Antipsychotic Monitoring

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Introduction
Evidence supporting what constitutes best practice in the monitoring of antipsychotics is lacking. Monitoring patients receiving antipsychotics can be seen as having two overall goals; firstly, to identify treatable pathology in a high-risk population and secondly, to link and track antipsychotic-induced adverse effects. Antipsychotics have been associated with causing a variety of cardiovascular, metabolic, hepatic, haematologic and endocrine diseases.

Physical health monitoring is the responsibility of the patient, case manager, GP and psychiatrist. Mental health services should ensure that a monitoring protocol is incorporated into the treatment plan of every patient. All monitoring protocols must include a workable, effective call-up system and a process to audit compliance.

Table 1 lists suggested baseline monitoring for patients starting on an antipsychotic drug and suggested ongoing monitoring. More frequent monitoring may be indicated in certain situations; these are discussed under the relevant monitoring parameter heading.

Medical History
Certain antipsychotics are contraindicated or must be used with caution in patients with other comorbidities. Judicious selection of an antipsychotic is particularly important in patients with a history of:

- Severe cardiac, renal or hepatic disease
- Conditions that are risk factors for arrhythmia eg bradycardia, electrolyte imbalance

Table 1: Key Monitoring Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Baseline and Early Treatment Monitoring</th>
<th>Ongoing Monitoring</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>At 1-2 weeks</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BSL</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>FBP</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>U+E</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>BP and pulse</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Key:
BMI= Body mass index (kg/m²)  
ECG= Electrocardiograph  
BSL= Blood sugar level (measure fasting venous glucose level)  
FBP= Full blood picture  
U+E= Urea and electrolytes  
LFT= Liver function test  
BP= Blood pressure

* Suggested monitoring dependent on risk factors
# For high-risk drugs for the first year, then annually

There is additional, specific monitoring for clozapine; refer to the clozapine monitoring section
- Parkinson’s disease
- Diabetes
- Closed angle glaucoma, increased intraocular pressure, Gl obstruction, prostatism, urinary retention, myasthenia gravis
- Epilepsy
- Bone marrow disorders or history of blood dyscrasias
- Prolactin-dependent tumours
- Respiratory failure
- Phaeochromocytoma
- Current pregnancy or lactation

Aside from a patient’s medical history, a medication history including any drug allergies or adverse drug reactions should also be elicited.

Body Mass Index
Most antipsychotics can cause weight gain, although the greatest mean weight gain has been associated with clozapine and olanzapine. Of the atypical antipsychotics, amisulpride and aripiprazole are considered the lowest risk of causing weight gain. BMI should be monitored monthly for the first six months or at every visit on an outpatient basis. Patients should be encouraged to maintain a BMI between 18.5-25kg/m². Antipsychotic treatment should be reviewed if BMI>30kg/m² or if there is >5% weight gain over baseline. Prevention of weight gain should be the primary objective by encouraging behavioural modification of diet and physical activity.

Lipid Profile
Antipsychotics considered a high-risk of causing hyperlipidaemia include clozapine, quetiapine, olanzapine and the phenothiazines. The National Heart Foundation recommends the following target lipid levels:

<table>
<thead>
<tr>
<th>Target Lipid Levels¹</th>
<th></th>
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<tbody>
<tr>
<td>LDL-cholesterol &lt; 2.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>(&lt;2.0mmol/L for high-risk patients)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol &lt;4.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol &gt; 1.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Triglycerides &lt;1.5 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Please note that these recommendations may differ from PBS criteria for eligibility for lipid lowering medications. Before lipid-lowering medications are commenced, secondary causes of dyslipidaemia and modifiable cardiovascular risk factors should be managed.

Blood Glucose Level
There is an increased risk of developing diabetes with certain antipsychotics, particularly olanzapine, clozapine and the phenothiazines. Although there is a correlation between diabetes and drug-induced weight gain, diabetes can occur independently.

Aside from the recommended regular monitoring, BSL should be measured at any time if weight loss, polydipsia, polyuria or unexplained tiredness occurs. The following table outlines the diagnostic criteria for diabetes.

<table>
<thead>
<tr>
<th>Blood Glucose Level¹⁰</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>≥7.0mmol/L (fasting) or ≥11.1mmol/L (random) Must occur on two occasions, or once with diabetic symptoms</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>5.5 –7.0 mmol/L (fasting) or 5.5 –11.0 mmol/L (random) (Diagnosis of diabetes if BSL ≥ 11.1 mmol/L at 2 hours following oral glucose tolerance test)</td>
</tr>
</tbody>
</table>

If diabetes is diagnosed, once daily antidiabetic medication should be used where possible, so that treatment can be more easily supervised. Metformin is considered the preferred first-line antidiabetic agent. HbA1c should be measured every 3-6 months to monitor glycaemic control. Ideal glycaemic control is represented by an HbA1c < 7%.

Electrocardiograph
QTc prolongation and resultant arrhythmia including torsades de pointes has been associated with a number of antipsychotics. A baseline ECG is recommended for all patients at the commencement of antipsychotic therapy. If the baseline QTc interval is >450ms, thioridazine should not be prescribed; other antipsychotics should be used with caution.

The ECG should be repeated 1-2 weeks after starting treatment and at 6-monthly intervals for patients with risk factors for arrhythmia, patients receiving high-dose or high-risk antipsychotics or patients receiving multiple medications known to prolong the QTc interval. Antipsychotics generally accepted as having a higher risk of causing torsades de pointes include: chlorpromazine, droperidol, haloperidol, pimozide and thioridazine (see www.qtdrugs.org for a complete list).

Additional ECG monitoring is also recommended when there are dose changes for high-risk drugs, or if patients experience signs of arrhythmia including shortness of breath, dizziness, loss of consciousness or palpitations.

If the QTc interval is prolonged to greater than 500ms, the causative drug should be stopped, and the patient referred to a cardiologist. Antipsychotic therapy should be reviewed if the QTc interval becomes prolonged by greater than 60ms over baseline or if there is abnormal T-wave morphology. Switching to a lower-risk antipsychotic should also be considered if the QTc interval is greater than 440ms (men) or greater than 470ms (women).
Full Blood Picture

Haematological abnormalities are frequently encountered with antipsychotic therapy; however, most of these are of little clinical significance. In a small minority of patients, potentially life-threatening haematologic abnormalities including neutropenia and agranulocytosis occur. Aside from regular monitoring, the FBP should also be monitored if a patient develops clinical signs of infection such as fever, sore throat or flu-like symptoms. If the neutrophil count is <1.5 x 10^9/L, treatment should be stopped and haematologist advice sought^1.

Urea and Electrolytes

Baseline U+E monitoring is required to assess renal function and to make any necessary dose adjustments. Electrolyte abnormalities, particularly hypokalaemia, hypomagnesaemia and hypocalcaemia can increase the risk of QTc prolongation and arrhythmia; these should be corrected before antipsychotic therapy is commenced^2. Antipsychotics have been associated with hyponatraemia caused by drug-induced syndrome of inappropriate antidiuretic hormone. U+Es should be monitored if a patient develops signs of hyponatraemia including confusion, nausea, headache and lethargy. If mild hyponatraemia is detected, fluid restriction with careful monitoring of serum sodium is recommended. Refer to specialist medical care if Na<125mmol/L^2.

Liver Function Test

A baseline LFT is required to determine any hepatic impairment. Although LFTs are a poor marker of hepatic metabolising capacity, if elevated, a lower starting dose of highly protein-bound, heptatically metabolised antipsychotics should be considered^3. If a patient has severe hepatic disease, avoid hepatotoxic drugs such as clozapine and phenothiazines and monitor LFTs weekly, at least initially^3. If LFTs deteriorate after a new drug is introduced, consider switching to another drug. Antipsychotics often cause asymptomatic increases in aminotransferase levels. Rarely, antipsychotics can cause hepatotoxicity or hepatocellular cholestasis. A LFT is indicated if a patient develops jaundice, pruritus, dark urine, pale stools, nausea or loss of appetite.

Blood Pressure

Monitor both recumbent and standing blood pressure and pulse at baseline and during dose titration for antipsychotics with alpha,-adrenergic blocking activity including clozapine, risperidone, quetiapine, chlorpromazine and thioridazine.

A prolactin level is indicated if a patient reports signs and symptoms of hyperprolactinaemia such as sexual dysfunction, galactorrhoea, amenorrhoea or gynaecomastia. If prolactin-related adverse reactions are intolerable, consider reducing the dose of medication or switching to a prolactin-sparing antipsychotic^4.

Creatine Kinase

Monitor creatine kinase (CK) as well as FBP (for leukocytosis) if a patient presents with fever, rigidity and diaphoresis to rule out neuroleptic malignant syndrome. Raised CK (>1000IU/L) may indicate possible neuroleptic malignant syndrome^5.

Electroencephalograph

Most antipsychotics produce a dose related reduction in seizure threshold. Monitor EEG if myoclonus or seizures occur. If EEG changes occur, consider switching to a drug with a low proconvulsive effect or adding an anticonvulsant.

Eye Examination

Phenothiazines may induce cataracts or pigmentary retinopathy, which is dependent on both the dose and duration of treatment. Ocular examinations should be performed annually or if changes in vision are reported^6.

Thyroid Function Test

Changes in thyroid function may occur in patients taking quetiapine. A baseline thyroid function test and follow up at one month may be advisable for patients at risk of hypothyroidism^7.

Clozapine Monitoring

For clozapine, monitoring of FBP is required weekly for the first 18 weeks of therapy and then monthly thereafter. Stop clozapine if neutrophils <1.5 x 10^9/L; total leukocyte count <3.0 x 10^9/L; or if eosinophils >3.0 x 10^9/L^11. The manufacturers of clozapine recommend monitoring baseline markers of myocardial damage using troponin I or T assay and serum creatinine as well as an ECG. The baseline cardiac enzymes and ECG should be repeated on days 7 and 14 of treatment to detect any early signs of acute myocarditis. Stop clozapine if ECG shows significant changes^13. After 6 months of treatment, it is advised that patients undergo echocardiography to test for the development of chronic cardiac adverse effects as well as to provide a baseline reading against which future events may be measured^13. More frequent haematological and cardiac monitoring may be indicated in certain cases; refer to the manufacturer published clozapine protocol.
### Therapeutic Drug Monitoring (TDM) of Psychotropics

#### Table 2: Interpretation of Sample Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Therapeutic Range</th>
<th>Sampling Time</th>
<th>Time to Steady State</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>350-600 µg/L</td>
<td>Trough</td>
<td>2-3 days</td>
<td>Plasma levels generally lower in males, younger patients and smokers.</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.5-1.2 mmol/L</td>
<td>12 hours post-dose</td>
<td>5 days</td>
<td>Aim for the upper end in acute mania and lower end in maintenance therapy.</td>
</tr>
<tr>
<td>Valproate</td>
<td>50-100 mg/L</td>
<td>Trough</td>
<td>2-3 days</td>
<td>Clinical value in bipolar disorder is controversial; dosing should be guided by clinical response and tolerability</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>6-12 mg/L</td>
<td>Trough</td>
<td>2 weeks</td>
<td>Time to steady state depends on its auto-induction.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1-14 mg/L</td>
<td>Trough</td>
<td>5 days</td>
<td>Recommended for compliance monitoring only</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20-80 µg/L</td>
<td>12 hours post-dose</td>
<td>1 week</td>
<td>Dosing should be guided by response and tolerability and TDM reserved for compliance monitoring and lack of response at maximum dosage.</td>
</tr>
<tr>
<td>Risperidone + 9-0H risperidone</td>
<td>20-60 µg/L</td>
<td>Trough</td>
<td>1 day</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>70-170 µg/L</td>
<td>Trough</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>100-400 µg/L</td>
<td>Trough</td>
<td>2-3 days</td>
<td></td>
</tr>
</tbody>
</table>

**TDM**

TDM is a valuable tool when used appropriately for optimising drug therapy in clinical psychiatry. Table 2 outlines practical issues of TDM for a number of psychotropic drugs.

**Sampling**

Before sampling, steady state plasma concentrations should be reached in order to prevent misinterpretation of drug concentrations. In practice, sampling for most psychotropic drugs is carried out one week after chronic daily dosing either 12 hours post-dose or immediately before the next dose depending on the drug. In both cases, samples taken more than 1-2 hours before or after the scheduled time are likely to lead to falsely low or high readings.

**Interpretation of Results**

If the drug concentration is within therapeutic range, modification of dosage is recommended only when justified by clinical reasons such as adverse effects or lack of clinical response. When plasma concentrations are unusually low, a repeat level is recommended; this may help to determine irregular compliance, or presence of environmental or genetic factors leading to rapid metabolism of the particular drug. Drug monitoring. Canadian Journal of Psychiatry. 2005;50(9):555-562.

References: