# Antipsychotics

Kalliopi Vallianatou

## Abstract

Antipsychotics are the mainstay of psychosis treatment. They are also used in the acute and long-term treatment of bipolar disorder, in depression and other conditions. They are classified as first-generation ('typical') and second-generation ('atypical') antipsychotics based on their ability to cause extrapyramidal symptoms (EPS). Metabolic adverse effects occur mainly with second-generation antipsychotics. Both classes have broadly similar efficacy in controlling the symptoms of psychosis with the exception of clozapine, which is unique in its improved efficacy in treatment resistant schizophrenia.

**Keywords** Adverse effects; antagonist; antipsychotic; dopamine; extrapyramidal; hyperprolactinaemia; psychosis; serotonin

## Key points

- Blockade of the $D_2$ receptors in the mesolimbic pathway mainly results in relief of positive symptoms of psychosis, while effects on other neuronal pathways result in the adverse effects seen with antipsychotics
- The choice of antipsychotic treatment should consider individual patient characteristics
- Physical health should be checked at baseline and monitored regularly during antipsychotic treatment.

## Introduction

Antipsychotic drugs reduce the severity of psychotic symptoms and prevent relapse in schizophrenia and other psychotic disorders (see Schizophrenia, *Medicine* 2016; **44(11)**: 649–653). They are also used in mania, depression and delirium, among other conditions. There are two main classes of antipsychotic: older, typical, conventional or first-generation antipsychotics (FGAs), and newer atypical or second-generation antipsychotics (SGAs).

## Basic principles of prescribing antipsychotics for psychosis and schizophrenia

- An antipsychotic should only be started in consultation with an experienced psychiatrist. Provide information on the likely benefits and adverse effects, and agree the choice of the antipsychotic with the patient.
- An oral antipsychotic should be offered in conjunction with psychological interventions (individual cognitive behavioural therapy and family intervention).
- The dose should be titrated as per the British National Formulary or Summaries of Product Characteristics to the lowest effective dosage, as many adverse effects are dose-related. If no or a poor response is seen after 1–2 weeks of assessment, the dose can be increased.
- Prescribing 'as required' antipsychotics for a calming effect increases the risk of the patient exceeding the maximum dose, resulting in a greater burden of adverse effects including oversedation or cardiac disorders and a greater risk of drug interactions.
- Antipsychotic combinations should be avoided, because of the increased risk of $QT_c$ prolongation, apart from during short periods of switching between two antipsychotics, and considered only in consultation with a psychiatrist.
- Physical health should be checked at baseline and monitored regularly throughout treatment in line with National Institute for Health and Care Excellence guidelines and clinical need.
- Risk of relapse is very high after treatment discontinuation, even 1–2 years after a first episode. If it is decided to stop the antipsychotic, the dose should be reduced slowly.

## First-generation antipsychotics

FGAs are those commonly associated with acute extrapyramidal symptoms (EPSs) even at therapeutic dosages. FGAs share some class-specific adverse effects but differ in chemical structure and receptor binding. Commonly prescribed FGAs in the UK include chlorpromazine, trifluoperazine, haloperidol, flupentixol, zuclopenthixol, pipotiazine, fluphenazine and sulpiride.

## Second-generation antipsychotics

SGAs are characterized by a lower incidence of EPSs at usual clinical doses and, with some exceptions (amisulpride, risperidone), a lack of sustained increase in plasma prolactin concentration (hyperprolactinaemia). The defining feature of atypicality for this group of drugs has not been concluded. Commonly prescribed SGAs in the UK include risperidone, olanzapine, quetiapine, aripiprazole, amisulpride, clozapine, paliperidone, asenapine and lurasidone. Other antipsychotics not currently licensed in the UK include ziprasidone, sertindole, brexpiprazole and cariprazine.

FGAs and SGAs have been formulated as depots or long-acting injections (LAIs) mainly to address the problem of non-adherence to maintenance treatment with antipsychotics. FGA LAIs have not previously been favoured as an early treatment option because of their side-effect profile and complex kinetics, which requires prolonged periods to achieve steady-state concentrations. The availability of more SGA LAIs (risperidone, olanzapine, paliperidone, aripiprazole) has offered greater options with the advantage of improved adherence.

## Mechanism of action[1]

Most antipsychotics act as antagonists at $D_2$ receptors in the mesolimbic pathway to reduce positive symptoms. $D_2$ receptor

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## Adverse effects of antipsychotics

| | Adverse effect | Antipsychotics |
|---|---|---|
| **EPSs**[3,4] | | |
| Dystonia[a] | Muscle spasm (e.g. eyes rolling, head and neck spasms) | More common with FGAs. Incidence is higher with haloperidol, fluphenazine, trifluoperazine, perphenazine. Risk is lower with lower doses. Dystonias are reported for several SGAs but incidence is low |
| Pseudo-parkinsonism | Resting tremor, rigidity, bradykinesia, mask-like face | Incidence rates as for dystonia |
| Akathisia[b] | Restlessness, nervousness, compulsion to keep moving | Rates of akathisia are about 25% less for SGAs than FGAs. More likely with aripiprazole and lurasidone than other SGAs |
| Tardive dyskinesia[c] | Lip-smacking, pill-rolling | More common in the elderly and in those with acute EPSs at start of treatment. Risk is higher with FGAs than SGAs |
| **Cardiac** | | |
| Postural hypotension | Drop in blood pressure on standing, light-headedness, blurred vision | Common with clozapine, risperidone, quetiapine, chlorpromazine and other low-potency FGAs |
| $QT_c$ prolongation | ($QT_c$ normal limits: men <440 milliseconds, women <470 milliseconds) | Usually plasma drug concentration-dependent. Common with haloperidol. Moderate effect with amisulpride, quetiapine, ziprasidone, chlorpromazine<br>Very low risk with aripiprazole and lurasidone |
| Tachycardia | Rapid heart rate (often >100 bpm) | Common with clozapine at start of treatment — usually benign but must exclude myocarditis or cardiomyopathy |
| **Other** | | |
| Metabolic | Weight gain, large waistline, dyslipidaemia, diabetes mellitus | Risk is highest with clozapine and olanzapine. Moderate with quetiapine and risperidone and paliperidone. Low with high-potency FGAs, aripiprazole, amisulpride, sulpiride, lurasidone, asenapine, ziprasidone |
| Hyperprolactinaemia | Galactorrhoea, gynaecomastia, amenorrhoea, loss of libido, sexual dysfunction, reduction in bone mineral density | Common with FGAs and some SGAs, namely risperidone, paliperidone and amisulpride.[4] Lowest risk with aripiprazole (low dose has been used as add-on treatment to reduce prolactin concentrations), clozapine and quetiapine. Olanzapine, asenapine, ziprasidone and lurasidone also have low risk of hyperprolactinaemia |
| Anticholinergic | Dry mouth, urinary retention, constipation and sedation | More common with some FGAs. Clozapine can cause constipation, which can be life-threatening, although hypersalivation rather than dry mouth is commonly problematic |

EPS, extrapyramidal symptoms; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.
[a] For treatment, anticholinergic drugs are given (orally, intramuscularly or intravenously depending on severity).
[b] Not responsive to anticholinergics. Dose reduction, β-blockers or benzodiazepines may help.
[c] Switch to an SGA; stop anticholinergics as they may worsen tardive dyskinesia.

**Table 1**

blockade in the striatum and tuberoinfundibular pathway mediates EPSs and hyperprolactinaemia adverse effects, respectively. $D_2$ receptor blockade in the mesocortical pathway has been thought to worsen negative symptoms.[1]

Both FGAs and SGAs affect many other receptors. Some also block serotonergic $5HT_2$, $\alpha_1$-adrenoceptors, $H_1$-histamine and muscarinic receptors. Most SGAs show lower affinity for $D_2$ and higher affinity for $5HT_{2A}$ receptors, which is thought to account



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