Drug points: second-generation antipsychotics

Steve Chaplin BPharm, MSc and Mark Taylor BSc, MD, FRCP, FRANZCP

Steve Chaplin and Dr Mark Taylor provide an overview of the properties of second-generation antipsychotics in the management of psychotic illnesses

KEY POINTS
- with the exception of clozapine, there is little difference in efficacy between the antipsychotics according to the BNF
- the adverse side-effect profile does generally distinguish first- and second-generation antipsychotics
- second-generation antipsychotics have been accepted as first-line treatment for both acute and maintenance phases of psychotic illness
- second-generation antipsychotics are associated with a large number of clinically significant drug interactions
- clozapine is uniquely effective in the treatment of schizophrenia
- older people are at increased risk of the adverse effects of antipsychotics

Steve Chaplin

The BNF categorises seven drugs as second-generation antipsychotics. All except aripiprazole (Abilify) and paliperidone (Invega, Xeplion) are available generically and as solid and/or liquid oral preparations. Amisulpride, clozapine and quetiapine are not available as depot formulations.

These agents are distinguished from first-generation antipsychotics such as haloperidol and chlorpromazine by their possibly superior efficacy against negative symptoms and different adverse effect profiles. However, they are a disparate group with antagonist and agonist activity at a range of receptors, different adverse effect profiles and different licensed indications (see Tables 1 and 2). Some prescribing points apply generally but there are many important differences within the group.

Elderly patients

Older people are at increased risk of the adverse effects of antipsychotics because clearance may be reduced. They are also vulnerable to postural hypotension and to hyper- and hypothermia in hot or cold weather. Those with dementia have a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack.

The BNF states that the balance of risks and benefit should be considered before prescribing antipsychotic drugs for older people. They should not be prescribed to treat mild to moderate symptoms of psychosis in elderly patients. When treatment is indicated, the initial dose should take into account factors such as the patient’s weight, co-morbidity and other drug treatment and should be half the adult dose or less. Treatment should be reviewed regularly.

Choice of treatment

The BNF states that, with the exception of clozapine, there is little difference in efficacy between the antipsychotics. The drug of choice depends on the medication history, whether a sedative effect is indicated (to which tolerance develops) and the risk of adverse effects. Second-generation agents are preferred to the first-generation alternatives when negative symptoms predominate and there is an increased risk of extrapyramidal effects. However, the risk of other adverse effects, including weight gain, impaired glucose tolerance and pro-
Longation of the QT-interval should be taken into account.

Two agents stand out from the group: aripiprazole is associated with a lower risk of adverse metabolic effects than other agents in this class and clozapine is uniquely effective in the treatment of schizophrenia when other antipsychotic drugs are not successful or are poorly tolerated.

Multiple antipsychotic therapy is associated with an increased risk of extrapyramidal effects, QT prolongation and sudden cardiac death. Prescribing more than one antipsychotic drug at a time should be avoided other than in exceptional circumstances such as augmentation with clozapine or when changing medication.

**Therapeutic trial**

Effectiveness should be assessed after a four to six week course of treatment. Clozapine is indicated if schizophrenia is not controlled despite the sequential use of two or more antipsychotics (one of which should be a second-generation agent) each for at least six to eight weeks. Patients must be registered with a clozapine patient monitoring service.

**Depot injection**

A depot formulation may be indicated when oral treatment has been well tolerated. Injections are usually given monthly but risperidone is administered every two weeks. There may need to be an initial overlap with oral administration until the dose is stabilised. Care should be taken with aripiprazole not to confuse the intramuscular injection intended for acute use (Abilify) with the depot formulation (Abilify Maintena).

**Monitoring**

Patients should be assessed before and periodically during treatment (see Table 3). Second-generation agents may be associated with a range of metabolic effects that increase cardiovascular risk and these require frequent assessment, particularly with clozapine and olanzapine.

Clozapine causes neutropenia and potentially fatal agranulocytosis. Leucocyte and differential blood counts must be normal before treatment and should be monitored every week for 18 weeks then at least every two weeks. If the blood count is stable after one year, monitoring frequency can be reduced to every four weeks, including four weeks after cessation. Treatment should be stopped and the patient referred to a haematologist if the leucocyte count falls below 3000 per mm$^3$ or if the absolute neutrophil count falls below 1500 per mm$^3$.

**Pregnancy and lactation**

Treatment with an antipsychotic during the third trimester may cause symptoms in the neonate including agitation, hypertonia, hypotonia, tremor, drowsiness, feeding problems, and respiratory distress. There is insufficient information to determine the risk of teratogenicity for individual second-generation agents; congenital anomalies associated with treatment are acknowledged only for aripiprazole but no causal link has been established.

There is evidence from animal studies that exposure to antipsychotics early in life may affect neurological development. All second-generation antipsychotics except risperidone are contraindicated during breastfeeding. The advice for risperidone is to weigh the risks and benefits, bearing in mind that the drug and its metabolite occur in milk but no adverse effects have been reported.

**Drug interactions**

Second-generation antipsychotics are associated with a large number of clinically significant drug interactions, notably with drugs that enhance their CNS and autonomic effects and others that affect their hepatic clearance or are affected by them. Details for a specific drug should be checked before prescribing.

Treatment with drugs that may increase the risk of blood dyscrasias should be avoided during treatment with clozapine, including the sulfonamides, chloramphenicol, cytotoxic drugs, penicillamine, risperidone, and depot antipsychotics (their prolonged duration of action means they cannot quickly be withdrawn).

**Adverse effects**

There is a wide overlap in activity at dopamine, 5-HT, histamine and muscarinic receptors among the second-generation antipsychotics. They have many adverse effects in common but the propensity to cause specific signs and
<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Indications*</th>
<th>Elderly</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>amisulpride</td>
<td>acute and chronic schizophrenia</td>
<td>caution</td>
<td>half dose at creatinine clearance (CRCL) 30–60ml/min; one-third dose at 10–30ml/min; no experience at &lt;10ml/min</td>
<td>no change in dose</td>
<td>tablets, oral solution</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>schizophrenia; moderate to severe manic episodes in bipolar I disorder, prevention of new manic episodes in adults; treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older; rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in bipolar I disorder</td>
<td>no experience; consider lower starting dose in &gt;65s</td>
<td>no change in dose</td>
<td>no dose change in mild to moderate impairment; caution in severe impairment</td>
<td>tablets, orodispersible tablets, oral solution, im injection (immediate-release), depot injection</td>
</tr>
<tr>
<td>clozapine</td>
<td>treatment-resistant schizophrenia; severe, untreatable neurological adverse reactions to other antipsychotic agents; treatment-resistant psychosis in Parkinson’s disease</td>
<td>in over-60s, initiate at 12.5mg/day and adjust in increments of 25mg/day</td>
<td>no change recommended</td>
<td>caution</td>
<td>tablets, oral suspension</td>
</tr>
<tr>
<td>olanzapine</td>
<td>schizophrenia; moderate to severe manic episode; prevention of mania in bipolar I disorder</td>
<td>consider 5mg/day starting dose when clinical factors indicate</td>
<td>consider 5mg/day starting dose</td>
<td>consider 5mg/day starting dose and increase with caution in moderate impairment</td>
<td>tablets, orodispersible tablets, depot injection</td>
</tr>
<tr>
<td>quetiapine</td>
<td>schizophrenia; manic episodes in bipolar disorder; major depression in bipolar disorder; maintenance bipolar disorder; augmentation of antidepressant therapy for depression</td>
<td>initiate at 50mg/day and adjust in increments of 50mg/day</td>
<td>no dose change</td>
<td>caution; initiate at 50mg/day and adjust in increments of 50mg/day</td>
<td>tablets, m/r tablets</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of second-generation antipsychotics
symptoms varies (see Table 1). Extrapyramidal effects are common to all antipsychotics that inhibit striatal dopamine function but the risk is relatively low with amisulpride, which selectively affects mesolimbic dopamine pathways. Most antipsychotics increase prolactin levels (except aripiprazole, which reduces them) but risperidone and amisulpride are most strongly associated with hyperprolactinaemia. Risperidone commonly causes sexual dysfunction, though this may improve with dose reduction.

Clozapine, olanzapine, quetiapine and risperidone are associated with the highest risk of hyperglycaemia and sometimes diabetes, and clozapine and olanzapine commonly cause weight gain. Postural hypotension is more frequent with clozapine and quetiapine. Clozapine is associated with hypersalivation.

**Declaration of interests**
Steve Chaplin has none to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.

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### Place in therapy

**Mark Taylor**

The second-generation antipsychotics were previously known as ‘atypical’ antipsychotics, although it is clear there are not huge class-related efficacy differences between the older typical or ‘first-generation’ antipsychotics and second-generation antipsychotics. The adverse side-effect profile does generally distinguish first- and second-generation antipsychotics (see Tables 1 and 2) with first-generation antipsychotics commonly being associated with parkinsonian-type movement disorders, whereas second-generation antipsychotics more usually have metabolic-related effects.

Nevertheless, second-generation antipsychotics have been accepted as first-line treatment for both acute and maintenance phases of psychotic illness. Indeed they are widely used in bipolar disorder and off label in other mental disorders. These medications
Antipsychotics are considered essential in aiding recovery from acute psychosis, and can facilitate the implementation of relevant psychosocial interventions.

Early in the disease course, a doctrine of ‘start low, go slow’ with regard to dosing is often employed, unless there are serious risks. In the maintenance phase of schizophrenia and related psychoses, evidence suggests duration of treatment of two to five years in order to minimise relapse potential.

More detail on these important clinical questions can be found in the major guidelines, eg SIGN 134, NICE CG78, British Association for Psychopharmacology guidelines or the Maudsley Prescribing Guidelines.

Adherence with second-generation antipsychotics continues to be a challenge to clinicians and patients alike, with many studies indicating a nonadherence rate of around 50 per cent even in the first two months of treatment. Non-adherence with treatment is a strong predictor of relapse1,2 with relapse being associated with social and functional deterioration and elevated risk of self-harm. Long-acting injectable or depot second-generation antipsychotics are now widely available, and are one strategy to address medication nonadherence.

Continuing challenges for the pharmacotherapy of schizophrenia include better tolerated treatments, better efficacy with regard to negative and cognitive symptoms, and adding to clozapine in treatment-resistant schizophrenia.

References

Declaration of interests
Mark Taylor has none to declare.

Mark Taylor is consultant psychiatrist and associate professor, University of Queensland, Australia

Table 2. Monitoring requirements during treatment with a second-generation antipsychotic

<table>
<thead>
<tr>
<th>Test</th>
<th>Initially</th>
<th>During treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients with schizophrenia</td>
<td></td>
<td>physical health monitoring (including cardiovascular disease risk assessment) at least once per year</td>
<td>amisulpride and aripiprazole, do not affect blood pressure to the same extent as other antipsychotics and blood pressure monitoring is not mandatory</td>
</tr>
<tr>
<td>blood pressure</td>
<td>before starting therapy</td>
<td>frequently during dose titration</td>
<td>especially if cardiovascular risk factors, personal history of cardiovascular disease, or if the patient is being admitted as an inpatient</td>
</tr>
<tr>
<td>ECG</td>
<td>before starting therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>full blood count, urea and electrolytes, and liver function</td>
<td>baseline</td>
<td>annually</td>
<td>amisulpride does not require liver function monitoring</td>
</tr>
<tr>
<td>blood lipids and weight</td>
<td>baseline</td>
<td>at 3 months (measure weight frequently first 3 months), then annually</td>
<td>more frequent monitoring for clozapine or olanzapine: every 3 months for the first year then annually</td>
</tr>
<tr>
<td>fasting blood glucose</td>
<td>baseline</td>
<td>at 4–6 months then annually</td>
<td>more frequent monitoring for clozapine or olanzapine: at baseline, after one month then every 4–6 months</td>
</tr>
<tr>
<td>prolactin</td>
<td>baseline</td>
<td>at 6 months then annually</td>
<td></td>
</tr>
<tr>
<td>clozapine</td>
<td>differential white blood cell monitoring weekly for 18 weeks, then fortnightly for up to one year, and then monthly</td>
<td>part of the clozapine patient monitoring service</td>
<td></td>
</tr>
</tbody>
</table>

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