Schizophrenia
long-term management

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Schizophrenia has been identified as one of the top 10 disabling medical conditions globally. Antipsychotics form the mainstay of treatment and, although the response to treatment is high for initial episodes, the relapse rate is around 80% within five years of initial response.

Relapse rates are five times higher for patients who discontinue antipsychotic therapy. For each patient, the aim of treatment is to find an antipsychotic medicine that offers the best balance of efficacy and tolerability to enhance adherence and prevent relapse.

This article discusses the pharmacological treatments used in the long-term management of schizophrenia. The management of acute psychosis is outside the scope of this article.

Antipsychotics

Antipsychotics are classified as either typical or atypical.

Typical antipsychotics

Typical antipsychotics — also referred to as first-generation antipsychotics or conventional antipsychotics — produce their therapeutic effect by blocking dopaminergic receptors in the mesolimbic pathway (see accompanying article, p41). The efficacy of antipsychotics is approximately proportional to their affinity for the dopamine (D2) receptor. Examples of typical antipsychotics include the phenothiazines (eg, chlorpromazine, trifluoperazine), butyrophenones (eg, haloperidol), thioxanthenes (eg, flupentixol, zuclopenthixol), diphenylbutylpiperidines (eg, pimozide) and substituted benzamides (eg, sulpiride).

Typical antipsychotics also block D2 receptors outside the mesolimbic pathway. Blockade in the basal ganglia (nigrostriatal pathway) causes involuntary movement disorders, also known as extrapyramidal side effects (EPS). There are four types of EPS:

- Acute dystonias — usually occur within 72 hours of starting an antipsychotic and include oculogyric crisis (rotating eyeballs), torticollis (head and neck twisting to the side), protrusion of the tongue and grimacing
- Akathisia — described as restlessness, leading to an urge to constantly move, which usually occurs within the first two weeks of starting an antipsychotic or after a rapid dose increase but sometimes occurring several months later
- Parkinsonism — usually occurs within a month of starting an antipsychotic and is characterised by

SUMMARY

The management of schizophrenia centres around the use of antipsychotic medicines. Antipsychotics can be classed as either typical or atypical. Typical antipsychotics are also known as first-generation antipsychotics and work by blocking dopaminergic receptors. Atypical antipsychotics (or second-generation antipsychotics) also block dopamine receptors; however, they also act on a range of other receptors, particularly serotonergic receptors.

Adverse effects are a problem with both classes and include extrapyramidal reactions, sedation and hyperprolactinaemia. Choice of antipsychotic should be based on factors such as the patient’s clinical presentation and comorbidities and the medicine’s side effect profile.
akinesia, a coarse tremor, an expressionless face and rigidity

- **Tardive dyskinesia** — a serious movement disorder of late onset which can develop in the course of long-term exposure to antipsychotics; characterised by a variety of involuntary movements affecting the muscles of the face, trunk or limbs and may include: facial tics; grimacing; tongue protrusion; lip smacking, puckering and pursing; rapid eye blinking; foot tapping; rocking, squirming or twisting; ankle movements; and abnormal posture or gait

Blockade of dopamine receptors in the tuberofundibular pathway can cause hyperprolactinaemia. It is a common adverse effect of the typical antipsychotics. It can also occur with the atypical antipsychotics (it is common with risperidone and amisulpride and less common or absent with olanzapine, aripiprazole, quetiapine and clozapine). Hyperprolactinaemia can be asymptomatic.

Generally, it is underdiagnosed because patients are often reluctant to report side effects such as sexual dysfunction and galactorrhoea. Persistent elevation of prolactin can cause long-term complications such as menstrual disturbances and infertility; there is also a possible increased risk of osteoporosis and breast cancer.

Baseline monitoring of prolactin is recommended before starting an antipsychotic and throughout treatment for patients on typical antipsychotics, risperidone and amisulpride. Prolactin levels should also be monitored if a patient complains of symptoms of hyperprolactinaemia. If prolactin levels are raised, consideration should be given to switching to an antipsychotic less likely to raise prolactin levels, reducing the dose of the existing antipsychotic or prescribing a dopamine agonist such as cabergoline or bromocriptine (however, these can exacerbate psychotic symptoms).

**Atypical antipsychotics** By definition, atypical antipsychotics, also known as second-generation antipsychotics, produce an antipsychotic effect without causing extrapyramidal side effects. In practice, not all atypical antipsychotics are free of these effects but the risk of them occurring is lower compared with the typical antipsychotics at usual therapeutic doses.

Generally atypical antipsychotics are highly selective D2 receptor antagonists. Most also have high affinity for the serotonergic receptor 5-HT2A and varying affinity for other receptors. This within-class variation, in terms of selectivity and affinity for various receptors, may explain the differences in their likelihood to cause adverse effects. (see Box 1). However, factors such as the location of receptors can also impact on the response and adverse effects experienced by patients. Receptor types that can be blocked and examples of likely corresponding adverse effects are outlined below:

- **Dopaminergic** — EPS and hyperprolactinaemia
- **Histaminergic** — sedation
- **Serotonergic** — weight gain
- **Muscarinic (cholinergic)** — blurred vision, dry mouth, constipation, precipitation of glaucoma
- **Alpha-adrenergic** — postural hypotension, sedation

Examples of atypical antipsychotics include amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine and risperidone. It is worthwhile noting that aripiprazole has a unique profile compared with the other atypical antipsychotics — it is a partial agonist of D2 and 5-HT1A and an antagonist at 5-HT2A.

**Clozapine** Between a fifth and a third of people with schizophrenia show a poor response to antipsychotics and are considered to have treatment-resistant schizophrenia (TRS). TRS is defined as a lack of satisfactory clinical improvement despite use of adequate doses of at least two different antipsychotic drugs, including an atypical antipsychotic, prescribed for adequate duration. The National Institute for Health and Clinical Excellence defines an adequate duration as four to six weeks at optimum dosage.
Clozapine is the only antipsychotic licensed for and with proven efficacy in TRS. It was first introduced in Europe in the 1970s. In 1975, the drug was voluntarily withdrawn from use by the manufacturer because of the risk of fatal agranulocytosis.

Additional clinical research, together with a proposal for a nationally co-ordinated, mandatory haematological monitoring service for all patients, enabled clozapine to be given a product licence in the UK in the late 1980s. Now all patients treated with clozapine in the UK must be registered with an approved clozapine monitoring service to minimise the risk of agranulocytosis or neutropenia (the clozapine product information sets out the specific monitoring requirements).

Clozapine has been shown to be better than typical and other atypical antipsychotic medicines for the treatment of patients with TRS.

The precise mechanism by which clozapine exerts its antipsychotic activity is not known (for receptor affinity see Box 1, p48). At therapeutic doses, clozapine only occupies 20–67% of striatal D2 receptors compared with 70–89% occupancy by typical antipsychotics. This appears to explain the low incidence of EPS associated with clinically effective doses of clozapine and hence its usefulness for patients who experience tardive dyskinesia with other antipsychotics. Clozapine is also blocks alpha-1, muscarinic (M1–5) and histamine (H1) receptors.

**Depot antipsychotics** Long-acting depot injections of antipsychotics are useful to prevent relapse in patients who cannot be relied on to take oral antipsychotic medicines regularly. All depots are administered intramuscularly. Most of the available depots contain typical antipsychotics; currently, there are two atypical antipsychotic depots available in the UK — risperidone and olanzapine.

**Choice of antipsychotic** Studies have shown that there is little difference in efficacy between typical and atypical antipsychotics and NICE no longer recommends the use of atypical antipsychotics first line.

NICE recommends that the choice of antipsychotic should be based on an informed discussion and made jointly by the patient and clinician. Treatment choice should also consider the:

- Patient’s clinical presentation
- Side effect profile (EPS, metabolic syndrome, weight gain, etc)
- Patient’s history of medication adherence
- Any patient comorbidities (such as diabetes or kidney disease) or other physical considerations (such as obesity)
- Possible interactions with any concomitant medicines
- Patient’s response to previous treatments
- Views of the patient’s carers

Self-rated side effect rating scales such as the “Glasgow antipsychotic side effect scale” (GASS) or the “Liverpool University neuroleptic side effect ratings scale” (LUNSERS) can be useful to identify and monitor the side effects of antipsychotics.

**Schizophrenia and the metabolic syndrome** Poor lifestyle choices (such as smoking, eating a high fat diet and a lack of physical activity) are common for people with schizophrenia, which can contribute to the development of diabetes, dyslipidaemia and cardiovascular disease. In addition, the atypical antipsychotics are associated with an increased likelihood of developing the metabolic syndrome — described as a cluster of abnormalities (namely obesity, hyperlipidaemia, hypertension and hyperglycaemia) that increase the risk of cardiovascular disease. It is therefore essential that all patients taking long-term antipsychotics undergo routine physical health screening.

It is recommended that the following physical health parameters are assessed before starting an antipsychotic:

- Blood pressure and pulse rate
- Blood glucose (fasting if possible)
- Lipid profile (fasting if possible)
- Weight and body mass index (BMI)
- Smoking and alcohol status
- Liver function
- Renal function
- Full blood count (note: there are special requirements for clozapine)
- Creatine phosphokinase (CPK)
- Prolactin

In addition, the following should be assessed if clinically warranted:

- Electrocardiogram (ECG) — before starting an antipsychotic, an ECG should be offered to patients if it is recommended in the summary of product characteristics and also for the following patients: inpatients; those with specific cardiovascular risk factors; those with a history of cardiovascular disease etc.
- Thyroid function tests — required before starting quetiapine or if thyroid dysfunction is suspected (see accompanying article, p41)
- Electroencephalogram, computerised tomography scan or magnetic resonance imaging — if organic cause of psychosis is suspected (see accompanying article, p41)
- Drug screening — if indicated by the patient’s clinical picture or history
- Chest X-ray — if indicated by the patient’s clinical picture or history

Depending on the individual risk factors and the antipsychotic chosen, more frequent monitoring of certain parameters may be required throughout treatment.

All patients also require an annual health check to assess weight and BMI, blood pressure and pulse, blood glucose levels, lipid levels, full blood count, liver and renal function tests, and smoking and alcohol status. An ECG should also be offered annually — especially for those with risk factors for cardiovascular disease identified from their physical examination, clinical picture or history.
Special populations

Elderly patients The general principles of schizophrenia management are the same for elderly patients (>65 years) as for other patient groups. However, the elderly are more prone to side effects because of increased sensitivity and reduced renal clearance. Generally, older patients require lower doses and more careful dose titration. The elderly are more likely to be taking other medicines concurrently, hence monitoring for potential interactions is particularly important (for more information on the role of pharmacists in the management of schizophrenia see Box 2).

Pregnant women NICE guidance on antenatal and postnatal mental health recommends a low-dose typical antipsychotic (such as haloperidol, chlorpromazine or trifluoperazine) for women with schizophrenia who are planning a pregnancy or who are already pregnant. The guidance advises against the use of depot antipsychotics because there are limited data on their safety and due to the risk of EPS occurring in the infant.

Breastfeeding women Due to the limited data on the use of antipsychotics in women who are breastfeeding, decisions must be made on a case-by-case basis. The decision should be based on the benefits of breastfeeding and the potential risks of exposure of the infant to the antipsychotic.

Discontinuing treatment

There is a significant increased risk of relapse following discontinuation of an antipsychotic. Abrupt discontinuation doubles the risk of relapse in the first six months and may lead to withdrawal symptoms such as headache, nausea and insomnia in some people. The decision to stop maintenance antipsychotic therapy requires careful consideration of the risks and benefits. The dose of antipsychotic should be reduced gradually and the patient should be monitored closely for signs of relapse and possible withdrawal symptoms.

References


Box 2: Role of the pharmacist

Long-term medication is essential to prevent relapse in patients with schizophrenia. One of the challenges in managing this patient group is poor adherence to prescribed medicines, either due to lack of insight or adverse drug reactions. Although there have been advances in the treatment of schizophrenia with the introduction of atypical antipsychotics, side effects such as hyperprolactinaemia, severe weight gain and metabolic syndrome can be distressing, embarrassing and stigmatising and may contribute partly to the poor adherence to medication. Poor adherence often results in numerous readmissions into hospital which has given rise to the term “revolving door patient”.

In the inpatient setting, pharmacists can help to educate patients and carers about the medicines prescribed and the importance of maintenance treatment to prevent relapse. For outpatients, expanding the role of the mental health pharmacist into the community through pharmacist-led clinics could improve the management of adverse effects, the monitoring of physical health parameters (such as weight and blood glucose) and the provision of support and education.

There is scope for pharmacists who have qualified as independent prescribers to work in the field of schizophrenia — helping to provide services that are more responsive to patients’ needs.

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