloperidol 1 to 5 mg either alone or in combination with oral Option 1 above | every 2 to 4 hours | 20 mg/24 hrs  |
| Option 3  | Either olanzapine 5 to 10 mg | every 2 to 4 hours | 30 mg/24 hrs  |
| OR quetiapine 25 to 100 mg | every 2 to 4 hours | 800 mg/24 hrs |
| OR risperidone 1 to 2 mg | every 2 to 4 hours | 8 mg/24 hrs  |

NOTE: These guidelines display normal adult doses. Dosage adjustment is required in the treatment of other patients, including the young, the frail and elderly, and those with comorbid conditions.
Pharmacological management of acute arousal

**TABLE 13: Moderate - Highly Aroused: Intramuscular Therapy**

<table>
<thead>
<tr>
<th>INTRAMUSCULAR THERAPY</th>
<th>Repeat dose (if required)</th>
<th>Max daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1</strong></td>
<td>midazolam 5 to 10 mg **</td>
<td>every 30 minutes</td>
</tr>
<tr>
<td>OR</td>
<td>clonazepam 1 to 2 mg #</td>
<td>every 30 minutes</td>
</tr>
<tr>
<td><strong>Option 2</strong></td>
<td>haloperidol 2.5 to 5 mg plus IM Option 1 above</td>
<td>every 30 minutes</td>
</tr>
<tr>
<td><strong>Option 3</strong></td>
<td>olanzapine 5 to 10 mg <strong>X</strong></td>
<td>2 to 4 hourly</td>
</tr>
</tbody>
</table>

**TABLE 14: Highly Aroused: Intravenous Therapy**

<table>
<thead>
<tr>
<th>INTRAVENOUS THERAPY (Rarely required)</th>
<th>Repeat dose (if required)</th>
<th>Max daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1</strong></td>
<td>midazolam 2.5 to 10 mg **</td>
<td>2.5mg every 5 to 10 minutes until adequate sedation is achieved</td>
</tr>
<tr>
<td><strong>Option 2</strong></td>
<td>diazepam 2.5 to 10 mg</td>
<td>2.5mg every 5 to 10 minutes until adequate sedation is achieved</td>
</tr>
<tr>
<td><strong>Option 3</strong></td>
<td>haloperidol 2.5 to 5 mg PLUS \midazolam 2.5 to 10 mg **</td>
<td>2.5mg every 5 to 10 minutes until adequate sedation is achieved</td>
</tr>
</tbody>
</table>

The selection of intravenous options in Table 14 should be based on the length of sedation required.

**NOTES**

**When using midazolam, first-line management of respiratory depression requires resuscitation equipment and experienced staff. Flumazenil should also be available for reversal of respiratory depression if required, but only under medical supervision and restricted to use in hospitals because of "on/off" effect.

#Use of intramuscular clonazepam for acute arousal is not an approved indication in Australia, but in the opinion of WATAG represents accepted clinical practice.

**XXTo avoid potential adverse effects, do not co-administer IM olanzapine with parenteral benzodiazepine drugs, and use with caution with oral benzodiazepine.
Pharmacological management of acute arousal

Precautions

• Monitor respiratory function when benzodiazepines are administered parenterally.
• Consider current medications, and their contribution to patient’s mental state.
• Lower doses should be considered in patients with low body weight, dehydration, and those with no prior neuroleptic exposure.
• Benzodiazepines occasionally produce disinhibition. This occurs up to 2-3 days after commencing benzodiazepine therapy, and requires that alternative treatment options (eg atypical antipsychotic at lower dosage than shown in Table 12, page 24) be considered.
• A sudden unexpected sedative effect sometimes occurs as a result of non-linear pharmacokinetics of drug(s) being administered. This effect occurs more often in patients who are frail, have low body fat, or have renal disease.

Comment

Use of atypical antipsychotics for acute arousal is gaining support in clinical practice despite limited evidence. Liquid or wafer presentations of risperidone and olanzapine are sometimes useful. Quetiapine requires individual titration and dosing is generally more unpredictable.

For complications involving acute dystonic reactions, add anticholinergic agent eg benztropine 2 mg intramuscularly or intravenously, up to a maximum of 6 mg in 24 hours.
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