Providing an overview on antipsychotics: schizophrenia a psychiatric challenge? A 2017 Update

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Abstract
Psychosis is an umbrella term used in the description of various conditions involving delusions and hallucinations. This article focuses mainly on the management of schizophrenia. Schizophrenia is a complex disorder, which provides many pharmacotherapy-related challenges. Advances have been made in the treatment of the condition; however, this requires a team approach, with the pharmacist having to monitor treatment both for safety and efficacy. The involvement of medicines that might modulate the N-methyl-D-aspartate (NMDA) receptors is an exciting development that should be monitored.

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Introduction
Psychosis has various definitions, with the most basic referring to a psychotic episode as an event that involves delusions and prominent hallucinations, without the affected patient being aware of the pathological nature of the hallucinations. Some definitions include the positive symptoms experienced in schizophrenia, such as disorganised speech and grossly disorganised or catatonic behaviour. The use of the term ‘psychotic’ also differs between schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and a psychotic disorder due to a general medical condition or substance-induced psychotic disorder, where the term refers to delusions or hallucinations that are not accompanied by insight.1

Schizophrenia is characterised by three major symptom domains: positive, negative (e.g. social withdrawal, flattened affect) and cognitive symptoms (e.g. deficits in working memory).1

As shown in Figure 1, three stages are identified in the evolution of schizophrenia and are of importance to the pharmacist when managing or evaluating treatment.2

Neurotransmitter involvement
Dopamine
The hypothesis of dopamine involvement in the development of schizophrenia follows two ideas:3

• Dopamine involved in antipsychotic action: Increased densities of D2 receptors have been shown in the caudate nucleus and decreased densities in the prefrontal cortex. The over-activity of these receptors in the mesolimbic part of the brain provides an explanation of the positive symptoms. These receptors provide the mechanistic basis for the antipsychotic action observed when blocked.

• Decreased activity in mesocortical dopaminergic pathway: Neuroimaging studies have shown that patients diagnosed with schizophrenia and suffering from psychosis show a decreased activity of D1 receptors in the mesocortical dopamine pathway.

To manage schizophrenia pharmacologically, inhibition of dopaminergic transmission has to be inhibited in the limbic pathway whilst enhancing the dopaminergic transmission in the prefrontal cortex. This makes managing schizophrenia challenging. Most current antipsychotics act on this system to manage mainly positive symptoms.

NMDA and glutamate
There is a growing body of evidence that supports glutamate dysfuntion as a contributing factor to the disease.4 Glutaminergic and GABAergic neurons have an important role in controlling...
neuronal activity in the mesolimbic pathway, where there is also
dopaminergic activity. It is for this reason that the glutamate
synapse has now received widespread attention as an important
target for pharmacological action. The synapse is target rich,
as it contains a large number of presynaptic, postsynaptic and
regulatory proteins that may be used in drug therapy to treat
symptoms refractive to other drug therapy. It has been postulated
that some of the negative symptoms seen in schizophrenia
might be due to a disruption in glutamate transmission at the
NMDA receptors owing to functional abnormalities of these
receptors. This has further been supported by the observation
that administration of NMDA receptor antagonists such as
ketamine induce a schizophrenia-like state. Drug development
for the management of schizophrenia might be steered towards
the development of agents that enhance the function of NMDA
receptors by activating the glycine site.

Glutamatergic agents are
at various stages of development, including the glycine transport
inhibitors bitopertin and sarcosine.

Serotonin
Serotonin does not seem to have a direct role in the pathogenesis
of schizophrenia; however, its receptors are present on the
dopaminergic axons. Stimulation of these receptors decreases
dopamine release, especially in the striatum. Drugs with
combined D2 antagonistic effects and 5-HT-receptor activity have
improved therapeutic effects, as discussed later.

Management of psychosis
Baseline investigations prior to initiation of therapy
All antipsychotics increase body weight, although to varying
degrees, and some second-generation antipsychotics (SGAs)
elevate lipid levels. Some first-generation antipsychotics (FGAs)
(e.g. clozapine) produce agranulocytosis. It is for this reason that
all patients undergo the following baseline investigations prior to
initiation of antipsychotic agents:

- body mass index (especially for olanzapine)
- waist-to-hip ratio
- fasting blood glucose
- liver function tests
- white cell count, specifically acute neutrophil count (especially
for clozapine)
- electrocardiogram.

These baseline investigations can be modified depending on the
regimen to be initiated or if there is a change in regimen. The
pharmacist can assist in monitoring the side effect profile.

Pharmacological management
Although psychosocial interventions are crucial in promoting
recovery and improving quality of life for the schizophrenia
patient during clinical management of different stages of the
illness, pharmacological management is the essential
component of treatment.
Benzamides

Amisulpride, a substituted benzamide analogue of sulpiride, is a highly selective antagonist of D₂ and D₃ receptors, with little affinity for D₁-like or non-dopaminergic receptors.8 FGAs differ in potency, not effectiveness.10 For example, haloperidol and fluphenazine have a high potency, perphenazine and loxapine have a mild potency and chlorpromazine has a low potency.

Table I provides an overview of the first-generation medicines used in the management of schizophrenia.

Table II: Recommended daily maximum doses of SGAs, their side effects and the associated management11

<table>
<thead>
<tr>
<th>Name</th>
<th>Brand name</th>
<th>Usual dose</th>
<th>Maximum dose</th>
<th>Indication(s)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>Solian®</td>
<td>400–800 mg</td>
<td>1200 mg</td>
<td>Acute and chronic schizophrenia</td>
<td>Neuroleptic malignancy syndrome</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify®</td>
<td>10–30 mg</td>
<td>30 mg</td>
<td>Schizophrenia, bipolar mania</td>
<td>Weight gain, anxiety, insomnia, headache</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril®</td>
<td>200–450 mg</td>
<td>900 mg</td>
<td>Schizophrenia</td>
<td>Agranulocytosis, weight gain, hypotension</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa®</td>
<td>10–20 mg</td>
<td>20 mg</td>
<td>Management of the manifestations of psychotic disorders, preventing the recurrence of manic episodes of bipolar disorder</td>
<td>Bradycardia, xerostomia, weight gain (dose dependent), hypercholesterolaemia, EPS (dose dependent), hyperglycaemia, weakness</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal®</td>
<td>4–6 mg</td>
<td>16 mg</td>
<td>Acute and chronic schizophrenia, conduct and disruptive behaviour disorders in children 5–12 years of age</td>
<td>Angioedema, body temperature dysregulation, hyperprolactinaemia in children, insomnia</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel®</td>
<td>300–450 mg</td>
<td>750 mg</td>
<td>Bipolar mood disorder associated with mania, schizophrenia</td>
<td>Abdominal, back, chest or ear pain, dry mouth, somnolence</td>
</tr>
<tr>
<td>Ziprazidone</td>
<td>Geodon®</td>
<td>80 mg</td>
<td>160 mg</td>
<td>Acute exacerbation and maintenance of clinical improvement during continuation therapy in schizophrenia</td>
<td>Headache, nausea, extrapyramidal symptoms, generalised tonic-clonic seizures</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega®</td>
<td>50 mg</td>
<td>800 mg</td>
<td>Schizophrenia, schizoaffective disorder in adults (unlicensed indication)</td>
<td>Somnolence, dizziness, liver enzyme abnormalities, orthostatic hypotension and syncpe, weight gain and metabolic dysfunction (particularly in adolescents)</td>
</tr>
</tbody>
</table>

Second-generation antipsychotics

There are two theories on the mechanism of action of SGAs:

- The serotonin–dopamine (S₂/D₂) antagonist theory suggests that an SGA has a higher affinity for the serotonin 5-HT₂₆ receptor than for the dopamine D₂ receptor.
- The fast-off D₂ theory suggests that although an SGA cannot function without some degree of binding to D₂ receptors, it is the rate at which the drug dissociates from the receptor that is responsible for the effect. The theory suggests that dissociation from the D₂ receptor quickly makes the antipsychotic more accommodating of physiological dopamine transmission.8,9,10

**Table I: Recommended daily maximum doses of typical antipsychotics, their side effects and the associated management11**

<table>
<thead>
<tr>
<th>Name</th>
<th>Brand name</th>
<th>Usual dose</th>
<th>Maximum dose</th>
<th>Indication(s)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Largactil®</td>
<td>75–300 mg</td>
<td>1000 mg</td>
<td>Schizophrenia, intractable hiccups, to reduce the manic phase of manic depressive disorders</td>
<td>Postural hypotension (especially in the elderly), anticholinergic effects</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Serenace®</td>
<td>1.5–15 mg</td>
<td>20 mg</td>
<td>Schizophrenia, secondary psychosis</td>
<td>Oligomenorrhea or amenorrhea, extrapyramidal</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Haloperidol LA®</td>
<td>50 mg</td>
<td>300 mg</td>
<td>Tourette's syndrome</td>
<td>Orthostatic hypotension, seizure (rare)</td>
</tr>
<tr>
<td>Flupenthixol decanoate</td>
<td>Fluanxol®</td>
<td>40 mg</td>
<td>400 mg</td>
<td>Mild to moderate depression with or without anxiety</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Modecate®</td>
<td>12.5 mg</td>
<td>100 mg</td>
<td>Psychotic disorders, especially schizophrenia</td>
<td>Blood dyscrasia</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Eglonyl®</td>
<td>200–800 mg</td>
<td>2400 mg</td>
<td>Acute schizophrenic episodes and prevention of relapse in chronic cases</td>
<td>Fatigue, weight gain, erectile dysfunction</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap®</td>
<td>2–20 mg</td>
<td>20 mg</td>
<td>Maintenance treatment of chronic schizophrenics who respond to the anti- hallucinatory and anti-delusional effects of classical neuroleptics but who do not need, or are handicapped by, the hyposedative action of such neuroleptics</td>
<td>Anorexia, akinesia, extrapyramidal side effects, sedation, visual disturbance, constipation, dry mouth</td>
</tr>
</tbody>
</table>
Table III: Management strategies for side effects of antipsychotic medicine\textsuperscript{12,13}

<table>
<thead>
<tr>
<th>Effect</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuromotor effects</strong></td>
<td></td>
</tr>
<tr>
<td>Acute dystonia (e.g. involuntary, sustained muscle spasms, oculogyric crisis)</td>
<td>Select antipsychotic with low incidence of extrapyramidal effects</td>
</tr>
<tr>
<td>Chronic dystonia (e.g. sustained, involuntary spasms of skeletal muscles)</td>
<td>• Start with low dose and increase gradually&lt;br&gt;• Add anticholinergic agent (e.g. benztropine)</td>
</tr>
<tr>
<td>Akathisia (feeling of ‘inner restlessness’, with a drive to move)</td>
<td>Reduce dose or switch medicine</td>
</tr>
<tr>
<td>Parkinsonism (e.g. masked facies, muscle rigidity, tremor, shuffling gait)</td>
<td>• Reduce dose or select antipsychotic with low risk for akathisia and increase dose slowly&lt;br&gt;• Add a beta blocker (e.g. propranolol), benzodiazepine or mirtazapine&lt;br&gt;• Reduce dose of antipsychotic medicine&lt;br&gt;• Switch from FGA to SGA&lt;br&gt;• Administer oral anticholinergic medicine</td>
</tr>
<tr>
<td>Tardive dyskinesia (e.g. orobuccofaciolingual movements)</td>
<td>• Select antipsychotic medicine with low risk for tardive dyskinesia&lt;br&gt;• Evaluate risk factors for tardive dyskinesia&lt;br&gt;• Switch to clozapine or other SGA</td>
</tr>
<tr>
<td><strong>Anticholinergic effects</strong></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>• Reduce dose or select antipsychotic agent with lower risk&lt;br&gt;• Drink small amounts of fluid frequently&lt;br&gt;• Use other oral hygiene products for dry mouth</td>
</tr>
<tr>
<td>Excessive saliva</td>
<td>Administer sublingual atropine, oral hyoscine hydrobromide or oral benztropine</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Advise high-fibre dietary supplementation&lt;br&gt;• Increase physical activity and fluid intake&lt;br&gt;• Administer laxatives</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>• Reduce dose, if feasible&lt;br&gt;• Switch to another antipsychotic agent&lt;br&gt;• Management depends on the underlying aetiology&lt;br&gt;• Avoid high intake of fluids in the evening and ensure adequate voiding at bedtime</td>
</tr>
<tr>
<td><strong>Cardiovascular effects</strong></td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>• Titrate dose gradually&lt;br&gt;• Advise patient to stand up slowly from a sitting or lying position&lt;br&gt;• Decrease or divide dose of antipsychotic medicine&lt;br&gt;• Switch to another antipsychotic without anti-adrenergic effects</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>• Switch medicine or add a low-dose peripheral beta blocker</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>• Avoid combining medicines with a known QTc prolongation&lt;br&gt;• If QTc &gt;450/470–500 ms or has increased more than 30–60 s, switch to another antipsychotic</td>
</tr>
<tr>
<td><strong>Hyperprolactinaemia</strong></td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>• Evaluation of prolactin levels&lt;br&gt;• Exclusion of pituitary tumour&lt;br&gt;• Switch to a prolactin-sparing agent if there are symptoms of sexual or menstrual dysfunction. In women, discuss the risk of pregnancy and appropriate contraception</td>
</tr>
<tr>
<td>Risk of osteoporosis</td>
<td>Bone density screening; switch medicine if abnormal</td>
</tr>
<tr>
<td>Sedation</td>
<td>• Titrate the dose slowly&lt;br&gt;• Reduce dose if applicable&lt;br&gt;• Avoid concomitant use of other CNS depressants</td>
</tr>
<tr>
<td><strong>Metabolic effects</strong></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>• Switch to an antipsychotic with low risk of weight gain&lt;br&gt;• Avoid polypharmacy if possible&lt;br&gt;• Provide appropriate advice about lifestyle interventions (diet and exercise)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>• Consider metformin&lt;br&gt;• Monitor serum glucose, treat with diet and hypoglycaemic medicines as indicated&lt;br&gt;• Monitor for complications of diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Monitor blood pressure, treat with antihypertensive medication if indicated</td>
</tr>
<tr>
<td>Elevated cholesterol and lipids</td>
<td>• Switch to antipsychotic medicine with low risk of elevating cholesterol and lipids&lt;br&gt;• Monitor lipid profile every 6–12 months&lt;br&gt;• Treat with statin if lifestyle interventions (diet and exercise) are insufficient</td>
</tr>
</tbody>
</table>

CNS, central nervous system; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic
SGAs are generally associated with a lower risk of extrapyramidal side effects and tardive dyskinesia compared with FGAs, but they may be associated with higher rates of weight gain and metabolic disorders. Table II provides an overview of the SGAs used in the management of schizophrenia, followed by Table III, which provides management strategies for side effects of antipsychotic medicine.

General management principles in schizophrenia

Owing to their lack of extrapyramidal side effects and tardive dyskinesia, SGAs, excluding clozapine, have become agents of choice when treating first-time episodes or younger patients. Monotherapy is recommended as there is no advantage to
combining antipsychotics. Rispiridone, amisulpride, olanzapine, quetiapine, aripiprazole and ziprazidone are effective agents in the treatment of a first episode in psychotic patients.

When the response to the first-line agent is not satisfactory, another SGA can be considered or the choice of FGA can be changed. The second agent should be tried for a period of 4–6 weeks before considering a third line of treatment.

Clozapine is commonly recommended for treatment of patients who experience inadequate control following trials with two different classes of antipsychotic or who display consistent aggression or persistent suicidal thoughts or behaviour. The main safety concerns for clozapine are, however, agranulocytosis, myocarditis and diabetes.

Clozapine is used as a third-line therapy, at the highest tolerable dose (<900 mg daily) for six months. Switching requires tapering and stopping the previous agent before initiating clozapine to reduce the risk of haematological side effects.

Various adjunctive treatments, including benzodiazepines, lithium, anticonvulsants, antidepressants, beta blockers and dopamine agonists, have been used to enhance the response to antipsychotic medications or to treat residual symptoms of chronic schizophrenia and comorbid conditions with schizophrenia.

Studies to determine the efficacy and effectiveness of FGAs compared with SGAs deliver conflicting results. A lower incidence of extrapyramidal side effects are seen with SGAs, although weight gain is a notable problem with these agents. Drugs from both groups are equally effective in treating psychosis, with the SGAs providing greater treatment results when managing negative symptoms. The choice of drug is consequently determined by:

- availability and accessibility of the drug
- shared patient-centred decision making
- previous experience (efficacy and side effects)
- tailoring the side effect profile to meet the needs of the patient
- choice of mode of administration (oral or parenteral)

The pharmacist can greatly assist in finding the right choice of drug for the patient. Figure 3 shows a treatment algorithm for the management of schizophrenia.

**Conclusion**

Schizophrenia is a complex disorder in which many aetiologies have a role. Management of the patient requires a multidisciplinary team, with each member of the team contributing to the patient’s best care. Side effect profiles differ between the two groups of antipsychotics and the choice of drug should not only focus on the patient’s characteristics but also involve the patient actively. Pharmacotherapy should be monitored according to the safety and efficacy of the drug with each patient visit.

**References**