Chapter 1

Schizophrenia and related psychoses

ANTIPSYCHOTIC DRUGS

General introduction

Classification of antipsychotics

Before the 1990s, antipsychotics (or major tranquillisers as they were then known) were classified according to their chemistry. The first antipsychotic, chlorpromazine, was a phenothiazine compound – a tricyclic structure incorporating a nitrogen and a sulphur atom. Further phenothiazines were generated and marketed, as were chemically similar thioxanthenes such as flupentixol. Later, entirely different chemical structures were developed according to pharmacological paradigms. These included butyrophenones (haloperidol), diphenylbutylpiperidines (pimozide) and substituted benzamides (sulpiride, amisulpride).

Chemical classification remains useful but is rendered somewhat redundant by the broad range of chemical entities now available and by the absence of any clear structure–activity relationships for newer drugs. The chemistry of some older drugs does relate to their propensity to cause movement disorders. Piperazine phenothiazines (e.g. fluphenazine, trifluoperazine), butyrophenones and thioxanthenes are most likely to cause extrapyramidal symptoms (EPS) while piperidine phenothiazines (e.g. pipotiazine) and benzamides are the least likely. Aliphatic phenothiazines (e.g. chlorpromazine) and diphenylbutylpiperidines (pimozide) are perhaps somewhere in between.

Relative liability for inducing EPS was originally the primary factor behind the typical/atypical classification. Clozapine had long been known as an atypical antipsychotic on the basis of its low liability to cause EPS and its failure in animal-based antipsychotic screening tests. Its re-marketing in 1990 signalled the beginning of a series of new
medications, all of which were introduced with claims (of varying degrees of accuracy) of ‘atypicality’. Of these medications, perhaps only clozapine and quetiapine are ‘fully’ atypical, seemingly having a very low liability for EPS. Others show dose-related effects, although, unlike with typical drugs, therapeutic activity can usually be achieved without EPS. This is possibly the real distinction between typical and atypical drugs: the ease with which a dose can be chosen (within the licensed dosage range) which is effective but which does not cause EPS (for example, compare haloperidol with olanzapine).

The typical/atypical dichotomy does not lend itself well to classification of antipsychotics in the middle ground of EPS liability. Thioridazine was widely described as atypical in the 1980s but is a ‘conventional’ phenothiazine. Sulpiride was marketed as an atypical but is often classified as typical. Risperidone, at its maximum dose of 16 mg/day (10 mg in the USA), is just about as ‘typical’ as a drug can be. Alongside these difficulties is the fact that there is nothing, either pharmacologically or chemically, which clearly binds these so-called ‘atypicals’ together as a group, save perhaps a general but not universal finding of preference for D₂ receptors outside the striatum. Nor are atypicals characterised by improved efficacy over older drugs (clozapine and one or two others excepted) or the absence of hyperprolactinaemia (which is worse with risperidone, paliperidone and amisulpride than with typical drugs).

In an attempt to get round some of these problems, typicals and atypicals were reclassified as first- or second-generation antipsychotics (FGA/SGA). All drugs introduced since 1990 are classified as SGAs (i.e. all atypicals) but the new nomenclature dispenses with any connotations regarding atypicality, whatever that may mean. However the FGA/SGA classification remains problematic because neither group is defined by anything other than time of introduction – hardly the most sophisticated pharmacological classification system. Perhaps more importantly, date of introduction is often wildly distant from date of first synthesis. Clozapine is one of the oldest antipsychotics (synthesised in 1959) while olanzapine is hardly in its first flush of youth, having first been patented in 1971. These two drugs are of course SGAs, apparently the most modern of antipsychotics.

In this edition of The Guidelines we conserve the FGA/SGA distinction more because of convention than some scientific basis. Also we feel that most people know which drugs belong to each group – it thus serves as a useful shorthand. However, it is clearly more sensible to consider the properties of individual antipsychotics when choosing drugs to prescribe or in discussions with patients and carers. With this in mind, the use of neuroscience-based nomenclature (NbN)¹ – a naming system that reflects pharmacological activity – is strongly recommended.

Choosing an antipsychotic

The NICE guideline for medicines adherence² recommends that patients should be as involved as possible in decisions about the choice of medicines that are prescribed for them, and that clinicians should be aware that illness beliefs and beliefs about medicines influence adherence. Consistent with this general advice that covers all of health care, the NICE guideline for schizophrenia emphasises the importance of patient choice rather than specifically recommending a class or individual antipsychotic as first-line treatment.³
Antipsychotics are effective in both the acute and maintenance treatment of schizophrenia and other psychotic disorders. They differ in their pharmacology, pharmacokinetics, overall efficacy/effectiveness and tolerability, but perhaps more importantly, response and tolerability differ between patients. This variability of individual response means that there is no clear first-line antipsychotic medication that is preferable for all.

Relative efficacy

Further to the publication of CATIE\(^4\) and CUtLASS,\(^5\) the World Psychiatric Association reviewed the evidence relating to the relative efficacy of 51 first-generation antipsychotics (FGAs) and 11 second-generation antipsychotics (SGAs) and concluded that, if differences in EPS could be minimised (by careful dosing) and anticholinergic use avoided, there was no convincing evidence to support any advantage for SGAs over FGAs.\(^6\) As a class, SGAs may have a lower propensity to cause EPS and tardive dyskinesia\(^7\) but this is somewhat offset by a higher propensity to cause metabolic adverse effects. A meta-analysis of antipsychotic medications for first-episode psychosis\(^8\) found few differences between FGAs and SGAs as groups of drugs but minor advantages for olanzapine and amisulpride individually. A more recent network meta-analysis of first-episode studies found small efficacy advantages for olanzapine and amisulpride and overall poor performance for haloperidol.\(^9\)

When individual non-clozapine SGAs are compared with each other, it would appear that olanzapine is more effective than aripiprazole, risperidone, quetiapine and ziprasidone, and that risperidone has the edge over quetiapine and ziprasidone.\(^10\) Differences were small. FGA-controlled trials also suggest an advantage for olanzapine, risperidone and amisulpride over older drugs.\(^11,12\) A network meta-analysis\(^13\) broadly confirmed these findings, ranking amisulpride second behind clozapine and olanzapine third. These three drugs were the only ones to show clear efficacy advantages over haloperidol. The magnitude of differences was again small (but potentially substantial enough to be clinically important)\(^15\) and must be weighed against the very different adverse-effect profiles associated with individual antipsychotics.

Clozapine is clearly the drug of choice in refractory schizophrenia\(^14\) although, bizarrely, this is not a universal finding,\(^15\) probably because of the nature and quality of many active-comparator trials.\(^16,17\)

Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, increases in plasma glucose/diabetes,\(^18,19\) hyperprolactinaemia, hip fracture,\(^20\) sexual dysfunction, EPS including neuroleptic malignant syndrome,\(^21\) anticholinergic effects, venous thromboembolism (VTE),\(^22\) sedation and postural hypotension. The exact profile is drug-specific (see individual sections on specific adverse effects), although comparative data are not robust\(^23\) (see the meta-analysis by Leucht et al.\(^13\) for rankings of some adverse-effect risks). Adverse effects are a common reason for treatment discontinuation,\(^24\) particularly when efficacy is poor.\(^13\) Patients do not always spontaneously report adverse effects, however,\(^25\) and psychiatrists’ views of the prevalence and importance of adverse effects differ markedly from patient experience.\(^26\) Systematic enquiry along with a physical examination and appropriate biochemical tests is the only way accurately to assess their presence and severity or perceived severity. Patient-completed checklists such as the Glasgow Antipsychotic
Side-effect Scale (GASS)\textsuperscript{27} can be a useful first step in this process. The clinician-completed Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS) facilitates more detailed and comprehensive assessment.\textsuperscript{28}

Non-adherence to antipsychotic treatment is common and here the guaranteed medication delivery associated with depot/long-acting injectable (LAI) antipsychotic preparations is potentially advantageous. In comparison with oral antipsychotics, there is strong evidence that depots are associated with a reduced risk of relapse and rehospitalisation.\textsuperscript{29–31} The introduction of SGA long-acting injections has to some extent changed the image of depots, which were sometimes perceived as punishments for miscreant patients. Their tolerability advantage probably relates partly to the better definition of their therapeutic dose range, meaning that the optimal dose is more likely to be prescribed (compare aripiprazole, with a licensed dose of 300 mg or 400 mg a month, with flupentixol, which has a licensed dose in the UK of 50 mg every 4 weeks to 400 mg a week).

As already mentioned, for patients whose symptoms have not responded sufficiently to adequate, sequential trials of two or more antipsychotic drugs, clozapine is the most effective treatment\textsuperscript{32–34} and its use in these circumstances is recommended by NICE.\textsuperscript{3} The biological basis for the superior efficacy of clozapine is uncertain.\textsuperscript{35} Olanzapine should probably be one of the two drugs used before clozapine.\textsuperscript{10,36}

This chapter covers the treatment of schizophrenia with antipsychotic drugs, the relative adverse-effect profile of these drugs and how adverse effects can be managed.

References

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66:541–552.

25. Yusufi B et al. Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and


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to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 2006; 333:224.
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32. Kane J et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry

33. McEvoy JP et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not

34. Lewis SW et al. Randomized controlled trial of the effect of prescription of clozapine versus other second-generation antipsychotic drugs in

36. Agid O et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retro-
CHAPTER 1

General principles of prescribing*

- The lowest possible dose should be used. For each patient, the dose should be titrated to the lowest known to be effective (see section on ‘Minimum effective doses’ in this chapter); dose increases should then take place only after 2 weeks of assessment during which the patient is clearly showing poor or no response. (There is gathering evidence that lack of response at 2 weeks is a potent predictor of later poor outcome, unless dose or drug is changed.)

- With regular dosing of depot medication, plasma levels rise for at least 6–12 weeks after initiation, even without a change in dose (see section on ‘Depot antipsychotics – pharmacokinetics’ in this chapter). Dose increases during this time are therefore difficult to evaluate. The preferred method is to establish efficacy and tolerability of oral medication at a particular dose and then give the equivalent dose of that drug in LAI form. Where this is not possible, the target dose of LAI for an individual should be that established to be optimal in clinical trials (although such data are not always available for older LAIs).

- For the large majority of patients, the use of a single antipsychotic (with or without additional mood stabiliser or sedatives) is recommended. Apart from exceptional circumstances (e.g. clozapine augmentation) antipsychotic polypharmacy should generally be avoided because of the risks associated with QT prolongation and sudden cardiac death (see section on ‘Combined antipsychotics’ in this chapter).

- Combinations of antipsychotics should only be used where response to a single antipsychotic (including clozapine) has been clearly demonstrated to be inadequate. In such cases, the effect of the combination against target symptoms and adverse effects should be carefully evaluated and documented. Where there is no clear benefit, treatment should revert to single antipsychotic therapy.

- In general, antipsychotics should not be used as pro re nata (‘PRN’, as required) sedatives. Short courses of benzodiazepines or general sedatives (e.g. promethazine) are recommended (see section on ‘Acutely disturbed or violent behaviour’).

- Responses to antipsychotic drug treatment should be assessed by recognised rating scales and be documented in patients’ records.

- Those receiving antipsychotics should undergo close monitoring of physical health (including blood pressure, pulse, electrocardiogram [ECG], plasma glucose and plasma lipids) (see appropriate sections in this chapter).

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*This section is not referenced. Please see relevant individual sections in this chapter for detailed and referenced guidance.
Minimum effective doses

Table 1.1 suggests the minimum dose of antipsychotic likely to be effective in first- or multi-episode schizophrenia. Most patients will respond to the dose suggested, although others may require higher doses. Given the variation in individual response, all doses should be considered approximate. Primary references are provided where available, but consensus opinion has also been used. Only oral treatment with commonly used drugs is covered.

### Table 1.1 Antipsychotics: minimum effective dose/day

<table>
<thead>
<tr>
<th>Drug</th>
<th>First episode</th>
<th>Multi-episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine¹</td>
<td>200 mg*</td>
<td>300 mg</td>
</tr>
<tr>
<td>Haloperidol²-⁶</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Sulpiride⁷</td>
<td>400 mg*</td>
<td>800 mg</td>
</tr>
<tr>
<td>Trifluoperazine⁸,⁹</td>
<td>10 mg*</td>
<td>15 mg</td>
</tr>
<tr>
<td><strong>SGAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amisulpride¹⁰-¹⁵</td>
<td>300 mg*</td>
<td>400 mg*</td>
</tr>
<tr>
<td>Aripiprazole¹⁶-²⁰</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Asenapine²¹</td>
<td>10 mg*</td>
<td>10 mg</td>
</tr>
<tr>
<td>Brexpiprazole²²</td>
<td>2 mg*</td>
<td>2 mg</td>
</tr>
<tr>
<td>Cariprazine²³</td>
<td>1.5 mg*</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Iloperidone²⁰,²⁴</td>
<td>4 mg*</td>
<td>8 mg</td>
</tr>
<tr>
<td>Lurasidone²⁵,²⁶</td>
<td>40 mg HCl/37 mg base*</td>
<td>40 mg HCl/37 mg base</td>
</tr>
<tr>
<td>Olanzapine⁴,²⁷-²⁹</td>
<td>5 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Quetiapine³⁰-³⁵</td>
<td>150 mg* (but higher doses often used³⁵)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Risperidone³,³⁷-⁴⁰</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Sertindole³⁷,⁴²</td>
<td>Not appropriate</td>
<td>12 mg</td>
</tr>
<tr>
<td>Ziprasidone²⁰,⁴³-⁴⁵</td>
<td>40 mg*</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

*Estimate – too few data available.

FGA, first-generation antipsychotic; HCl, hydrochloride; SGA, second-generation antipsychotic.
References


Further reading

### Licensed maximum doses

Table 1.2 lists the EU licensed maximum doses of antipsychotics, according to the EMA labelling (as of March 2018).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGAs – oral</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>18 mg/day</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Pimozide</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>2400 mg/day</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>None (suggest 30 mg/day)</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>150 mg/day</td>
</tr>
<tr>
<td><strong>SGAs – oral</strong></td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>1200 mg/day</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Asenapine</td>
<td>20 mg (sublingual)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>900 mg/day</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>160 mg (HCl)/148 mg (base)/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>750 mg/day schizophrenia (800 mg/day for MR preparation)</td>
</tr>
<tr>
<td></td>
<td>800 mg/day bipolar disorder</td>
</tr>
<tr>
<td>Risperidone</td>
<td>16 mg/day</td>
</tr>
<tr>
<td>Sertindole</td>
<td>24 mg/day</td>
</tr>
<tr>
<td><strong>Depots</strong></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole depot</td>
<td>400 mg/month</td>
</tr>
<tr>
<td>Flupentixol depot</td>
<td>400 mg/week</td>
</tr>
<tr>
<td>Fluphenazine depot</td>
<td>100 mg every 2 weeks</td>
</tr>
<tr>
<td>Haloperidol depot</td>
<td>300 mg every 4 weeks</td>
</tr>
<tr>
<td>Paliperidone depot – 1 monthly</td>
<td>150 mg/month</td>
</tr>
<tr>
<td>Paliperidone depot – 3 monthly</td>
<td>525 mg every 3 months</td>
</tr>
<tr>
<td>Pipotiazine depot</td>
<td>200 mg every 4 weeks</td>
</tr>
<tr>
<td>Risperidone</td>
<td>50 mg every 2 weeks</td>
</tr>
<tr>
<td>Zuclopenthixol depot</td>
<td>600 mg/week</td>
</tr>
</tbody>
</table>

FGA, first-generation antipsychotic; HCl, hydrochloride; MR, modified-release; SGA, second-generation antipsychotic.
Table 1.3 lists the licensed maximum doses of antipsychotics available outside the EU, according to FDA labelling (March 2018).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA – oral</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>6 mg/day</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Molindone</td>
<td>225 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>160 mg/day</td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration; SGA, second-generation antipsychotic.

Table 1.3 lists the licensed maximum doses of antipsychotics available outside the EU, according to FDA labelling (as of March 2018).
Equivalent doses

Knowledge of equivalent dosages is useful when switching between FGAs. Estimates of ‘neuroleptic’ or ‘chlorpromazine’ equivalence, in mg/day, between these medications are based on clinical experience, expert panel opinion and/or early dopamine binding studies.

Table 1.4 provides approximate equivalent doses for FGAs.1–4 The values given should be seen as a rough guide when switching from one FGA to another and are no substitute for clinical titration of the new medication dose against adverse effects and response.

Equivalent doses of SGAs may be less clinically relevant as these medications tend to have tighter, evidence-based licensed dose ranges. Nevertheless, a rough guide to equivalent SGA daily dosages is given in Table 1.5.3–7 Clozapine is not included as this has a distinct initial titration schedule, partly for safety and tolerability reasons, and because it probably has a different mechanism of action.

Comparing potencies of FGAs with SGAs introduces yet more uncertainty with respect to dose equivalence. Very approximately, 100 mg chlorpromazine is equivalent to 1.5 mg risperidone.3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent dose (consensus)</th>
<th>Range of values in literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>100 mg/day</td>
<td>Reference</td>
</tr>
<tr>
<td>Fluphenazine depot</td>
<td>10 mg/week</td>
<td>1–5 mg/day</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2 mg/day</td>
<td>1.5–5 mg/day</td>
</tr>
<tr>
<td>Haloperidol depot</td>
<td>15 mg/week</td>
<td>5–25 mg/week</td>
</tr>
<tr>
<td>Pericystazine</td>
<td>10 mg/day</td>
<td>5–10 mg/day</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2 mg/day</td>
<td>1.33–2 mg/day</td>
</tr>
<tr>
<td>Pimotiazine depot</td>
<td>10 mg/week</td>
<td>10–12.5 mg/week</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>200 mg/day</td>
<td>133–300 mg/day</td>
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<tr>
<td>Trifluoperazine</td>
<td>5 mg/day</td>
<td>2.5–5 mg/day</td>
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<tr>
<td>Zuclopenthixol</td>
<td>25 mg/day</td>
<td>25–60 mg/day</td>
</tr>
<tr>
<td>Zuclopenthixol depot</td>
<td>100 mg/week</td>
<td>40–100 mg/week</td>
</tr>
</tbody>
</table>
References


Table 1.5 Second-generation antipsychotics: approximate equivalent doses3–7

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate equivalent dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>400 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15 mg</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Brexpiprazole*</td>
<td>2 mg</td>
</tr>
<tr>
<td>Cariprazine*</td>
<td>3 mg</td>
</tr>
<tr>
<td>Clotiapine†</td>
<td>100 mg</td>
</tr>
<tr>
<td>Iloperidone*</td>
<td>12 mg</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>80 mg (74 mg)</td>
</tr>
<tr>
<td>Molindone*</td>
<td>100 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Paliperidone LAI</td>
<td>75 mg/month</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300 mg</td>
</tr>
<tr>
<td>Risperidone oral</td>
<td>3 mg</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>37.5 mg/2 weeks</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

* Not available in EU at time of writing.
† Limited availability (not UK/USA).
LAI, long-acting injection.
High-dose antipsychotics: prescribing and monitoring

‘High-dose’ antipsychotic medication can result from the prescription of either a single antipsychotic medication at a dose above the recommended maximum, or two or more antipsychotic medications concurrently that, when expressed as a percentage of their respective maximum recommended doses and added together, result in a cumulative dose of more than 100%.1 In clinical practice, antipsychotic polypharmacy and PRN antipsychotic medication are strongly associated with high-dose prescribing.2,3

Efficacy

There is no firm evidence that high doses of antipsychotic medication are any more effective than standard doses for schizophrenia. This holds true for the use of antipsychotic medication for rapid tranquilisation, relapse prevention, persistent aggression and management of acute psychotic episodes.1 Despite this, in the UK, approximately a quarter to a third of hospitalised patients on antipsychotic medication have been observed to be on a high dose,2 while the national audit of schizophrenia in 2013, reporting on prescribing practice for over 5000 predominantly community-based patients, found that, overall, 10% were prescribed a high dose of antipsychotics.4

Review of the dose–response effects of a variety of antipsychotic medications has not found any evidence of greater efficacy for doses above accepted licensed ranges.5,6 Efficacy appears to be optimal at relatively low doses: 4 mg/day risperidone;7 300 mg/day quetiapine;8 olanzapine 10 mg9,10 etc. Similarly, 100 mg 2-weekly risperidone depot offers no benefits over 50 mg 2-weekly,11 and 320 mg/day ziprasidone12 is no better than 160 mg/day. All currently available antipsychotics (with the possible exception of clozapine) exert their antipsychotic effect primarily through antagonism (or partial agonism) at post-synaptic dopamine receptors. There is increasing evidence that in some patients with schizophrenia, refractory symptoms do not seem to be driven through dysfunction of dopamine pathways,13–15 and so increasing dopamine blockade in such patients is of uncertain value.

Dold et al.16 conducted a meta-analysis of randomised controlled trials (RCTs) that compared continuation of standard-dose antipsychotic medication with dose escalation in patients whose schizophrenia had proved to be unresponsive to a prospective trial of standard-dose pharmacotherapy with the same antipsychotic medication. In this context, there was no evidence of any benefit associated with the increased dosage. There are a small number of RCTs that have examined the efficacy of high versus standard dosage in patients with a diagnosis of treatment-resistant schizophrenia (TRS).1 Some demonstrated benefit17 but the majority of these studies are old, the number of patients randomised is small and study design is poor by current standards. Some studies used daily doses equivalent to more than 10 g of chlorpromazine. In a study of patients with first-episode schizophrenia, increasing the dose of olanzapine up to 30 mg/day and the dose of risperidone up to 10 mg/day in non-responders to standard doses yielded only a 4% absolute increase in overall response rate; switching to an alternative antipsychotic, including clozapine, was considerably more successful.18 One small (n = 12) open study of high-dose quetiapine (up to 1400 mg/day) found modest benefits in a
third of subjects\textsuperscript{19} but other, larger studies of quetiapine have shown no benefit for higher doses.\textsuperscript{8,20,21} A further RCT of high-dose olanzapine (up to 45 mg/day) versus clozapine for TRS found similar efficacy for the two treatments but concluded that, given the small sample size, it would be premature to conclude that they were equivalent.\textsuperscript{22} A systematic review of relevant studies comparing olanzapine at above standard dosage with clozapine for TRS concluded that while olanzapine, particularly in higher dosage, might be considered as an alternative to clozapine in TRS, clozapine still had the most robust evidence for efficacy.\textsuperscript{23}

**Adverse effects**

The majority of adverse effects associated with antipsychotic treatment are dose-related. These include EPS, sedation, postural hypotension, anticholinergic effects, QTc prolongation and coronary heart disease mortality.\textsuperscript{24–27} High-dose antipsychotic treatment is clearly associated with a greater adverse-effect burden.\textsuperscript{12,21,27–29} There is some evidence that antipsychotic dose reduction from very high (mean 2253 mg chlorpromazine equivalents per day) to high (mean 1315 mg chlorpromazine equivalents per day) leads to improvements in cognition and negative symptoms.\textsuperscript{30}

**Recommendations**

- The use of high-dose antipsychotic medication should be an exceptional clinical practice and only ever employed when adequate trials of standard treatments, including clozapine, have failed.
- Documentation of target symptoms, response and adverse effects, ideally using validated rating scales, should be standard practice so that there is ongoing consideration of the risk–benefit ratio for the patient. Close physical monitoring (including ECG) is essential.

**Prescribing high-dose antipsychotic medication**

**Before using high doses, ensure that:**

- Sufficient time has been allowed for response (see section on ‘Antipsychotic response – to increase the dose, to switch, to add or wait?’ in this chapter).
- At least two different antipsychotic medications have been tried sequentially (including, if possible, olanzapine).
- Clozapine has failed or not been tolerated due to agranulocytosis or other serious adverse effect. Most other adverse effects can be managed. A very small proportion of patients may also refuse clozapine.
- Medication adherence is not in doubt (use of blood tests, liquids/dispersible tablets, depot preparations, etc).
- Adjunctive medications such as antidepressants or mood stabilisers are not indicated.
- Psychological approaches have failed or are not appropriate.
The decision to use high doses should:

- Be made by a senior psychiatrist.
- Involve the multidisciplinary team.
- Be done, if possible, with a patient’s informed consent.

Practice points

- Rule out contraindications (ECG abnormalities, hepatic impairment).
- Consider and minimise any risks posed by concomitant medication (e.g. potential to cause QTc prolongation, electrolyte disturbance or pharmacokinetic interactions via CYP inhibition).
- Document the decision to prescribe high dosage in the clinical notes along with a description of target symptoms. The use of an appropriate rating scale is advised.
- Adequate time for response should be allowed after each dosage increment before a further increase is made.

Monitoring

- Physical monitoring should be carried out as outlined in the section on ‘Monitoring’ in this chapter.
- All patients on high doses should have regular ECGs (baseline, when steady-state serum levels have been reached after each dosage increment, and then every 6–12 months). Additional biochemical/ECG monitoring is advised if drugs that are known to cause electrolyte disturbances or QTc prolongation are subsequently co-prescribed.
- Target symptoms should be assessed after 6 weeks and 3 months. If insufficient improvement in these symptoms has occurred, the dose should be decreased to the normal range.

References


CHAPTER 1

Combined antipsychotics

A systematic review of the efficacy of monotherapy with an antipsychotic medication concluded that the magnitude of the clinical improvement achieved is generally modest. It is therefore unsurprising that the main clinical rationale for prescribing combined antipsychotics is to improve residual psychotic symptoms. Nonetheless, there is no robust objective evidence that treatment with combined antipsychotics is superior to a single antipsychotic. A meta-analysis of 16 randomised trials in schizophrenia, comparing augmentation with a second antipsychotic with continued antipsychotic monotherapy, found that combining antipsychotic medication lacked double-blind/high-quality evidence for overall efficacy. However, in patients with schizophrenia, the effects of a change from antipsychotic polypharmacy to monotherapy, even when carefully conducted, are uncertain. While the findings of two randomised studies suggested that the majority of patients may be successfully switched from antipsychotic polypharmacy to monotherapy without loss of symptom control, another reported greater increases in symptoms after 6 months in those participants who had switched to antipsychotic monotherapy.

Much of the evidence supporting antipsychotic combination therapy consists of small open studies and case series. Placebo response and reporting bias (nobody reports the failure of polypharmacy) are clearly important factors in this flimsy evidence base. However, some antipsychotic polypharmacy has a valid rationale. It has been shown that co-prescribed aripiprazole reduces weight in patients receiving clozapine and normalises prolactin in those on haloperidol and risperidone LAI (although not amisulpride). Polypharmacy with aripiprazole in such circumstances may thus represent worthwhile, evidence-based practice, albeit in the absence of regulatory trials demonstrating safety. In many cases, however, using aripiprazole alone might be a more logical choice.

Evidence for harm is perhaps more compelling. There are a number of published reports of clinically significant adverse effects associated with combined antipsychotics, such as an increased prevalence of EPS, severe EPS, increased metabolic adverse effects and diabetes, sexual dysfunction, increased risk of hip fracture, paralytic ileus, grand mal seizures, prolonged QTc and arrhythmias. Switching from antipsychotic polypharmacy to monotherapy has been shown to lead to worthwhile improvements in cognitive functioning. With respect to systematic studies, one that followed a cohort of patients with schizophrenia prospectively over a 10-year period found that receiving more than one antipsychotic concurrently was associated with substantially increased mortality. But there was no association between mortality and any measure of illness severity, suggesting that the increased mortality was related to the co-prescription of antipsychotic medication rather than the more severe or refractory illness for which the combined antipsychotics may have been prescribed. Another study, which involved the follow-up of 99 patients with schizophrenia over a 25-year period, found that those prescribed three antipsychotics simultaneously were twice as likely to die as those who had been prescribed only one. Overall, however, the evidence regarding increased mortality is inconclusive: a negative case-control study and a negative database study have also been published. Further, combined antipsychotics have been associated with longer admissions to hospital alongside more frequent adverse effects.
It follows that it should be standard practice to document the rationale for combined antipsychotics in individual cases in the clinical records, along with a clear account of any benefits and adverse effects. Medico-legally, this would seem to be prudent although in practice it is rarely done.29

Despite the adverse risk–benefit balance, prescriptions for combined antipsychotics are common30–32 and often long term.33 Combined antipsychotics are likely to involve depots/LAIs,34,35 quetiapine36 and FGAs,37 the last of these perhaps reflecting their frequent use as PRN medications. Focused, assertive interventions can reduce the prevalence of prescribing of antipsychotic polypharmacy38 but persistence with such programmes over several years may be required to achieve a significant change in practice.39,40 In the UK there may have been some gradual reduction in the use of antipsychotic polypharmacy over recent years. National clinical audits conducted as part of a Prescribing Observatory for Mental Health (POMH-UK) quality improvement programme40 found that combined antipsychotics were prescribed for 43% of patients on acute adult wards in the UK in 2006 while the respective figure in 2017 was 32%. It should be noted that only half of the in-patients receiving combined antipsychotics in the 2017 sample were prescribed more than one regular antipsychotic medication; the other half were prescribed a single regular antipsychotic plus PRN antipsychotic medication. The most common clinical reasons for prescribing regular, combined antipsychotics were a poor response to antipsychotic monotherapy and a period of crossover while switching from one antipsychotic to another. The use of combined antipsychotics has been found to be associated with younger patient age, male gender, and increased illness severity, acuity, complexity and chronicity, as well as poorer functioning, in-patient status and a diagnosis of schizophrenia.2,31,36,41,42 These associations largely reinforce the notion that polypharmacy is used where monotherapy proves inadequate.43

The situation in the community appears to be different. A systematic audit conducted in the UK in 2011 involved 5000 adult patients with a diagnosis of schizophrenia or schizoaffective disorder who were living in the community, from nearly 60 different NHS Trusts. It found that just over 60% of these patients were receiving a single antipsychotic (FGA or SGA; oral or injectable) and a further 18% were receiving clozapine, while 5% were not prescribed any antipsychotic medication.44 Thus, in this large sample of community patients, around one in six (16%) received combined antipsychotic medication. These data suggest some disparity between in-patient and outpatient practice, which probably reflects factors such as patient selection, disease severity and prescribing culture.

On the basis of the lack of evidence for efficacy and the potential for serious adverse effects, the routine use of combined antipsychotics should be avoided. But antipsychotic polypharmacy is clearly an established custom and practice. A questionnaire survey of US psychiatrists45 found that for illnesses that had failed to respond to a single antipsychotic, two-thirds of psychiatrists switched to another single antipsychotic, while a third added a second antipsychotic. Those who switched were more positive about clinical outcomes than those who had augmented. Another questionnaire study, conducted in Denmark, revealed that almost two-thirds of psychiatrists would rather combine antipsychotics than prescribe clozapine.46 An observational study found that patients whose illnesses had derived no benefit from antipsychotic monotherapy were likely to be switched to an alternative antipsychotic while those with a partial response
were more likely to have a second antipsychotic added.\textsuperscript{47} Such findings may partly explain why some patients are prescribed combined antipsychotics early in a treatment episode\textsuperscript{3,48} and the use of combined antipsychotics in up to a third of patients prior to the initiation of clozapine.\textsuperscript{49,50} They also indicate that the general consensus across treatment guidelines that the use of combined antipsychotic medication for the treatment of refractory psychotic illness should be considered only after other, evidence-based, pharmacological treatments such as clozapine have been exhausted is not consistently followed in clinical practice.\textsuperscript{9} A UK study of patients newly prescribed continuing, combined, antipsychotic medication found that only a third had previously been trialled on clozapine.\textsuperscript{42} However, it should be noted that clozapine augmentation strategies often involve combining antipsychotics and this is perhaps the sole therapeutic area where such practice is supportable\textsuperscript{51–55} (see section on ‘Optimising clozapine treatment’ in this chapter). While there is little evidence to support starting polypharmacy, stopping may not always be easy. Switching to monotherapy, even when done in a graded fashion, may involve some increase in the risk of exacerbation of psychiatric symptoms, though it is usually rewarded with fewer/less severe adverse effects and the expectation is that such exacerbations can be successfully managed.\textsuperscript{5}

Summary

- There is very little evidence supporting the efficacy of combined, non-clozapine, antipsychotic medications.
- There is substantial evidence supporting the potential for harm and so the use of combined antipsychotics should generally be avoided.
- Combined antipsychotics are commonly prescribed and this practice seems to be relatively resistant to change.
- As a minimum requirement, all patients who are prescribed combined antipsychotics should be systematically monitored for adverse effects (including an ECG) and any beneficial effect on symptoms should be carefully documented.
- Some antipsychotic polypharmacy (e.g. combinations with aripiprazole) shows clear benefits for tolerability but not efficacy.

References

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Antipsychotic prophylaxis

First episode of psychosis

Antipsychotics provide effective protection against relapse, at least in the short to medium term. A meta-analysis of placebo-controlled trials found that 26% of first-episode patients randomised to receive maintenance antipsychotics relapsed after 6–12 months compared with 61% randomised to receive placebo. Although the current consensus is that antipsychotics should be prescribed for 1–2 years after a first episode of schizophrenia, Gitlin et al. found that withdrawing antipsychotic treatment in line with this consensus led to a relapse rate of almost 80% after 1 year medication-free and 98% after 2 years. Other studies in first-episode patients have found that discontinuing antipsychotics increases the risk of relapse five-fold and confirmed that only a small minority of patients who discontinue remain well 1–2 years later. However, a 5-year follow-up of a 2-year RCT, during which patients received either maintenance antipsychotic treatment or had their antipsychotic dose reduced or discontinued completely, found that while there was a clear advantage for maintenance treatment with respect to reducing short-term relapse this advantage was lost in the medium term. Further, the dose-reduction/discontinuation group were receiving lower doses of antipsychotic drugs at follow-up and had better functional outcomes. There are numerous interpretations of these outcomes but the most that can be concluded at this stage is that dose reduction is a possible option in first-episode psychosis. There are certainly other studies showing disastrous outcomes from antipsychotic discontinuation, albeit over shorter periods with fewer subjects.

Clearly some patients with first-episode psychosis will not need long-term antipsychotics to stay well – figures of 18–30% have been quoted. However, there are no reliable patient factors linked to good outcome following discontinuation of antipsychotics and there remains more evidence in favour of continuing antipsychotics than for stopping them.

It should be noted that definitions of relapse usually focus on the severity of positive symptoms, and largely ignore cognitive and negative symptoms: positive symptoms are more likely to lead to hospitalisation while cognitive and negative symptoms (which respond less well, and in some circumstances may even be exacerbated by antipsychotic treatment) have a greater overall impact on quality of life.

With respect to antipsychotic choice, in the context of an RCT, clozapine did not offer any advantage over chlorpromazine in the medium term in first-episode patients with non-refractory illness. However, in a large naturalistic study of patients with a first admission for schizophrenia, clozapine and olanzapine fared better with respect to preventing re-admission than other oral antipsychotics. In this same study, the use of a long-acting antipsychotic injection seemed to offer advantages over oral antipsychotics despite confounding by indication (depots will have been prescribed to those considered to be poor adherers, oral to those perceived to have good adherence). Later studies show a huge advantage for long-acting risperidone over oral risperidone in first-episode patients and a smaller but substantial benefit for paliperidone LAI over oral antipsychotics in ‘recently diagnosed schizophrenia’. 
In practice, a firm diagnosis of schizophrenia is rarely made after a first episode and the majority of prescribers and/or patients will have at least attempted to stop antipsychotic treatment within 1 year. Ideally, patients should have their dose reduced gradually and all relevant family members and health-care staff should be aware of the discontinuation (such a situation is most likely to be achieved by using LAI). It is vital that patients, carers and key-workers are aware of the early signs of relapse and how to access help. Antipsychotics should not be considered the only intervention. Evidence-based psychosocial and psychological interventions are clearly also important.

**Multi-episode schizophrenia**

The majority of those who have one episode of schizophrenia will go on to have further episodes. Patients with residual symptoms, a greater adverse-effect burden and a less positive attitude to treatment are at greater risk of relapse. With each subsequent episode, the baseline level of functioning can deteriorate and the majority of this decline is seen in the first decade of illness. Suicide risk (10%) is also concentrated in the first decade of illness. Antipsychotic drugs, when taken regularly, protect against relapse in the short, medium and (with less certainty) long term. Those who receive targeted antipsychotics (i.e. only when symptoms re-emerge) seem to have a worse outcome than those who receive prophylactic antipsychotics and the risk of tardive dyskinesia (TD) may also be higher. Similarly, low-dose antipsychotics are less effective than standard doses.

Table 1.6 summarises the known benefits and harms associated with maintenance antipsychotic treatment as reported in a meta-analysis by Leucht et al. (2012).

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Relapse at 7–12 months</td>
<td>27%</td>
</tr>
<tr>
<td>Re-admission</td>
<td>10%</td>
</tr>
<tr>
<td>Improvement in mental state</td>
<td>30%</td>
</tr>
<tr>
<td>Violent/aggressive behaviour</td>
<td>2%</td>
</tr>
</tbody>
</table>

NNT, number needed to treat for one patient to benefit; NNH, number treated for one patient to be harmed.

* Likely to be a considerable underestimate as adverse effects are rarely systematically assessed in clinical trials.
10% lower, respectively, than with oral treatment.\textsuperscript{2,28} Long-acting preparations of antipsychotics may thus be preferred by both prescribers and patients. A large meta-analysis concluded that the risk of relapse with newer antipsychotics is similar to that associated with older drugs.\textsuperscript{2} (Note that lack of relapse is not the same as good functioning.\textsuperscript{29}) The proportion of multi-episode patients who achieve remission is small and may differ between antipsychotic drugs. The CATIE study reported that only 12% of patients treated with olanzapine achieved remission for at least 6 months, compared with 8% treated with quetiapine and 6% with risperidone.\textsuperscript{30} The advantage seen here for olanzapine is consistent with that seen in an acute efficacy network meta-analysis.\textsuperscript{31}

Patients with schizophrenia often receive a number of sequential antipsychotic drugs during the maintenance phase.\textsuperscript{32} Such switching is a result of a combination of suboptimal efficacy and poor tolerability. In both CATIE\textsuperscript{33} and SOHO,\textsuperscript{34,35} the attrition rate from olanzapine was lower than the attrition rate from other antipsychotic drugs, suggesting that olanzapine may be more effective than other antipsychotic drugs (except clozapine). However, prescribing choice should be based on potential risk–benefit and it should be noted that olanzapine is associated with a high propensity for metabolic adverse effects. In the SOHO study, the relapse rate over a 3-year period was relatively constant, supporting the benefit for maintenance treatment.\textsuperscript{36,37}

**Summary**

- Relapse rates in patients discontinuing antipsychotics are extremely high.
- Antipsychotics significantly reduce relapse, re-admission and violence/aggression.
- Long-acting depot formulations provide the best protection against relapse.

**Adherence to antipsychotic treatment**

Amongst people with schizophrenia, non-adherence with antipsychotic treatment is high. Only 10 days after discharge from hospital up to 25% are partially or non-adherent, rising to 50% at 1 year and 75% at 2 years.\textsuperscript{38} Not only does non-adherence increase the risk of relapse, it may also increase the severity of relapse and the duration of hospitalisation.\textsuperscript{38} The risk of suicide attempts also increases four-fold\textsuperscript{38} (see Chapter 14 ‘Enhancing medication adherence’).

**Dose for prophylaxis**

Many patients probably receive higher doses than necessary (particularly of the older drugs) when acutely psychotic.\textsuperscript{39,40} In the longer term, a balance needs to be struck between effectiveness and adverse effects. Lower doses of the older drugs (8 mg haloperidol/day or equivalent) are, when compared with higher doses, associated with less severe adverse effects,\textsuperscript{41} better subjective state and better community adjustment.\textsuperscript{42} Very low doses increase the risk of psychotic relapse.\textsuperscript{39,43,44} There are no data to support the use of lower than standard doses of the newer drugs as prophylaxis. Doses that are acutely effective should generally be continued as prophylaxis\textsuperscript{45,46} although an exception to this is prophylaxis after a first episode where very careful dose reduction is supportable.
How and when to stop antipsychotic treatment

The decision to stop antipsychotic drugs requires a thorough risk–benefit analysis for each patient. Withdrawal of antipsychotic drugs after long-term treatment should be gradual and closely monitored. The relapse rate in the first 6 months after abrupt withdrawal is double that seen after gradual withdrawal (defined as slow taper down over at least 3 weeks for oral antipsychotics or abrupt withdrawal of depot preparations). One analysis of incidence of relapse after switch to placebo found time to relapse to be very much longer for 3-monthly paliperidone than for 1-monthly and oral. Overall percentage relapse was also reduced. Abrupt withdrawal of oral treatment may also lead to discontinuation symptoms (e.g. headache, nausea, insomnia) in some patients.

The following factors should be considered:

- Is the patient symptom-free, and, if so, for how long? Long-standing, non-distressing symptoms which have not previously been responsive to medication may be excluded.
- What is the severity of adverse effects (EPS, TD, sedation, obesity, etc.)?
- What was the previous pattern of illness? Consider the speed of onset, duration and severity of episodes and any danger posed to self and others.
- Has dosage reduction been attempted before, and, if so, what was the outcome?
- What are the patient’s current social circumstances? Is it a period of relative stability, or are stressful life events anticipated?
- What is the social cost of relapse (e.g. is the patient the sole breadwinner for a family)?
- Is the patient/carer able to monitor symptoms, and, if so, will they seek help?

As with first-episode patients, patients, carers and key-workers should be aware of the early signs of relapse and how to access help. Be aware that targeted relapse treatment is much less effective than continuous prophylaxis. Those with a history of aggressive behaviour or serious suicide attempts and those with residual psychotic symptoms should be considered for life-long treatment.

Key points that patients should know

- Antipsychotics do not ‘cure’ schizophrenia. They treat symptoms in the same way that insulin treats diabetes.
- Some antipsychotic drugs may be more effective than others.
- Many antipsychotic drugs are available. Different drugs suit different patients. Perceived adverse effects should always be discussed, so that the best tolerated drug can be found.
- Long-term treatment is generally required to prevent relapses.
- Antipsychotics should never be stopped suddenly.
- Psychological and psychosocial interventions increase the chance of staying well.

Alternative views

While it is clear that antipsychotics effectively reduce symptom severity and rates of relapse, a minority view is that antipsychotics might also sensitise patients to psychosis. The hypothesis is that relapse on withdrawal can be seen as a type of discontinuation
reaction resulting from super-sensitivity of dopamine receptors, although the evidence for this remains uncertain. This phenomenon might explain better outcomes seen in first-episode patients who receive lower doses of antipsychotics but it also suggests the possibility that the use of antipsychotics might ultimately worsen outcomes.

The concept of ‘super-sensitivity psychosis’ was much discussed decades ago and has recently seen a resurgence. It is also striking that dopamine antagonists used for non-psychiatric conditions can induce withdrawal psychosis (although, to our knowledge, these three references are the only ones in the medical literature). Whilst these theories and observations do not alter recommendations made in this section, they do emphasise the need for using the lowest possible dose of antipsychotic in all patients and the balancing of observed benefit with adverse outcomes, including those that might be less clinically obvious (e.g. the possibility of structural brain changes).

References

Negative symptoms in schizophrenia represent the absence or diminution of normal behaviours and functions and constitute an important dimension of psychopathology. A subdomain of ‘expressive deficits’ manifests as a decrease in verbal output or verbal expressiveness and flattened or blunted affect, assessed by diminished facial emotional expression, poor eye contact, decreased spontaneous movement and lack of spontaneity. A second ‘avolition/amotivation’ subdomain is characterised by a subjective reduction in interests, desires and goals, and a behavioural reduction in purposeful acts, including a lack of self-initiated social interactions.\(^1\)\(^2\)

Persistent negative symptoms are held to account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.\(^3\)\(^4\)\(^5\) However, the aetiology of negative symptoms is complex and it is important to determine the most likely cause in any individual case before embarking on a treatment regimen. An important clinical distinction is between primary negative symptoms, which comprise an enduring deficit state, predict a poor prognosis and are stable over time, and secondary negative symptoms, which are consequent upon positive psychotic symptoms, depression or demoralisation, or medication adverse effects such as bradykinesia as part of drug-induced parkinsonism.\(^5\)\(^7\) Other sources of secondary negative symptoms may include chronic substance/alcohol use, high-dose antipsychotic medication, social deprivation, lack of stimulation and hospitalisation.\(^8\) Secondary negative symptoms may be best tackled by treating the relevant underlying cause. In people with established schizophrenia, negative symptoms are seen to a varying degree in up to three-quarters, with up to 20% having persistent primary negative symptoms.\(^9\)\(^10\)

The literature pertaining to the pharmacological treatment of negative symptoms largely consists of sub-analyses of acute efficacy studies, correlational analysis and path analyses.\(^11\) There is often no reliable distinction between primary and secondary negative symptoms or between the two subdomains of expressive deficits and avolition/amotivation, and few studies specifically recruit patients with persistent negative symptoms. While the evidence suggests short-term efficacy for a few interventions, there is no robust evidence for an effective treatment for persistent primary negative symptoms.

In general:

- In first-episode psychosis, the presence of negative symptoms has been related to poor outcome in terms of recovery and level of social functioning.\(^4\)\(^9\) There is evidence to suggest that the earlier a psychotic illness is effectively treated, the less likely is the development of negative symptoms over time.\(^12\)\(^13\)\(^14\) However, when interpreting such data it should be borne in mind that an early clinical picture characterised by negative symptoms, being less socially disruptive and more subtle as signs of psychotic illness than positive symptoms, may contribute to delay in presentation to clinical services and thus be associated with a longer duration of untreated psychosis. In other words, patients with an inherently poorer prognosis in terms of persistent negative symptoms may be diagnosed and treated later.

- While antipsychotic medication has been shown to improve negative symptoms, this benefit seems to be limited to secondary negative symptoms in acute psychotic
episodes.\textsuperscript{15} There is no consistent evidence for any superiority of SGAs over FGAs in the treatment of negative symptoms.\textsuperscript{16–20} Similarly, there is no consistent evidence for the superiority of any individual SGA.\textsuperscript{21} While a meta-analysis of 38 RCTs found a statistically significant reduction in negative symptoms with SGAs, the effect size did not reach a threshold for ‘minimally detectable clinical improvement over time’.\textsuperscript{22}

- Nevertheless, there are some data suggesting efficacy for negative symptoms with certain antipsychotic treatment strategies, such as amisulpride,\textsuperscript{23–26} cariprazine,\textsuperscript{27,28} and augmentation with aripiprazole.\textsuperscript{29,30}

- While clozapine remains the only medication with convincing superiority for TRS, whether it has superior efficacy for negative symptoms, at least in the short term, in such cases remains uncertain.\textsuperscript{31–33} One potential confounder in studies of clozapine for negative symptoms is that the medication has a low liability for parkinsonian adverse effects, including bradykinesia, which have a phenomenological overlap with negative symptoms, particularly the subdomain of expressive deficits.

- With respect to non-antipsychotic pharmacological interventions, several drugs that modulate glutamate pathways have been directly tested as adjuncts, but this approach has proved disappointing. Metabotropic glutamate 2/3 (mGlu2/3) receptor agonists have not been found to have any clear effect on negative symptoms over placebo.\textsuperscript{34,35} Drugs modulating N-methyl-D-aspartate (NMDA) receptors in other ways have been tested: for example, there are negative RCTs of glycine,\textsuperscript{36} D-serine,\textsuperscript{37} modafinil,\textsuperscript{38} armodafinil,\textsuperscript{39} and bitopertin\textsuperscript{40,41} augmentation of antipsychotic medication. There is a small preliminary positive RCT of pregnenolone.\textsuperscript{42} With respect to decreasing glutamate transmission, there are inconsistent meta-analysis findings for lamotrigine augmentation of clozapine\textsuperscript{43,44} and one positive\textsuperscript{45} and one negative\textsuperscript{46} RCT of memantine (the negative study being much larger). The antibiotic minocycline may have neuroprotective effects and modulate glutamate neurotransmission. There is some suggestion from meta-analyses of relevant studies that adding minocycline may improve negative symptoms, but the total sample size remains small.\textsuperscript{47,48}

- With respect to antidepressant augmentation of an antipsychotic for negative symptoms, a Cochrane review concluded that this may be an effective strategy for reducing affective flattening, alogia and avolition,\textsuperscript{49} although RCT findings for antidepressant augmentation of antipsychotic medication have found only inconsistent evidence of modest efficacy.\textsuperscript{50–53} One review of meta-analyses of relevant studies concluded that the evidence supported the efficacy of mirtazapine and mianserin (postulated to be related to their α₂-adrenergic antagonist effects).\textsuperscript{15} Another review concluded from the results of meta-analyses that adjunctive topiramate (a noradrenaline reuptake inhibitor) was effective for negative symptoms in schizophrenia spectrum disorders, being perhaps more efficacious when used to augment clozapine than non-clozapine antipsychotic medication.\textsuperscript{54,55}

- Meta-analyses support the efficacy of augmentation of an antipsychotic with *Ginkgo biloba*\textsuperscript{56} and a COX-2 inhibitor (albeit with a small effect size)\textsuperscript{57} while small RCTs have demonstrated some benefit for selegiline,\textsuperscript{58,59} pramipexole,\textsuperscript{60} testosterone (applied topically),\textsuperscript{61} ondansetron\textsuperscript{62} and granisetron.\textsuperscript{63} The findings from studies of repetitive transcranial magnetic stimulation (rTMS) are mixed but promising.\textsuperscript{64–66} The evidence for transcranial direct current stimulation (tDCS) as a treatment for negative symptoms is limited and inconclusive.\textsuperscript{15,67} A large (n = 250) RCT in adults\textsuperscript{68}
and a smaller RCT in elderly patients each found no benefit for donepezil and there is a further negative RCT of galantamine.

Patients who misuse psychoactive substances experience fewer negative symptoms than patients who do not. But rather than any pharmacological effect, it may be that this association at least partly reflects that those people who develop psychosis in the context of substance use, specifically cannabis, have fewer neurodevelopmental risk factors and thus better cognitive and social function.

Summary and recommendations

The following recommendations are derived from the BAP schizophrenia guideline, Veerman et al. 2017, Aleman et al. 2017 and Remington et al.

- There are no well-replicated, large trials, or meta-analyses of trials, with negative symptoms as the primary outcome measure that have yielded convincing evidence for enduring and clinically significant benefit.
- Where some improvement has been demonstrated in clinical trials, this may be limited to secondary negative symptoms.
- Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms.
- For any given patient, the antipsychotic medication that provides the best balance between overall efficacy and adverse effects should be used, at the lowest dose that maintains control of positive symptoms.
- Where negative symptoms persist beyond an acute episode of psychosis:
  - Ensure EPS (specifically bradykinesia) and depression are detected and treated if present, and consider the contribution of the environment to negative symptoms (e.g. institutionalisation, lack of stimulation).
  - There is insufficient evidence at present to support a recommendation for any specific pharmacological treatment for negative symptoms. Nevertheless, a trial of add-on medication for which there is some RCT evidence for efficacy, such as an antidepressant, may be worth considering in some cases, ensuring that the choice of the augmenting agent is based on minimising the potential for compounding adverse effects through pharmacokinetic or pharmacodynamic drug interactions.

References

CHAPTER 1

35. Stauffer VL et al. Pomaglumetad methionil: no significant difference as an adjunctive treatment for patients with prominent negative symptoms of schizophrenia compared to placebo. Schizophr Res 2013; 150:434–441.
42. Marx CE et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. Neuropsychopharmacology 2008; 33:375–383.
Table 1.7 summarises suggested monitoring for those receiving antipsychotic drugs. More detail and background are provided in specific sections in this chapter.

References

<table>
<thead>
<tr>
<th>Parameter/test</th>
<th>Suggested frequency</th>
<th>Action to be taken if results outside reference range</th>
<th>Drugs with special precautions</th>
<th>Drugs for which monitoring is not required</th>
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</table>
| **Urea and electrolytes**  
(including creatinine or estimated GFR) | Baseline and yearly as part of a routine physical health check | Investigate all abnormalities detected | Amisulpride and sulpiride renally excreted – consider reducing dose if GFR reduced | None |
| **Full blood count (FBC)** | Baseline and yearly as part of a routine physical health check and to detect chronic bone marrow suppression (small risk associated with some antipsychotics) | Stop suspect drug if neutrophils fall below $1.5 \times 10^9/L$  
Refer to specialist medical care if neutrophils below $0.5 \times 10^9/L$. Note high frequency of benign ethnic neutropenia in certain ethnic groups | Clozapine – FBC weekly for 18 weeks, then fortnightly up to 1 year, then monthly (schedule varies from country to country) | None |
| **Blood lipids**  
(cholesterol; triglycerides)  
Fasting sample, if possible | Baseline, at 3 months then yearly to detect antipsychotic-induced changes, and generally monitor physical health | Offer lifestyle advice. Consider changing antipsychotic and/or initiating statin therapy | Clozapine, olanzapine – 3-monthly for first year, then yearly | Some antipsychotics (e.g. aripiprazole, lurasidone) not clearly associated with dyslipidaemia but prevalence is high in this patient group so all patients should be monitored |
| **Weight**  
(include waist size and BMI, if possible) | Baseline, frequently for 3 months then yearly to detect antipsychotic-induced changes, and generally monitor physical health | Offer lifestyle advice. Consider changing antipsychotic and/or dietary/pharmacological intervention | Clozapine, olanzapine – frequently for 3 months then 3-monthly for first year, then yearly | Aripiprazole, ziprasidone, brexpiprazole, cariprazine and lurasidone not clearly associated with weight gain but monitoring recommended nonetheless – obesity prevalence high in this patient group |
| **Plasma glucose**  
(fasting sample, if possible) | Baseline, at 4–6 months, then yearly to detect antipsychotic-induced changes and generally monitor physical health | Offer lifestyle advice. Obtain fasting sample or non-fasting and HbA1c  
Refer to GP or specialist | Clozapine, olanzapine, chlorpromazine – test at baseline, 1 month, then 4–6-monthly | Some antipsychotics not clearly associated with IFG but prevalence is high in this patient group so all patients should be monitored |
| **ECG** | Baseline and when target dose is reached (ECG changes rare in practice) on admission to hospital and before discharge if drug regimen changed | Discuss with/refer to cardiologist if abnormality detected | Haloperidol, pimozide, sertindole – ECG mandatory  
Ziprasidone – ECG mandatory in some situations | Risk of sudden cardiac death increased with most antipsychotics. Ideally, all patients should be offered an ECG at least yearly |

*(Continued)*
<table>
<thead>
<tr>
<th>Parameter/test</th>
<th>Suggested frequency</th>
<th>Action to be taken if results outside reference range</th>
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<th>Drugs for which monitoring is not required</th>
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<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td>Baseline; frequently during dose titration to detect antipsychotic-induced changes, and generally monitor physical health</td>
<td>If severe hypotension or hypertension (clozapine) observed, slow rate of titration. Consider switching to another antipsychotic if symptomatic postural hypotension. Treat hypertension in line with NICE guidelines</td>
<td>Clozapine, chlorpromazine and quetiapine most likely to be associated with postural hypotension</td>
<td>Amisulpride, aripiprazole, brexpiprazole, cariprazine, lurasidone, trifluoperazine, sulpiride</td>
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<td><strong>Prolactin</strong></td>
<td>Baseline, then at 6 months, then yearly to detect antipsychotic-induced changes</td>
<td>Switch drugs if hyperprolactinaemia confirmed and symptomatic. Consider tests of bone mineral density (e.g. DEXA scanning) for those with chronically raised prolactin</td>
<td>Amisulpride, sulpiride, risperidone and paliperidone particularly associated with hyperprolactinaemia</td>
<td>Asenapine, aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, quetiapine, olanzapine (&lt;20mg), ziprasidone usually do not elevate prolactin, but worth measuring if symptoms arise</td>
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<tr>
<td><strong>Liver function tests (LFTs)</strong></td>
<td>Baseline, then yearly as part of a routine physical health check and to detect chronic antipsychotic-induced changes (rare)</td>
<td>Stop suspect drug if LFTs indicate hepatits (transaminases x 3 normal) or functional damage (PT/albumin change)</td>
<td>Clozapine and chlorpromazine associated with hepatic failure</td>
<td>Amisulpride, sulpiride</td>
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<td><strong>Creatinine phosphokinase</strong></td>
<td>Baseline, then if NMS suspected</td>
<td>See section on 'Neuroleptic malignant syndrome' in this chapter</td>
<td>NMS more likely with first-generation antipsychotics</td>
<td>None</td>
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</table>

**Other tests:**
Patients on clozapine may benefit from an EEG as this may help determine the need for anticonvulsant treatment (although interpretation is obviously complex). Those on quetiapine should have thyroid function tests yearly although the risk of abnormality is very small.

Note: this table is a summary – see individual sections for detail and discussion.

BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; ECG, electrocardiograph; EEG, electroencephalogram; GFR, glomerular filtration rate; IFG, impaired fasting glucose; NMS, neuroleptic malignant syndrome; PT, prothrombin time.
Relative adverse effects – a rough guide

Table 1.8 is made up of approximate estimates of relative incidence and/or severity, based on clinical experience, manufacturers’ literature and published research. This is a very rough guide – see individual sections for more precise information.

Other adverse effects not mentioned in Table 1.8 do occur. Please see dedicated sections on other adverse effects included in this book for more information.

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<th>Drug</th>
<th>Sedation</th>
<th>Weight gain</th>
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*Availability varies from country to country.
+++ high incidence/severity; ++ moderate; + low; – very low.
Treatment algorithms for schizophrenia

First-episode schizophrenia

See Figure 1.1.

Either:
Agree the choice of antipsychotic medication with patient\(^1\) and/or carer
Or, if not possible:
Start second-generation antipsychotic medication\(^2,3\)

Titrate, as necessary, to minimum effective dose (see section on ‘Minimum effective doses’ in this chapter)

Adjust dosage regimen according to therapeutic response and tolerability/safety

Assess over 2–3 weeks*  

**Effective**
Continue at dose established as effective  
Consider switching to depot/long-acting injection before discharge\(^7\)

**Not effective**
Change drug and follow above process

If poor adherence related to poor tolerability, discuss with patient and change to drug with more favourable adverse-effect profile
If poor adherence related to other factors, consider early use of depot/long-acting injection\(^1\)

Not tolerated or poor medication adherence

If not effective

Clozapine\(^6\)

* Any improvement is likely to be apparent within 2–3 weeks of receiving an effective dose.\(^4\) Most improvement occurs during this period.\(^5\) If no effect by 2–3 weeks, change dose or drug. If some response detected, continue for a total of at least 4 weeks before abandoning treatment.

\(^1\) Relapse and readmission rates are vastly reduced by early use of depot/long-acting injections in this patient group.\(^6,8\)

\(^6\) Early use of clozapine much more likely than anything else to be successful.\(^9\)
Relapse or acute exacerbation of schizophrenia (full adherence confirmed)

See Figure 1.2.

- Investigate social or psychological precipitants
- Provide appropriate support and/or therapy
- Continue usual drug treatment

**Acute drug treatment required**

- Add short-term sedative
  - or
- Switch to a different, more acceptable antipsychotic medication if appropriate
- Discuss medication choice with patient and/or carer
- Assess over 6 weeks

**Treatment ineffective**

- Switch to clozapine

**Notes:**
- First-generation drugs may be slightly less efficacious than some SGAs. FGA should probably be reserved for second-line use because of the possibility of poorer outcome compared with SGAs and the higher risk of movement disorder, particularly tardive dyskinesia.
- Choice should be based largely on comparative adverse-effect profile and relative toxicity. Patients seem able to make informed choices based on these factors, although in practice they have in the past only very rarely been involved in drug choice. Allowing patients informed choice seems to improve outcomes.
- Where there is prior treatment failure (but not confirmed treatment refractoriness), olanzapine or risperidone may be a better option than quetiapine. Olanzapine, because of the wealth of evidence suggesting slight superiority over other antipsychotics, should always be tried before clozapine unless contraindicated.
- Before considering clozapine, ensure adherence to prior therapy using depot/LAI formulation or plasma drug level monitoring of oral treatment. Most non-adherence is undetected in practice and apparent treatment resistance may simply be a result of inadequate treatment.
- Where there is confirmed treatment resistance (failure to respond to adequate trials of at least two antipsychotic medications), evidence supporting the use of clozapine (and only clozapine) is overwhelming.

**Figure 1.2** Treatment algorithm for relapse or acute exacerbation of schizophrenia (full adherence to medication confirmed). FGA, first-generation antipsychotic; LAI, long-acting injection; SGA, second-generation antipsychotic.
Relapse or acute exacerbation of schizophrenia (adherence in doubt)

See Figure 1.3.

Figure 1.3 Treatment of relapse or acute exacerbation of schizophrenia (adherence doubtful or known to be poor). LAI, long-acting injection.

References

17. Stroup TS et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discon-
18. Haro JM et al. Remission and relapse in the outpatient care of schizophrenia: three-year results from the Schizophrenia Outpatient Health
20. Tihonen J et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due
to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ 2006; 333:224.
137:39–46.
26. Lewis SW et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in
First-generation antipsychotics – place in therapy

Nomenclature

First-generation (‘typical’) and second-generation (‘atypical’) antipsychotic medications are not categorically differentiated, the medications in both groups being heterogeneous in terms of pharmacological and adverse-effect profiles. First-generation medications tend to be associated with acute EPS, hyperprolactinaemia and, in the longer term, TD. There are expectations that such adverse effects are less likely with SGAs although in practice most show dose-related EPS, some induce hyperprolactinaemia (often to a greater extent than with FGAs) and all may eventually give rise to TD. Second-generation medications tend to be associated with metabolic and cardiac complications.\(^1\)\(^-\)\(^3\) To complicate matters further, it has been suggested that the therapeutic and adverse effects of FGAs can be separated by careful dosing\(^4\) – essentially turning them into SGAs if used in small doses (although there is much evidence to the contrary\(^5\)\(^-\)\(^7\)).

Given these observations, it seems unwise and unhelpful to consider so-called ‘FGAs’ and ‘SGAs’ as distinct groups of drugs. Perhaps the essential difference between the two groups is the size of the therapeutic index in relation to acute EPS: for instance haloperidol has an extremely narrow index (probably less than 0.5 mg/day); olanzapine a wide index (20–40 mg/day).

The use of neuroscience-based nomenclature (NbN)\(^8\)\(^,\)\(^9\) (for which there is a free app for iPhone and other devices) obviates the need for classification as FGA or SGA and describes an individual drug by its pharmacological activity. The wider use of NbN will undoubtedly improve understanding of individual drug effects and perhaps forestall future redundant categorisation.

Role of older antipsychotics

FGAs still play an important role in schizophrenia: for example, chlorpromazine and haloperidol are frequent choices for PRN medication, and depot preparations of fluphenazine, zuclopenthixol and flupentixol are commonly prescribed. FGAs can offer a valid alternative to SGAs where these are poorly tolerated (usually because of metabolic changes) or where FGAs are preferred by patients themselves. Some FGAs may be less effective than some non-clozapine SGAs (amisulpride, olanzapine and risperidone may be more efficacious\(^10\)\(^,\)\(^11\)) but any differences in therapeutic efficacy seem to be modest. Two large pragmatic studies, CATIE\(^12\) and CUtLASS,\(^13\) found few important differences between SGAs and FGAs (mainly perphenazine and sulpiride, respectively).

The main drawbacks of FGAs are, inevitably, acute EPS, hyperprolactinaemia and TD. Hyperprolactinaemia is probably unavoidable in practice (the dose that achieves efficacy is too close to the dose that causes hyperprolactinaemia) and, even when not symptomatic, may grossly affect hypothalamic function.\(^14\) It is also associated with sexual dysfunction,\(^15\) but be aware that the autonomic effects of some SGAs may also cause sexual dysfunction.\(^16\) Also, some SGAs (risperidone, paliperidone, amisulpride) increase prolactin to a greater extent than FGAs.\(^17\)

Some FGAs, like haloperidol, are potent dopamine antagonists and are liable to induce dysphoria.\(^18\) Perhaps as a consequence, some FGAs may produce smaller benefits in quality of life than some SGAs.\(^19\)
TD probably occurs more frequently with FGAs than with SGAs\(^{20-23}\) (notwithstanding difficulties in defining what is ‘atypical’), although there remains some uncertainty\(^{23-25}\) and the dose of FGA used is a crucial factor. Careful observation of patients and the prescribing of the lowest effective dose are essential to help reduce the risk of this serious adverse event\(^{26,27}\). Even with these precautions, the risk of TD with some FGAs may be unacceptably high\(^{28}\).

A good example of the relative merits of SGAs and a carefully dosed FGA comes from a trial comparing paliperidone palmitate with low-dose haloperidol decanoate\(^{29}\). Paliperidone produced more weight gain and prolactin change but haloperidol was associated with significantly more akathisia and parkinsonism, and numerically more TD. Efficacy was identical.

### References

NICE guidelines for the treatment of schizophrenia

The 2009 NICE guidelines differed importantly from previous guidelines. There was no longer an imperative to prescribe an ‘atypical’ as first-line treatment and it was recommended only that clozapine be ‘offered’ (rather than prescribed) after the prior failure of two antipsychotics. These differences pointed respectively towards disillusionment with SGAs and recognition of the delay in prescribing clozapine in practice. Much emphasis was placed on involving patients and their carers in prescribing decisions. There is some evidence that this is rarely done but that it can be done. New NICE guidelines appeared in February 2014 and were reviewed in November 2017. Few changes were made to recommendations regarding drug treatment but psychological treatments are now more strongly promoted (perhaps reflecting the make-up of the NICE review panel).

NICE guidelines – a summary

- For people with newly diagnosed schizophrenia, offer oral antipsychotic medication. Provide information and discuss the benefits and adverse-effect profile of each drug with the service user. The choice of drug should be made by the service user and health-care professional together, considering:
  - the relative potential of individual antipsychotic drugs to cause EPS (including akathisia), cardiovascular adverse effects, metabolic adverse effects (including weight gain), hormonal adverse effects and other adverse effects (including unpleasant subjective experiences)
  - the views of the carer where the service user agrees.

- Before starting antipsychotic medication, undertake and record the following baseline investigations:
  - weight
  - waist circumference
  - pulse and blood pressure
  - fasting blood glucose, HbA₁c, blood lipid profile, prolactin
  - assessment of movement disorders
  - assessment of nutritional status, diet and level of physical activity.

- Before starting antipsychotic medication, offer the person with schizophrenia an electrocardiogram (ECG) if:
  - specified in the summary of product characteristics (SPC)
  - a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
  - there is personal history of cardiovascular disease, or
  - the service user is being admitted as an in-patient.

- Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following:
  - Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of adverse effects.
At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British National Formulary (BNF) or SPC.

- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication and the effects of such changes.
- Carry out a trial of medication at optimum dosage for 4–6 weeks (although half of this period is probably sufficient if no effect at all is seen).

- Monitor and record the following regularly and systematically throughout treatment, but especially during titration:
  - efficacy, including changes in symptoms and behaviour
  - adverse effects of treatment, taking into account overlap between certain adverse effects and clinical features of schizophrenia, for example the overlap between akathisia and agitation or anxiety
  - adherence
  - weight, weekly for the first 6 weeks, then at 12 weeks, 1 year and annually
  - waist circumference annually
  - pulse and blood pressure at 12 weeks, 1 year and annually
  - fasting blood glucose, HbA1c and blood lipids at 12 weeks, 1 year and annually
  - nutritional status, diet and physical activity.

- Physical monitoring is to be the responsibility of the secondary care team for 1 year or until the patient is stable.

- Do not use a loading dose of antipsychotic medication (often referred to as ‘rapid neuroleptisation’). (Note that this does not apply to loading doses of depot forms of olanzapine and paliperidone.)

- Do not routinely initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).

- If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.

- Consider offering depot/LAI antipsychotic medication to people with schizophrenia:
  - who would prefer such treatment after an acute episode
  - where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

- Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs alongside psychological therapies. At least one of the drugs should be a non-clozapine SGA. (See Figure 1.1 – we recommend that one of the drugs should be olanzapine).

- For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, health-care professionals should establish prior compliance with optimised antipsychotic treatment (including measuring drug levels) and engagement with psychological treatment before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks (some data suggest 6 weeks may be enough). Choose a drug that does not compound the common adverse effects of clozapine.
References


Antipsychotic response – to increase the dose, to switch, to add or just wait – what is the right move?

For any clinician taking active care of patients with schizophrenia, the single most common clinical dilemma is what to do when the current antipsychotic medication is not optimal for the patient. This may be for two broad reasons: first, while the symptoms are well controlled, the adverse effects are problematic and, second, there is an inadequate therapeutic response. Fortunately, with regard to the first reason, the diversity of the available antipsychotic medications means that it is usually possible to find one that has an adverse-effect profile that is appropriate and acceptable to the patient. What to do next is a more difficult question with regard to the second reason – an insufficient symptom response. If the patient has already had adequate trials, in terms of dosage, duration and adherence, of two antipsychotic medications then clozapine should clearly be considered. However, the majority of the patients in the clinic are those who are either not yet ready for clozapine or unwilling to choose that option. In those instances, the clinician has four main choices: to increase the dose of the current medication; to switch to another antipsychotic; to add an adjunct medication; or just to wait.

When to increase the dose?

While optimal doses of FGAs were always a matter of debate, the recommended doses of the SGAs were generally based on careful and extensive clinical trials, but even then the consensus on optimal doses has changed with time. For example, when risperidone was first launched it was suggested that optimal titration was from 2 mg to 4 mg to 6 mg or more for all patients; however, the field has tended towards lower doses.\(^1\) On the other hand, when quetiapine was introduced, 300 mg was considered the optimal dose and the overall consensus now is towards higher doses,\(^2\) although RCT and other evidence does not support this shift.\(^2,3\) Nonetheless, most clinicians feel comfortable in navigating within the recommended clinical dose range. The more critical question is what should be done if one has hit the upper limit of these dose ranges and the patient is tolerating the medication well but with limited benefit.

Dose–response observations

Davis and Chen performed a systematic meta-analysis of relevant dose–response data available up to 2004 and concluded that the average dose that produces maximal benefit was 4 mg for risperidone, 16 mg of olanzapine, 120 mg of ziprasidone and 10–15 mg of aripiprazole (they could not determine such a dose for quetiapine using their method).\(^4\) More recent trials have tried to compare ‘high-dose’ with standard dosage. For example, one group\(^5\) studied the dose–response relationship of standard and higher doses of olanzapine in a randomised, double-blind, 8-week, fixed-dose study comparing olanzapine 10 mg, 20 mg and 40 mg and found no additional benefit with the higher doses (i.e. 40 mg was no better than 10 mg) but clear evidence for an increasing adverse-effect burden (weight gain and prolactin) with dose. Similarly, the initial licensing studies of risperidone compared the usual doses of 2–6 mg with higher doses of 8–16 mg/day. While they found no additional benefit with the higher doses, there
was a clear signal for a greater risk of adverse effects (EPS and increased prolactin). The findings of these studies are in accord with older studies involving fixed doses of haloperidol. However, it is important to keep in mind that these doses are extracted from group evidence where patients are assigned to different doses, which is a different situation from the clinical one where the prescriber considers increasing the dose only in those patients whose illnesses have failed to respond to the initial dosage regimen. The potential benefits and risks of such a strategy remain uncertain and warrant further investigation. Kinon et al. examined patients who failed to respond to the (then) standard dose of fluphenazine (20 mg) and tested three strategies: increasing the dose to 80 mg, switching to haloperidol or watchful waiting (on the original dose). All three strategies proved to be equivalent in terms of efficacy. These findings provide little supportive evidence at a group level (as opposed to an individual level) for treatment beyond the recommended dose range. Such RCT evidence is corroborated by the clinical practice norms – Hermes and colleagues examined the CATIE data to identify clinical factors that predicted a prescriber’s decision to increase the dose and found that decisions for dose change (within the therapeutic ranges) were only weakly associated with clinical measures. More recently a trial of lurasidone showed that patients failing to respond at 2 weeks did somewhat better if their dose was doubled than if the dose was kept the same. It is not clear if these results are generalisable to other antipsychotics.

**Plasma level variations**

Group level evidence cannot completely determine individual decisions. There are significant inter-individual variations in plasma drug levels in patients treated with antipsychotic medication. One can often encounter a patient who, when receiving medication at the higher end of the dose range (say 6 mg of risperidone or 20 mg of olanzapine), would have plasma drug levels that are well below the range expected for 2 mg risperidone or 10 mg of olanzapine, respectively. In such patients, a rational case could be made for increasing the dose, provided the patient is informed and the adverse effects are tolerable, to bring the plasma levels to the median optimal range for the particular medication. (More details on plasma levels and their interpretation are provided in Chapter 11.) However, one often encounters an unresponsive patient, adherent to their medication, whose dose has reached the ceiling and plasma levels are also sufficient – what next?

**Treatment choices**

There are essentially three options here: clozapine, switch to another drug or add another (non-clozapine) drug. If the patient meets the criteria for clozapine it is undoubtedly the preferred option. Yet, in a clinical audit of community (not in-patient) practice in the UK, covering some 5000 patients in 60 different NHS Trusts, it was found that nearly 40% of the patients who met criteria for treatment resistance did not receive clozapine; of those who did, the vast majority (85%) received their clozapine after a much longer wait after the failure of two serial trials of antipsychotic medication than is advised in most guidelines.
Nonetheless, there is a group of patients who do not like the idea of regular blood testing, the adverse-effect profile and the regular appointments required to receive clozapine. In such patients, the choice is to switch to another medication or to add another antipsychotic. The data on switching are sparse. While almost every clinical trial in patients with established schizophrenia has entailed the patient switching from one antipsychotic medication to another, there are no rigorous studies of preferred switch combinations (e.g. if risperidone fails – what next: olanzapine, quetiapine, aripiprazole or ziprasidone?). If one looks at only the switching trials that have been sponsored by the drug companies it leads to a rather confusing picture, with the trial results being very closely linked to the sponsor’s interest (see Heres et al. ‘Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics’).

CATIE, the major US-based publicly-funded comparative trial, examined patients who had failed their first SGA and were then randomly assigned to a different second one. Patients switched to olanzapine and risperidone did better than those switched to quetiapine and ziprasidone. This greater effectiveness is supported by a meta-analysis that compared a number of SGAs with FGAs and concluded that, other than clozapine, only amisulpride, risperidone and olanzapine were superior to FGAs in efficacy, and a meta-analysis comparing SGAs amongst themselves which suggests that olanzapine and risperidone (in that order) may be more effective than the others, although these differences in efficacy between medications may be judged as modest. Nevertheless, if a patient has not tried olanzapine or risperidone as yet, it would be a reasonable decision to switch to these drugs provided the adverse-effect balance is favourable. Comparing these two drugs the data are somewhat limited. However, a number of controlled but open-label studies do show an asymmetrical advantage (i.e. switching to olanzapine being more effective than risperidone), providing some direction, albeit incomplete.

The best medication regimen (aside from clozapine) to choose for a patient who fails on olanzapine and risperidone remains unclear. Should one switch (to, say, aripiprazole or ziprasidone or even an older FGA) or should one add another antipsychotic medication? It should be borne in mind that after ‘switching’, adding another antipsychotic is probably the second most common clinical move as around 40% of patients in routine care are on more than one antipsychotic. Often a second antipsychotic is added to get an additional profile (e.g. sedation with quetiapine, or decrease in prolactin with the addition of aripiprazole) – these matters are discussed elsewhere. Here we are concerned solely with the addition of an antipsychotic to another antipsychotic to increase efficacy. From a theoretical point of view, because all antipsychotics block D2 receptors (unlike, say, antihypertensives which use different mechanisms), there is limited rationale for addition. Studies of add-ons have often chosen combinations of convenience or those based on clinical lore. Perhaps the most systematic evidence is available for the addition of a second antipsychotic to clozapine, possibly supported by the rationale that because clozapine has low D2 occupancy, increasing its D2 occupancy may yield additional benefits. However, a meta-analysis of RCTs comparing augmentation with a second antipsychotic with continuing antipsychotic monotherapy in schizophrenia found a lack of double-blind/high-quality evidence for efficacy for the combination in terms of treatment response and symptom improvement. Further, compared with
antipsychotic monotherapy, combined antipsychotics seem to be associated with an increased adverse-effect burden and a greater risk of high-dose prescribing.\textsuperscript{22,23}

Although augmentation with another antipsychotic as a treatment strategy should probably be avoided, under some conditions of acute exacerbation or agitation the prescriber may see this as the only practicable solution. Or quite often the prescriber may inherit the care of a patient on antipsychotic polypharmacy. Most RCT evidence suggests that such a regimen can be safely switched back to antipsychotic monotherapy without symptom exacerbation, at least in the majority of patients,\textsuperscript{24–26} although this is not a universal finding.\textsuperscript{27} Essock et al.\textsuperscript{26} conducted a relatively large trial involving 127 patients with schizophrenia who were stable on antipsychotic polypharmacy. Over a 12-month period, a switch to monotherapy was successful in about two-thirds of the patients in whom it was tested. In those cases where the move to monotherapy resulted in a return of symptoms, the most common recourse was a return to the original polypharmacy; this was achieved without any significant worsening in this group. The advantages for the monotherapy group were exposure to less medication, equivalent symptom severity and some loss of weight.

So, when should the prescriber just continue with the current regimen? The evidence reviewed above suggests that no one strategy, such as increasing the dose or switching or augmenting, is the clear winner in all situations. Increase the dose if plasma drug levels are low; switch if the patient has not tried olanzapine or risperidone; and if treatment with clozapine is failing, augmentation may help. Given the limited efficacy of these manoeuvres, perhaps an equally important call by the treating doctor is to just stay with the current pharmacotherapy and focus on non-pharmacological means: engagement in case management, targeted psychological treatments and vocational rehabilitation as means of enhancing patient well-being. While it may seem a passive option, staying may often do less harm than aimless switching.

**Summary – when treatment fails**

- If the dose has been optimised, consider watchful waiting.
- Consider increasing the antipsychotic dose according to tolerability and plasma levels (little supporting evidence).
- If this fails, consider switching to olanzapine or risperidone (if not already used).
- If this fails, use clozapine (supporting evidence very strong).
- If clozapine fails, use time-limited augmentation strategies (supporting evidence variable).

**References**

27. Constantine RJ et al. The risks and benefits of switching patients with schizophrenia or schizoaffective disorder from two to one antipsychotic medication: a randomized controlled trial. Schizophr Res 2015; 166:194–200.
**Acutely disturbed or violent behaviour**

Acute behavioural disturbance can occur in the context of psychiatric illness, physical illness, substance abuse or personality disorder. Psychotic symptoms are common and the patient may be aggressive towards others secondary to persecutory delusions or auditory, visual or tactile hallucinations.

The clinical practice of rapid tranquillisation (RT) is used when appropriate psychological and behavioural approaches have failed to de-escalate acutely disturbed behaviour. It is, essentially, a treatment of last resort. Patients who require RT are often too disturbed to give informed consent and therefore participate in randomised controlled trials (RCTs), but with the use of a number of creative methodologies, the evidence base with respect to the efficacy and tolerability of pharmacological strategies has grown substantially in recent years. However, recommendations remain based partly on research data, partly on theoretical considerations and partly on clinical experience.

Several studies supporting the efficacy of oral SGAs have been published. The level of behavioural disturbance exhibited by the patients in these studies was moderate at best, and all subjects accepted oral treatment (this degree of compliance would be unusual in clinical practice). Note too that patients recruited to these studies received the SGA as antipsychotic monotherapy. The efficacy and safety of adding a second antipsychotic as ‘PRN’ has not been explicitly tested in formal RCTs.

A single-dose RCT showed sublingual asenapine to be more effective than placebo for acute agitation. The efficacy of inhaled loxapine (in behavioural disturbance that is moderate in severity) is also supported by RCTs and case series. Note that use of this preparation requires the co-operation of the patient, and that bronchospasm is an established but rare adverse effect.

Large, placebo-controlled RCTs support the efficacy of intramuscular (IM) preparations of olanzapine, ziprasidone and aripiprazole. When considered together, these trials suggested that IM olanzapine is more effective than IM haloperidol, which in turn is more effective than IM aripiprazole. Again, the level of behavioural disturbance in these studies was moderate at most.

A large observational study supported the efficacy and tolerability of IM olanzapine in clinical emergencies (where disturbance was severe). A study comparing IM haloperidol with a combination of IM midazolam and IM haloperidol found the combination more effective than haloperidol alone for controlling agitation in palliative care patients.

Several RCTs have now investigated the effectiveness of parenteral medication in ‘real-life’ acutely disturbed patients. Overall:

- Compared with intravenous (IV) midazolam alone, a combination of IV olanzapine or IV droperidol with IV midazolam was more rapidly effective and resulted in fewer subsequent doses of medication being required.
- IM midazolam 7.5–15 mg was more rapidly sedating than a combination of haloperidol 5–10 mg and promethazine 50 mg (TREC 1).
- Olanzapine 10 mg was as effective as a combination of haloperidol 10 mg and promethazine 25–50 mg in the short term, but the effect did not last as long (TREC 4).
- A combination of haloperidol 5–10 mg and promethazine 50 mg was more effective and better tolerated than haloperidol 5–10 mg alone (TREC 3).
A combination of haloperidol 10 mg and promethazine 25–50 mg was more effective than lorazepam 4 mg (TREC 2).18
- A combination of IV midazolam and IV droperidol was more rapidly sedating than either IV droperidol or IV olanzapine alone. Fewer patients in the midazolam–droperidol group required additional medication doses to achieve sedation.19
- IM olanzapine was more effective than IM aripiprazole in the treatment of agitation in schizophrenia in the short term (at 2 hours) but there was no significant difference between treatments at 24 hours.20
- In an open-label study the combination of IM haloperidol and IM lorazepam was found to be similar in efficacy to IM olanzapine.21
- IM droperidol and IM haloperidol were equally effective.22

Note that TREC 317 found IM haloperidol alone to be poorly tolerated; 6% of patients had an acute dystonic reaction. A Cochrane review concluded that haloperidol alone is effective in the management of acute behavioural disturbance but poorly tolerated, and that co-administration of promethazine but not lorazepam improves tolerability.23,24 However, NICE considers the evidence relating to the use of promethazine for this purpose to be inconclusive.25 When assessing haloperidol plus promethazine, Cochrane concluded that the combination is effective for use in patients who are aggressive due to psychosis and its use is based on good evidence. The resumption of aggression and need for further injections was more likely with olanzapine than with the haloperidol–promethazine combination. The authors also state that ‘haloperidol used on its own without something to offset its frequent and serious adverse effects does seem difficult to justify’.26 Cochrane recently concluded that available data for aripiprazole are rather poor. Available evidence suggests that aripiprazole is more effective than placebo and haloperidol, but not olanzapine. However, the authors advise caution when generalising these results to real-world practice.27 A systematic review and meta-analysis of IM olanzapine for agitation found IM olanzapine and IM haloperidol to be equally effective, but IM olanzapine was associated with a lower incidence of EPS.28 Cochrane suggests that droperidol is effective and may be used to control people with very disturbed and aggressive behaviours caused by psychosis.29 Having become available again, droperidol is seeing a resurgence in use in some countries (its initial withdrawal was voluntary, so reintroduction is not prohibited).

In a meta-analysis that examined the tolerability of IM antipsychotics when used for the treatment of agitation, the incidence of acute dystonia with haloperidol was reported to be 5%, with SGAs faring considerably better.30 Acute EPS may adversely affect longer-term compliance.31 In addition, the SPC for haloperidol requires a pre-treatment ECG32,33 and recommends that concomitant antipsychotics are not prescribed. The mean increase in QTc after 10 mg IM haloperidol has been administered has been reported to be 15 ms but the range is wide.34 Note that promethazine may inhibit the metabolism of haloperidol,35 a pharmacokinetic interaction that is potentially clinically significant given the potential of haloperidol to prolong QTc. While this is unlikely to be problematic if a single dose is administered, repeat dosing may confer risk.

Droperidol is also associated with QT changes (the reason for its withdrawal). In an observational study set in hospital emergency departments, of the 1009 patients administered parenteral droperidol only 13 patients (1.28%) had an abnormal QT recorded
after dose administration. However, in seven of these cases another contributory factor was identified. There were no cases of torsades de pointes.22

Intravenous treatment is now rarely used in RT but where benefits are thought to outweigh risks it may be considered as a last resort. A small study comparing high-dose IV haloperidol with IV diazepam found both drugs to be effective at 24 hours.36 Two large observational studies have examined the safety of IV olanzapine when used in the emergency department. The indications for its use varied, agitation being the most common. In one study,37 in the group treated for agitation (n=265), over a third of patients required an additional sedative dose after the initial IV olanzapine dose. Hypoxia was reported in 17.7% of cases and supplemental oxygen was used in 20.4% of cases. Six patients required intubation: in two this was likely to have been due to olanzapine treatment. In the other study,38 IV olanzapine (n=295) was compared with IM olanzapine (n=489). Additional doses were not required for 81% of patients in the IV group and 84% of patients in the IM group. Respiratory depression was more commonly observed in the group receiving IV olanzapine. Five patients in the IM group and two in the IV group required intubation.

In an acute psychiatric setting, high-dose sedation (defined as a dose of more than 10 mg of haloperidol, droperidol or midazolam) was not more effective than lower doses but was associated with more adverse effects (hypotension and oxygen desaturation).39 Consistent with this, a small RCT supports the efficacy of low-dose haloperidol, although both efficacy and tolerability were superior when midazolam was co-prescribed.40 These data support the use of standard doses in clinical emergencies.

A small observational study supports the effectiveness of buccal midazolam in a psychiatric intensive care unit (PICU) setting.41 Parenteral administration of midazolam, particularly in higher doses, may cause over-sedation accompanied by respiratory depression.42 Lorazepam IM is an established treatment and TREC 218 supports its efficacy, although combining all results from the TREC studies suggests midazolam 7.5–15 mg is probably more effective. A Cochrane review of benzodiazepines for psychosis-induced aggression and agitation concluded that most trials were too small to highlight differences in either positive or negative effects and that although adding a benzodiazepine to another drug may not be clearly advantageous it may lead to unnecessary adverse effects.43

With respect to those who are behaviourally disturbed secondary to acute intoxication with alcohol or illicit drugs, there are fewer data to guide practice. A large observational study of IV sedation in patients intoxicated with alcohol found that combination treatment (most commonly haloperidol 5 mg and lorazepam 2 mg) was more effective and reduced the need for subsequent sedation than either drug given alone.44 A case series (n=59) of patients who received modest doses of oral, IM or IV haloperidol to manage behavioural disturbance in the context of phencyclidine (PCP) consumption reported that haloperidol was effective and well tolerated (one case each of mild hypotension and mild hypoxia).45

Data are emerging from hospital emergency departments on the use of ketamine for agitation. IM ketamine was shown to be effective, with minimal adverse effects, in a small group of patients who failed to respond to IM droperidol.46 A small retrospective study found ketamine to be associated with few major adverse effects. However, many
patients in the study (62%) required additional sedation. An observational study comparing ketamine (IM or IV) first line with midazolam, lorazepam, haloperidol or a combination of haloperidol and benzodiazepine found that significantly more patients in the ketamine group were no longer agitated at 5, 10 and 15 minutes. Two patients receiving ketamine were intubated compared with one patient in the other group. In a prospective study comparing IM ketamine with IM haloperidol, mean time to adequate sedation was significantly shorter with IM ketamine. Complications, including intubation, vomiting, hypersalivation and laryngospasm, were higher in the ketamine group.

**Practical measures**

Plans for the management of individual patients should ideally be made in advance. The aim is to prevent disturbed behaviour and reduce risk of violence. Nursing interventions (de-escalation, time out, seclusion), increased nursing levels, transfer of the patient to a PICU and pharmacological management are options that may be employed. Care should be taken to avoid combinations and high cumulative doses of antipsychotic drugs. The monitoring of routine physical observations after RT is essential. Note that RT is often viewed as punitive by patients. There is little research into the patient experience of RT.

The aims of RT are three-fold:

- to reduce suffering for the patient – psychological or physical (through self-harm or accidents)
- to reduce risk of harm to others by maintaining a safe environment
- to do no harm (by prescribing safe regimes and monitoring physical health).

Note: Despite the need for rapid and effective treatment, concomitant use of two or more antipsychotics (antipsychotic polypharmacy) should be avoided on the basis of risk associated with QT prolongation (common to almost all antipsychotics). This is a particularly important consideration in RT where the patient’s physical state predisposes to cardiac arrhythmia.

**Zuclopenthixol acetate**

Zuclopenthixol acetate (ZA) is widely used in the UK and elsewhere and is best known by its trade name Acuphase. Zuclopenthixol itself is a thioxanthine dopamine antagonist and was first introduced in the early 1960s. Its elimination half-life is around 20 hours. IM injection of zuclopenthixol base results in rapid absorption and a duration of action of 12–24 hours. By slowing absorption after IM injection, the biological half-life (and so duration of action) becomes dependent on the rate of release from the IM reservoir. This can be achieved by esterification of the zuclopenthixol molecule, the rate of release being broadly in proportion to the length of the ester carbon chain. Thus, zuclopenthixol decanoate is slow to act but very long-acting as a result of retarded release after IM injection. ZA (with eight fewer carbon atoms) would be expected to provide relatively prompt release but with an intermediate duration of action. The intention of the
The use of ZA would obviate the need for repeated IM injections in disturbed patients.

An initial pharmacokinetic study of ZA included 19 patients ‘in whom calming effect by parenteral neuroleptic was considered necessary’. Zuclopenthixol was detectable in the plasma after 1–2 hours but did not reach peak concentrations until around 36 hours after dosing. At 72 hours, plasma levels were around a third of those at 36 hours. The clinical effect of ZA was not rapid – 10 of 17 patients exhibited minimal or no change in psychotic symptoms at 4 hours. Sedation was evident at 4 hours but it had effectively abated by 72 hours.

A follow-up study by the same research group examined more closely the clinical effects of ZA in 83 patients. The authors concluded that ZA produced ‘pronounced and rapid reduction in psychotic symptoms’. In fact, psychotic symptoms were first assessed only after 24 hours and so a claim of rapid effect is not reasonably supported. Sedative effects were measured after 2 hours, when a statistically significant effect was observed – at baseline mean sedation score was 0.0 (0 = no sign of sedation) and at 2 hours 0.6 (1 = slightly sedated). Maximum sedation was observed at 8 hours (mean score 2.2; 2 = moderately sedated). At 72 hours mean score was 1.1. Dystonia and rigidity were the most commonly reported adverse effects.

Two independently conducted open studies produced similar results – a slow onset of effect peaking at 24 hours and still being evident at 72 hours. The first UK study was reported in 1990. In the trial, a significant reduction in psychosis score was first evident at 8 hours and scores continued to fall until the last measurement at 72 hours. Of 25 patients assessed, only 4 showed signs of tranquillisation at 1 hour (19 at 2 hours and 22 at 24 hours).

A comparative trial of ZA examined its effects and those of IM/oral haloperidol and IM/oral zuclopenthixol base (in multiple doses over 6 days). The two non-ester, IM/oral preparations produced a greater degree of sedation at 2 hours than did ZA but the effect of ZA and zuclopenthixol was more sustained than with haloperidol over 144 hours (although patients received more zuclopenthixol doses). No clear differences between treatments were detected with the exception of the slow onset of effect of ZA. The number of doses given varied substantially: ZA 1–4, haloperidol 1–26 and zuclopenthixol 1–22. This is the key (and perhaps unique) advantage of ZA – it reduces the need for repeat doses in acute psychosis. Indeed, this was the principal finding of the first double-blind study of ZA. Participants were given either ZA or haloperidol IM and assessed over 3 days. Changes in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scores were near identical on each daily assessment. However, only 1 of 23 ZA patients required a second injection whereas 7 of 21 haloperidol patients required a repeat dose. Speed of onset was not examined. Similar findings were reported by Thai researchers comparing the same treatments and in three other studies of moderate size (n = 44, n = 40, n = 50). In each study, the timing of assessments was such that time to onset of effect could not be determined.

A Cochrane review included all of the above comparative studies as well as three further studies for which the authors were unable to obtain full details. The Cochrane authors concluded that all studies were methodologically flawed and poorly reported and that ZA did not appear to have a ‘rapid onset of action’. They noted that...
ZA was probably no less effective than other treatments and that its use might ‘result in less numerous coercive injections’.

Overall, the utility of ZA in RT is limited by a somewhat delayed onset of both sedative and antipsychotic actions. Sedation may be apparent in a minority of patients after 2–4 hours, but antipsychotic action is evident only after 8 hours. If ZA is given to a restrained patient, their behaviour on release from restraint is likely to be unchanged and will remain as such for several hours. ZA has a role in reducing the number of restraints for IM injection but it has no role in RT.

Guidelines for the use of ZA are summarised in Box 1.1.

**Box 1.1 Guidelines for the use of zuclopenthixol acetate (Acuphase)**

**Zuclopenthixol acetate (ZA) is not a rapidly tranquillising agent. It should be used only after an acutely psychotic patient has required repeated injections of short-acting antipsychotic drugs such as haloperidol or olanzapine, or sedative drugs such as lorazepam. It is perhaps best reserved for those few patients who have a prior history of good response to Acuphase.**

ZA should be given only when enough time has elapsed to assess the full response to previously injected drugs: allow 15 minutes after IV injections, 60 minutes after IM.

ZA should **never** be administered:

- in an attempt to ‘hasten’ the antipsychotic effect of other antipsychotic therapy
- for rapid tranquillisation (onset of effect is too slow)
- at the same time as other parenteral antipsychotics or benzodiazepines (may lead to over-sedation which is difficult to reverse)
- as a ‘test dose’ for zuclopenthixol decanoate depot
- to a patient who is physically resistant (risk of intravasation and oil embolus).

ZA should **never** be used for, or in, the following:

- patients who accept oral medication
- patients who are neuroleptic-naïve
- patients who are sensitive to EPS
- patients who are unconscious
- patients who are pregnant
- those with hepatic or renal impairment
- those with cardiac disease.

ZA was probably no less effective than other treatments and that its use might ‘result in less numerous coercive injections’.

Summary – rapid tranquillisation

A summary of rapid tranquillisation is provided in Box 1.2.

Rapid tranquillisation – physical monitoring

A summary of physical monitoring in RT is provided in Box 1.3.

Remedial measures in rapid tranquillisation

Remedial measures in RT are summarised in Table 1.9 and the use of flumazenil in Box 1.4.
In an emergency situation
Assess to see if there may be a medical cause. Optimise regular prescription. The aim of pharmacological treatment is to calm the patient but not to oversedate. Note: lower doses should be used for children, adolescents and older adults. Patients’ levels of consciousness and physical health should be monitored after administration of parenteral medication (see Box 1.3).

Step intervention
1. De-escalation, time out, placement, etc., as appropriate.

2. Offer oral treatment

If patient is prescribed a regular antipsychotic:
- Lorazepam 1–2 mg
- Promethazine 25–50 mg

Monotherapy with buccal midazolam may avoid the need for IM treatment. Dose: 10 mg. Note that this preparation is unlicensed.

Repeat after 45–60 minutes, if necessary. Consider combining sedative and antipsychotic treatment. Go to step 3 if two doses fail or sooner if the patient is placing themselves or others at significant risk.

3. Consider IM treatment

- Lorazepam 2 mg Have flumazenil to hand in case of benzodiazepine-induced respiratory depression.
- Promethazine 50 mg IM promethazine is a useful option in a benzodiazepine-tolerant patient.
- Olanzapine 10 mg IM olanzapine should not be combined with an IM benzodiazepine, particularly if alcohol has been consumed.
- Aripiprazole 9.75 mg Less hypotension than olanzapine, but possibly less effective.
- Haloperidol 5 mg Haloperidol should be the last drug considered. The incidence of acute dystonia is high; combine with IM promethazine and ensure IM procyclidine is available. The SPC recommends a pre-treatment ECG. Recommended by NICE.

Repeat after 30–60 minutes if insufficient effect. Combinations of haloperidol and lorazepam or haloperidol and promethazine may be considered if single-drug treatment fails. Drugs must not be mixed in the same syringe. IM olanzapine must never be combined with IM benzodiazepine.

4. Consider IV treatment

- Diazepam 10 mg over at least 2 minutes
- Repeat after 5–10 minutes if insufficient effect (up to 3 times)
- Have flumazenil to hand.

5. Seek expert advice from the consultant or senior clinical pharmacist on call.

Carefully check administration instructions, which differ between manufacturers. With respect to Ativan (the most commonly used preparation), mix lorazepam 1:1 with water for injections before injecting. Some centres use 2–4 mg. An alternative is midazolam 7.5–15 mg. The risk of respiratory depression is dose-related with both but generally greater with midazolam.
b Caution in the very young and elderly and those with pre-existing brain damage or impulse control problems, as disinhibition reactions are more likely.69

c Promethazine has a slow onset of action but is often an effective sedative. Dilution is not required before IM injection. May be repeated up to a maximum of 100 mg/day. Wait 1–2 hours after injection to assess response. Note that promethazine alone has been reported, albeit very rarely, to cause neuroleptic malignant syndrome70 although it is an extremely weak dopamine antagonist. Note the potential pharmacokinetic interaction between promethazine and haloperidol (reduced metabolism of haloperidol) which may confer risk if repeated doses of both are administered.

d Recommended by NICE only for moderate behavioural disturbance, but data from a large observational study also support efficacy in clinical emergencies.

e Use Diazemuls to avoid injection site reactions. IV therapy may be used instead of IM when a very rapid effect is required. IV therapy also ensures near immediate delivery of the drug to its site of action and effectively avoids the danger of inadvertent accumulation of slowly absorbed IM doses. Note also that IV doses can be repeated after only 5–10 minutes if no effect is observed.

f Options at this point are limited. IM amylobarbitone and paraldehyde have been used in the past but are used now only extremely rarely and are generally not readily available. IV olanzapine, IV/IM droperidol and IV haloperidol are possible but serious adverse effects are fairly common. Ketamine is an option in medical units. Electroconvulsive therapy (ECT) is probably a better option. Behavioural disturbance secondary to the use of illicit drugs can be very difficult to manage. Time and supportive care may be safer than administering more sedative medication.

### Box 1.2 (Continued)

Temperature

Pulse

Blood pressure

Respiratory rate.

Every 15 minutes for 1 hour, and then hourly until the patient is ambulatory. Patients who refuse to have their vital signs monitored or who remain too behaviourally disturbed to be approached should be observed for signs/symptoms of pyrexia, hypoxia, hypotension, oversedation and general physical well-being.

If the patient is asleep or unconscious, the continuous use of pulse oximetry to measure oxygen saturation is desirable. A nurse should remain with the patient until ambulatory.

ECG and haematological monitoring are also strongly recommended when parenteral antipsychotics are given, especially when higher doses are used.71,72 Hypokalaemia, stress and agitation place the patient at risk of cardiac arrhythmia73 (see section on ‘QT prolongation’ in this chapter). ECG monitoring is formally recommended for all patients who receive haloperidol.
### References


50. Huf G et al. Physical restraints versus seclusion room for management of people with acute agitation or agitation due to psychotic illness (TREC-SAVE); a randomized trial. Psychol Med 2012; 42:2265–2273.
Further reading

Antipsychotic depots/long-acting injections (LAIs)

Antipsychotic depots/long-acting injections (LAIs) are recommended where a patient has expressed a preference for such a formulation because of its convenience or where avoidance of covert non-adherence is a clinical priority. LAIs do not assure compliance but they do assure awareness of compliance. With the advent of better tolerated SGA LAIs, these formulations are increasingly seen as treatments of choice by both patients and health professionals. Another advantage for LAIs over oral medication is that they provide the opportunity for regular scrutiny of a patient's mental state and adverse effects by the health-care professional administering the injection. It has been estimated that, in the UK, between a quarter and a third of people with schizophrenia are prescribed an LAI, depending on the clinical setting. This prevalence varies from country to country. Some years ago, approximately half were also prescribed an oral antipsychotic drug, one possible reason being to allow for more rapid dose titration, but the combination of an oral and LAI antipsychotic preparation often resulted in high-dose prescribing which is associated with an increased adverse-effect burden and has implications for physical health monitoring. It goes without saying that monotherapy with an LAI is likely to be optimal.

Advice on prescribing depots/LAIs

- **For FGAs, give a test dose.** Because of its long half-life, any adverse effects that result from the administration of an LAI are likely to be long-lived. Therefore, LAIs should be avoided in patients with a history of serious adverse effects that would warrant immediate discontinuation of the medication, such as neuroleptic malignant syndrome (NMS). For FGAs, a test dose consisting of a small dose of active drug in a small volume of oil serves a dual purpose: it is a test both of the patient’s sensitivity to EPS and of any sensitivity to the base oil. For SGAs, test doses may not be required (less propensity to cause EPS and aqueous base not known to be allergic) although they could be considered appropriate where a patient is suspected of being non-adherent to oral antipsychotic medication and the LAI will be the first exposure to guaranteed antipsychotic medication delivery. For both types of LAI prior treatment with the equivalent oral formulation is preferred, to assess efficacy and tolerability.

- **Begin with the lowest therapeutic dose.** There are few data showing clear dose–response effects for LAIs. There is some information indicating that low doses (within the licensed range) are at least as effective as higher ones. Low doses are likely to be better. Perhaps the key problem with FGA LAIs is that, unlike with SGAs, the optimal dose range is not known.

- **Administer at the longest possible licensed interval.** All LAIs can be safely administered at their licensed dosing intervals, bearing in mind the maximum recommended single dose. There is no evidence to suggest that shortening the dose interval improves efficacy. Moreover, the injection site can be a cause of discomfort and pain, so less frequent administration is desirable. Although some patients are reported to deteriorate in the days before their next LAI is due, plasma levels may continue to fall, albeit slowly, for some hours (or even days with some preparations) after each injection (see Figure 1.11). Thus, patients may conceivably be most at risk of deterioration.
immediately after an LAI. Moreover, in trials, relapse seems only to occur 3–6 months after withdrawing LAI therapy, roughly the time required to clear steady-state drug levels from the blood.

- **Adjust doses only after an adequate period of assessment.** Attainment of peak plasma levels, therapeutic effect and steady-state plasma levels are all delayed with LAIs. Doses may be **reduced** if adverse effects occur, but should only be increased after careful assessment over at least 1 month, and preferably longer. The use of adjunctive oral medication to assess dosage requirements of LAIs may be helpful, but is complicated by the slow emergence of antipsychotic effects. Note that at the start of therapy, plasma levels of antipsychotic released from a LAI increase over several weeks to months without increasing the given dose. (This is due to accumulation: steady state is only achieved after at least 6–8 weeks.) Dose increases during this time to steady-state plasma levels are thus illogical and impossible to evaluate properly. The monitoring and recording of therapeutic efficacy, adverse effects and any impact on physical health during therapy are recommended.

- **LAI are not recommended for those who are antipsychotic-naïve.** Tolerance to some LAIs can be established by using the oral form of the same drug for 2 weeks before starting the LAI. Good examples here are haloperidol, aripiprazole and paliperidone (using oral risperidone).

**Differences between LAIs**

There are few differences between individual FGA LAIs. Pipotiazine (now withdrawn in most countries) may be associated with relatively less frequent EPS, and fluphenazine (which also has limited availability) with relatively more EPS but perhaps less weight gain. Cochrane reviews have been completed for pipotiazine, flupentixol, zuclopenthixol, haloperidol and fluphenazine. With the exception of zuclopenthixol, these preparations are equally effective with respect to each other. Standard doses are said to be as effective as high doses for flupentixol.

Two differences that possibly do exist between FGA LAIs are:

- Zuclopenthixol may be more effective in preventing relapses than others, although this may be at the expense of an increased burden of adverse effects.
- Flupentixol decanoate can be given in very much higher ‘neuroleptic equivalent’ doses than the other LAI preparations and still remain ‘within licensed dosing limits’. It is doubtful that this confers any real therapeutic advantage.

Aripiprazole, paliperidone, risperidone and olanzapine LAIs have a relatively lower propensity for EPS compared with FGA LAIs. At least some of this difference is a result of higher equivalent doses being used with FGAs but even when low doses are used there is still an advantage for SGAs. Risperidone, however, increases prolactin, and dosage adjustment can be complex because of its pharmacokinetic profile. Olanzapine can cause significant weight gain and is associated with inadvertent intravascular injection or post-injection syndrome. Unlike risperidone LAI, it is effective within a few days. Paliperidone 1-monthly is also rapidly released and effective within a few days, as is aripiprazole LAI.
<table>
<thead>
<tr>
<th>Drug</th>
<th>UK trade name</th>
<th>Licensed injection site</th>
<th>Test dose (mg)</th>
<th>Dose range (mg/week)</th>
<th>Dosing interval (weeks)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify Maintena</td>
<td>Buttock</td>
<td>Not required</td>
<td>300–400 mg monthly</td>
<td>Monthly</td>
<td>Does not increase prolactin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral loading required</td>
</tr>
<tr>
<td>Flupentixol decanoate</td>
<td>Depixol</td>
<td>Buttock or thigh</td>
<td>20</td>
<td>50 mg every 4 weeks to 400 mg a week</td>
<td>2–4</td>
<td>Maximum licensed dose is high relative to other LAIs</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Modecate</td>
<td>Gluteal region</td>
<td>12.5</td>
<td>12.5 mg every 2 weeks to 100 mg every 2 weeks</td>
<td>2–5</td>
<td>High EPS</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Haldol</td>
<td>Gluteal region</td>
<td>25*</td>
<td>50–300 mg every 4 weeks</td>
<td>4</td>
<td>High EPS</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>ZypAdhera</td>
<td>Gluteal</td>
<td>Not required</td>
<td>150 mg every 4 weeks to 300 mg every 2 weeks</td>
<td>2–4</td>
<td>Risk of post-injection syndrome</td>
</tr>
<tr>
<td>Paliperidone palmitate (monthly)</td>
<td>Xepion</td>
<td>Deltoid or gluteal</td>
<td>Not required</td>
<td>50–150 mg monthly</td>
<td>Monthly</td>
<td>Loading dose required at treatment initiation</td>
</tr>
<tr>
<td>Paliperidone palmitate (3-monthly)</td>
<td>Trevicta</td>
<td>Deltoid or gluteal</td>
<td>Not required</td>
<td>175–525 mg every 3 months</td>
<td>3 months</td>
<td>? Lower incidence of EPS (relative to other FGAs)</td>
</tr>
<tr>
<td>Pipotiazine palmitate</td>
<td>Piportil</td>
<td>Gluteal region</td>
<td>25</td>
<td>50–200 mg every 4 weeks</td>
<td>4</td>
<td>? Slightly better efficacy than FGA LAIs</td>
</tr>
<tr>
<td>Risperidone microspheres</td>
<td>Risperidal Consta</td>
<td>Deltoid or gluteal</td>
<td>Not required</td>
<td>25–50 mg every 2 weeks</td>
<td>2</td>
<td>Drug release delayed for 2–3 weeks – oral therapy required</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Clopixol</td>
<td>Buttock or thigh</td>
<td>100</td>
<td>200 mg every 3 weeks to 600 mg a week</td>
<td>2–4</td>
<td>? Slightly better efficacy than FGA LAIs</td>
</tr>
</tbody>
</table>

Notes:
- The doses in the table are for adults. Check formal labelling for appropriate doses in the elderly.
- After a test dose, wait 4–10 days then titrate to maintenance dose according to response (see product information for individual drugs).
- Avoid using shorter dose intervals than those recommended except in exceptional circumstances (e.g. long interval necessitates high-volume [>3–4 mL] injection). Maximum licensed single dose overrides longer intervals and lower volumes. For example, zuclopenthixol 500 mg every week is licensed whereas 1000 mg every 2 weeks is not (more than the licensed maximum of 600 mg is administered). Always check official manufacturer’s information.
- Test dose not stated by manufacturer.
- Tolerability and response to the oral preparation should be established before administering the LAI. With respect to paliperidone LAI, oral risperidone can be used for this purpose.
- May not be started until the completion of 4 months’ treatment with monthly LAI.

EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; LAI, long-acting injection.
The use of LAIs does not guarantee good treatment adherence, and there is a lack of robust and consistent RCT evidence that LAIs offer better efficacy or tolerability than oral preparations. Nevertheless, non-randomised, observational, ‘real-world’ data have suggested an overall better global outcome with LAIs compared with oral antipsychotics, with a reduced risk of relapse and rehospitalisation. It has been argued that adherence to oral antipsychotic medication decreases over time and that relapse rates in patients prescribed LAIs decrease in comparison with oral antipsychotics only in the longer term. That is, LAIs reveal advantages over oral treatment only after several years. It is also probably true that patients volunteering for RCTs do not properly represent those treated in everyday practice.

Table 1.10 summarises suggested doses and frequencies for administration of antipsychotic LAIs.

## Intramuscular anticholinergic medication and depots/LAIs

Antipsychotic LAIs do not produce acute movement disorders at the time of administration: this may take hours to days. The administration of IM procyclidine routinely with each dose is illogical as the effects of the anticholinergic drug will have worn off before plasma antipsychotic levels rise or peak.

### References


Further reading
**Depot/LAI antipsychotics – pharmacokinetics**

Table 1.11 summarises the pharmacokinetics of depot antipsychotics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>UK trade name</th>
<th>Time to peak (days)*</th>
<th>Plasma half-life (days)</th>
<th>Time to steady state (weeks)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify Maintena</td>
<td>7</td>
<td>30–46</td>
<td>~20</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>Aristada (in US)</td>
<td>44–50</td>
<td>~30</td>
<td>~16</td>
</tr>
<tr>
<td>Flupentixol decanoate</td>
<td>Depirol</td>
<td>7</td>
<td>8–17</td>
<td>~9</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Modecate</td>
<td>8–12‡</td>
<td>10</td>
<td>~8</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Haldol</td>
<td>7</td>
<td>21</td>
<td>~14</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>ZypAdhera</td>
<td>2–3</td>
<td>30</td>
<td>~12</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Xepion</td>
<td>13</td>
<td>29–45</td>
<td>~20</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Trecvicta</td>
<td>25</td>
<td>~75</td>
<td>~52</td>
</tr>
<tr>
<td>Pipotiazine palmitate</td>
<td>Piportil</td>
<td>7–14</td>
<td>15</td>
<td>~9</td>
</tr>
<tr>
<td>Risperidone microspheres</td>
<td>Risperdal Consta</td>
<td>~30</td>
<td>4</td>
<td>~8</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Clopixol</td>
<td>4–7</td>
<td>19</td>
<td>~12</td>
</tr>
</tbody>
</table>

* Time to peak is not the same as time to reach therapeutic plasma concentration but both are dependent on dose. For large (loading) doses, therapeutic activity is often seen before peak levels are attained. For low (test) doses, the initial peak level may be subtherapeutic.

† Attainment of steady state (SS) follows logarithmic, not linear characteristics: around 90% of SS levels are achieved in three half-lives. Time to attain steady state is independent of dose and dosing frequency (i.e. you cannot hurry it up by giving more, more often). Loading doses can be used to produce prompt therapeutic plasma levels but time to SS remains the same.

‡ Some estimates suggest peak concentrations after only a few hours. It is likely that fluphenazine decanoate produces two peaks – one on the day of injection and a second slightly higher peak a week or so later.

**References**

CHAPTER 1

Management of patients on long-term depots/LAIs

All patients receiving long-term treatment with antipsychotic medication should be seen by the psychiatrist responsible for them at least once a year (ideally more frequently) in order to review their progress and treatment. A systematic assessment of tolerability and safety should constitute part of this review. The assessment of adverse effects should include EPS (principally parkinsonism, akathisia and TD). TD can be assessed by recording the score on the Abnormal Involuntary Movement Scale (AIMS). Some study findings have suggested that depot/LAI antipsychotic medication is more likely to cause TD but this remains uncertain and not all studies confirm these observations.

For most people with multi-episode schizophrenia, continuing antipsychotic treatment, even lifelong, may be necessary. However, with long-term LAI treatment, dose reduction may be considered in stable patients. There is some evidence to suggest that FGA depots are sometimes prescribed in excessive doses: haloperidol decanoate is optimally effective at 75 mg every 4 weeks, paliperidone palmitate at 50 mg a month. Further to this, dopamine occupancy required for relapse prevention may be lower than that for acute treatment – continuous occupancy above 65% may not be necessary.

Long-term follow-up is required when antipsychotic dosage is decreased as such reduction, at least to very low doses, is associated with a greater risk of treatment failure, hospitalisation and relapse, which may only become evident over the longer term. One study comparing fluphenazine decanoate at 5 mg or 25 mg every 2 weeks found no difference in outcome at 1 year but a substantial disadvantage for the lower dose at 2 years (69% vs 36% relapse). In the same study, the facility to increase dose when symptoms emerged removed the advantage for the higher dose. Interestingly, in another trial which used low-dose (5 mg every 2 weeks) fluphenazine decanoate, this dose was substantially inferior to standard doses (56% vs 7% relapse at 1 year, respectively). The lowest dose at which fluphenazine decanoate can be shown to be effective is 25 mg every 6 weeks.

There is no simple formula for deciding when or whether to reduce the dose of maintenance antipsychotic treatment; therefore, a risk–benefit analysis must be done for every patient. Many patients, it should be noted, prefer to receive depots/LAIs. When considering dose reduction, the following prompts may be helpful:

- Is the patient symptom-free and, if so, for how long? Long-standing, non-distressing symptoms which have not previously been responsive to medication may be excluded.
- What is the severity of the adverse effects (EPS including TD, metabolic adverse effects including obesity, etc.)? When patients report no or minimal adverse effects it is usually sensible to continue treatment and monitor closely for signs of TD.
- What is the previous pattern of illness? Consider the speed of onset, duration and severity of past relapses and any dangers or risks posed to self or others.
- Has dosage reduction been attempted before? If so, what was the outcome?
- What are the patient’s current social circumstances? Is it a period of relative stability, or are stressful life events anticipated?
- What is the potential social cost of relapse (e.g. is the patient the sole breadwinner for a family)?
- Is the patient able to monitor his/her own symptoms? If so, will he/she seek help?
If, after consideration of the above, the decision is taken to reduce medication dose, the patient’s family should be involved and a clear explanation given of what should be done if symptoms return or worsen. It would then be reasonable to proceed in the following manner:

- If it has not already been done, any co-prescribed oral antipsychotic medication should be discontinued.
- Where the product labelling allows, the interval between injections should be increased to up to 4 weeks before decreasing the dose given each time.
- The dose should be reduced by no more than a third at any one time. Note: special considerations apply to risperidone.
- Decrements should, if possible, be made no more frequently than every 3 months, preferably every 6 months. The slower the rate of withdrawal, the longer the time to relapse.13
- Discontinuation should not be seen as the ultimate aim of the above process although it sometimes results. NICE14 (2014) now suggests that intermittent treatment (symptom-triggered) is preferable to no treatment.

If the patient becomes symptomatic, this should be seen not as a failure, but rather as an important step in determining the minimum effective dose that the patient requires.

For more discussion see section on ‘Antipsychotic long-acting injections’ in this chapter.

References

Aripiprazole long-acting injection

Aripiprazole lacks the prolactin-related and metabolic adverse effects of other SGA LAIs and so is a useful alternative to them. Placebo-controlled studies show a good acute and longer-term effect\(^1\) but aripiprazole LAI has not been compared with other depots. For most patients, a suitable dosing regimen is oral aripiprazole 10 mg/day for 14 days (to establish tolerability and response) then 400 mg aripiprazole LAI once monthly. Oral aripiprazole should be continued for 14 days after the first injection. In such a regimen, peak plasma levels are seen 7 days after injection and the lowest trough at 4 weeks.\(^2\) At steady state, peak plasma levels are up to 50% higher than the first dose peak and trough plasma levels only slightly below the first dose peak.\(^2\) Dose adjustments should take this into account. A lower dose of 300 mg a month can be used in those not tolerating 400 mg. A dose of 200 mg a month may only be used for those patients receiving particular enzyme-inhibiting drugs. The incidence of akathisia, insomnia, nausea and restlessness is similar to that seen with oral aripiprazole.\(^3,4\)

There are no formal recommendations for switching to aripiprazole but Table 1.12 presents recommendations based on our interpretation of available pharmacokinetic data.

A new long-acting formulation of aripiprazole has been approved by the FDA for the treatment of schizophrenia. Aripiprazole lauroxil is a pro-drug formulated to be administered at monthly, 6-weekly or 2-monthly intervals by IM injection into the deltoid or gluteal muscle depending on the dose.\(^5,6\) It is available as four strengths: 441 mg, 662 mg, 882 mg and 1064 mg doses to deliver 300 mg, 450 mg, 600 mg and 724 mg of aripiprazole respectively (see section on ‘Depot antipsychotics – pharmacokinetics’ in this chapter).

### Table 1.12 Switching to aripiprazole LAI

<table>
<thead>
<tr>
<th>Switching from</th>
<th>Aripiprazole LAI regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antipsychotics</td>
<td>Cross taper antipsychotic with oral aripiprazole* over 2 weeks. Start LAI, continue aripiprazole oral for 2 weeks then stop</td>
</tr>
<tr>
<td>Depot antipsychotics (not risperidone LAI)</td>
<td>Start oral aripiprazole* on day last depot injection was due. Start aripiprazole LAI after 2 weeks then stop oral aripiprazole 2 weeks later</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>Start oral aripiprazole* 4–6 weeks after the last risperidone injection. Start aripiprazole LAI 2 weeks later; discontinue oral aripiprazole 2 weeks after that</td>
</tr>
</tbody>
</table>

*If prior response and tolerability to aripiprazole is known, oral aripiprazole may not be strictly required but attainment of effective aripiprazole plasma levels is dependent upon 4 weeks of oral supplementation so this is recommended in every situation.

LAI, long-acting injection.

### References

Olanzapine long-acting injection

Like all esters, olanzapine pamoate (embonate, in some countries) is very poorly water soluble. An aqueous suspension of olanzapine pamoate, when injected intramuscularly, affords both prompt and sustained release of olanzapine. Peak plasma levels are seen within a week of injection (in most people within 2–4 days) and efficacy can be demonstrated after only 3 days. Only gluteal injection is licensed; deltoid injection is less effective. Olanzapine LAI is effective when given every 4 weeks, with 2-weekly administration only required when the highest dose is prescribed. Half-life is around 30 days. It has not been compared with other LAIs in RCTs but naturalistic data suggest similar effectiveness to paliperidone LAI. Loading doses are recommended in some dose regimens (see Table 1.13). Formal labelling/SPC suggests that patients be given oral olanzapine to assess response and tolerability. This rarely happens in practice but is strongly recommended. Oral supplementation after the first depot injection is not necessary.

Switching

Direct switching to olanzapine LAI, ideally following an oral trial, is usually possible. So, when switching from another LAI (but not risperidone), olanzapine oral or LAI can be started on the day the last LAI was due. Likewise for switching from oral treatment – a direct switch is possible but prior antipsychotics are probably best reduced slowly after starting olanzapine (either oral or LAI). When switching from risperidone LAI, olanzapine should be started, we suggest, 2 weeks after the last injection was due (peak risperidone plasma levels can be expected 4–6 weeks after the last injection).

Post-injection syndrome

Post-injection syndrome occurs when olanzapine pamoate is inadvertently exposed to high blood volumes (probably via accidental intravasation). Olanzapine plasma levels may reach 600 µg/L and delirium and somnolence result. The incidence of post-injection syndrome is less than 0.1% of injections; almost all reactions (86%) occur within 1 hour of injection. A more recent study suggested an incidence of 0.044% of injections (less than 1 in 2000) with 91% of reactions being apparent within 1 hour. In most countries, olanzapine LAI may only be given in health-care facilities under

Table 1.13 Olanzapine LAI: dosing schedules

<table>
<thead>
<tr>
<th>Oral olanzapine equivalent</th>
<th>Loading dose</th>
<th>Maintenance dose (given 8 weeks after the first dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg/day</td>
<td>210 mg every 2 weeks</td>
<td>300 mg every 2 weeks (or 150 mg every 2 weeks)</td>
</tr>
<tr>
<td></td>
<td>405 mg every 4 weeks</td>
<td></td>
</tr>
<tr>
<td>15mg/day</td>
<td>300 mg every 2 weeks</td>
<td>405 mg every 2 weeks (or 210 mg every 2 weeks)</td>
</tr>
<tr>
<td></td>
<td>None – give 300 mg every 2 weeks</td>
<td>300 mg every 2 weeks</td>
</tr>
</tbody>
</table>
supervision and patients need to be kept under observation for 3 hours after the injection is given. Given the tiny number of cases appearing only after 2 hours, a good case can be made for shortening the observation period to 2 hours (as is the situation in New Zealand\textsuperscript{10} and some other countries).

In the EU, the exact wording of the SPC\textsuperscript{11} is as follows:

\textit{After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.}

\textit{Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.}

\textit{For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery.}

This monitoring requirement undoubtedly has adversely affected the popularity of olanzapine LAI. No patient or medical factor has been identified that might predict post-injection syndrome\textsuperscript{7} except that those experiencing the syndrome are more likely to have previously had an injection-site-related adverse effect.\textsuperscript{12} Male gender and higher doses have more recently been suggested to be risk factors for post-injection syndrome (the study examined 46 events occurring in 103,505 injections).\textsuperscript{9}

\textbf{References}

Paliperidone palmitate long-acting injection

Paliperidone is the major active metabolite of risperidone: 9-hydroxyrisperidone.

Paliperidone LAI 1-monthly

Following an IM injection, active paliperidone plasma levels are seen within a few days, therefore co-administration of oral paliperidone or risperidone during initiation is not required.\(^1\) Dosing consists of two initiation doses (deltoid) followed by monthly maintenance doses (deltoid or gluteal) (Table 1.14). Following administration of a single IM dose to the deltoid muscle, on average 28% higher peak concentration is observed compared with IM injection to the gluteal muscle.\(^1\) Thus the two deltoid muscle injections on days 1 and 8 help to quickly attain therapeutic drug concentrations.

Paliperidone LAI has been compared with haloperidol depot given in a loading dose schedule matching that of paliperidone.\(^2\) The two formulations were equally effective in preventing relapse but paliperidone increased prolactin to a greater extent and caused more weight gain. Haloperidol caused more akathisia and more acute movement disorder, and there was a trend for a higher incidence of TD. The average dose of haloperidol was around 75 mg a month, a dose rarely used in practice.

The second initiation dose may be given 4 days before or after day 8 (after the first initiation dose on day 1).\(^3\) Similarly, the manufacturer recommends that patients may be given maintenance doses up to 7 days before or after the monthly time point.\(^3\) This flexibility should help minimise the number of missed doses. See manufacturer’s information for full recommendations around missed doses.\(^3\)

Points to note:

- No test dose is required for paliperidone palmitate (but patients should ideally be currently stabilised on or have previously responded to oral paliperidone or risperidone).
- The median time to maximum plasma concentrations is 13 days.\(^3\)

The approximate dose equivalents of different formulations of risperidone and paliperidone are shown in Table 1.15. Switching to paliperidone palmitate is shown in Table 1.16.

<table>
<thead>
<tr>
<th>Table 1.14 Paliperidone dose and administration information(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Day 8 (±4 days)</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td>Every month (±7 days) thereafter</td>
</tr>
</tbody>
</table>

* The maintenance dose is perhaps best judged by consideration of what might be a suitable dose of oral risperidone and then giving paliperidone palmitate in an equivalent dose (see Table 1.15).
IM, intramuscularly.
### Table 1.15 Approximate dose equivalence\(^1,3\)

<table>
<thead>
<tr>
<th>Risperidone oral (mg/day) (bioavailability = 70%)(^4)</th>
<th>Paliperidone oral (mg/day) (bioavailability = 28%)(^5)</th>
<th>Risperidone LAI (Consta) (mg/2 weeks)</th>
<th>Paliperidone palmitate (mg/monthly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>37.5</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>–</td>
<td>150</td>
</tr>
</tbody>
</table>

### Table 1.16 Switching to paliperidone palmitate 1-monthly LAI

<table>
<thead>
<tr>
<th>Switching from</th>
<th>Recommended method of switching</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>Give the two initiation doses: 150 mg IM deltoid on day 1 and 100 mg IM deltoid on day 8 Maintenance dose starts 1 month later</td>
<td>In general the lowest most effective maintenance dose should be used The manufacturer recommends a dose of 75 mg monthly for the general adult population.(^1) This is approximately equivalent to 3 mg/day oral risperidone (see Table 1.15). In practice the modal dose is 100 mg/month(^6) Maintenance dose adjustments should be made monthly. However, the full effect of the dose adjustment may not be apparent for several months(^3)</td>
</tr>
<tr>
<td>Oral paliperidone/riperidone</td>
<td>Give the two initiation doses followed by the maintenance dose (see Table 1.15 and prescribe equivalent dose)</td>
<td>Oral paliperidone/risperidone supplementation during initiation is not necessary</td>
</tr>
<tr>
<td>Oral antipsychotics</td>
<td>Reduce the dose of the oral antipsychotic over 1–2 weeks following the first injection of paliperidone. Give the two initiation doses followed by the maintenance dose</td>
<td></td>
</tr>
<tr>
<td>Depot antipsychotic</td>
<td>Start paliperidone (at the maintenance dose) when the next injection is due N.B. No initiation doses are required</td>
<td>Doses of paliperidone palmitate IM may be difficult to predict. The manufacturer recommends a dose of 75 mg monthly for the general adult population. If switching from risperidone LAI see Table 1.15 and prescribe equivalent dose Maintenance dose adjustments should be made monthly. However, the full effect of the dose adjustment may not be apparent for several months(^3)</td>
</tr>
<tr>
<td>Antipsychotic polypharmacy with depot</td>
<td>Start paliperidone (at the maintenance dose) when the next injection is due N.B. No initiation doses are required Reduce the dose of the oral antipsychotic over 1–2 weeks following the first injection of paliperidone</td>
<td>Aim to treat the patient with paliperidone palmitate IM as the sole antipsychotic The maintenance dose should be governed as far as possible by the total dose of oral and injectable antipsychotic (see Table 1.15)</td>
</tr>
</tbody>
</table>
Paliperidone LAI 3-monthly

Paliperidone LAI 3-monthly is indicated for patients who are clinically stable on paliperidone LAI 1-monthly (preferably for 4 months or more) and do not require dose adjustment.7

Paliperidone LAI 3-monthly is generally well tolerated, with a tolerability profile similar to the 1-monthly preparation,8,9 and is non-inferior to paliperidone 1-monthly in terms of relapse rate.8

When initiating paliperidone LAI 3-monthly, give the first dose in place of the next scheduled dose of paliperidone LAI 1-monthly. The dose of paliperidone LAI 3-monthly should be based on the previous paliperidone LAI 1-monthly dose, see Table 1.17.

<table>
<thead>
<tr>
<th>Dose of paliperidone LAI 1-monthly</th>
<th>Dose of paliperidone LAI 3-monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>175 mg</td>
</tr>
<tr>
<td>75 mg</td>
<td>263 mg</td>
</tr>
<tr>
<td>100 mg</td>
<td>350 mg</td>
</tr>
<tr>
<td>150 mg</td>
<td>525 mg</td>
</tr>
</tbody>
</table>

References

Risperidone long-acting injection

Risperidone was the first ‘atypical’ drug to be made available as a depot, or LAI, formulation. Doses of 25–50 mg every 2 weeks appear to be as effective as oral doses of 2–6 mg/day. The long-acting injection (RLAI) also seems to be well tolerated – fewer than 10% of patients experienced EPS and fewer than 6% withdrew from a long-term trial because of adverse effects. Oral risperidone increases prolactin, as does RLAI, but levels appear to reduce somewhat following a switch from oral to injectable risperidone. Rates of TD are said to be low. There are no direct comparisons with standard depots using randomised controlled designs but comparisons from observational studies are available and results have been mixed. Switching from FGA depots in stable patients to RLAI has been shown to be less successful than remaining on the FGA depot; in contrast, discontinuation rates were lower with RLAI when compared with FGAs.

Uncertainty remains over the dose–response relationship for RLAI. Studies randomising subjects to different fixed doses of RLAI show no differences in response according to dose. One randomised, fixed-dose, year-long study suggested better outcome for 50 mg every 2 weeks than with 25 mg, although no observed difference reached statistical significance. Naturalistic studies indicate doses higher than 25 mg/2 weeks are frequently used. One study suggested higher doses were associated with better outcome.

Plasma levels afforded by 25 mg/2 weeks seem to be similar to, or even lower than, levels provided by 2 mg/day oral risperidone. (One study found that 9.5% of plasma samples from people apparently receiving risperidone LAI contained no risperidone or 9-hydroxyrisperidone.) Striatal dopamine D<sub>2</sub> occupancies are similarly low in people receiving 25 mg/2 weeks. So, although fixed-dose studies have not revealed clear advantages for doses above 25 mg/2 weeks, other indicators cast doubt on the assumption that 25 mg/2 weeks will be adequate for all or even most patients. While this conundrum remains unresolved the need for careful dose titration becomes of great importance.

Titrination is perhaps most efficiently achieved by establishing the required dose of oral risperidone and converting this dose into the equivalent injection dose. Trials have clearly established that switching from 2 mg oral to 25 mg injection and 4 mg oral to 50 mg injection is usually successful (switching from 4 mg/day to 25 mg/2 weeks increases the risk of relapse). There remains a question over the equivalent dose for 6 mg oral: in theory, patients should be switched to 75 mg injection but this showed no advantage over lower doses in clinical trials and is in any case above the licensed maximum dose. Nevertheless, an observational study reported successful outcomes in patients treated with doses in excess of 75 mg/2 weeks (range 75–200 mg) with continuation rates of 95% after 3 years. Paliperidone palmitate 150 mg a month is equivalent to oral risperidone 6 mg/day. In fact, for many reasons, paliperidone palmitate (9-hydroxyrisperidone) may be preferred to risperidone injection: it acts acutely, can be given monthly, does not require cold storage and has a wider, more useful dose range (see section on ‘Paliperidone palmitate long-acting injection’ in this chapter).

RLAI differs importantly from other depots and the following should be noted:

- Risperidone depot is not an esterified form of the parent drug. It contains risperidone coated in polymer to form microspheres. These microspheres have to be suspended in an aqueous base immediately before use.
The injection must be stored in a fridge (consider the practicalities for community staff).

It is available as doses of 25, 37.5 and 50mg. The whole vial must be used (because of the nature of the suspension). This means that there is limited flexibility in dosing.

### Table 1.18 Switching to risperidone long-acting injection (RLAI)

<table>
<thead>
<tr>
<th>Switching from</th>
<th>Recommended method of switching</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No treatment</strong> (new patient or recently non-compliant)</td>
<td>Start risperidone oral at 2 mg/day and titrate to effective dose. If tolerated, prescribe equivalent dose of RLAI Continue with oral risperidone for at least 3 weeks then taper over 1–2 weeks. Be prepared to continue oral risperidone for longer</td>
<td>Use oral risperidone before giving injection to assure good tolerability Those stabilised on 2 mg/day, start on 25 mg/2 weeks Those on higher doses, start on 37.5 mg/2 weeks and be prepared to use 50 mg/2 weeks (Manufacturer advice may differ from this – our guidance is based on numerous studies of dose-related outcome and on comparative plasma levels)</td>
</tr>
<tr>
<td><strong>Oral risperidone</strong></td>
<td>Prescribe equivalent dose of RLAI</td>
<td>See above</td>
</tr>
</tbody>
</table>
| **Oral antipsychotics** (not risperidone) | Either: Switch to oral risperidone and titrate to effective dose. If tolerated, prescribe equivalent dose of RLAI Continue with oral risperidone for at least 3 weeks then taper over 1–2 weeks. Be prepared to continue oral risperidone for longer  
**Or:**  
b. Give RLAI and then slowly discontinue oral antipsychotics after 3–4 weeks. Be prepared to continue oral antipsychotics for longer | Dose assessment is difficult in those switching from another antipsychotic. Broadly speaking, those on low oral doses should be switched to 25 mg/2 weeks 'Low' in this context means towards the lower end of the licensed dose range or around the minimum dose known to be effective Those on higher oral doses should receive 37.5 mg or 50 mg every 2 weeks. The continued need for oral antipsychotics after 3–4 weeks may indicate that higher doses of RLAI are required |
| **Depot antipsychotic**             | Give RLAI 1 week before the last depot injection is given                                      | Dose of RLAI difficult to predict. For those on low doses (see above) start at 25 mg/2 weeks and then adjust as necessary  
Start RLAI at 37.5 mg/2 weeks in those previously maintained on doses in the middle or upper range of licensed doses. Be prepared to increase to 50 mg/2 weeks |
| **Antipsychotic polypharmacy with depot** | Give RLAI 1 week before the last depot injection is given  
Slowly taper oral antipsychotics 3–4 weeks later. Be prepared to continue oral antipsychotics for longer | Aim to treat patient with RLAI as the sole antipsychotic. As before, RLAI dose should be dictated, as far as is possible, by the total dose of oral and injectable antipsychotic |

RLAI, risperidone long-acting injection.
A test dose is not required or sensible. (Testing tolerability with oral risperidone is desirable but not always practical.)

It takes 3–4 weeks for the first injection to produce therapeutic plasma levels. Patients must be maintained on a full dose of their previous antipsychotic for at least 3 weeks after the administration of the first risperidone injection. Oral antipsychotic cover is sometimes required for longer (6–8 weeks). If the patient is not already receiving an oral antipsychotic, oral risperidone should be prescribed. (See Table 1.18 for advice on switching from depots.) **Patients who refuse oral treatment and are acutely ill should not be given RLAI because of the long delay in drug release.**

Risperidone depot must be administered every 2 weeks. The product licence does not allow longer intervals between doses. There is little flexibility to negotiate with patients about the frequency of administration, although monthly injections may be effective.26

The most effective way of predicting response to RLAI is to establish dose and response with oral risperidone.

Risperidone injection is not considered suitable for patients with treatment-refractory schizophrenia, although there are studies showing positive effects.27,28

For guidance on switching to RLAI see Table 1.18.

Two new RLAs are in development at the time of writing and are designed to deliver risperidone through monthly injections. RBP-7000 is a subcutaneous injection that has been approved by the FDA for the treatment of schizophrenia. Risperidone-ISM, which is undergoing Phase 3 trials, is designed to be given via the IM route. Both preparations form a biodegradable implant after injection to deliver risperidone in a sustained-release fashion.29,30

References
Electroconvulsive therapy and psychosis

A Cochrane systematic review reviewed randomised controlled clinical trials that compared ECT with placebo (sham ECT), non-pharmacological interventions and antipsychotic medication for patients with schizophrenia, schizoaffective disorder or chronic mental disorder. Where ECT was compared with placebo or sham ECT, more people improved in the real ECT group and there was a suggestion that real ECT resulted in fewer relapses in the short term and a greater likelihood of being discharged from hospital. The review concluded that ECT combined with continuing antipsychotic medication is a valid treatment option for schizophrenia, particularly when rapid global improvement and reduction of symptoms were desired, and where the illness had shown only a limited response to medication alone. Treatment guidelines for schizophrenia suggest the use of ECT for catatonia and treatment-resistant illness.

Recent studies have focused on ECT augmentation of antipsychotic medication for treatment-resistant schizophrenia (TRS). For example, in a relatively small sample of patients with TRS characterised by ‘dominant negative symptoms’, ECT augmentation of a variety of antipsychotic medications produced a significant decrease in symptom severity. A meta-analysis of RCTs examined the efficacy of the combination of ECT and (non-clozapine) antipsychotic medication versus the same antipsychotic medication as monotherapy, in TRS. The combination proved to be superior in terms of symptom improvement, study-defined response and remission rate.

Augmentation of clozapine may be at least as effective as ECT augmentation of other antipsychotic medications, if not more so. In a retrospective study assessing the effectiveness and safety of the combination of clozapine and ECT in a sample of patients with TRS, almost two-thirds were responders (defined as a 30% or greater reduction in PANSS total score). Follow-up data on a sub-sample of these patients, over a mean of 30 months, revealed that the majority had maintained their symptomatic improvement or improved further. In a randomised, single-blind study assessing the effectiveness and safety of the combination of clozapine and ECT in a sample of patients with clozapine-refractory schizophrenia either continued solely on their clozapine treatment or had it augmented with a course of bilateral ECT. After 8 weeks, a predefined response criterion (including a 40% or greater reduction in symptoms) was met by half the patients receiving clozapine plus ECT but none of the group on clozapine alone. When the non-responders from the clozapine-alone group crossed over to an 8-week, open trial of ECT, nearly half met the response criterion. A systematic review and meta-analysis looking specifically at ECT augmentation of clozapine found a paucity of controlled studies, although the authors acknowledged the methodological challenges of such investigations. Analysis of the data from the controlled and open trials and case reports identified suggested that ECT augmentation of clozapine may be an efficacious and safe strategy in TRS, but the authors considered that double-blind studies of ECT augmentation were required, particularly given the potentially strong placebo effect.

Although ECT augmentation of continuing antipsychotic medication appears to be generally well tolerated, adverse effects such as transient memory impairment and headache have been reported for a minority of cases and there are reports of an increase in blood pressure after ECT and prolonged seizures.
In summary, the evidence supports ECT augmentation of pharmacotherapy, particularly clozapine, as an effective combination to improve mental state in TRS, although further, well-controlled trials are required to establish the benefit–risk balance of the combination in both the short and long term.

References

Omega-3 fatty acid (fish oils) in schizophrenia

Fish oils contain the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), also known as polyunsaturated fatty acids or PUFAs. These compounds are thought to be involved in maintaining neuronal membrane structure, in the modulation of membrane proteins and in the production of prostaglandins and leukotrienes. High dietary intake of PUFAs may protect against psychosis and antipsychotic treatment seems to normalise PUFA deficits. Animal models suggest a protective effect for PUFAs. PUFAs have been suggested as treatments for a variety of psychiatric illnesses; in schizophrenia, case reports, case series and prospective trials originally suggested useful efficacy.

A meta-analysis of these RCTs concluded that EPA has ‘no beneficial effect in established schizophrenia’, although the estimate of effect size (0.242) approached statistical significance. Since then, an RCT comprising 71 patients with first-episode schizophrenia given 2.2 g EPA + DHA daily for 6 months showed a reduction in symptom severity for patients in the active arm, finding an NNT (number needed to treat for one patient to benefit) of 4 to produce a 50% reduction in symptoms measured by Positive and Negative Syndrome Scale (PANSS). However, a further RCT of 97 subjects with acute psychosis showed no advantage for EPA 2 g daily and a relapse prevention study of EPA 2 g + DHA 1 g a day failed to demonstrate any value for PUFAs over placebo (relapse rate was 90% with PUFAs, 75% with placebo).

On balance, evidence now suggests that EPA (2–3 g daily) is unlikely to be a worthwhile option in schizophrenia when added to standard treatment. Set against doubts over efficacy are the observations that fish oils are relatively cheap, well tolerated (mild gastrointestinal symptoms may occur) and benefit physical health. In addition, a study of 700 mg EPA + 480 mg DHA in adolescents and young adults at high risk of psychosis showed that such treatment greatly reduced emergence of psychotic symptoms compared with placebo (although a review described this study as ‘very low quality evidence’). Since this single-site study, the large, multisite NEURAPRO trial gave adult patients at high risk of psychosis 840 mg EPA + 560 mg DHA for 6 months, and failed to find any evidence of efficacy either for reduction in transition to psychosis or improvement in symptoms. Two further multisite trials are currently ongoing.

PUFAs are no longer recommended for the treatment of residual symptoms of schizophrenia or for the prevention of transition to psychosis in young people at high risk. If used, careful assessment of response is important and fish oils should be withdrawn if no effect is observed after 3 months’ treatment unless they are required for their beneficial metabolic effects.

Recommendations

- Patients at high risk of first-episode psychosis. Not recommended. If used, suggest EPA 700 mg/day (2 × Omacor or 6 × Maxepa capsules).
- Residual symptoms of multi-episode schizophrenia (added to antipsychotic). Not recommended. If used, suggest dose of EPA 2 g/day (5 × Omacor or 10 × Maxepa capsules).
References

Details of the extrapyramidal symptoms (EPS) caused by antipsychotic drug treatment are shown in Table 1.19.

EPS are:

- dose-related
- most likely with high doses of high-potency FGAs
- less common with other antipsychotics, particularly clozapine, olanzapine, quetiapine and aripiprazole, but once present may be persistent. Note that CUTLASS reported no difference in EPS between FGAs and SGAs (although sulpiride was widely used in the FGA group). Vulnerability to EPS may be genetically determined.

Note that in never-medicated patients with first-episode schizophrenia, 1% have dystonia, 8% parkinsonian symptoms and 11% akathisia. Parkinsonian symptoms in such patients are associated with cognitive impairment. In never-treated patients with established illness, 9% exhibit spontaneous dyskinesias and 17% parkinsonian symptoms. Patients who experience one type of EPS may be more vulnerable to developing others. Substance misuse increases the risk of dystonia, akathisia and TD. There is some evidence for an association between alcohol use and akathisia.

References

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Dystonia (uncontrolled muscular spasm)</th>
<th>Pseudoparkinsonism (bradykinesia, tremor, etc.)</th>
<th>Akathisia (restlessness)</th>
<th>Tardive dyskinesia (abnormal involuntary movements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasm in any part of the body, e.g.:</td>
<td>Muscle spasm in any part of the body, e.g.:</td>
<td>Tremor and/or rigidity</td>
<td>A subjectively unpleasant state of inner restlessness where there is a strong desire or compulsion to move, e.g.:</td>
<td>A wide variety of movements can occur such as:</td>
</tr>
<tr>
<td>eyes rolling upwards (ouclogyric crisis)</td>
<td>eyes rolling upwards (ouclogyric crisis)</td>
<td>Bradykinesia (decreased facial expression, flat monotone voice, slow body movements, inability to initiate movement)</td>
<td>foot stamping when seated</td>
<td>lip smacking or chewing</td>
</tr>
<tr>
<td>head and neck twisted to the side (torticollis)</td>
<td>head and neck twisted to the side (torticollis)</td>
<td>Bradyphrenia (slowed thinking)</td>
<td>constantly crossing/uncrossing legs</td>
<td>tongue protrusion (fly catching)</td>
</tr>
<tr>
<td>The patient may be unable to swallow or speak clearly. In extreme cases, the back may arch or the jaw dislocate</td>
<td>The patient may be unable to swallow or speak clearly. In extreme cases, the back may arch or the jaw dislocate</td>
<td>Salivation</td>
<td>rocking from foot to foot</td>
<td>choreiform hand movements (pill rolling or piano playing)</td>
</tr>
<tr>
<td>Acute dystonia can be both painful and very frightening</td>
<td>Acute dystonia can be both painful and very frightening</td>
<td>Pseudoparkinsonism can be mistaken for depression or the negative symptoms of schizophrenia</td>
<td>constantly pacing up and down</td>
<td>pelvic thrusting</td>
</tr>
<tr>
<td>A wide variety of movements can occur such as:</td>
<td>A wide variety of movements can occur such as:</td>
<td>Akathisia can be mistaken for psychotic agitation and has been linked with suicidal ideation and aggression towards others</td>
<td>Severe orofacial movements can lead to difficulty speaking, eating or breathing.</td>
<td>Severe orofacial movements can lead to difficulty speaking, eating or breathing.</td>
</tr>
<tr>
<td>Simpson–Angus EPS Rating Scale</td>
<td>Simpson–Angus EPS Rating Scale</td>
<td>Barnes Akathisia Scale</td>
<td>Barnes Akathisia Scale</td>
<td>Barnes Akathisia Scale</td>
</tr>
<tr>
<td>No specific scale</td>
<td>No specific scale</td>
<td>Abnormal Involuntary Movement Scale (AIMS)</td>
<td>Abnormal Involuntary Movement Scale (AIMS)</td>
<td>Abnormal Involuntary Movement Scale (AIMS)</td>
</tr>
<tr>
<td>Approximately 10%, but more common in:</td>
<td>Approximately 10%, but more common in:</td>
<td>Approximately 20%, but more common in:</td>
<td>Wide variation but approximately 25% for acute akathisia with FGAs; lower with SGAs</td>
<td>5% of patients per year of antipsychotic exposure.</td>
</tr>
<tr>
<td>in young males</td>
<td>in the neuroleptic-naïve</td>
<td>in elderly females</td>
<td>In decreasing order: aripiprazole, risperidone, olanzapine, quetiapine and clozapine</td>
<td>elderly females</td>
</tr>
<tr>
<td>in the neuroleptic-naïve</td>
<td>with high-potency drugs (e.g. haloperidol)</td>
<td>those with pre-existing neurological damage (head injury, stroke, etc.)</td>
<td>those with affective illness</td>
<td>those with affective illness</td>
</tr>
<tr>
<td>Dystonic reactions are rare in the elderly</td>
<td>Dystonic reactions are rare in the elderly</td>
<td>Dystonic reactions are rare in the elderly</td>
<td>those who have had acute EPS early in treatment</td>
<td>those who have had acute EPS early in treatment</td>
</tr>
<tr>
<td>TD may be associated with neurocognitive deficits</td>
<td>TD may be associated with neurocognitive deficits</td>
<td>TD may be associated with neurocognitive deficits</td>
<td>TD may be associated with neurocognitive deficits</td>
<td>TD may be associated with neurocognitive deficits</td>
</tr>
</tbody>
</table>

(Continued)
Table 1.19 (Continued)

<table>
<thead>
<tr>
<th>Dystonia (uncontrolled muscular spasm)</th>
<th>Pseudoparkinsonism (bradykinesia, tremor, etc.)</th>
<th>Akathisia (restlessness)(^1)</th>
<th>Tardive dyskinesia (abnormal involuntary movements)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time taken to develop</strong></td>
<td>Days to weeks after antipsychotic drugs are started or the dose is increased</td>
<td>Acute akathisia occurs within hours to weeks of starting antipsychotics or increasing the dose</td>
<td>Months to years</td>
</tr>
<tr>
<td>Acute dystonia can occur within hours of starting antipsychotics (minutes if the IM or IV route is used)</td>
<td>TD occurs after months to years of antipsychotic treatment</td>
<td>Akathisia that has persisted for several months or so is called ‘chronic akathisia’. Tardive akathisia tends to occur later in treatment and may be exacerbated or provoked by antipsychotic dose reduction or withdrawal(^1)</td>
<td>Approximately 50% of cases are reversible(^13,14)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Several options are available depending on the clinical circumstances:</td>
<td>Reduce the antipsychotic dose</td>
<td>Stop anticholinergic if prescribed</td>
</tr>
<tr>
<td>Anticholinergic drugs given orally, IM or IV depending on the severity of symptoms(^9)</td>
<td>Reduce the antipsychotic dose</td>
<td>Change to an antipsychotic drug with lower propensity for akathisia (see sections on ‘Akathisia’ and ‘Relative adverse effects – a rough guide’)</td>
<td>Reduce dose of antipsychotic medication</td>
</tr>
<tr>
<td>■ Remember the patient may be unable to swallow</td>
<td>Change to an antipsychotic with lower propensity for pseudoparkinsonism (see section on ‘Relative adverse effects – a rough guide’)</td>
<td>A reduction in symptoms may be seen with: (^{18}) propranolol 30–80 mg/day (evidence poor); clonazepam (low dose)</td>
<td>Change to an antipsychotic with lower propensity for TD(^24–27) (note that data are conflicting(^28,29))</td>
</tr>
<tr>
<td>■ Response to IV administration will be seen within 5 minutes</td>
<td>Prescribe an anticholinergic. The majority of patients do not require long-term anticholinergic agents. Use should be reviewed at least every 3 months. Do not prescribe at night (symptoms usually absent during sleep)</td>
<td>5-HT(_{2}) antagonists such as cyproheptadine, (^{15}) mirtazapine, (^{18}) trazodone, (^{19,20}) mianserin(^21) and cyproheptadine(^{15}) may help, as may diphenhydramine(^{19})</td>
<td>Clozapine is the antipsychotic most likely to be associated with resolution of symptoms.(^{19}) Quetiapine may also be useful in this regard(^9)</td>
</tr>
<tr>
<td>■ Response to IM administration takes around 20 minutes</td>
<td>■ Reduce the antipsychotic dose</td>
<td>All are unlicensed for this indication</td>
<td>Both valbenazine and deutetrabenazine have a positive risk–benefit balance as add-on treatments(^32–35)</td>
</tr>
<tr>
<td>■ TD may respond to ECT(^15)</td>
<td>■ Change to an antipsychotic drug with lower propensity for EPS (see section on ‘Relative adverse effects – a rough guide’)</td>
<td>Anticholinergics are generally unhelpful(^23)</td>
<td>There is also some evidence for tetrabenazine and <strong>Ginkgo biloba</strong>(^36) as add-on treatments. For other treatment options see the review by the American Academy of Neurology(^37) and the section on ‘Tardive dyskinesia’</td>
</tr>
<tr>
<td>■ Where symptoms do not respond to simpler measures, including switching to an antipsychotic with a lower propensity for EPS, botulinum toxin may be effective(^16)</td>
<td>■ A reduction in symptoms may be seen with: (^{18}) propranolol 30–80 mg/day (evidence poor); clonazepam (low dose)</td>
<td>■ Both valbenazine and deutetrabenazine have a positive risk–benefit balance as add-on treatments(^32–35)</td>
<td></td>
</tr>
<tr>
<td>■ rTMS may be helpful(^17)</td>
<td>■ 5-HT(_{2}) antagonists such as cyproheptadine, (^{15}) mirtazapine, (^{18}) trazodone, (^{19,20}) mianserin(^21) and cyproheptadine(^{15}) may help, as may diphenhydramine(^{19})</td>
<td>■ There is also some evidence for tetrabenazine and <strong>Ginkgo biloba</strong>(^36) as add-on treatments. For other treatment options see the review by the American Academy of Neurology(^37) and the section on ‘Tardive dyskinesia’</td>
<td></td>
</tr>
</tbody>
</table>

ECT, electroconvulsive therapy; EPS, extrapyramidal symptoms; IM, intramuscularly; IV, intravenously; rTMS, repetitive transcranial magnetic stimulation; TD, tardive dyskinesia.
Further reading

**Akathisia**

Akathisia is a relatively common adverse effect of most antipsychotic medications although some SGAs have a lower liability for the condition. The core feature of akathisia is mental unease and dysphoria characterised by a sense of restlessness.\(^1\,\)^\(^2\) This is usually accompanied by observable motor restlessness, which, when severe, can cause patients to pace up and down and be unable to stay seated for more than a short time.\(^1\,\)^\(^2\) An association between the discomfiting subjective experience of akathisia and suicidal ideation has been postulated\(^3\,\)^\(^4\) but remains uncertain.

There is some evidence to suggest that akathisia may be prevented by avoiding high-dose antipsychotic medication, antipsychotic polypharmacy and rapid increase in dosage.\(^1\,\)^\(^5\,\)^\(^6\) There is limited evidence for efficacy for any pharmacological treatment for akathisia, even those most commonly used, such as switching to an antipsychotic medication with a lower liability for the condition, or adding a beta-adrenergic blocker, a 5-HT\(_{2A}\) antagonist or an anticholinergic agent. Figure 1.4 suggests a programme of treatment options for persistent, drug-induced akathisia.

**References**

Figure 1.4 Suggested treatment options for persistent, drug-induced akathisia. EPS, extrapyramidal symptoms; tds, *ter die sumendum* (three times a day).
Notes:
- Akathisia is sometimes difficult to diagnose with certainty. Clinical physical examination schedules for EPS have been proposed. A careful history of symptoms, medication and co-morbid substance use is essential.
- Evaluate the efficacy of each treatment option over at least 1 month. Some effect may be seen after a few days but it may take much longer to become apparent in those with chronic akathisia.
- Withdraw previously ineffective akathisia treatments before starting the next option in the algorithm.
- Combinations of treatment may be considered for refractory cases if carefully monitored.
- Other possible treatments for acute akathisia that have been investigated include vitamin B₆, pregabalin, diphenhydramine, trazodone, and zolmitriptan. Always read the primary literature before considering any of the treatment options.
- Parenteral midazolam (1.5 mg) has been successfully used to prevent akathisia associated with IV metoclopramide, suggesting a specific therapeutic effect for midazolam and perhaps benzodiazepines more generally.

Figure 1.4 (Continued)

Weight gain

Antipsychotics have long been recognised as weight-inducing agents. Suggested mechanisms include 5-HT_{2C} antagonism, H_{1} antagonism, D_{2} antagonism, and increased serum leptin (leading to leptin desensitisation).\textsuperscript{1–3} There is no evidence that drugs exert any direct metabolic effect: weight gain seems to result from increased food intake and, in some cases, reduced energy expenditure.\textsuperscript{4} Risk of weight gain appears to be related to clinical response\textsuperscript{5} (although the association is too small to be clinically important\textsuperscript{6}) and may also have a genetic basis.\textsuperscript{7} Weight gain may also be more pronounced in antipsychotic-naïve patients.\textsuperscript{8}

All available antipsychotics have been associated with weight gain, although mean weight gained varies substantially between drugs. With all drugs, some patients lose weight, some gain no weight and some gain a great deal of weight. Knowledge of the mean weight gained is often not useful in predicting how much weight an individual might gain. Assessment of relative risk for different drugs is based largely on short-term studies. Notwithstanding these limitations, the results of indirect and direct meta-analyses suggest that antipsychotics can be clustered into three groups based on their weight gain liability.\textsuperscript{9} Table 1.20 suggests approximate relative risk of weight gain and the extent of mean weight gain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk/extent of weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>High</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Moderate</td>
</tr>
<tr>
<td>Iloperidone</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Low</td>
</tr>
<tr>
<td>Asenapine</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>Cariprazine</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td></td>
</tr>
<tr>
<td>Sulpiride</td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td></td>
</tr>
</tbody>
</table>
See section on ‘Treatment of antipsychotic-induced weight gain’ in this chapter for advice on treating drug-induced weight gain.

References

**Treatment of antipsychotic-induced weight gain**

Weight gain is an important adverse effect of nearly all antipsychotics with obvious consequences for self-image, morbidity and mortality. Prevention and treatment are therefore matters of clinical urgency.

**Monitoring**

Patients starting antipsychotic treatment or changing drugs should, as an absolute minimum, be weighed and their weight clearly recorded. Estimates of body mass index (BMI) and waist circumference should, ideally, also be made at baseline and at least every 6 months. Weekly monitoring of weight is recommended early in treatment, for the first 3 months at least. Rapid weight gain in early treatment (≥5% above baseline after 1 month of treatment) strongly predicts long-term weight gain and should prompt consideration of preventative or remedial measures.

There is somewhat dated evidence that only a minority of patients have anywhere near adequate monitoring of weight. Clearly, monitoring of weight parameters is essential to assess the value of preventative and remedial measures.

**Treatment and prevention**

Most of the relevant literature in this area relates to attempts at reversing antipsychotic-related weight gain, although there are now useful data suggesting that early interventions can prevent or mitigate weight gain.

When weight gain occurs, initial options involve switching drugs or instituting behavioural programmes (or both). Switching always presents a risk of relapse and treatment discontinuation but there is fairly strong support for switching to aripiprazole, ziprasidone or lurasidone as a method for reversing weight gain. It is possible that switching to other drugs with a low propensity for weight gain is also beneficial.

Another option is to add aripiprazole to existing treatment: weight loss has been observed when aripiprazole was added to clozapine and to olanzapine. Stopping antipsychotic treatment altogether will reverse weight gain but this course of action would not be sensible for the large majority of people with multi-episode schizophrenia. Note that, while some switching and augmentation strategies may minimise further weight gain or facilitate weight loss, the overall effect is generally modest and many patients continue to be overweight. Additional lifestyle interventions are often required if BMI is to remain in/move towards the normal range.

A variety of lifestyle interventions have been proposed and evaluated with good results. Interventions vary, but they are mainly ‘behavioural lifestyle programmes’ aimed at improving diet and increasing physical activity. Meta-analyses of RCTs have shown a robust effect for both prevention and intervention with these non-pharmacological interventions. Pharmacological methods should be considered only where behavioural methods or switching have failed or where obesity presents clear immediate physical risk to the patient. Some options are described in Table 1.21. Metformin is now probably considered to be the drug of choice for the prevention and treatment of
Table 1.21 Drug treatment of antipsychotic-induced weight gain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine23,24 (100–300 mg/day)</td>
<td>May attenuate olanzapine-related weight gain. Seems to be well tolerated apart from insomnia and abdominal discomfort. May (theoretically, at least) exacerbate psychosis. Evidence base too limited to recommend22</td>
</tr>
<tr>
<td>Alpha-lipoic acid25–27 (1200 mg/day)</td>
<td>Supplementation may lead to a small short-term weight loss. Limited data for antipsychotic-induced weight gain. Not recommended</td>
</tr>
<tr>
<td>Aripiprazole6,28 (5–15 mg/day)</td>
<td>Three RCTs show beneficial effects on weight loss and possibly other metabolic parameters when used as an adjunct to clozapine or olanzapine. Adjunctive use appears to be safe and unlikely to worsen psychosis. Recommended as a possible option for weight gain associated with clozapine or olanzapine. Not recommended with other antipsychotics</td>
</tr>
<tr>
<td>Betahistine29,30 (48 mg/day)</td>
<td>May attenuate olanzapine-induced weight gain. Limited data. Not recommended</td>
</tr>
<tr>
<td>Bupropion31,32 (amfebutamone)</td>
<td>Seems to be effective in obesity when combined with calorie-restricted diets. Appears not to exacerbate psychosis symptoms, at least when used for smoking cessation.33 Few data on its effects on drug-induced weight gain. Not recommended</td>
</tr>
<tr>
<td>Bupropion + naltrexone (Contrave/Mysimba)34</td>
<td>Combination approved for weight management as an adjunct to diet and exercise. No data in drug-induced weight gain. Not recommended, but should not be ruled out</td>
</tr>
<tr>
<td>Fluoxetine6 (20–60 mg/day)</td>
<td>Two negative RCTs. Not recommended</td>
</tr>
<tr>
<td>Fluvoxamine35–37 (50 mg/day)</td>
<td>Earlier conflicting data but one short-term RCT shows attenuated clozapine-induced weight gain (possibly related to a higher clozapine to norclozapine ratio). Co-administration markedly increases clozapine levels, requiring extreme caution. Evidence base is too limited to recommend</td>
</tr>
<tr>
<td>H2 antagonists38 (e.g. nizatidine 300 mg bd, ranitidine 300 mg bd or famotidine 40 mg/day)</td>
<td>Meta-analysis of RCTs suggests no effect on weight gain</td>
</tr>
<tr>
<td>Liraglutide39,40 (3 mg/day via subcutaneous injection)</td>
<td>GLP-1 agonist that was previously approved for type 2 diabetes and more recently approved as an anti-obesity agent in non-diabetic patients. Dose for weight loss (3 mg/day) is higher than the dose used for diabetes (≤1.8 mg). Limited data in drug-induced weight gain. One RCT shows significant weight loss in overweight pre-diabetic patients stable on olanzapine or clozapine. Beneficial effects on other metabolic parameters. Well tolerated but can cause gastrointestinal disturbances. Recommended option in pre-diabetic/diabetic patients and clozapine-induced weight gain</td>
</tr>
<tr>
<td>Metformin43 (500–2000 mg/day)</td>
<td>Now a substantial database (in non-diabetic patients) supporting the use of metformin in both reducing and reversing weight gain caused by antipsychotics (mainly olanzapine). Beneficial effects on other metabolic parameters. Some negative studies, but clear and significant effect in meta-analyses. One positive RCT44 and extension study45 in children and adolescents with ASD published since then. Ideal for those with weight gain and diabetes or polycystic ovary syndrome. Note that metformin treatment increases the risk of vitamin B12 deficiency46</td>
</tr>
</tbody>
</table>
antipsychotic-induced weight gain although GLP-1 agonists may ultimately prove more effective and better tolerated. Bariatric surgery may rarely have a role in severe cases when all else fails. However, the efficacy of bariatric surgery for drug-induced weight gain is not known. Table 1.21 lists drug treatment options for antipsychotic-induced weight gain (in alphabetical order).

### References


Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is an acute disorder of thermoregulation and neuromotor control. It is characterised by muscular rigidity, hyperthermia, altered consciousness and autonomic dysfunction following exposure to antipsychotic medication, although there is considerable heterogeneity in the clinical presentation. Although widely seen as an acute, severe syndrome, NMS may, in many cases, have few signs and symptoms and ‘full-blown’ NMS may thus represent the extreme of a range of non-malignant-related symptoms. Certainly, asymptomatic rises in plasma creatine kinase (CK) are fairly common.

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Fever, diaphoresis, rigidity, confusion, fluctuating level of consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluctuating blood pressure, tachycardia</td>
</tr>
<tr>
<td></td>
<td>Elevated CK, leukocytosis, altered liver function tests</td>
</tr>
<tr>
<td>Risk factors</td>
<td>High potency FGAs, recent or rapid dose increase, rapid dose reduction, abrupt withdrawal of anticholinergic agents, antipsychotic polypharmacy</td>
</tr>
<tr>
<td></td>
<td>Psychosis, organic brain disease, alcoholism, Parkinson’s disease, hyperthyroidism, psychomotor agitation, mental retardation</td>
</tr>
<tr>
<td></td>
<td>Male gender, younger age</td>
</tr>
<tr>
<td></td>
<td>Agitation, dehydration</td>
</tr>
<tr>
<td>Treatments</td>
<td>In the psychiatric unit:</td>
</tr>
<tr>
<td></td>
<td>Withdraw antipsychotic medication, monitor temperature, pulse, blood pressure.</td>
</tr>
<tr>
<td></td>
<td>Consider benzodiazepines if not already prescribed – IM lorazepam has been used.</td>
</tr>
<tr>
<td></td>
<td>In the medical/A&amp;E unit:</td>
</tr>
<tr>
<td></td>
<td>Rehydration, bromocriptine + dantrolene, sedation with benzodiazepines, artificial ventilation if required</td>
</tr>
<tr>
<td></td>
<td>L-dopa, apomorphine and carbamazepine have also been used, among many other drugs. Consider ECT for treatment of psychosis</td>
</tr>
<tr>
<td>Re-starting antipsychotics</td>
<td>Antipsychotic treatment will be required in most instances and re-challenge is associated with acceptable risk</td>
</tr>
<tr>
<td></td>
<td>Stop antipsychotics for at least 5 days, preferably longer. Allow time for symptoms and signs of NMS to resolve completely</td>
</tr>
<tr>
<td></td>
<td>Begin with very small dose and increase very slowly with close monitoring of temperature, pulse and blood pressure. CK monitoring may be used, but is controversial. Close monitoring of physical and biochemical parameters is effective in reducing progression to ‘full-blown’ NMS</td>
</tr>
<tr>
<td></td>
<td>Consider using an antipsychotic medication structurally unrelated to that previously associated with NMS or a drug with low dopamine affinity (quetiapine or clozapine). Aripiprazole may also be considered but it has a long plasma half-life and has been linked to an increased risk of NMS</td>
</tr>
<tr>
<td></td>
<td>Avoid depot/LAI antipsychotic preparations (of any kind) and high potency FGAs</td>
</tr>
</tbody>
</table>

A&E, accident and emergency; CK, creatine kinase; ECT, electroconvulsive therapy; FGA, first-generation antipsychotic; IM, intramuscular; LAI, long-acting injection; NMS, neuroleptic malignant syndrome.
NMS occurs as a rare but potentially serious or even fatal adverse effect of antipsychotics, as medications with dopamine receptor-antagonist properties. Risk factors include being male, dehydration, exhaustion and confusion/agitation. Young adult males seem to be particularly at risk, while the condition is most likely to be lethal in older people.

The incidence and mortality rates of NMS are difficult to establish and probably vary as drug use changes and recognition of NMS increases. It has been estimated that fewer than 1% of all patients treated with FGAs will experience NMS. NMS is probably less common with SGAs but most have been reported to be associated with the syndrome, including later SGAs such as ziprasidone, iloperidone, aripiprazole, paliperidone (including paliperidone palmitate), asenapine and risperidone injection. Mortality is probably lower with SGAs than with FGAs although the clinical picture is essentially similar except that rigidity and fever may be less common.

NMS is also sometimes seen with other medications, such as antidepressants, valproate, phenytoin and lithium. Combinations of antipsychotics with SSRIs or cholinesterase inhibitors may increase the risk of NMS. NMS-type syndromes induced by SGA/SSRI combinations may share their symptoms and pathogenesis with serotonin syndrome. The use of benzodiazepines has been linked to an important increase in the risk of NMS.

NMS is also occasionally seen in people given non-antipsychotic dopamine antagonists such as metoclopramide.

The characteristics of NMS and its management are summarised in Table 1.22.

References

Catatonia

The term ‘catatonia’ usually refers to a state of stupor (akinetic mutism) occurring in the context of a psychotic illness. There are two problems with this. First, catatonic schizophrenia may manifest as immobile stupor or a state of chaotic physical and psychological agitation.\(^1\) Second, stupor is seen in many other non-organic conditions such as depression, mania and conversion disorder.\(^2\)–\(^6\)

Catatonia is thus one type of stupor, characterised by at least two of the following symptoms:

- marked psychomotor retardation, sometimes with complete immobility
- mutism
- waxy flexibility (no resistance from a patient to an attempt to move a limb into the most awkward position and maintenance of its position)
- negativism (strong opposite direction movement responses to an attempt to move a patient’s limb) or automatic obedience
- peculiar voluntary movements, e.g. posturing, mannerisms, stereotyped movements and grimacing
- echolalia, echopraxia
- refusal to eat and/or drink.

If psychiatric stupor is left untreated, physical health complications are unavoidable and develop rapidly. Prompt treatment is crucial as it may prevent complications, which include dehydration, venous thrombosis, pulmonary embolism, pneumonia, and ultimately death.\(^7\)

There are three major psychiatric illnesses that can present with stupor. Amongst them, stupor is mostly seen in psychotic illness. As outlined earlier, catatonic schizophrenia presents not only with an immobile mute picture of stupor, but also with a catatonic excitement, when a patient experiences the opposite of stupor – a chaotic psychomotor agitation and pronouncedly increased volume of speech, most of which is incoherent. The second psychiatric cause of stupor is affective illness, where an immobile mute clinical picture can occur in both depressive and, less commonly, manic states.\(^2\)–\(^4\),\(^8\)–\(^11\) The third cause is one of the most intriguing and rare psychiatric conditions – conversion disorder stupor, which sometimes is referred to as psychosomatic or hysterical catatonia.\(^12\)–\(^15\)

There are also developmental disorders such as autism, as well as neurodegenerative\(^16\),\(^17\) and organic disorders, which can present with a catatonia-like picture of a mute and immobile patient. These include a number of medical disorders such as:

- subarachnoid haemorrhages
- basal ganglia disorders
- non-convulsive status epilepticus
- locked-in and akinetic mutism states
- endocrine and metabolic disorders, e.g. Wilson’s disease\(^18\)
- Prader–Willi syndrome
- antiphospholipid syndrome\(^19\)
- systemic lupus erythematosus (SLE)\(^20\)
Infections
Dementia
Drug withdrawal and toxic drug states – can precipitate catatonic symptoms, e.g. after abrupt withdrawal of clozapine and withdrawal of zolpidem, temazepam and many non-psychotropics including the medicines used in oncology.

The treatment of stupor is dependent on its cause. Benzodiazepines are the drugs of choice for stupor occurring in the context of affective and conversion disorders. It is postulated that benzodiazepines may act by increasing GABAergic transmission or reducing levels of brain-derived neurotropic factor. There is most clinical experience with lorazepam. Many patients will respond to standard doses (up to 4 mg per day), but repeated and higher doses (between 8 and 24 mg per day) may be needed. One observational study lasting 9 years in patients with stupor of a mood disorder causality, either major depressive episodes or bipolar I, reported an 83.3% response to IM lorazepam 2 mg administered within the first 2 hours of presentation and a 100% response if 10 mg diazepam IV in 500 mL normal saline was added in cases of IM treatment failure. A very similar protocol achieved an 85.7% success rate in catatonia caused by general medical conditions or substance misuse.

Where benzodiazepines are effective, their benefit is seen very quickly. A test dose of zolpidem (10 mg) is said to predict response to benzodiazepines and frequent dosing of zolpidem may provide effective treatment.

Catatonia in schizophrenia is somewhat less likely to respond to benzodiazepines, with a response in the range of 40–50%. A double-blind, placebo-controlled, crossover trial with lorazepam up to 6 mg per day demonstrated no effect on catatonic symptoms in patients with chronic schizophrenia, similar to the poor effect of lorazepam in a non-randomised trial. A further complication in schizophrenia is that of differential diagnosis. Debate continues on the similarities and differences between catatonic stupor in psychosis and NMS. Two terms, lethal catatonia and malignant catatonia, have been coined to describe stupor that is accompanied by autonomic instability or hyperthermia. This potentially fatal condition cannot be distinguished either clinically or by laboratory testing from NMS, leading to a suggestion that NMS is a variant form of malignant catatonia. However, the absence of any prior or recent administration of a dopamine antagonist can help rule out NMS.

In stupor associated with schizophrenia, ECT and benzodiazepines remain the treatments of first choice (Figure 1.5). The vast majority of evidence published recently as well as over previous decades suggests that prompt ECT remains the most successful treatment. As with benzodiazepines, response to ECT may be lower in patients with schizophrenia (or in those who have been treated with antipsychotics) than in patients with mood disorders. In malignant catatonia, every effort should be made to maximise the effect of ECT by using liberal stimulus dosing to induce well-generalised seizures. Physical health needs should also be a priority and in-patient medical care obtained when necessary, especially for those showing autonomic imbalance and those whose dietary intake cannot be managed in psychiatric care.

The use of antipsychotic medication should be carefully considered (Table 1.23). Some authors recommend that antipsychotics should be avoided altogether in catatonic patients, although there are case reports of successful treatment with aripiprazole,
risperidone, olanzapine, ziprasidone and clozapine. There is probably most evidence supporting clozapine and olanzapine. Simple guidance on the usage of antipsychotic medication is to consider the history of a patient, their previous diagnosis and previous response to antipsychotic treatment, and the likelihood that non-adherence precipitated stupor. It needs to be noted that physical health problems, as in the examples listed in the beginning of this section, can present as a catatonia-like clinical picture, warranting treatment of the underlying medical condition. Antipsychotic medication should be avoided where there are clear signs of NMS: where stupor develops during treatment with antipsychotics and muscle rigidity is accompanied by autonomic instability. Where NMS can be ruled out and stupor occurs in the context of non-adherence to antipsychotic treatment, early re-establishment of antipsychotic medication is recommended. This is particularly important where stupor represents a withdrawal syndrome (as sometimes seen with clozapine).
References


Table 1.23 Alternatives to benzodiazepines in catatonia/stupor (listed in alphabetical order – no preference implied by order)

<table>
<thead>
<tr>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
</tr>
<tr>
<td>clozapine</td>
</tr>
<tr>
<td>olanzapine</td>
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<tr>
<td>risperidone</td>
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<tr>
<td>ziprasidone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experimental treatments*</th>
</tr>
</thead>
<tbody>
<tr>
<td>amantadine</td>
</tr>
<tr>
<td>amitriptyline</td>
</tr>
<tr>
<td>carbamazepine</td>
</tr>
<tr>
<td>fluoxetine</td>
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<tr>
<td>fluvoxamine</td>
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<tr>
<td>lithium</td>
</tr>
<tr>
<td>memantine</td>
</tr>
<tr>
<td>methylphenidate</td>
</tr>
<tr>
<td>mirtazapine</td>
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<tr>
<td>tramadol</td>
</tr>
<tr>
<td>valproate</td>
</tr>
<tr>
<td>zolpidem</td>
</tr>
</tbody>
</table>

* Always read the primary literature before using anything in this section.
CHAPTER 1

ECG changes – QT prolongation

Introduction

Many psychotropic drugs are associated with ECG changes and some are causally linked to serious ventricular arrhythmia and sudden cardiac death. Specifically, some antipsychotics block cardiac potassium channels and are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsades de pointes, which is often fatal. Case-control studies have suggested that the use of most antipsychotics is associated with an increase in the rate of sudden cardiac death.\(^1\)\(^{-7}\) This risk is probably a result of the arrhythmogenic potential of antipsychotics\(^8\),\(^9\) although schizophrenia itself may be associated with QT prolongation.\(^10\) Nonetheless, a study in first-episode patients showed that the use of antipsychotics produced clear prolongation of the QT interval after 2–4 weeks.\(^11\) Overall risk is probably dose-related and, although the absolute risk is low, it is substantially higher than, say, the risk of fatal agranulocytosis with clozapine.\(^8\) The effect of antipsychotic polypharmacy on QT is somewhat uncertain,\(^12\) but the extent of QT prolongation is probably a function of overall dose.\(^13\)

ECG monitoring of drug-induced changes in mental health settings is complicated by a number of factors. Psychiatrists may have limited expertise in ECG interpretation, for example, and still less expertise in manually measuring QT intervals. Even cardiologists show an inter-rater reliability in QT measurement of up to 20 ms.\(^14\) Self-reading, computerised ECG devices are available and to some extent compensate for some lack of expertise, but different models use different algorithms and different correction formulae.\(^15\) In addition, ECG machines may not be as readily available in all clinical areas as they are in general medicine. Also, time for ECG determination may not be available in many areas (e.g. out-patients). Lastly, ECG determination may be difficult to perform in acutely disturbed, physically uncooperative patients.

ECG monitoring is essential for all patients prescribed antipsychotics. An estimate of QTc interval should be made on admission to in-patient units (in the UK this is recommended in the NICE schizophrenia guideline\(^16\)) and yearly thereafter.

QT prolongation

- The cardiac QT interval (usually cited as QTc – QT corrected for heart rate) is a useful, but imprecise indicator of risk of torsades de pointes and of increased cardiac mortality.\(^17\) Different correction factors and methods may give markedly different values.\(^18\)
- The QT interval broadly reflects the duration of cardiac repolarisation. Lengthening of repolarisation duration induces heterogeneity of electrical phasing in different ventricular structures (a phenomenon known as dispersion) which in turn allows the emergence of early afterdepolarisations (EADs) which may provoke ventricular extrasystole and torsades de pointes.
- There is some controversy over the exact association between QTc and risk of arrhythmia. Very limited evidence suggests that risk is exponentially related to the extent of prolongation beyond normal limits (440 ms for men, 470 ms for women), although there are well-known exceptions that appear to disprove this theory\(^19\) (some
drugs prolong QT without increasing dispersion). Rather stronger evidence links QTc values over 500 ms to a clearly increased risk of arrhythmia.\textsuperscript{20} QT intervals of >6.50 ms may be more likely than not to induce torsades.\textsuperscript{21} Despite some uncertainties, QTc determination remains an important measure in estimating risk of arrhythmia and sudden death.

- Individual components of the QT interval may have particular importance. The time from the start of the T wave to T-wave peak has been shown to be the only aspect of QT prolongation associated with sudden cardiac deaths.\textsuperscript{22}

- QTc measurements and evaluation are complicated by:
  - difficulty in determining the end of the T wave, particularly where U waves are present (this applies both to manual and self-reading ECG machines)\textsuperscript{20}
  - normal physiological variation in QTc interval: QT varies with gender, time of day, food intake, alcohol intake, menstrual cycle, ECG lead, etc.\textsuperscript{18,19}
  - variation in the extent of drug-induced prolongation of QTc because of changes in plasma levels. QTc prolongation is most prominent at peak drug plasma levels and least obvious at trough levels.\textsuperscript{18,19}

Other ECG changes

Other reported antipsychotic-induced changes include atrial fibrillation, giant P waves, T-wave changes and heart block.\textsuperscript{19}

Quantifying risk

Drugs are categorised in Table 1.24 according to data available on their effects on the cardiac QTc interval (as reported; mostly using Bazett’s correction formula). ‘No-effect’ drugs are those with which QTc prolongation has not been reported either at therapeutic doses or in overdose. ‘Low-effect’ drugs are those for which severe QTc prolongation has been reported only following overdose or where only small average increases (<10 ms) have been observed at clinical doses. ‘Moderate-effect’ drugs are those which have been observed to prolong QTc by >10 ms on average when given at normal clinical doses or where ECG monitoring is officially recommended in some circumstances. ‘High-effect’ drugs are those for which extensive average QTc prolongation (usually >20 ms at normal clinical doses).

Note that, as outlined previously, effect on QTc may not necessarily equate directly to risk of torsades de pointes or sudden death,\textsuperscript{68} although this is often assumed. (A good example here is ziprasidone – a drug with a moderate effect on QTc but with no evidence of cardiac toxicity.\textsuperscript{69}) Note also that categorisation is inevitably approximate given the problems associated with QTc measurements. Lastly, keep in mind that differences in the effects of different antipsychotics on the QT interval rarely reach statistical significance even in meta-analyses.\textsuperscript{70}

Outside these guidelines, readers are directed to the RISQ-PATH study\textsuperscript{71} which provides a scoring system for the prediction of QT prolongation (to above normal ranges) in any patient. RISQ-PATH has a 98\% negative predictive value, so allowing a reduction in monitoring in low-risk patients. The RISQ-PATH method uses CredibleMeds categorisation for drug effects on QT – this, too, is recommended.\textsuperscript{72}
Other risk factors

A number of physiological/pathological factors are associated with an increased risk of QT changes and of arrhythmia (Table 1.25) and many non-psychotropic drugs are linked to QT prolongation (Table 1.26). These additional risk factors seem almost always to be present in cases of antipsychotic-induced TDP.

ECG monitoring

Measure QTc in all patients prescribed antipsychotics:
- on admission
- if previous abnormality or known additional risk factor, at annual physical health check.

Consider measuring QTc within a week of achieving a therapeutic dose of a newly prescribed antipsychotic that is associated with a moderate or high risk of QTc prolongation or of newly prescribed combined antipsychotics. See Table 1.27 for the management of QT prolongation in patients receiving antipsychotic drugs.
### Table 1.25 Physiological risk factors for QTc prolongation and arrhythmia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptom</th>
</tr>
</thead>
</table>
| **Cardiac** | Long QT syndrome  
Bradyarrhythmia  
Ischaemic heart disease  
Myocarditis  
Myocardial infarction  
Left ventricular hypertrophy |
| **Metabolic** | Hypokalaemia  
Hypomagnesaemia  
Hypocalcaemia |
| **Others** | Extreme physical exertion  
Stress or shock  
Anorexia nervosa  
Extremes of age – children and elderly people may be more susceptible to QT changes  
Female gender |

Hypokalaemia-related QTc prolongation is more commonly observed in acute psychotic admissions.\(^7)^4 Also, be aware that there are a number of physical and genetic factors which may not be discovered on routine examination but which probably predispose patients to arrhythmia.\(^7)^5,\(^7)^6

### Table 1.26 Non-psychotropics associated with QT prolongation (see Crediblemeds.org for latest information)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
</tr>
</thead>
</table>
| **Antibiotics** | Erythromycin  
Clarithromycin  
Ampicillin  
Co-trimoxazole  
Pentamidine  
(Some 4 quinolones affect QTc – see manufacturers’ literature) |
| **Antimalarials** | Chloroquine  
Mefloquine  
Quinine |
| **Antiarrhythmics** | Quinidine  
Disopyramide  
Procanamide  
Sotalol  
Amiodarone  
Bretylium |
| **Others** | Amantadine  
Cyclosporin  
Diphenhydramine  
Hydroxyzine  
Methadone  
Nicardipine  
Tamoxifen |

Beta-2 agonists and sympathomimetics may provoke torsades de pointes in patients with prolonged QTc.
Metabolic inhibition

The effect of drugs on the QTc interval is usually plasma level-dependent. Drug interactions are therefore important, especially when metabolic inhibition results in increased plasma levels of the drug affecting QTc. Commonly used metabolic inhibitors include fluvoxamine, fluoxetine, paroxetine and valproate.

Other cardiovascular risk factors

The risk of drug-induced arrhythmia and sudden cardiac death with psychotropics is an important consideration. With respect to cardiovascular disease, note that other risk factors such as smoking, obesity and impaired glucose tolerance present a much greater risk to patient morbidity and mortality than the uncertain outcome of QT changes. See relevant sections for discussion of these problems.

Summary

- In the absence of conclusive data, assume all antipsychotics are linked to sudden cardiac death.
- Prescribe the lowest dose possible and avoid polypharmacy/metabolic interactions.
- Perform ECG on admission, and, if previous abnormality or additional risk factor, at yearly check-up.
- Consider measuring QTc within a week of achieving a therapeutic dose of a moderate-/high-risk antipsychotic.

References

Effect of antipsychotic medications on plasma lipids

Morbidity and mortality from cardiovascular disease are higher in people with schizophrenia than in the general population. Dyslipidaemia is an established risk factor for cardiovascular disease along with obesity, hypertension, smoking, diabetes and sedentary lifestyle. The majority of patients with schizophrenia have several of these risk factors and can be considered at ‘high risk’ of developing cardiovascular disease. Dyslipidaemia is treatable and intervention is known to reduce morbidity and mortality. Aggressive treatment is particularly important in people with diabetes, the prevalence of which is increased two- to three-fold over population norms in people with schizophrenia (see section on ‘Diabetes and impaired glucose tolerance’ in this chapter).

Effect of antipsychotic drugs on lipids

First-generation antipsychotics

Phenothiazines are known to be associated with increases in triglycerides and low-density lipoprotein (LDL) cholesterol and decreases in high-density lipoprotein (HDL) cholesterol, but the magnitude of these effects is poorly quantified. Haloperidol seems to have minimal effect on lipid profiles.

Second-generation antipsychotics

Although there are relatively more data pertaining to some SGAs, they are derived from a variety of sources and are reported in different ways, making it difficult to compare drugs directly. While cholesterol levels can rise, the most profound effect of these drugs seems to be on triglycerides. Raised triglycerides are, in general, associated with obesity and diabetes. From the available data, olanzapine would seem to have the greatest propensity to increase lipids, and quetiapine and risperidone moderate propensity. Aripiprazole, lurasidone and ziprasidone have minimal adverse effect on blood lipids and may even modestly reverse dyslipidaemias associated with previous antipsychotics. Olanzapine has been shown to increase triglyceride levels by 40% over the short (12 weeks) and medium (16 months) term. Levels may continue to rise for up to a year. Up to two-thirds of olanzapine-treated patients have raised triglycerides and just under 10% may develop severe hypertriglyceridaemia. While weight gain with olanzapine is generally associated with both increases in cholesterol and triglycerides, severe hypertriglyceridaemia can occur independently of weight gain. In one study, patients treated with olanzapine and risperidone gained a similar amount of weight, but in olanzapine patients serum triglyceride levels increased by four times as much (80 mg/dL) as in risperidone patients (20 mg/dL). Quetiapine seems to have more modest effects than olanzapine, although data are conflicting.
A case-control study conducted in the UK found that patients with schizophrenia who were treated with olanzapine were five times more likely to develop hyperlipedemia than controls and three times more likely to develop hyperlipidaemia than patients receiving typical antipsychotics. Risperidone-treated patients could not be distinguished from controls.

**Clozapine**

Mean triglyceride levels have been shown to double and cholesterol levels to increase by at least 10% after 5 years’ treatment with clozapine. Patients treated with clozapine have triglyceride levels that are almost double those of patients who are treated with FGA drugs. Cholesterol levels are also increased.

Particular care should be taken before prescribing clozapine or olanzapine for patients who are obese, diabetic or known to have pre-existing hyperlipidaemia.

**Screening and monitoring**

All patients should have their lipids measured at baseline, 3 months after starting treatment with a new antipsychotic, and then annually. Those prescribed clozapine and olanzapine should ideally have their serum lipids measured every 3 months for the first year of treatment, and then annually. Clinically significant changes in cholesterol are unlikely over the short term but triglycerides can increase dramatically. In practice, dyslipidaemia is widespread in patients taking long-term antipsychotics irrespective of drug prescribed or of diagnosis. Screening for this potentially serious adverse effect of antipsychotics is not yet routine in clinical practice, but is strongly recommended by NICE.

Severe hypertriglyceridaemia (fasting level of >5 mmol/L) is a risk factor for pancreatitis. Note that antipsychotic-induced dyslipidaemia can occur independent of weight gain.

**Treatment of dyslipidaemia**

If moderate to severe hyperlipidaemia develops during antipsychotic treatment, a switch to another antipsychotic less likely to cause this problem should be considered in the first instance. Although not recommended as a strategy in patients with treatment-resistant illness, clozapine-induced hypertriglyceridaemia has been shown to reverse after a switch to risperidone. This may hold true with other switching regimens but data are scarce. Aripiprazole (or ziprasidone outside the UK) seems at present to be the treatment of choice in those with prior antipsychotic-induced dyslipidaemia.

Patients with raised cholesterol may benefit from dietary advice, lifestyle changes and/or treatment with statins. Statins seem to be effective in this patient group but interactions are possible. Risk tables and treatment guidelines can be found in the *British National Formulary* (*BNF*). Evidence supports the treatment of cholesterol concentrations as low as 4 mmol/L in high-risk patients and this is the highest level recommended by NICE for secondary prevention of cardiovascular events. NICE makes no recommendations on target levels for primary prevention but recent advice...
promotes the use of statins for anyone with a >10% 10-year risk of cardiovascular disease.49 Coronary heart disease and stroke risk can be reduced by a third by reducing cholesterol to as low as 3.5 mmol/L.2 When triglycerides alone are raised, diets low in saturated fats and the taking of fish oil and fibrates are effective treatments24,50,51 although there is no proof that mortality is reduced. Such patients should be screened for impaired glucose tolerance and diabetes.

The recommended procedure for monitoring lipid levels in patients on antipsychotics is summarised in Table 1.28.

### Table 1.28 Monitoring lipid concentrations in patients on antipsychotic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Fasting lipids at baseline, then every 3 months for a year, then annually</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Fasting lipids at baseline, then every 3 months for a year, then annually</td>
</tr>
<tr>
<td>Other antipsychotics</td>
<td>Fasting lipids at baseline and at 3 months, and then annually</td>
</tr>
</tbody>
</table>

References

Diabetes and impaired glucose tolerance

Schizophrenia

Schizophrenia is associated with relatively high rates of insulin resistance and diabetes\(^1,2\) — an observation that predates the discovery and widespread use of antipsychotics.\(^3-5\) Lifestyle interventions (lower weight, more activity) are effective in preventing diabetes\(^6\) and should be considered for all people with a diagnosis of schizophrenia.

Antipsychotics

Data relating to diabetes and antipsychotic use are numerous but less than perfect.\(^7-10\) The main problem is that incidence and prevalence studies assume full or uniform screening for diabetes. Neither assumption is likely to be correct.\(^7\) Many studies do not account for other factors affecting risk of diabetes.\(^10\) Small differences between drugs are therefore difficult to substantiate but may in any case be ultimately unimportant: risk is probably increased for all those with schizophrenia receiving any antipsychotic.

The mechanisms involved in the development of antipsychotic-related diabetes are unclear, but may include 5-HT\(_{2A}/5\text{-HT}\(_{2C}\) antagonism, increased plasma lipids, weight gain and leptin resistance.\(^11\) Insulin resistance may occur in the absence of weight gain.\(^12\)

First-generation antipsychotics

Phenothiazine derivatives have long been associated with impaired glucose tolerance and diabetes.\(^13\) Diabetes prevalence rates were reported to have increased substantially following the introduction and widespread use of FGA drugs.\(^14\) The prevalence of impaired glucose tolerance seems to be higher with aliphatic phenothiazines than with fluphenazine or haloperidol.\(^15\) Hyperglycaemia has also been reported with other FGAs, such as loxapine,\(^16\) and other data confirm an association with haloperidol.\(^17\) Some studies even suggest that FGAs are no different from SGAs in their propensity to cause diabetes,\(^18,19\) whereas others suggest a modest but statistically significant excess incidence of diabetes with SGAs.\(^20\)

Second-generation antipsychotics

Clozapine

Clozapine is strongly linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis.\(^21\) The risk of diabetes appears to be higher with clozapine than with other SGAs and conventional drugs, especially in younger patients,\(^22-25\) although this is not a consistent finding.\(^26,27\)

As many as a third of patients might develop diabetes after 5 years of treatment.\(^28\) Many cases of diabetes are noted in the first 6 months of treatment and some occur within 1 month,\(^29\) some only after many years.\(^27\) Death from ketoacidosis has also been reported.\(^29\) Diabetes associated with clozapine is not necessarily linked to obesity or to family history of diabetes,\(^21,30\) although these factors greatly increase the risk of developing diabetes on clozapine.\(^31\)
Clozapine appears to increase plasma levels of insulin in a clozapine level-dependent fashion.\textsuperscript{32,33} It has been shown to be more likely than FGAs to increase plasma glucose and insulin following oral glucose challenge.\textsuperscript{34} Testing for diabetes is essential given the high prevalence of diabetes in people receiving clozapine.\textsuperscript{35}

\textbf{Olanzapine}

As with clozapine, olanzapine has been strongly linked to impaired glucose tolerance, diabetes and diabetic ketoacidosis.\textsuperscript{36} Olanzapine and clozapine appear to directly induce insulin resistance.\textsuperscript{37,38} Risk of diabetes has also been reported to be higher with olanzapine than with FGA drugs,\textsuperscript{39} again with a particular risk in younger patients.\textsuperscript{23} The time course of development of diabetes has not been established but impaired glucose tolerance seems to occur even in the absence of obesity and family history of diabetes.\textsuperscript{21,30} Olanzapine is probably more diabetogenic than risperidone.\textsuperscript{40-44} Olanzapine is also associated with plasma levels of glucose and insulin higher than those seen with FGAs (after oral glucose load).\textsuperscript{34,45}

\textbf{Risperidone}

Risperidone has been linked, mainly in case reports, to impaired glucose tolerance, diabetes\textsuperscript{47} and ketoacidosis.\textsuperscript{48} The number of reports of such adverse effects is substantially smaller than with either clozapine or olanzapine.\textsuperscript{49} At least one study has suggested that changes in fasting glucose are significantly less common with risperidone than with olanzapine\textsuperscript{40} but other studies have detected no difference.\textsuperscript{50}

Risperidone seems no more likely than FGA drugs to be associated with diabetes,\textsuperscript{23,39,41} although there may be an increased risk in patients under 40 years of age.\textsuperscript{23} Risperidone has, however, been observed adversely to affect fasting glucose and plasma glucose (following glucose challenge) compared with levels seen in healthy volunteers (but not compared with patients taking conventional drugs).\textsuperscript{54}

\textbf{Quetiapine}

Like risperidone, quetiapine has been linked to cases of new-onset diabetes and ketoacidosis.\textsuperscript{51-53} Again, the number of reports is much lower than with olanzapine or clozapine. Quetiapine appears to be more likely than FGA drugs to be associated with diabetes.\textsuperscript{23,54} Two studies showed quetiapine to be equal to olanzapine in incidence of diabetes.\textsuperscript{50,55} Risk with quetiapine may be dose-related, with daily doses of 400 mg or more being clearly linked to changes in HbA\textsubscript{1C}.\textsuperscript{56}

\textbf{Other SGAs}

Amisulpride appears not to elevate plasma glucose\textsuperscript{57} and seems not to be associated with diabetes.\textsuperscript{58} There is one reported case of ketoacidosis occurring in a patient given the closely related sulpiride.\textsuperscript{59} Data for aripiprazole\textsuperscript{60-63} and ziprasidone\textsuperscript{64,65} suggest that neither drug alters glucose homeostasis. Aripiprazole may even reverse diabetes caused by other drugs\textsuperscript{66} (although ketoacidosis has been reported with aripiprazole\textsuperscript{67-69}).
A large case-control study has confirmed that neither amisulpride nor aripiprazole increase the risk of diabetes. These three drugs (amisulpride, aripiprazole and ziprasidone) are recommended for those with a history of or predisposition to diabetes mellitus or as an alternative to other antipsychotics known to be diabetogenic. Data suggest neither lurasidone nor asenapine has any effect on glucose homeostasis. Likewise, initial data for brexpiprazole and cariprazine suggest minimal effects on glucose tolerance.

**Predicting antipsychotic-related diabetes**

Risk of diabetes is increased to a much greater extent in younger adults than in the elderly (in whom antipsychotics may show no increased risk). First-episode patients seem particularly prone to the development of diabetes when given a variety of antipsychotics. During treatment, rapid weight gain and a rise in plasma triglycerides seem to predict the development of diabetes.

**Monitoring**

Diabetes is a growing problem in Western society and has a strong association with obesity, (older) age, (lower) educational achievement and certain ethnic groups. Diabetes markedly increases cardiovascular mortality, largely as a consequence of atherosclerosis. Likewise, the use of antipsychotics also increases cardiovascular mortality. Intervention to reduce plasma glucose levels and minimise other risk factors (obesity, hypercholesterolaemia) is therefore essential.

There is no clear consensus on diabetes-monitoring practice for those receiving antipsychotics and recommendations in formal guidelines vary considerably. Given the previous known parlous state of testing for diabetes in the UK and elsewhere, arguments over precisely which tests are done and when seem to miss the point. There is an overwhelming need to improve monitoring by any means and so any tests for diabetes are supported – urine glucose and random plasma glucose included (Table 1.29).

<table>
<thead>
<tr>
<th>Table 1.29</th>
<th>Recommended monitoring for diabetes in patients receiving antipsychotic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideally</strong></td>
<td><strong>Minimum</strong></td>
</tr>
<tr>
<td>Baseline</td>
<td>OGTT or FPG</td>
</tr>
<tr>
<td></td>
<td>Hba1c if fasting not possible</td>
</tr>
<tr>
<td>Continuation</td>
<td>All drugs: OGTT or FPG + Hba1c at 4–6 months then every 12 months</td>
</tr>
<tr>
<td></td>
<td>For clozapine and olanzapine or if other risk factors present: OGTT or FPG after 1 month, then every 4–6 months</td>
</tr>
<tr>
<td></td>
<td>For ongoing regular screening, Hba1c is a suitable test. Note that this test is not suitable for detecting short-term change</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; OGTT, oral glucose tolerance tests; RPG, random plasma glucose.
Ideally, though, all patients should have oral glucose tolerance tests (OGTT) performed as this is the most sensitive method of detection.\textsuperscript{97,98} Fasting plasma glucose (FPG) tests are less sensitive but recommended.\textsuperscript{99} Any abnormality in FPG should provoke an OGTT. Fasting tests are often difficult to obtain in acutely ill, disorganised patients so measurement of random plasma glucose or glycosylated haemoglobin (HbA\textsubscript{1c}) may also be used (fasting not required). HbA\textsubscript{1c} is now recognised as a useful tool in detecting and monitoring diabetes.\textsuperscript{100} Frequency of monitoring should then be determined by physical factors (e.g. weight gain) and known risk factors (e.g. family history of diabetes, lipid abnormalities, smoking status). The absolute minimum is yearly testing for diabetes for all patients. In addition, all patients should be asked to look out for and report signs and symptoms of diabetes (fatigue, candida infection, thirst polyuria).

### Treatment of antipsychotic-related diabetes

Switching to a drug of low or minimal risk of diabetes is often effective in reversing changes in glucose tolerance. In this respect the most compelling evidence is for switching to aripiprazole\textsuperscript{101,102} but also to ziprasidone\textsuperscript{102} and perhaps lurasidone.\textsuperscript{72} Standard antidiabetic treatments are otherwise recommended. Pioglitazone\textsuperscript{103} may have particular benefit but note the hepatotoxic potential of this drug. GLP-1 agonists such as liraglutide are increasingly used.\textsuperscript{104} The overall risk of impaired glucose tolerance and diabetes for different antipsychotics is summarised in Table 1.30.

<table>
<thead>
<tr>
<th>Degree of risk</th>
<th>Antipsychotic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Clozapine, olanzapine</td>
</tr>
<tr>
<td>Moderate</td>
<td>Quetiapine, risperidone, phenothiazines</td>
</tr>
<tr>
<td>Low</td>
<td>High-potency FGAs (e.g. haloperidol)</td>
</tr>
<tr>
<td>Minimal</td>
<td>Aripiprazole, amisulpride, brexpiprazole, cariprazine, asenapine, lurasidone, ziprasidone</td>
</tr>
</tbody>
</table>

FGA, first-generation antipsychotic.

### References


64. Simpson GM et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004; 161:1837–1847.
84. Mokdad AH et al. The continuing increase of diabetes in the US. Diabetes Care 2001; 24:412.
89. Goff DC et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005; 80:45–53.
104. Larsen JR et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry 2017; 74:719–728.
Blood pressure changes

Orthostatic hypotension

Orthostatic hypotension is one of the most common cardiovascular adverse effects of antipsychotics and some antidepressants. Orthostatic hypotension generally presents acutely, during the initial dose titration period, but there is evidence to suggest it can also be a chronic problem. Symptoms may include dizziness, light-headedness, asthenia, headache and visual disturbance. Patients may not be able to communicate the nature of these symptoms effectively and subjective reports of postural dizziness correlate weakly with the magnitude of measured postural hypotension.

Factors increasing the risk for orthostatic hypertension relate to:

- **Treatment:**
  - intramuscular administration route (as peak levels are achieved more rapidly)
  - rapid dose increases
  - antipsychotic polypharmacy
  - drug interactions (e.g. beta blockers and other antihypertensive drugs).

- **Patient:**
  - old age (young patients often develop sinus tachycardia with minimal changes in orthostatic blood pressure)
  - disease states associated with autonomic dysfunction (e.g. Parkinson’s disease)
  - dehydration
  - cardiovascular disease.

Blood pressure monitoring is recommended in suspected cases to confirm orthostatic hypotension (defined as a ≥20 mmHg fall in systolic blood pressure or a ≥10 mmHg fall in diastolic blood pressure within 2–5 minutes of standing). Orthostatic hypotension may result in syncope and falls-related injuries. It has also been associated with an increased risk of coronary heart disease, heart failure and death.

Slow dose titration is a commonly used and often effective strategy to avoid or minimise orthostatic hypotension. However, in some cases orthostasis may be a dose-limiting adverse effect, preventing optimal treatment. Potential management strategies are shown in Table 1.31.

Antipsychotics with a high affinity for postsynaptic α1-adrenergic receptors are most frequently implicated. Among the SGAs, the reported incidence is highest with clozapine (24%), quetiapine (27%) and iloperidone (19.5%), and lowest with lurasidone (<2%) and asenapine (<2%). There are limited quantitative data for FGAs, but low-potency phenothiazines (e.g. chlorpromazine) are considered most likely to cause orthostatic hypotension. All reported frequencies are somewhat dependent on titration schedules used.

Hypertension

There are two ways in which antipsychotic drugs may be associated with the development or worsening of hypertension:

- **Slow steady rise in blood pressure over time.** This may be linked to weight gain. Being overweight increases the risk of developing hypertension. The magnitude of the effect
Schizophrenia and related psychoses

CHAPTER 1

has been modelled using the Framingham data: for every 30 people who gain 4 kg, one will develop hypertension over the next 10 years. Note that this is a very modest weight gain; the majority of patients treated with some antipsychotics gain more than this, increasing further the risk of developing hypertension.

- Unpredictable rapid sharp increase in blood pressure on starting a new drug or increasing the dose. Increases in blood pressure occur shortly after starting, ranging from within hours of the first dose to a month. The following information relates to the pharmacological mechanism behind this and the antipsychotic drugs that are most implicated.

Table 1.31 Management of antipsychotic-induced orthostatic hypotension

<table>
<thead>
<tr>
<th>Minimise the risk of treatment</th>
<th>Non-pharmacological therapies</th>
<th>Pharmacological therapies for patients with a compelling indication for treatment where alternatives are not suitable (e.g. clozapine) and management strategies have failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Limit initial doses and titrate slowly according to tolerability (most develop a tolerance to the hypotensive effect)</td>
<td>1. Advice to patients, e.g. to sit on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position, may be helpful</td>
<td>1. Sodium chloride supplementation has been used to treat antidepressant-induced orthostatic hypotension</td>
</tr>
<tr>
<td>2. Consider a temporary dose reduction if hypotension develops</td>
<td>2. Abdominal binders and compression stockings have been recommended in postural hypotension</td>
<td>2. Fludrocortisone has been used to treat clozapine-induced orthostatic hypotension where other measures have failed (electrolyte and blood pressure monitoring essential)</td>
</tr>
<tr>
<td>3. Avoid antipsychotics that are potent α1-adrenergic receptor antagonists</td>
<td>3. Increasing fluid intake to 1.25–2.5 L/day is advisable for all patients who are not fluid restricted</td>
<td>3. A single case report describes the use of midodrine (an α1-receptor agonist) for tricyclic antidepressant-induced orthostatic hypotension</td>
</tr>
<tr>
<td>4. Reduce peak plasma levels by using smaller and more frequent doses or by using modified-release preparations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Postural hypotension is commonly associated with antipsychotic drugs that are antagonists at postsynaptic α1-adrenergic receptors. Some antipsychotics are also antagonists at presynaptic α2-adrenergic receptors; this can lead to increased release of norepinephrine and vasoconstriction. As all antipsychotics that are antagonists at α2 receptors are also antagonists at α1 receptors, the end result for any given patient can be difficult to predict, but for a very small number the result can be hypertension. Some antipsychotics are more commonly implicated than others, but individual patient factors are undoubtedly also important.

Receptor binding studies have demonstrated that clozapine, olanzapine and risperidone have the highest affinity for α2-adrenergic receptors so it might be predicted that these drugs would be most likely to cause hypertension. Most case reports implicate clozapine, with some clearly describing normal blood pressure before clozapine was introduced, a sharp rise during treatment and return to normal when clozapine was discontinued. Blood pressure has also been reported to rise again on re-challenge, and increased plasma catecholamines have been noted in some cases. Case reports also implicate aripiprazole, sulpiride, risperidone, quetiapine and ziprasidone.
Data available through the UK Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system indicate that clozapine is the antipsychotic drug most associated with hypertension. There are a very small number of reports with aripiprazole, olanzapine, quetiapine and risperidone. The timing of the onset of hypertension in these reports with respect to antipsychotic initiation is unknown, and likely to be variable.

In long-term treatment, hypertension is seen in around 30–40% of patients regardless of antipsychotic prescribed. A cross-sectional study found an increased risk of hypertension only for perphenazine, a finding not readily explained by its pharmacology.

No antipsychotic is contraindicated in essential hypertension but extreme care is needed when clozapine is prescribed. Concomitant treatment with SSRIs may increase risk of hypertension, possibly via inhibition of the metabolism of the antipsychotic. It is also (theoretically) possible that $\alpha_2$ antagonism may be at least partially responsible for clozapine-induced tachycardia and nausea.

Treatment of antipsychotic-associated hypertension should follow standard protocols. There is specific evidence for the efficacy of valsartan and telmisartan in antipsychotic-related hypertension.

References

Hyponatraemia

Hyponatraemia can occur in the context of:

- **Water intoxication** where water consumption exceeds the maximal renal clearance capacity. Serum and urine osmolality are low. Cross-sectional studies of chronically ill, hospitalised psychiatric patients have found the prevalence of water intoxication to be approximately 5%.\(^1,2\) A longitudinal study found that 10% of severely ill patients with a diagnosis of schizophrenia had episodic hyponatraemia secondary to fluid overload.\(^3\) The primary aetiology is poorly understood. It has been postulated that it may be driven, at least in part, by an extreme compensatory response to the anticholinergic adverse effects of some antipsychotic drugs.\(^4\)

- **Drug-induced syndrome of inappropriate antidiuretic hormone (SIADH)** where the kidney retains an excessive quantity of solute-free water. Serum osmolality is low and urine osmolality relatively high. The prevalence of SIADH has been estimated to be as high as 11% in acutely ill psychiatric patients.\(^5\) Risk factors for antidepressant-induced SIADH (increasing age, female gender, medical co-morbidity and polypharmacy) seem to be less relevant in the population of patients treated with antipsychotic drugs.\(^6\) SIADH usually develops in the first few weeks of treatment with the offending drug. Case reports and case series implicate phenothiazines, haloperidol, pimozide, risperidone, paliperidone, quetiapine, olanzapine, aripiprazole, cariprazine and clozapine.\(^6-15\) A systematic review\(^16\) and a case-control study\(^17\) each suggested a clear increase in risk of hyponatraemia with antipsychotics. Another review\(^18\) confirmed that drug-induced hyponatraemia is associated with concentrated urine and suggested that an antipsychotic was five times more likely than water intoxication to be the cause of hyponatraemia. Overall prevalence of antipsychotic-induced hyponatraemia has been estimated at 0.004%\(^19\) and 26.1%\(^20\) of patients. It is assumed that the true figure lies somewhere between these two extremes. Desmopressin use (for clozapine-induced enuresis) can also result in hyponatraemia.\(^21\) Other drugs, including antidepressants and anticonvulsants (especially carbamazepine\(^22\)), have also been implicated.\(^23\)

- **Severe hyperlipidaemia** and/or **hyperglycaemia** lead to secondary increases in plasma volume and ‘pseudohyponatraemia’.\(^*4\)** Both are more common in people treated with antipsychotic drugs than in the general population and should be excluded as causes.

Mild to moderate hyponatraemia presents as confusion, nausea, headache and lethargy. As the plasma sodium falls, these symptoms become increasingly severe and seizures and coma can develop.

Monitoring of plasma sodium is desirable for all those receiving antipsychotics. Signs of confusion or lethargy should provoke thorough diagnostic analysis, including plasma sodium determination and urine osmolality.

Standard treatments for antipsychotic-induced hyponatraemia are summarised in Table 1.32. More recently introduced drugs such as tolvaptan,\(^32\) a so-called ‘vaptan’ (non-peptide arginine-vasopressin antagonist – also known as aquaretics because they induce a highly hypotonic diuresis\(^33\)), show promise in the treatment of hyponatraemia of varying aetiology, including that caused by drug-related SIADH.
Table 1.32 Treatment of antipsychotic-induced hyponatraemia

<table>
<thead>
<tr>
<th>Cause of hyponatraemia</th>
<th>Antipsychotic drugs implicated</th>
<th>Treatment&lt;sup&gt;4,5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water intoxication</td>
<td>Only very speculative evidence to support drugs as a cause</td>
<td>Fluid restriction with careful monitoring of serum sodium, particularly diurnal variation (Na drops as the day progresses). Refer to specialist medical care if Na &lt; 125 mmol/L. Note that the use of IV saline to correct hyponatraemia has been reported to precipitate rhabdomyolysis&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Core part of illness in a minority of patients (e.g. psychotic polydipsia)</td>
<td>Consider treatment with clozapine: shown to increase plasma osmolality into the normal range and increase urine osmolality (not usually reaching the normal range).&lt;sup&gt;25,26&lt;/sup&gt; These effects are consistent with reduced fluid intake. This effect is not clearly related to improvements in mental state&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ There are both&lt;sup&gt;6&lt;/sup&gt; positive and negative reports for olanzapine&lt;sup&gt;28&lt;/sup&gt; and risperidone&lt;sup&gt;29&lt;/sup&gt; and one positive case report for quetiapine.&lt;sup&gt;30&lt;/sup&gt; Compared with clozapine, the evidence base is weak</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ There is no evidence that either reducing or increasing the dose of an antipsychotic results in improvements in serum sodium in water-intoxicated patients&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Demeclocycline should not be used (this exerts its effect by interfering with ADH and increasing water excretion, which is already at capacity in these patients)</td>
</tr>
<tr>
<td>SIADH</td>
<td>All antipsychotic drugs</td>
<td>If mild, fluid restriction with careful monitoring of serum sodium. Refer to specialist medical care if Na &lt; 125 mmol/L</td>
</tr>
<tr>
<td>(serum osmolality low; urine osmolality relatively high)</td>
<td></td>
<td>■ Switching to a different antipsychotic drug. There are insufficient data available to guide choice. Be aware that cross-sensitivity may occur (the individual may be predisposed and the choice of drug relatively less important)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Consider demeclocycline (see formal prescribing instruction for details)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Lithium may be effective&lt;sup&gt;6&lt;/sup&gt; but is a potentially toxic drug. Remember that hyponatraemia predisposes to lithium toxicity</td>
</tr>
</tbody>
</table>

ADH, antidiuretic hormone; IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone.

References


Further reading

Hyperprolactinaemia

Dopamine inhibits prolactin release and so dopamine antagonists can be expected to increase prolactin plasma levels. The degree of prolactin elevation is probably dose-related, and for most antipsychotic medications the threshold activity (D₂ occupancy) for increased prolactin is very close to that of therapeutic efficacy. Genetic differences may also play a part. Table 1.33 groups individual antipsychotics according to their effect on prolactin concentrations.

Hyperprolactinaemia is often superficially asymptomatic (i.e. the patient does not spontaneously report problems) and there is some evidence that hyperprolactinaemia does not affect subjective quality of life. Nonetheless, persistent elevation of plasma prolactin is associated with suppression of the hypothalamic–pituitary–gonadal axis. Symptoms of this include sexual dysfunction (but note that other pharmacological activities also give rise to sexual dysfunction), menstrual disturbances, breast growth and galactorrhoea, and may include delusions of pregnancy. Long-term adverse consequences are reductions in bone mineral density and a possible increase in the risk of breast cancer.

Prolactin can also be raised because of stress, pregnancy and lactation, seizures, renal impairment and other medical conditions, including prolactinoma. When measuring prolactin, the sample should be taken early in the morning and stress during venepuncture should be minimised.

Contraindications

Prolactin-elevating drugs with high risk should, if possible, be avoided in the following patient groups:

- patients under 25 years of age (i.e. before peak bone mass)
- patients with osteoporosis
- patients with a history of hormone-dependent breast cancer
- young women.

<table>
<thead>
<tr>
<th>Table 1.33 Effects of antipsychotic medication on prolactin concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolactin-sparing</strong> (prolactin increase very rare)</td>
</tr>
<tr>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Asenapine</td>
</tr>
<tr>
<td>Brexpiprazole*</td>
</tr>
<tr>
<td>Cariprazine*</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Iloperidone*</td>
</tr>
<tr>
<td>Quetiapine</td>
</tr>
</tbody>
</table>

* Not available in the EU at the time of writing. FGAs, first-generation antipsychotic.
For all patients, measure plasma prolactin level at baseline.

At 3 months:
- Ask about prolactin-related symptoms
- If hyperprolactinaemia suspected or patient is prescribed a prolactin-elevating antipsychotic, obtain plasma prolactin level

**Prolactin concentration interpretation**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Women</th>
<th>0–25 ng/mL (0–530 mIU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0–20 ng/mL (0–424 mIU/L)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elevated</th>
<th>25–118 ng/mL (530–2500 mIU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematically assess prolactin-related adverse effects</td>
<td></td>
</tr>
<tr>
<td>Discuss clinical consequences of prolonged raised prolactin levels</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highly elevated</th>
<th>&gt;118 ng/mL &gt;2500 mIU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer for tests to rule out prolactinoma</td>
<td></td>
</tr>
</tbody>
</table>

**Elevated**

- Symptomatic: Switch to an antipsychotic with a lower liability for plasma prolactin elevation
- Asymptomatic: Discuss clinical implications of the test results with the patient and take a joint decision on whether to continue current treatment with annual monitoring or switch to another antipsychotic

**Not appropriate/not successful**

- Add adjunctive aripiprazole*

**Successful**

- Consider slowly reducing dose of prolactin-raising drug and aim for aripiprazole as sole treatment
- Only if this strategy fails or is considered clinically inappropriate should long-term combined antipsychotics be considered

**Not tolerated**

- Consider treatment with dopamine agonists or peony–glycyrrhiza decoction

*May not normalise prolactin levels in amisulpride-induced hyperprolactinaemia

---

**Figure 1.6** Interpretation and management of antipsychotic-induced hyperprolactinaemia.
Management

Treatment of hyperprolactinaemia depends more on symptoms and long-term risk than on the reported plasma prolactin level.

Figure 1.6 presents a suggested algorithm for managing antipsychotic-induced hyperprolactinaemia. If treatment of hyperprolactinaemia is required, switching to an antipsychotic with a lower liability for prolactin elevation is usually the first choice although switching always carries a risk of destabilising the illness and relapse. An alternative is to add aripiprazole to existing treatment. Aripiprazole lowers prolactin levels in a dose-dependent manner: 3 mg/day is effective but 6 mg/day more so. Higher doses appear unnecessary. Other strategies to reduce long-term risk to bone mineral density should also be discussed (e.g. stopping smoking, increasing weight-bearing exercise, and ensuring adequate calcium and vitamin D intake).

For patients who need to remain on a prolactin-elevating antipsychotic medication and who cannot tolerate aripiprazole, dopamine agonists can be effective. Amantadine, cabergoline and bromocriptine have all been used, but each has, theoretically at least, the potential to worsen psychosis (although this has not been reported in trials). A herbal remedy – peony–glycyrrhiza decoction – has also been shown to improve prolactin-related symptoms, but the data are limited. A reduction in prolactin levels was also achieved by high daily doses (2.5–3 g) of metformin in a study of diabetic women on antipsychotic medication.

Management of hyperprolactinaemia is summarised in Table 1.34.

<table>
<thead>
<tr>
<th>First choice</th>
<th>Aripiprazole 5 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second choice (in no particular order)</td>
<td>Dopamine agonists – cabergoline, bromocriptine, amantadine</td>
</tr>
<tr>
<td></td>
<td>Peony–glycyrrhiza decoction</td>
</tr>
<tr>
<td></td>
<td>Metformin 2.5–3 g/day</td>
</tr>
</tbody>
</table>

References

Sexual dysfunction

Primary sexual disorders are common, although reliable normative data are lacking. Physical illness, psychiatric illness, substance misuse and prescribed drug treatment can all cause sexual dysfunction. It has been estimated that 50–60% of people with schizophrenia have problems with sexual dysfunction compared with 30% of the general population, but note that in both groups reported prevalence rates vary depending on the method of data collection (low numbers with spontaneous reports, increasing with confidential questionnaires and further still with direct questioning). In one study of patients with psychosis, 37% spontaneously reported sexual problems but 46% were found to be experiencing difficulties when directly questioned.

Baseline sexual functioning should be determined if possible (questionnaires may be useful) because sexual function can affect quality of life and compliance with medication (sexual dysfunction is one of the major causes of treatment dropout). Complaints of sexual dysfunction may also indicate progression or inadequate treatment of underlying medical or psychiatric conditions. Sexual problems may also be caused by drug treatment where intervention may greatly improve quality of life.

The human sexual response

There are four phases of the human sexual response, as detailed in Table 1.35.

Effects of psychosis

Sexual dysfunction is a well-established phenomenon in first-episode schizophrenia and up to 82% of men and 96% of women with established illness report problems, with associated reductions in quality of life. Men complain of reduced desire, inability to achieve an erection and premature ejaculation whereas women complain more generally about reduced enjoyment. Women with psychosis are known to have reduced fertility. People with psychosis are less able to develop good psychosexual relationships and, for some, treatment with an antipsychotic can improve sexual

<table>
<thead>
<tr>
<th>Table 1.35 Phases of the human sexual response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Desire</td>
</tr>
<tr>
<td>Related to testosterone levels in men</td>
</tr>
<tr>
<td>Possibly increased by dopamine and decreased by prolactin</td>
</tr>
<tr>
<td>Psychosocial context and conditioning significantly affect desire</td>
</tr>
<tr>
<td>2. Arousal</td>
</tr>
<tr>
<td>Influenced by testosterone in men and oestrogen in women</td>
</tr>
<tr>
<td>Other potential mechanisms include: central dopamine stimulation, modulation of the cholinergic/adrenergic balance, peripheral α agonism and nitric oxide pathways</td>
</tr>
<tr>
<td>Physical pathology such as hypertension or diabetes can have a significant effect</td>
</tr>
<tr>
<td>3. Orgasm</td>
</tr>
<tr>
<td>May be related to oxytocin</td>
</tr>
<tr>
<td>Inhibition of orgasm may be caused by an increase in serotonin activity and raised prolactin, as well as α blockade</td>
</tr>
<tr>
<td>4. Resolution</td>
</tr>
<tr>
<td>Occurs passively after orgasm</td>
</tr>
</tbody>
</table>

Note: Many other hormones and neurotransmitters may interact in a complex way at each phase.
functioning.\textsuperscript{16} Assessment of sexual functioning can clearly be difficult in someone who is psychotic. The Arizona Sexual Experience Scale (ASEX) may be useful in this respect.\textsuperscript{17}

\section*{Effects of antipsychotic medications}

Sexual dysfunction has been reported as an adverse effect of all antipsychotics, and up to 45\% of people taking older or conventional antipsychotics experience sexual dysfunction.\textsuperscript{18} Individual susceptibility varies and all effects are reversible. Note though that physical illness and drugs other than antipsychotics can cause sexual dysfunction and many studies do not control for either, making the prevalence of sexual dysfunction with different antipsychotics difficult to compare.\textsuperscript{19}

Antipsychotics decrease dopaminergic transmission, which in itself can decrease libido but may also increase prolactin levels via negative feedback. It has been estimated that prolactin elevation explains 40\% of the sexual dysfunction that is associated with antipsychotic medication.\textsuperscript{3} Hyperprolactinaemia can also cause amenorrhoea in women, and breast enlargement and galactorrhoea in both men and women.\textsuperscript{20} Although it has been suggested that the overall propensity of an antipsychotic to cause sexual dysfunction is related to propensity to raise prolactin, i.e. risperidone > haloperidol > olanzapine > quetiapine > aripiprazole,\textsuperscript{7,19,21} it should be noted that in the CUtLASS-1 study, FGAs (primarily sulpiride, but also other FGAs known to be associated with prolactin elevation) did not fare any worse than SGAs (70\% of patients in this arm were prescribed an antipsychotic not associated with prolactin elevation) with respect to worsening sexual dysfunction. In fact, sexual functioning improved in both arms over the 1-year duration of the study.\textsuperscript{16} Aripiprazole is relatively free of sexual adverse effects when used as monotherapy\textsuperscript{22} and possibly also in combination with another antipsychotic.\textsuperscript{23,24}

Anticholinergic effects can cause disorders of arousal,\textsuperscript{25} and drugs that block peripheral \(\alpha_1\) receptors cause particular problems with erection and ejaculation in men.\textsuperscript{9} Drugs that are antagonists at both peripheral \(\alpha_1\) receptors and cholinergic receptors can cause priapism.\textsuperscript{26} Antipsychotic-induced sedation and weight gain may reduce sexual desire.\textsuperscript{26} These principles can be used to predict the sexual adverse effects of different antipsychotic drugs (Table 1.36).

\section*{Treatment}

Before attempting to treat sexual dysfunction, a thorough assessment is essential to determine the most likely cause. Assuming that physical pathology (diabetes, hypertension, cardiovascular disease, etc.) has been excluded, the following principles apply.

Spontaneous remission may occasionally occur.\textsuperscript{26} The most obvious first step is to decrease the dose or discontinue the offending drug where appropriate. The next step is to switch to a different drug that is less likely to cause the specific sexual problem experienced (see Table 1.36). Another option is to add 5–10 mg aripiprazole – this can normalise prolactin and improve sexual function.\textsuperscript{57-59} If this fails or is not practicable, ‘antidote’ drugs can be tried: for example, cyproheptadine (a 5-HT\textsubscript{2} antagonist at doses of 4–16 mg/day) has been used to treat SSRI-induced sexual dysfunction but sedation is a common adverse effect. There is some evidence that mirtazapine (also a 5-HT\textsubscript{2} antagonist as well as an \(\alpha_2\) antagonist) may relieve orgasmic dysfunction in FGA-treated
### Table 1.36 Sexual adverse effects of antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>- No effect on prolactin or α&lt;sub&gt;1&lt;/sub&gt; receptors. No reported adverse effects on sexual function.&lt;br&gt;- Improves sexual function in those switched from other antipsychotics&lt;sup&gt;22,24,27&lt;/sup&gt;&lt;br&gt;- Case reports of aripiprazole-induced hypersexuality have been published&lt;sup&gt;28,29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asenapine</td>
<td>- Does not appear to significantly affect prolactin levels&lt;sup&gt;30&lt;/sup&gt;&lt;br&gt;- No reported cases of sexual dysfunction</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>- Similar mechanism of action to aripiprazole (5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist, 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist and partial D&lt;sub&gt;2&lt;/sub&gt; agonist)&lt;br&gt;- Causes negligible increases in prolactin&lt;sup&gt;31&lt;/sup&gt;&lt;br&gt;- No problems with sexual dysfunction reported in clinical trials&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>- Similar mechanism of action to aripiprazole (5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist, 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist and partial D&lt;sub&gt;2&lt;/sub&gt; agonist)&lt;br&gt;- Not associated with hyperprolactinaemia&lt;sup&gt;33&lt;/sup&gt;&lt;br&gt;- No reported cases of sexual dysfunction</td>
</tr>
<tr>
<td>Clozapine</td>
<td>- Significant α&lt;sub&gt;1&lt;/sub&gt;-adrenergic blockade and anticholinergic effects.&lt;sup&gt;34&lt;/sup&gt; No effect on prolactin&lt;sup&gt;35&lt;/sup&gt;&lt;br&gt;- Probably fewer problems than with typical antipsychotics&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>- Similar problems to the phenothiazines&lt;sup&gt;37&lt;/sup&gt; but anticholinergic effects reduced&lt;sup&gt;38&lt;/sup&gt;&lt;br&gt;- Prevalence of sexual dysfunction reported to be up to 70%&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>- Does not appear significantly to affect prolactin levels&lt;sup&gt;40&lt;/sup&gt;&lt;br&gt;- No reported cases of sexual dysfunction</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>- Possibly less sexual dysfunction due to relative lack of prolactin-related effects&lt;sup&gt;37&lt;/sup&gt;&lt;br&gt;- Priapism reported rarely&lt;sup&gt;41,42&lt;/sup&gt;&lt;br&gt;- Prevalence of sexual dysfunction reported to be &gt;50%&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>- Similar prolactin elevations to risperidone&lt;br&gt;- One small study&lt;sup&gt;43&lt;/sup&gt; and one case report&lt;sup&gt;44&lt;/sup&gt; showing reduction in sexual dysfunction following switching from risperidone oral or depot to paliperidone depot</td>
</tr>
<tr>
<td>Phenothiazines (e.g. chlorpromazine)</td>
<td>- Hyperprolactinaemia and anticholinergic effects. Reports of delayed orgasm at lower doses followed by normal orgasm but without ejaculation at higher doses&lt;sup&gt;14&lt;/sup&gt;&lt;br&gt;- Priapism has been reported with thioridazine, risperidone and chlorpromazine (probably due to α&lt;sub&gt;1&lt;/sub&gt; blockade)&lt;sup&gt;38,45,46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>- No effect on serum prolactin&lt;sup&gt;47&lt;/sup&gt;&lt;br&gt;- Possibly associated with low risk of sexual dysfunction, but studies are conflicting&lt;sup&gt;52,53&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risperidone</td>
<td>- Potent elevator of serum prolactin&lt;br&gt;- Less anticholinergic&lt;br&gt;- Specific peripheral α&lt;sub&gt;1&lt;/sub&gt;-adrenergic blockade leads to a moderately high reported incidence of ejaculatory problems such as retrograde ejaculation&lt;sup&gt;54,55&lt;/sup&gt;&lt;br&gt;- Priapism reported rarely&lt;sup&gt;26&lt;/sup&gt;&lt;br&gt;- Prevalence of sexual dysfunction reported to be 60–70%&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulpiride/amisulpride</td>
<td>- Potent elevators of serum prolactin&lt;sup&gt;18&lt;/sup&gt; but note that sulpiride (as the main FGA prescribed in the study) was not associated with greater sexual dysfunction than SGAs (with variable ability to raise prolactin) in the CUltASS-1 study&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thioxanthenes (e.g. flupentixol)</td>
<td>- Arousal problems and anorgasmia&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.
patients. Amantadine, bupropion, buspirone, bethanechol and yohimbine have all been used with varying degrees of success but have a number of unwanted adverse effects and interactions with other drugs (Table 1.37). Given that hyperprolactinaemia may contribute to sexual dysfunction, selegiline (enhances dopamine activity) has been...
tested in an RCT. This was negative.\textsuperscript{74} Testosterone patches have been shown to increase libido in women, although be aware that breast cancer risk may be significantly increased.\textsuperscript{75,76}

The evidence base supporting the use of ‘antidotes’ is poor.\textsuperscript{26} Drugs such as sildenafil (Viagra) or alprostadil (Caverject) are effective only in the treatment of erectile dysfunction (they have no effect on libido). Psychological approaches used by sexual dysfunction clinics may be difficult for clients with mental health problems to engage in.\textsuperscript{9}

References

32. Citrome L. Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2015; 69:978–997.


Further reading
Pneumonia

Recent systematic reviews\textsuperscript{1,2} have found that antipsychotic medication is associated with a 70–100% increase in risk of pneumonia in patients across a range of diagnoses. The risk was highest in the first week or first month of treatment and was seen with both SGAs and FGAs, with no difference between the two classes of antipsychotics.\textsuperscript{2} The risk associated with clozapine persisted beyond 30 days in one study of people with schizophrenia, though effects estimates of risk were notably lower than in the first month of treatment.\textsuperscript{3} A dose-related increase in risk has been reported, especially for clozapine\textsuperscript{3–5} and other antipsychotics.\textsuperscript{6} Polypharmacy involving FGAs and SGAs\textsuperscript{3,5,7} and combinations involving a mood stabiliser\textsuperscript{7} have been found to be associated with increased risk of pneumonia. In people with bipolar disorder, the risk with combinations involving all three classes of medication was higher than any other combinations.\textsuperscript{5}

A study of bipolar patients found that clozapine, olanzapine and haloperidol were linked to increased rates of pneumonia while lithium was protective.\textsuperscript{5} Another study suggests amisulpride is not linked to pneumonia.\textsuperscript{3} Clozapine re-exposure was associated with a greater risk for recurrent pneumonia than the risk of baseline pneumonia with initial clozapine treatment in one study.\textsuperscript{4} Schizophrenia itself seems to afford a higher risk of complications (e.g. admission to intensive care) in people diagnosed with pneumonia\textsuperscript{8} though neither diagnosis nor age appears to modify the effect of antipsychotic use on pneumonia.\textsuperscript{1} Likewise, risk of antipsychotic-associated pneumonia was increased in patients with Alzheimer’s disease and those without.\textsuperscript{9}

The mechanism by which antipsychotics increase the risk of pneumonia is not known. Possibilities include sedation (risk seems to be highest with drugs that show greatest H\textsubscript{1} antagonism\textsuperscript{3,7}); dystonia or dyskinesia; dry mouth causing poor bolus transport and so increasing the risk of aspiration (hypersalivation in the case of clozapine); general poor physical health\textsuperscript{3}; or perhaps some ill-defined effect on immune response.\textsuperscript{7,10} Nevertheless, the fact that antipsychotics can increase the risk of aspiration pneumonia and not other pneumonia types offers support to this as a plausible (perhaps sole) mechanism.\textsuperscript{11} With clozapine, pneumonia may also be secondary to constipation.\textsuperscript{12}

An increased risk of pneumonia should be assumed for all patients (regardless of age) taking any antipsychotic for any period. All patients should be very carefully monitored for signs of chest infection and effective treatment started promptly. Extra vigilance should be taken when re-exposing to clozapine patients with previous history of clozapine-induced pneumonia. Early referral to general medical services should be considered where there is any doubt about the severity or type of chest infection.

Summary

- Assume the use of all antipsychotics will increase the risk of pneumonia.
- Monitor all patients for signs of chest infection and treat promptly.

References

Switching antipsychotics

General recommendations for switching antipsychotics because of poor tolerability are shown in Table 1.38.

Table 1.38 General recommendations for switching antipsychotic drugs

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Suggested drugs</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute EPS1–8 – dystonia, parkinsonism, bradykinesia</td>
<td>Aripiprazole, Olanzapine, Quetiapine</td>
<td>Brexpiprazole*, Cariprazine*, Clozapine, Lurasidone, Ziprasidone</td>
</tr>
<tr>
<td>Akathisia2,9</td>
<td>Olanzapine, Quetiapine</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Dyslipidaemia7,8,10–15</td>
<td>Amisulpride, Aripiprazole*, Lurasidone, Ziprasidone*</td>
<td>Asenapine, Brexpiprazole*, Cariprazine*</td>
</tr>
<tr>
<td>Impaired glucose tolerance7,8,14,16–19</td>
<td>Amisulpride, Aripiprazole*, Lurasidone, Ziprasidone*</td>
<td>Brexpiprazole*, Cariprazine*, Haloperidol</td>
</tr>
<tr>
<td>Hyperprolactinaemia7,8,14,20–25</td>
<td>Aripiprazole*, Brexpiprazole*, Cariprazine*, Lurasidone, Quetiapine</td>
<td>Clozapine, Olanzapine, Ziprasidone*</td>
</tr>
<tr>
<td>Postural hypotension8,14,26</td>
<td>Amisulpride, Aripiprazole, Lurasidone</td>
<td>Brexpiprazole*, Cariprazine*, Haloperidol, Sulpiride, Trifluoperazine</td>
</tr>
<tr>
<td>QT prolongation25,27–33</td>
<td>Brexpiprazole*, Cariprazine*, Lurasidone, Paliperidone (all with ECG monitoring)</td>
<td>Low-dose monotherapy of any drug not formally contraindicated in QT prolongation (with ECG monitoring)</td>
</tr>
<tr>
<td>Sedation7,8,25</td>
<td>Amisulpride, Aripiprazole, Brexpiprazole*, Cariprazine*, Risperidone, Sulpiride</td>
<td>Haloperidol, Trifluoperazine, Ziprasidone*</td>
</tr>
<tr>
<td>Sexual dysfunction8,34–40</td>
<td>Aripiprazole, Lurasidone, Quetiapine</td>
<td>Brexpiprazole*, Cariprazine*, Clozapine</td>
</tr>
</tbody>
</table>
### References

12. Chrzanowski WK et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. Psychopharmacology (Berl) 2006; 189:259–266.

### Table 1.38 (Continued)

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Suggested drugs</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tardive dyskinesia&lt;sup&gt;41–44&lt;/sup&gt;</td>
<td>Clozapine</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Weight gain&lt;sup&gt;15,32,45–52&lt;/sup&gt;</td>
<td>Amisulpride</td>
<td>Asenapine</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Brexpiprazole&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Cariprazine&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lurasidone</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>†</sup> There is evidence that both switching to and co-prescription of aripiprazole are effective in reducing weight, prolactin and dyslipidaemia and in reversing impaired glucose tolerance.<sup>53–55</sup>

ECG, electrocardiogram; EPS, extrapyramidal symptoms.

* Not available in all countries; limited clinical experience with brexpiprazole and cariprazine.
Evidence of an association

Antipsychotic treatment was first linked to an increased risk of thromboembolism in 1965. Over a 10-year observation period, 3.1% of 1590 patients developed thromboembolism, of whom 9 (0.6%) died. However, the use of continuing antipsychotic medication is a proxy for severe mental illness and so observed associations with antipsychotics may reflect inherent pathological processes in the conditions for which they are prescribed. To some extent the relative contributions to risk of thromboembolism of antipsychotic treatment and the conditions they treat remain to be clearly defined.

In a landmark case-control study of nearly 30,000 patients an attempt was made to control for age and gender (but not for diagnosed psychiatric conditions). Risk of thromboembolism was greatly increased overall in people prescribed antipsychotics compared with controls (odds ratio [OR] 7.1). The increased risk was driven by the effect of low-potency phenothiazines (thioridazine, chlorpromazine [OR 24.1]) and was seen chiefly in the first few weeks on treatment. Absolute risk of venous thromboembolism was very small – 0.14% of patients. A secondary analysis suggested no association with diagnosis (not all prescribing was for schizophrenia).

A later meta-analysis of seven case-control studies confirmed an increased risk of thromboembolism with low-potency drugs (OR 2.91) and suggested lower but significantly increased risks with all types of antipsychotics. More recently a meta-analysis of 17 studies reported a small increased risk of thromboembolism with antipsychotics as a whole (OR 1.54) and with FGAs (OR 1.74) and SGAs (OR 2.07) as individual groups. Risk of thromboembolism clearly decreased with age. The authors suggested that the best that could be said was that antipsychotics probably increased the risk by about 50% but that residual confounding could not be discounted (i.e. other factors may have accounted for the effect seen).

Since this time, several more case-control studies have confirmed both the slightly increased risk of thromboembolism and the small risk overall; one study reported a risk for older people taking antipsychotics as 43 per 10,000 patient years. Other noteworthy findings were a substantially increased association with thromboembolism for prochlorperazine, a drug not always (or even often) prescribed for psychotic disorders, and an increased risk linked to antipsychotic dosage (risk was quadrupled in high-dose patients). An association with prochlorperazine prescribing had previously been suggested by a UK study. These findings add weight to the theory that antipsychotic medication (and not only the conditions it treats) is responsible for the increased hazard of thromboembolism. The highest risk of pathological blood clotting may be in the first 3 months or so of treatment.

Mechanisms

Several mechanisms have been suggested to explain the association between antipsychotics and thromboembolism. These proposed mechanisms are outlined in Box 1.5.
Increased risk of thromboembolism is reflected in numerous published reports of elevated incidence of pulmonary embolism,13 stroke14 and myocardial infarction.15,16

Summary

Antipsychotics are almost certainly associated with a small but important increased risk of venous thromboembolism and associated hazards of pulmonary embolism, stroke and myocardial infarction. Risk appears to be greatest during the early part of treatment and in younger people, and is probably dose-related.

Practice points

- Monitor closely all patients (but especially younger patients) starting antipsychotic treatment for signs of venous thromboembolism:
  - calf pain or swelling
  - sudden breathing difficulties
  - signs of myocardial infarction (chest pain, nausea, etc.)
  - signs of stroke (sudden unilateral weakness, etc.).
- Use the lowest therapeutic dose.
- Encourage good hydration and physical mobility.

References

REFRACTORY SCHIZOPHRENIA AND CLOzapine

Clozapine – dosing regimen

Many of the adverse effects of clozapine are dose-dependent and associated with speed of titration. Adverse effects also tend to be more common and severe at the beginning of therapy. Standard maintenance doses may even prove fatal in clozapine-naïve subjects. To minimise these problems it is important to start treatment at a low dose and to increase dosage slowly.

Clozapine should normally be started at a dose of 12.5 mg once a day, at night. Blood pressure should be monitored hourly for 6 hours because of the hypotensive effect of clozapine. This monitoring is not usually necessary if the first dose is given at night. On day 2, the dose can be increased to 12.5 mg twice daily. If the patient is tolerating

<table>
<thead>
<tr>
<th>Day</th>
<th>Morning dose (mg)</th>
<th>Evening dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>25</td>
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<tr>
<td>4</td>
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<td>50</td>
<td>75</td>
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<td>9</td>
<td>75</td>
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<td>10</td>
<td>75</td>
<td>100</td>
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<tr>
<td>11</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>125</td>
</tr>
<tr>
<td>13</td>
<td>125</td>
<td>125*</td>
</tr>
<tr>
<td>14</td>
<td>125</td>
<td>150</td>
</tr>
<tr>
<td>15</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>18</td>
<td>150</td>
<td>200†</td>
</tr>
<tr>
<td>21</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>28</td>
<td>200</td>
<td>250‡</td>
</tr>
</tbody>
</table>

* Target dose for female non-smokers (250 mg/day).
† Target dose for male non-smokers (350 mg/day).
‡ Target dose for female smokers (450 mg/day).
clozapine, the dose can be increased by 25–50 mg a day, until a dose of 300 mg a day is reached. This can usually be achieved in 2–3 weeks. Further dosage increases should be made slowly in increments of 50–100 mg each week. A plasma level of 350 µg/L should be aimed for to ensure an adequate trial, but response may occur at a lower plasma level. The average (there is substantial variation) dose at which this plasma level is reached varies according to gender and smoking status. The range is approximately 250 mg/day (female non-smoker) to 550 mg/day (male smoker). The total clozapine dose should be divided (usually twice daily) and, if sedation is a problem, the larger portion of the dose can be given at night.

Table 1.39 is a suggested starting regimen for clozapine. This is a cautious regimen – more rapid increases have been used. Slower titration may be necessary where sedation or other dose-related adverse effects are severe, in the elderly, the very young, those who are physically compromised or those who have poorly tolerated other antipsychotics. If the patient is not tolerating a particular dose, decrease to one that was previously tolerated. If the adverse effect resolves, increase the dose again but at a slower rate.

If for any reason a patient misses fewer than 2 days’ clozapine, re-start at the dose prescribed before the event. Do not administer extra tablets to catch up. If more than 2 days are missed, re-start and increase slowly (but at a faster rate than in drug-naïve patients). Please see section on ‘Re-starting clozapine after a break in treatment’ in this chapter.

References
Optimising clozapine treatment

Using clozapine alone

**Target dose**

Note that dose is best adjusted according to patient tolerability and plasma level.

- The average dose in UK is around 450 mg/day.\(^1\)
- Response usually seen in the range 150–900 mg/day.\(^2\)
- Lower doses are required in the elderly, females and non-smokers, and in those prescribed certain enzyme inhibitors\(^3,4\): See Table 1.39.

**Plasma levels**

- Most studies indicate that the threshold for response is in the range 350–420 µg/L.\(^5,6\)
  - The threshold may be as high as 500 µg/L.\(^7\)
- In male smokers who cannot achieve therapeutic plasma levels, metabolic inhibitors (fluvoxamine\(^8\) or cimetidine\(^9\) for example) can be co-prescribed but extreme caution is required.
- The importance of norclozapine levels has not been established but the clozapine/norclozapine ratio may aid assessment of recent compliance.

**Clozapine augmentation**

Clozapine ‘augmentation’ has become common practice because inadequate response to clozapine alone is a frequent clinical event. The evidence base supporting augmentation strategies is growing but remains insufficient to allow the development of any algorithm or schedule of treatment options. In practice, the result of clozapine augmentation is often disappointing and substantial changes in symptom severity are rarely observed. This clinical impression is supported by the equivocal results of many studies, which suggest a small effect size at best. Meta-analyses of antipsychotic augmentation suggest no effect,\(^10\) a small effect in long-term studies\(^11\) or, in the largest meta-analysis, a very small effect overall.\(^12\) An update on this last study\(^13\) confirmed this small effect size. Investigations into dopaminergic activity in refractory schizophrenia suggest there is no overproduction of dopamine.\(^14,15\) Dopamine antagonists are thus unlikely to be effective.

It is recommended that all augmentation attempts are carefully monitored and, if no clear benefit is forthcoming, abandoned after 3–6 months. The addition of another drug to clozapine treatment must be expected to worsen overall adverse-effect burden and so continued ineffective treatment is not appropriate. In some cases, the addition of an augmenting agent may reduce the severity of some adverse effects (e.g. weight gain, dyslipidaemia – see Table 1.40) or allow a reduction in clozapine dose. The addition of aripiprazole to clozapine may be particularly effective in reversing metabolic effects.\(^16,17\)

Table 1.40 shows suggested treatment options (in alphabetical order) where 3–6 months of optimised clozapine alone has not provided satisfactory benefit.
### Table 1.40  Suggested options for augmenting clozapine

<table>
<thead>
<tr>
<th>Option</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add amisulpride 18-23 (400–800 mg/day)</td>
<td>Some evidence and experience suggests amisulpride augmentation may be worthwhile. Two small RCTs, one of which found an increased adverse-effect burden, including cardiac adverse effects.24 May allow clozapine dose reduction25</td>
</tr>
<tr>
<td>Add aripiprazole 16,26-28 (15–30 mg/day)</td>
<td>Very limited evidence of therapeutic benefit, although a meta-analysis suggests some effect.29 Reduces weight and LDL cholesterol29</td>
</tr>
<tr>
<td>Add haloperidol 29,30,31 (2–3 mg/day)</td>
<td>Modest evidence of benefit</td>
</tr>
<tr>
<td>Add lamotrigine 32-34 (25–300 mg/day)</td>
<td>May be useful in partial or non-responders. May reduce alcohol consumption.35 Several equivocal reports36-38 but meta-analyses suggest moderate effect size39,40</td>
</tr>
<tr>
<td>Add omega-3 triglycerides 41,42 (2–3 g EPA daily)</td>
<td>Modest, and somewhat contested, evidence to support efficacy in non- or partial responders to antipsychotics, including clozapine</td>
</tr>
<tr>
<td>Add risperidone 43,44 (2–6 mg/day)</td>
<td>Supported by an RCT but there are also two negative RCTs, each with minuscule response rates.45,46 Small number of reports of increases in clozapine plasma levels. Long acting injection also an option47</td>
</tr>
<tr>
<td>Add sulpiride 46 (400 mg/day)</td>
<td>May be useful in partial or non-responders. Supported by a single randomised trial in English and three in Chinese.49 Overall effect modest</td>
</tr>
<tr>
<td>Add topiramate 50-54 (50–300 mg/day)</td>
<td>Two positive RCTs, two negative. Can worsen psychosis in some.33,55 Two meta-analyses including hitherto unknown Chinese data60,66 suggested robust effect on positive and negative symptoms, substantial weight loss but with psychomotor slowing and attention difficulties</td>
</tr>
<tr>
<td>Add ziprasidone 57-60 (80–160 mg/day)</td>
<td>Supported by three RCTs.60,61 Associated with QTc prolongation. Rarely used</td>
</tr>
</tbody>
</table>

Notes:
- Always consider the use of mood stabilisers and/or antidepressants, especially where mood disturbance is thought to contribute to symptoms.62-64
- Other options include adding pimozide, olanzapine or sertindole. None is recommended: pimozide and sertindole have important cardiac toxicity and the addition of olanzapine is poorly supported65 and likely to exacerbate metabolic adverse effects. Studies of pimozide66,67 and sertindole68 have shown no effect. One small RCT supports the use of Ginkgo biloba,69 another two support the use of memantine.70,71 Another study suggests possible benefit of augmentation with acetyl-L-carnitine72 and a case study reports good outcome with thyroxine.73

EPA, eicosapentaenoic acid; RCT, randomised controlled trial.

### References
8. Papetti F et al. [Clozapine-resistant schizophrenia related to an increased metabolism and benefit of fluvoxamine: four case reports]. Encephale 2007;33:811–818.
42. Puri BK et al. Sustained remission of positive and negative symptoms of schizophrenia following treatment with eicosapentaenoic acid. Arch Gen Psychiatry 1998; 55:188–189.
Alternatives to clozapine

Clozapine has the strongest evidence for efficacy for schizophrenia that has proved refractory to adequate trials of standard antipsychotic medication. Where treatment resistance has been established, clozapine treatment should not be delayed or withheld.\(^1\)\(^,\)\(^2\) The practice of using successive antipsychotic medications (or the latest) instead of clozapine is widespread but not supported by research. Where clozapine cannot be used (because of toxicity or patient refusal to take the medication or comply with the mandatory monitoring tests), other drugs or drug combinations may be tried (see Table 1.41) but, in practice, outcome is usually disappointing. Long-term data on efficacy and safety/tolerability are generally lacking. The data that are available do not allow any distinction between treatment regimens to be drawn, particularly choice of antipsychotic medication,\(^3\)\(^,\)\(^4\) but it seems wise to use single drugs before trying multiple drug options. Olanzapine is perhaps most often used as antipsychotic monotherapy, usually in dosage above the licensed range. If this fails, then the addition of a second antipsychotic (amisulpride, for example) is a possible next step, although the risk–benefit balance of combined antipsychotic medication regimens remains unclear.\(^5\) Amongst unconventional agents, minocycline and ondansetron have the advantage of low toxicity and good tolerability. A depot/LAI antipsychotic preparation is an option where the avoidance of covert non-adherence is a clinical priority.

Many of the treatments listed in Table 1.41 are somewhat experimental and some of the compounds are difficult to obtain (e.g. glycine, D-serine, sarcosine, etc.).

### Table 1.41 Alternatives to clozapine. Treatments are listed in alphabetical order: no preference is implied by position in table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol (+ antipsychotic)(^8)(^,)(^9)(^,)(^11)</td>
<td>Increases adenosinergic transmission which may reduce effects of dopamine. Three positive RCTs(^8)(^,)(^9)(^,)(^11)</td>
</tr>
<tr>
<td>Amisulpride (up to 1200 mg/day)</td>
<td>Single, small open study</td>
</tr>
<tr>
<td>Aripiprazole (15–30 mg/day)</td>
<td>Single randomised controlled study indicating moderate effect in patients resistant to risperidone or olanzapine (+ others). Higher doses (60 mg/day) have been used(^1)(^5)</td>
</tr>
<tr>
<td>Asenapine (+ antipsychotic)(^1)(^6)</td>
<td>Two case reports</td>
</tr>
<tr>
<td>Bexarotene (+ antipsychotic)(^7)(^5)(^1)(^7)</td>
<td>Retinoid receptor agonist. One RCT (n = 90) in non-refractory but suboptimally treated patients suggesting worthwhile effect on positive symptoms</td>
</tr>
<tr>
<td>Blonanserin (+ antipsychotic)(^1)(^5)</td>
<td>Atypical antipsychotic licensed in Japan and Korea. One case series found it to be effective and well tolerated</td>
</tr>
<tr>
<td>CBT(^1)(^9)</td>
<td>Non-drug therapies should always be considered</td>
</tr>
<tr>
<td>Celecoxib + risperidone(^2)(^0) (400 mg + 6 mg/day)</td>
<td>COX-2 inhibitors modulate immune response and may prevent glutamate-related cell death. One RCT showed useful activity in all main symptom domains. Associated with increased cardiovascular mortality</td>
</tr>
<tr>
<td>Donepezil (+ antipsychotic)(^2)(^1)(^2)(^3)</td>
<td>Three RCTs, one negative,(^2)(^2) two positive,(^2)(^1)(^,)(^2)(^3) suggesting a small effect on cognitive and negative symptoms</td>
</tr>
</tbody>
</table>
### Treatment Comments

**D-alanine** 100 mg/kg/day (+ antipsychotic)\(^{14}\)
- Glycine (NMDA) agonist. One positive RCT

**D-serine** 30 mg/kg/day (+ olanzapine)\(^{32}\)
- Glycine (NMDA) agonist. One positive RCT

**D-serine** up to 3 g as monotherapy\(^{26}\)
- Improved negative symptoms in one RCT, but inferior to high-dose olanzapine for treatment of positive symptoms

**ECT**\(^{27}\)
- Open studies suggest moderate effect, as does a retrospective study.\(^{28}\) Often reserved for last-line treatment in practice but can be successful in the short\(^{29}\) and long\(^{30}\) term

**Estradiol** 100–200 µg transdermal/day (+ antipsychotic)\(^{31}\)
- Oestrogens may be psychoprotective and/or antipsychotic. RCT (n = 183) in women of child-bearing age suggested benefits on positive symptoms, especially at higher doses. Note contraindications include being post-menopausal, history of venous thromboembolism, stroke, breast cancer, migraine with aura. Unopposed estradiol over long periods increases the risk of endometrial hyperplasia and malignancy – consider consulting an endocrinologist. Evidence in men is lacking

**Famotidine** 100 mg bd (+ antipsychotic)\(^{32}\)
- H\(_2\) antagonist. One short (4-week) RCT suggested some benefit in overall PANSS and CGI scores

**Ginkgo biloba** (+ antipsychotic)\(^{6,7}\)
- Possibly effective in combination with haloperidol. Unlikely to give rise to additional adverse effects but clinical experience limited

**Lurasidone** up to 240 mg/day\(^{33}\)
- One RCT of high-dose lurasidone, full results not yet reported. Appears to be well tolerated, may be effective but no clozapine comparison arm included

**Memantine** 20 mg/day (+ antipsychotic)\(^{34–36}\)
- Memantine is an NMDA antagonist. Two RCTs. The larger of the two (n = 138) was negative. In the smaller (n = 21), memantine improved positive and negative symptoms when added to clozapine. In another study in non-refractory schizophrenia, memantine improved negative symptoms when added to risperidone

**Mianserin + FGA** 30 mg/day\(^{32}\)
- 5-HT\(_2\) antagonist. One, small positive RCT

**Minocycline** 200 mg/day (+ antipsychotic)\(^{37,38}\)
- May be anti-inflammatory and neuroprotective. One open study (n = 22) and one RCT (n = 54) suggest good effect on negative and cognitive symptoms. Also one RCT (n = 50) of augmentation of clozapine.\(^{39}\) RCT evidence of neuroprotective effect in early psychosis\(^{40}\)

**Mirtazapine** 30 mg/day (+ antipsychotic)\(^{41–43}\)
- 5-HT\(_2\) antagonist. Two RCTs, one negative,\(^{42}\) one positive.\(^{41}\) Effect seems to be mainly on positive symptoms

**N-acetylcysteine** 2 g/day (+ antipsychotic)\(^{45}\)
- One RCT suggests small benefits in negative symptoms and rates of akathisia. Another RCT showed benefits in chronic schizophrenia.\(^{44}\) Case study of successful use of 600 mg a day.\(^{45}\) Large RCT in progress\(^{46}\)

**Olanzapine**\(^{47–52}\)
- 5–25 mg/day
  - Supported by some well-conducted trials but clinical experience disappointing. Some patients show moderate response

**Olanzapine**\(^{53–59}\)
- 30–60 mg/day
  - Contradictory findings in the literature but possibly effective. High-dose olanzapine is not atypical\(^{60}\) and can be poorly tolerated\(^{61}\) with gross metabolic changes\(^{59}\)

**Olanzapine + amisulpride**\(^{62}\)
- (up to 800 mg/day)
  - Small open study suggests benefit
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine + aripiprazole&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Single case report suggests benefit. Probably reduces metabolic toxicity</td>
</tr>
<tr>
<td>Olanzapine + glycine&lt;sup&gt;64&lt;/sup&gt; (0.8 g/kg/day)</td>
<td>Small, double-blind crossover trial suggests clinically relevant improvement in negative symptoms</td>
</tr>
<tr>
<td>Olanzapine + lamotrigine&lt;sup&gt;61,65&lt;/sup&gt; (up to 400 mg/day)</td>
<td>Reports contradictory and rather unconvincing. Reasonable theoretical basis for adding lamotrigine, which is usually well tolerated</td>
</tr>
<tr>
<td>Olanzapine + risperidone&lt;sup&gt;66&lt;/sup&gt; (various doses)</td>
<td>Small study suggests some patients may benefit from combined therapy after sequential failure of each drug alone</td>
</tr>
<tr>
<td>Olanzapine + sulpiride&lt;sup&gt;67&lt;/sup&gt; (600 mg/day)</td>
<td>Some evidence that this combination improves mood symptoms</td>
</tr>
<tr>
<td>Omega-3 triglycerides&lt;sup&gt;68,69&lt;/sup&gt;</td>
<td>Suggested efficacy but data very limited</td>
</tr>
<tr>
<td>Ondansetron 8 mg/day (+ antipsychotic)&lt;sup&gt;70–72&lt;/sup&gt;</td>
<td>Three RCTs. All show improvements in negative and cognitive symptoms</td>
</tr>
<tr>
<td>Propentofylline + risperidone&lt;sup&gt;73&lt;/sup&gt; (900 mg + 6 mg/day)</td>
<td>One RCT suggests some activity against positive symptoms</td>
</tr>
<tr>
<td>Quetiapine&lt;sup&gt;74–77&lt;/sup&gt;</td>
<td>Very limited evidence and clinical experience not encouraging. High doses (&gt;1200 mg/day) have been used but are no more effective&lt;sup&gt;78&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quetiapine + amisulpride&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Single naturalistic observation of 19 patients suggested useful benefit. Doses averaged 700 mg quetiapine and 950 mg amisulpride</td>
</tr>
<tr>
<td>Quetiapine + haloperidol&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Two case reports</td>
</tr>
<tr>
<td>Raloxifene 60–120 mg/day (+ antipsychotic)&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Selective oestrogen receptor modulator; may offer benefits of estradiol without long-term risks. One case report&lt;sup&gt;85&lt;/sup&gt; in post-menopausal treatment-resistant schizophrenia. Data in non-treatment resistance are rather conflicting, with two overlapping positive trials&lt;sup&gt;82,83&lt;/sup&gt; and one negative trial&lt;sup&gt;84&lt;/sup&gt;. One positive RCT in refractory women&lt;sup&gt;85&lt;/sup&gt;. Evidence in men is lacking</td>
</tr>
<tr>
<td>Riluzole 100 mg/day + risperidone up to 6 mg/day&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Glutamate modulating agent. One RCT demonstrated improvement in negative symptoms</td>
</tr>
<tr>
<td>Risperidone&lt;sup&gt;87–89&lt;/sup&gt; 4–8 mg/day</td>
<td>Doubtful efficacy in true treatment-refractory schizophrenia but some supporting evidence. May also be tried in combination with glycine&lt;sup&gt;64&lt;/sup&gt; or lamotrigine&lt;sup&gt;60&lt;/sup&gt; or indeed with other atypicals&lt;sup&gt;90&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risperidone LAI 50/100 mg 2/52&lt;sup&gt;91&lt;/sup&gt;</td>
<td>One RCT showing good response for both doses in refractory schizophrenia. Plasma levels for 100 mg dose similar to 6–8 mg/day oral risperidone</td>
</tr>
<tr>
<td>Ritanserin + risperidone (12 mg + 6 mg/day)&lt;sup&gt;92&lt;/sup&gt;</td>
<td>5-HT&lt;sub&gt;2A/2C&lt;/sub&gt; antagonist. One RCT suggests small effect on negative symptoms</td>
</tr>
<tr>
<td>Sarcosine (2 g/day)&lt;sup&gt;93,94&lt;/sup&gt; (+ antipsychotic)</td>
<td>Enhances glycine action. Supported by two RCTs</td>
</tr>
<tr>
<td>Sertindole&lt;sup&gt;95&lt;/sup&gt; (12–24 mg/day)</td>
<td>One large RCT (conducted in 1996–1998 but published in 2011) suggested good effect and equivalence to risperidone. Around half of subjects responded. Another RCT&lt;sup&gt;96&lt;/sup&gt; showed no effect at all when added to clozapine. Little experience in practice</td>
</tr>
<tr>
<td>Topiramate (300 mg/day) (+ antipsychotic)&lt;sup&gt;97&lt;/sup&gt;</td>
<td>Small effect shown in single RCT. Induces weight loss. Cognitive adverse effects likely</td>
</tr>
</tbody>
</table>
Before using any of the regimens outlined, readers should consult the primary literature cited. Particular care should be taken to inform patients where prescribing is off-label and to ensure that they understand the potential adverse effects of the more experimental treatments.

Non-clozapine treatment of refractory schizophrenia is an area of active research. Glutamatergic drugs may hold promise (although bitopertin is inactive), as may 5-HT$_{2A}$ inverse agonists.

References

84. Weiser M et al. Raloxifene plus antipsychotics versus placebo plus antipsychotics in severely ill decompensated postmenopausal women with schizophrenia or schizoaffective disorder: a randomized controlled trial. J Clin Psychiatry 2017;78:e758–e765.
Re-starting clozapine after a break in treatment

Re-titration of clozapine is somewhat constrained by the manufacturer’s recommendation that re-titration should be the same as initial titration if clozapine has been missed for more than 48 hours. While somewhat arbitrary, this recommendation certainly recognises the dangers of giving clozapine to those who are intolerant of its effects (clozapine has been used in criminal poisonings). However, there is evidence that faster titrations may be safe in both those naïve to clozapine and those re-starting it. It has been suggested that the starting dose of 12.5 mg or 25 mg can be seen as a pharmacological challenge test; where this is well tolerated, rapid titration may be beneficial without an increased risk of problematic adverse effects. Nevertheless, more cautious dosage titration may still be suitable for certain patients, such as elderly patients, people with Parkinson’s disease and out-patients starting clozapine who are uncertain about the potential benefits of the medication.

Table 1.42 provides general advice on re-starting clozapine after gaps of various lengths. It takes account of the need to regain antipsychotic activity with clozapine while ensuring safety during titration. The key feature is flexibility: the dose prescribed for a patient depends upon their ability to tolerate previous doses.

<table>
<thead>
<tr>
<th>Time since last clozapine dose</th>
<th>Action to re-start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 48 hours</td>
<td>Re-start at previous dose – no re-titration required</td>
</tr>
</tbody>
</table>
| 48–72 hours                   | Begin rapid re-titration as soon as possible  
On day 1, re-start with half of the previously prescribed total daily dose given in divided doses 12 hours apart. Then give 75% of previous daily dose on day 2 and, if prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule on day 3 |
| 72 hours to 1 week            | Begin re-titration with 12.5 mg or 25 mg clozapine  
Try a second dose 12 hours later if the first is well tolerated. Increase to ‘normal’ dose according to patient tolerability over at least 3 days |
| More than 1 week              | Re-titrate as if new patient  
Aim to reach previously prescribed dose within 2–4 weeks. Increase according to tolerability |

References

Initiation of clozapine for community-based patients

Contraindications to community initiation

- History of seizures, significant cardiac disease, unstable diabetes, paralytic ileus, blood dyscrasia, NMS or other disorder that increases the risk of serious adverse effects (initiation with close monitoring in hospital may still be possible).
- Previous severe adverse effects on titration of clozapine or other antipsychotics.
- Unreliable or chaotic lifestyle that may affect adherence to the medication or the monitoring regimen.
- Significant abuse of alcohol or other drugs likely to increase the risk of adverse effects (e.g. cocaine).

Suitability for community initiation

All the answers should be yes.

- Is the patient likely to be adherent with oral medication and to monitoring requirements?
- Has the patient understood the need for regular physical monitoring and blood tests?
- Has the patient understood the possible adverse effects and what to do about them (particularly the rare but serious ones)?
- Is the patient readily contactable (e.g. in the event of a result that needs follow-up)?
- Is it possible for the patient to be seen every day during the early titration phase?
- Is the patient able to collect medication every week or can medication be delivered to their home?
- Is the patient likely to be able to seek help out of hours if they experience potentially serious adverse effects (e.g. indicators of myocarditis or infection such as fever, malaise, chest pain)?

Initial work-up

To screen for risk factors and provide a baseline:

- physical examination, full blood count, liver function tests, urea and electrolytes (U&Es), lipids, glucose/HbA1C. Consider troponin, C-reactive protein (CRP), beta-natriuretic peptide, erythrocyte sedimentation rate (ESR) (as baseline for further tests)
- ECG – particularly to screen for evidence of past myocardial infarction or ventricular abnormality
- echocardiogram if clinically indicated.

Mandatory blood monitoring and registration

- Register with the relevant monitoring service.
- Perform baseline blood tests (white cell count and differential count) before starting clozapine.
Further blood testing continues weekly for the first 18 weeks and then every 2 weeks for the remainder of the year. After that, the blood monitoring is usually done monthly.

Inform the patient’s GP.

**Dosing**

Starting clozapine in the community requires a slow and flexible titration schedule. Prior antipsychotics should be slowly discontinued during the titration phase (depots can usually be stopped at the start of titration). Clozapine can cause marked postural hypotension. The initial monitoring is partly aimed at detecting and managing this.

There are two basic methods for starting clozapine in the community. One is to give the first dose in the morning in clinic and then monitor the patient for at least 3 hours. If the dose is well tolerated, the patient is then allowed home with a dose to take before going to bed. This dosing schedule is described in Table 1.43. This is a very cautious schedule: most patients will tolerate faster titration. The second method involves giving the patient the first dose to take immediately before bed, so avoiding the need for close physical monitoring immediately after administration. Subsequent dosing and monitoring is as for the first method. All initiations should take place early in the week (e.g. on a Monday) so that adequate staffing and monitoring are assured.

**Adverse effects**

Sedation, hypersalivation and hypotension are common at the start of treatment. These effects can usually be managed (see section on ‘Clozapine: common adverse effects’ in this chapter) but require particular attention in community titration.

The formal carer (usually the Community Psychiatric Nurse) should inform the prescriber if:

- temperature rises above 38 °C (this is very common and is not a good reason, on its own, for stopping clozapine)
- pulse is >100 bpm (also common and not, on its own, a reason for stopping, but may sometimes be linked to myocarditis)
- postural drop of >30 mmHg
- patient is clearly over-sedated
- any signs of constipation
- flu-like symptoms (malaise, fatigue, etc.)
- chest pain, dyspnoea, tachypnoea
- any other adverse effect that is intolerable.

A doctor should see the patient at least once a week for the first month to assess mental and physical state.

**Recommended additional monitoring**

Recommended additional monitoring is summarised in Table 1.44.

Consider monitoring plasma troponin, beta-natriuretic peptide and CRP weekly in the first 6 weeks of treatment, particularly where there is any suspicion of myocarditis.
## Table 1.43 Suggested titration regimen for initiation of clozapine in the community. Note that much faster titrations can be undertaken in many patients where tolerability allows

<table>
<thead>
<tr>
<th>Day</th>
<th>Day of the week</th>
<th>Morning dose (mg)</th>
<th>Evening dose (mg)</th>
<th>Monitoring</th>
<th>Percentage dose of previous antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monday</td>
<td>6.25</td>
<td>6.25</td>
<td>A</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Tuesday</td>
<td>6.25</td>
<td>6.25</td>
<td>A</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Wednesday</td>
<td>6.25</td>
<td>6.25</td>
<td>A</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Thursday</td>
<td>6.25</td>
<td>12.5</td>
<td>A, B, FBC</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Friday</td>
<td>12.5</td>
<td>12.5</td>
<td>A</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Check results from day 4. Remind patient of out-of-hours arrangements for weekend</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Saturday</td>
<td>12.5</td>
<td>12.5</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sunday</td>
<td>12.5</td>
<td>12.5</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Monday</td>
<td>12.5</td>
<td>25</td>
<td>A</td>
<td>75*</td>
</tr>
<tr>
<td>9</td>
<td>Tuesday</td>
<td>12.5</td>
<td>25</td>
<td>A</td>
<td>75*</td>
</tr>
<tr>
<td>10</td>
<td>Wednesday</td>
<td>25</td>
<td>25</td>
<td>A</td>
<td>75*</td>
</tr>
<tr>
<td>11</td>
<td>Thursday</td>
<td>25</td>
<td>37.5</td>
<td>A, B, FBC</td>
<td>75*</td>
</tr>
<tr>
<td>12</td>
<td>Friday</td>
<td>25</td>
<td>37.5</td>
<td>A</td>
<td>75*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Check results from day 1. Remind patient of out-of-hours arrangements for weekend</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Saturday</td>
<td>25</td>
<td>37.5</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Sunday</td>
<td>25</td>
<td>37.5</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Monday</td>
<td>37.5</td>
<td>37.5</td>
<td>A</td>
<td>50*</td>
</tr>
<tr>
<td>16</td>
<td>Tuesday</td>
<td>37.5</td>
<td>37.5</td>
<td>Not seen unless problems</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Wednesday</td>
<td>37.5</td>
<td>50</td>
<td>A</td>
<td>25*</td>
</tr>
<tr>
<td>18</td>
<td>Thursday</td>
<td>37.5</td>
<td>50</td>
<td>Not seen unless problems</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Friday</td>
<td>50</td>
<td>50</td>
<td>A, B, FBC</td>
<td>25*</td>
</tr>
<tr>
<td>20</td>
<td>Saturday</td>
<td>50</td>
<td>50</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Sunday</td>
<td>50</td>
<td>50</td>
<td>No routine monitoring unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Monday</td>
<td>50</td>
<td>75</td>
<td>A</td>
<td>25*</td>
</tr>
<tr>
<td>23</td>
<td>Tuesday</td>
<td>50</td>
<td>75</td>
<td>Not seen unless problems</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Wednesday</td>
<td>75</td>
<td>75</td>
<td>A</td>
<td>25*</td>
</tr>
</tbody>
</table>
Switching from other antipsychotics

- The switching regimen will be largely dependent on the patient’s mental state.
- Consider potential additive adverse effects of antipsychotics (e.g. hypotension, sedation, effect on QTc interval).
- Consider drug interactions (e.g. some SSRIs may increase clozapine levels).
- All depots, sertindole, pimozide and ziprasidone should be stopped before clozapine is started.
- Other antipsychotics and clozapine may be cross-tapered with varying degrees of caution. ECG monitoring is prudent when clozapine is co-prescribed with other drugs known to affect QT interval.
Serious cardiac adverse effects

Patients should be closely observed for signs or symptoms of myocarditis, particularly during the first 2 months, and advised to inform staff if they experience these, and to seek out-of-hours review if necessary. These include persistent tachycardia (although commonly benign), palpitations, shortness of breath, fever, arrhythmia, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure. (See section on ‘Clozapine: serious haematological and cardiovascular adverse effects’ in this chapter.)

Further reading

### CLOZAPINE ADVERSE EFFECTS

#### Clozapine: common adverse effects

Table 1.45 describes some more common adverse effects of clozapine (no particular frequency implied by order).

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Time course</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>First few months, may persist, but usually wears off to some extent</td>
<td>Give smaller dose in the morning&lt;br&gt;Reduce dose if possible</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>First few months, may persist, but sometimes wears off&lt;br&gt;Often very troublesome at night</td>
<td>Give hyoscine 300µg sucked and swallowed up to three times a day. Many other options (see section on ‘Clozapine-induced hypersalivation’ in this chapter). Note anticholinergics worsen constipation and cognition</td>
</tr>
<tr>
<td>Constipation</td>
<td>First 4 months are the highest risk, usually persists</td>
<td>Advise patients of the risks before starting, screen regularly, ensure adequate fibre, fluid and exercise. Bulk-forming laxatives are usually first line, but have a low threshold for adding osmotic and/or stimulant laxatives early. Stop other medicines that may be contributing and reduce clozapine dose if possible. Effective treatment or prevention of constipation is essential as death may result.1–5 See section on ‘Clozapine-induced gastrointestinal hypomotility (CIGH)’ in this chapter</td>
</tr>
<tr>
<td>Hypotension</td>
<td>First 4 weeks</td>
<td>Advise patient to take time when standing up&lt;br&gt;Reduce dose or slow down rate of increase. Increase fluid intake to 2L daily.6 If severe, consider moclobemide and Bovril,7 or fludrocortisone. Over longer term, weight gain may lead to hypertension</td>
</tr>
<tr>
<td>Hypertension</td>
<td>First 4 weeks, sometimes longer</td>
<td>Monitor closely and increase dose as slowly as is necessary. Hypotensive therapy is sometimes necessary8</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>First 4 weeks, but sometimes persists</td>
<td>Very common in early stages of treatment but usually benign. May be dose-related.9 Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate myocarditis11,12 (see section on ‘Clozapine: serious haematological and cardiovascular adverse effects’ in this chapter). Referral to a cardiologist is advised. Clozapine should be stopped if tachycardia occurs in the context of chest pain or heart failure. Benign sinus tachycardia can be treated with bisoprolol or atenolol,13 although evidence base is poor.14 Ibradine may be used if hypotension or contraindications limit the use of beta blockers.15 Note that prolonged tachycardia can itself precipitate cardiomyopathy16</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Usually during the first year of treatment, but may continue</td>
<td>Dietary counselling is essential. Advice may be more effective if given before weight gain occurs&lt;br&gt;Weight gain is common and often profound (&gt;10lb). Many treatments available (see section on ‘Weight gain’ in this chapter)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Time course</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>First 4 weeks</td>
<td>Clozapine induces inflammatory response (increased CRP and interleukin-6).17–19 Give paracetamol but check FBC for neutropenia. Reduce rate of dose titration.20 This fever is not usually related to blood dyscrasias21,22 but beware myocarditis and NMS</td>
</tr>
<tr>
<td>Seizures23</td>
<td>May occur at any time24</td>
<td>Related to dose, plasma level and rapid dose escalation.25 Consider prophylactic topiramate, lamotrigine, gabapentin or valproate* if on high dose (≥500 mg/day) or with high plasma level (≥500 µg/L). Some suggest risk of seizures below 1300 µg/L (about 1 in 20 people) is not enough to support primary prophylaxis.26 After a seizure: withhold clozapine for 1 day; re-start at half previous dose; give anticonvulsant.1 EEG abnormalities are common in those on clozapine27</td>
</tr>
<tr>
<td>Nausea</td>
<td>First 6 weeks</td>
<td>May give anti-emetic. Avoid prochlorperazine and metoclopramide if previous EPS. Avoid domperidone if underlying cardiac risk or QTc prolongation. Ondansetron is a good choice, but it may worsen constipation</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td>May occur at any time</td>
<td>Try reducing the dose or manipulating dose schedule to avoid periods of deep sedation. Avoid fluids before bedtime. Consider scheduled night-time toileting. May resolve spontaneously28 but may persist for months or years.29 Seems to affect 1 in 5 people on clozapine.30 In severe cases, desmopressin nasal spray (10–20 µg nocte) is usually effective31 but is not without risk: hyponatraemia may result.32 Anticholinergic agents may be effective33 but support for this approach is weak and constipation and sedation may worsen. Ephedrine,34 pseudoephedrine35 and aripiprazole36,37 have also been used</td>
</tr>
<tr>
<td>Neutropenia/agranulocytosis</td>
<td>First 18 weeks (but may occur at any time)</td>
<td>Stop clozapine; admit to hospital if agranulocytosis confirmed</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease (GORD)38,39</td>
<td>Any time</td>
<td>Proton pump inhibitors often prescribed but some are CYP1A2 inducers and possibly increase risk of neutropenia and agranulocytosis.40,41 Reasons for GORD association unclear – clozapine is an H₂ antagonist42</td>
</tr>
<tr>
<td>Myoclonus25,43–45</td>
<td>During dose titration or plasma level increases</td>
<td>May precede full tonic-clonic seizure. Reduce dose. Anticonvulsants may help, and will reduce the likelihood of progression to seizures. Valproate is first choice; lamotrigine may worsen some types of myoclonus</td>
</tr>
</tbody>
</table>

* Usual dose is 1000–2000 mg/day. Plasma levels may be useful as a rough guide to dosing – aim for 50–100 mg/L. Use of modified-release preparation (Epilim Chrono) may aid compliance: can be given once-daily and may be better tolerated.

† Use valproate if schizoaffective; lamotrigine if poor response to clozapine or continued negative symptoms; topiramate if weight loss required (but beware cognitive adverse effects); gabapentin if other anticonvulsants are poorly tolerated.25

CRP, C-reactive protein; EEG, electroencephalogram; EPS, extrapyramidal symptoms; FBC, full blood count; NMS, neuroleptic malignant syndrome.
References


Further reading

### Clozapine: uncommon or unusual adverse effects

Table 1.46 gives brief details (in alphabetical order) of unusual or uncommon adverse effects of clozapine.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Time course</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranulocytosis/neutropenia (delayed)</td>
<td>Usually first 3 months but may occur at any time</td>
<td>Occasional reports of apparent clozapine-related blood dyscrasia even after 1 year of treatment. Risk may be elevated for up to 9 years. It is possible that clozapine is not the causative agent in some cases. See section on ‘Clozapine: serious haematological and cardiovascular adverse effects’ in this chapter.</td>
</tr>
<tr>
<td>Colitis</td>
<td>Any time</td>
<td>A few reports in the literature, but clear causative link to clozapine not determined. Any severe or chronic diarrhoea should prompt specialist referral as there is a substantial risk of death. Anticholinergic use probably increases risk of colitis and necrosis.</td>
</tr>
<tr>
<td>Delirium</td>
<td>Any time</td>
<td>Reported to be fairly common, but rarely seen in practice if dose is titrated slowly and plasma level determinations are used.</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>First 4 weeks</td>
<td>Reasonably common but significance unclear. Some suggestion that eosinophilia predicts neutropenia but this is disputed. May be associated with colitis and related symptoms. Occasional reports linking eosinophilia with myocarditis and interstitial nephritis. Usually benign but investigate for signs of other organ damage. Successful re-challenge in the absence of organ inflammation is possible. Concomitant antidepressants may increase risk.</td>
</tr>
<tr>
<td>Heat stroke</td>
<td>Any time</td>
<td>Occasional case reported. May be mistaken for NMS.</td>
</tr>
<tr>
<td>Hepatic failure/enzyme abnormalities</td>
<td>First few months</td>
<td>Benign changes in LFTs are common (up to 50% of patients) but worth monitoring because of the very small risk of fulminant hepatic failure. Rash may be associated with clozapine-related hepatitis.</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Usually first 2 weeks, possibly up to 3 months</td>
<td>A handful of reports implicating clozapine. Immune-mediated; may occur after only a few doses. Symptoms may include fever, skin rash and eosinophilia.</td>
</tr>
<tr>
<td>Ocular effects</td>
<td>Any time</td>
<td>Single case report of ocular pigmentation. Clozapine may cause dry eye syndrome.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Usually first 6 weeks, possibly later in treatment</td>
<td>Several reports of asymptomatic and symptomatic pancreatitis sometimes associated with eosinophilia. Some authors recommend monitoring serum amylase in all patients treated with clozapine. No cases of successful re-challenge after pancreatitis.</td>
</tr>
<tr>
<td>Parotid gland swelling</td>
<td>Usually first few weeks, but may occur later</td>
<td>Several case reports. Unclear mechanism, possibly immunological or thickening of saliva leading to calcium precipitation. May be recurrent. May resolve spontaneously. Treatment of hypersalivation with terazosin in combination with benzatropine may be helpful.</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Any time</td>
<td>Several reports in the literature. Symptoms include fatigue, chest pain, dyspnoea and tachycardia, but may be asymptomatic. Signs include raised inflammatory markers (specifically trop I) and proBNP levels. Use echocardiogram to confirm/rule out effusion. Successful re-challenge possible.</td>
</tr>
</tbody>
</table>

(Continued)
Table 1.46 (Continued)

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Time course</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia(^{78-85})</td>
<td>Usually early in treatment, but may be any time</td>
<td>May result from saliva aspiration (this may be why pneumonia sometimes appears to be dose-related(^{86,87}), very rarely constipation.(^{88}) Pneumonia is a common cause of death in people on clozapine.(^{79}) Infections in general may be more common in those on clozapine(^{89}) and use of antibiotics is also increased.(^{90}) Note that respiratory infections may give rise to elevated clozapine levels(^{91-94}) (possibly an artefact: smoking usually ceases during an infection). Clozapine is often successfully continued after the pneumonia has resolved, but recurrence may be more likely(^{95-97}).</td>
</tr>
<tr>
<td>Stuttering(^{98-106})</td>
<td>Any time</td>
<td>Case reports. May be a result of EPS or epileptiform activity. Check plasma levels, consider dose reduction and/or anticonvulsant – may be a warning sign for impending generalised seizures(^{107}).</td>
</tr>
<tr>
<td>Thrombocytopenia(^{108-111})</td>
<td>First 3 months</td>
<td>Few data but apparently fairly common (incidence over 1 year of 3%(^{112})). Probably transient and clinically unimportant, but persistent in some cases.(^{113,114}) Thrombocytosis also reported(^{115}).</td>
</tr>
<tr>
<td>Skin reactions(^{116})</td>
<td>Any time</td>
<td>Presence of skin diseases in general is higher in those with schizophrenia.(^{117}) Two reports of vasculitis(^{118,119}) in which patients developed confluent erythematous rash on lower limbs. One report of Stevens–Johnson syndrome,(^{120}) two reports of pityriasis rosea,(^{121,122}) one report of a papular rash,(^{123}) one report of exanthematic pustulosis(^{124}) and one fatal case of Sweet’s syndrome(^{125}).</td>
</tr>
<tr>
<td>Thromboembolism(^{126-130})</td>
<td>Any time</td>
<td>Weight increase and sedation may contribute to risk of thromboembolism, but other mechanisms including increased platelet aggregation via 5-HT(_2A) receptor activation may also be responsible.(^{131}) Hyperprolactinaemia also increases the risk. Clozapine appears to increase risk of pulmonary thromboembolism by 28 times.(^{132}) Threshold for prophylactic antithrombotic treatment where additional risk factors are present (surgery, immobility) should probably be low. Continuation of therapy after embolism may be possible(^{133}) but consult haematologist as without prophylactic antithrombotic treatment recurrence is likely(^{134,135}).</td>
</tr>
</tbody>
</table>

BNP, beta-natriuretic peptide; EPS, extrapyramidal symptoms; LFT, liver function test; NMS, neuroleptic malignant syndrome.

References

76. Prisco V et al. Brain natriuretic peptide as a biomarker of asymptomatic clozapine-related heart dysfunction: a criterion for a more cautious administration. Clin Schizophr Relat Psychoses 2016; [Epub ahead of print]
Clozapine: serious haematological and cardiovascular adverse effects

Agranulocytosis, thromboembolism, cardiomyopathy and myocarditis

Clozapine is a somewhat toxic drug, but it may reduce overall mortality in schizophrenia, largely because of a reduction in the rate of suicide.\textsuperscript{1,2} Clozapine can cause serious, life-threatening adverse effects, of which \textit{agranulocytosis} is the best known. Early US data suggested a mortality rate of 12 in 99,502 (0.012\%).\textsuperscript{3} Risk is clearly well managed by the approved clozapine monitoring systems.

\textit{Thromboembolism}

A possible association between clozapine and \textit{thromboembolism} has been suggested.\textsuperscript{4} Initially, Walker et al.\textsuperscript{1} uncovered a risk of fatal pulmonary embolism of 1 in 4,500 — about 20 times the risk in the population as a whole. Following a case report of non-fatal pulmonary embolism possibly related to clozapine,\textsuperscript{5} data from the Swedish authorities were published.\textsuperscript{6} Twelve cases of venous thromboembolism were described, of which five were fatal. The risk of thromboembolism was estimated to be 1 in 2000 to 1 in 6000 patients treated. Thromboembolism may be related to clozapine’s observed effects on antiphospholipid antibodies\textsuperscript{7} and platelet aggregation.\textsuperscript{8} It seems most likely to occur in the first 3 months of treatment but can occur at any time. Other antipsychotic drugs are also strongly linked to thromboembolism\textsuperscript{9–15} although clozapine appears to have the most reports.\textsuperscript{16}

With all drugs, the causes of thromboembolism are probably multifactorial.\textsuperscript{10} Sedation may lead to a reduction in movement and consequent venous stasis. Obesity, hyperprolactinaemia and smoking are additional independent risk factors for thromboembolism.\textsuperscript{17,18} Encouraging exercise and ensuring good hydration are essential precautionary measures.\textsuperscript{19}

\textit{Myocarditis and cardiomyopathy}

Clozapine is associated with \textit{myocarditis} and \textit{cardiomyopathy}. Myocarditis is a hypersensitivity response to clozapine, resulting in inflammation of the myocardium. Some debate surrounds the prevalence of myocarditis, with several Australian studies finding it to occur in around 3\% of patients.\textsuperscript{20–22} Studies conducted elsewhere\textsuperscript{23–25} have suggested a much lower incidence of 1\% or less. The reason for such variation in reported incidence is unclear; some authors propose that a lack of robust monitoring leads to missed diagnoses in those countries reporting lower incidences.\textsuperscript{26} Myocarditis is potentially fatal, and is most likely to occur in the first 6–8 weeks of starting clozapine treatment (median 3 weeks),\textsuperscript{27} but may occur at any time.

Cardiomyopathy is usually diagnosed from echocardiography to establish left ventricular dilatation (resulting in a reduced ejection fraction) and/or hypertrophy. It may develop following myocarditis (if clozapine is not stopped), but other causative factors may include persistent tachycardia, obesity, diabetes, and previous personal or familial cardiac events.\textsuperscript{26} Most incidence data originate from Australia and rates range from 0.02\% to 5\%.\textsuperscript{22,28} Cardiomyopathy may occur later in treatment than myocarditis (median 9 months),\textsuperscript{27} but as with myocarditis it may occur at any time.
Despite uncertainty over incidence, patients should be closely monitored for signs of myocarditis, especially in the first few months of treatment. Symptoms include hypotension, tachycardia, fever, flu-like symptoms, fatigue, dyspnoea (with increased respiratory rate) and chest pain. Signs include ECG changes (ST depression), enlarged heart on radiography/echocardiography and eosinophilia. Many of these symptoms occur in patients on clozapine not developing myocarditis and, conversely, their absence does not rule out myocarditis. Nonetheless, signs of heart failure should provoke immediate cessation of clozapine and referral to a cardiologist. Re-challenge has been successfully completed (the use of beta blockers and angiotensin-converting enzyme [ACE] inhibitors may help) but recurrence is also possible. Use of echocardiography and measurement of CRP and troponin are essential in cases of re-challenge.

Autopsy findings suggest that fatal myocarditis can occur in the absence of clear cardiac symptoms, although tachycardia and fever are usually present. A group from Melbourne, Australia, has put forward a monitoring programme which is said to detect 100% of symptomatic cases of myocarditis using measurement of troponin I or T and C-reactive protein (see Table 1.47). Echocardiography at baseline, 6 months and yearly thereafter is routine practice in Australia, although the benefit of this monitoring in the absence of other symptoms has recently been questioned. The absence of resources to provide monitoring beyond routine blood tests (including CRP and troponin) and ECG should not be a barrier to prescribing for most patients.

Factors that may increase the risk of developing myocarditis include rapid dose increases, concurrent use of sodium valproate, and older age (31% increased risk for each additional decade). Other psychotropic drugs, including lithium, risperidone, haloperidol, chlorpromazine and fluphenazine, have also been associated with myocarditis. It is probably preferable to avoid concomitant use of other medicines that may contribute to the risk, but this may be practically difficult. Any pre-existing cardiac disorder, previous cardiac event, use of illicit drugs or family history of cardiac disease should provoke extra caution.

Cardiomyopathy should be suspected in any patient showing signs of heart failure, which should provoke immediate cessation of clozapine and referral. Presentation of cardiomyopathy varies somewhat and is often asymptomatic in the early stages, so any reported symptoms of palpitations, chest pain, syncope, sweating, decreased exercise capacity or breathing difficulties should be closely investigated. Successful re-challenge with rigorous cardiac monitoring (including echocardiography) may be possible.

Note also that, despite an overall reduction in mortality, younger patients may have an increased risk of sudden death, perhaps because of clozapine-induced ECG changes. The overall picture remains very unclear but caution is required. There may, of course, be similar problems with other antipsychotics.

Summary

- Overall mortality is lower for those on clozapine than in schizophrenia as a whole.
- Risk of fatal agranulocytosis is less than 1 in 8000 patients treated.
- Risk of fatal pulmonary embolism is estimated to be around 1 in 4500 patients treated.
- Risk of fatal myocarditis or cardiomyopathy may be as high as 1 in 1000 patients.
- Careful monitoring is essential during clozapine treatment, particularly during the first 3 months (see Table 1.47).

**Table 1.47** Suggested monitoring for myocarditis

<table>
<thead>
<tr>
<th>Time/condition</th>
<th>Signs/symptoms to monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Pulse, blood pressure, temperature, respiratory rate</td>
</tr>
<tr>
<td></td>
<td>Full blood count (FBC)</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein (CRP)</td>
</tr>
<tr>
<td></td>
<td>Troponin</td>
</tr>
<tr>
<td></td>
<td>Echocardiography (if available)</td>
</tr>
<tr>
<td></td>
<td>Electrocardiogram (ECG)</td>
</tr>
<tr>
<td>Daily, if possible</td>
<td>Pulse, blood pressure, temperature, respiratory rate</td>
</tr>
<tr>
<td></td>
<td>Ask about: chest pain, fever, cough, shortness of breath, exercise capacity</td>
</tr>
<tr>
<td>On days 7, 14, 21, and 28</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td>Troponin</td>
</tr>
<tr>
<td></td>
<td>FBC</td>
</tr>
<tr>
<td></td>
<td>ECG if possible</td>
</tr>
<tr>
<td>If CRP &gt;100 mg/L or troponin &gt; twice upper limit of normal</td>
<td>Stop clozapine; repeat echo</td>
</tr>
<tr>
<td>If fever + tachycardia + raised CRP or troponin (but not as above)</td>
<td>Daily CRP and troponin measures</td>
</tr>
</tbody>
</table>

**References**


Further reading
Clozapine is well known to be causally associated with hypersalivation (sialorrhoea), with excess salivary pooling in the mouth and drooling, particularly at night. The problem tends to occur in the early stages of treatment and is probably dose-related. Clinical observation suggests that hypersalivation reduces somewhat in severity over time (usually several months) but may persist. Clozapine-induced hypersalivation is socially embarrassing, has a negative impact on quality of life and, given that it has been implicated as a contributory factor in the development of aspiration pneumonia, could be potentially life-threatening. Treatment is therefore a matter of some urgency.

The pharmacological basis of clozapine-related hypersalivation remains unclear. Suggested mechanisms include muscarinic M₄ agonism, adrenergic α₂ antagonism and inhibition of the swallowing reflex. The last of these is supported by trials which suggest that saliva production is not increased in clozapine-treated patients, although at least one study has observed marked increases in salivary flow in the first 3 weeks of treatment.

Whatever the mechanism, drugs that reduce saliva production are likely to diminish the severity of this adverse effect. Non-drug treatments may be used if appropriate – these include chewing gum, elevating pillows and placing a towel on the pillow to prevent soaking of clothes. Table 1.48 describes the pharmacological treatments so far examined.

<table>
<thead>
<tr>
<th>Table 1.48 Clozapine-related hypersalivation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Amisulpride</td>
</tr>
<tr>
<td>100–400 mg/day¹¹,¹²</td>
</tr>
<tr>
<td>Amitriptyline</td>
</tr>
<tr>
<td>25–100 mg/day¹⁷,¹⁸</td>
</tr>
<tr>
<td>Atropine eye drops (1%) given sublingually⁹–¹¹ or as solution (1 mg/10 mL) used as a mouthwash</td>
</tr>
<tr>
<td>Benzhexol (trihexyphenidyl)</td>
</tr>
<tr>
<td>5–15 mg/day²³</td>
</tr>
<tr>
<td>Benzatropine 2 mg/day + terazosin 2 mg/day²⁵</td>
</tr>
<tr>
<td>Botulinum toxin²⁶–²⁹ (Botox) bilateral parotid gland injections (150 IU into each gland)</td>
</tr>
<tr>
<td>Bupropion</td>
</tr>
<tr>
<td>100–150 mg/day³⁰</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>0.1–0.2 mg patch weekly or 0.1 mg orally at night³¹,³²</td>
</tr>
</tbody>
</table>

(Continued)
### Table 1.48 (Continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycopyrrrolate</strong>&lt;br&gt;0.5–4 mg bd&lt;sup&gt;33–36&lt;/sup&gt;</td>
<td>One RCT showed glycopyrrolate to be more effective than biperiden without worsening cognitive function while another found significant clinical improvement of ‘nocturnal sialorrhoea’ with 2 mg a day compared with placebo</td>
</tr>
<tr>
<td><strong>Guanfacine</strong>&lt;br&gt;1 mg daily&lt;sup&gt;37&lt;/sup&gt;</td>
<td>α&lt;sub&gt;2&lt;/sub&gt; agonist. Single case report. May cause hypotension</td>
</tr>
<tr>
<td><strong>Hyoscine</strong>&lt;br&gt;0.3 mg tablet sucked or chewed up to 3 times daily or 1.5 mg/72 h patch&lt;sup&gt;38,39&lt;/sup&gt;</td>
<td>Peripheral and central anticholinergic. Very widely used but no published data available on oral treatment. May cause cognitive impairment and drowsiness and worsens constipation</td>
</tr>
<tr>
<td><strong>Ipratropium</strong>&lt;br&gt;nasal spray&lt;br&gt;(0.03% or 0.06%) given sublingually up to two sprays three times a day of the 0.06% or intranasally, one spray into each nostril daily of the 0.03%&lt;sup&gt;40,41&lt;/sup&gt;</td>
<td>Limited literature support. The only placebo-controlled RCT conducted was negative&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lofexidine</strong>&lt;br&gt;0.2 mg twice daily&lt;sup&gt;43&lt;/sup&gt;</td>
<td>α&lt;sub&gt;2&lt;/sub&gt; agonist. Very few data. May exacerbate psychosis and depression and cause hypotension</td>
</tr>
<tr>
<td><strong>Metoclopramide</strong>&lt;br&gt;Starting dose of 10 mg a day&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Double-blind, placebo-controlled trial found metoclopramide was associated with a significant reduction in nocturnal hypersalivation and drooling</td>
</tr>
<tr>
<td><strong>Moclobemide</strong>&lt;br&gt;150–300 mg/day&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Effective in 9 of 14 patients treated in one open study. Appears to be as effective as amisulpride (see above)</td>
</tr>
<tr>
<td><strong>Oxybutynin</strong>&lt;br&gt;5 mg up to twice daily&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Single case report</td>
</tr>
<tr>
<td><strong>Pirenzepine</strong>&lt;br&gt;50–150 mg/day&lt;sup&gt;47–49&lt;/sup&gt;</td>
<td>Selective M&lt;sub&gt;1&lt;/sub&gt;, M&lt;sub&gt;2&lt;/sub&gt; antagonist. Extensive clinical experience suggests efficacy in some but the only randomised trial suggested no effect. Still widely used. Does not have a UK licence for any indication. May cause constipation</td>
</tr>
<tr>
<td><strong>Propantheline</strong>&lt;br&gt;7.5 mg at night&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Peripheral anticholinergic. No central effects. Two Chinese RCTs (one positive). May worsen constipation</td>
</tr>
<tr>
<td><strong>Quetiapine</strong>&lt;sup&gt;51&lt;/sup&gt;</td>
<td>May reduce hypersalivation by allowing lower doses of clozapine to be used</td>
</tr>
<tr>
<td><strong>Sulpiride</strong>&lt;br&gt;150–300 mg/day&lt;sup&gt;52,53&lt;/sup&gt;</td>
<td>Supported by one, small positive RCT and a Cochrane review of clozapine augmentation with sulpiride (at higher sulpiride doses). May allow dose reduction of clozapine</td>
</tr>
</tbody>
</table>

bd, bis die (twice a day); RCT, randomised controlled trial.

### References


Further reading

Clozapine-induced gastrointestinal hypomotility (CIGH)

Constipation is a common adverse effect of clozapine treatment with a prevalence of more than 30%, three times that seen with other antipsychotics. The mechanism of action is not completely understood but is thought to be a combination of the drug’s anticholinergic and antihistaminergic properties, which are further complicated by antagonism at 5-HT3 receptors. In addition, clozapine-induced sedation can result in a sedentary lifestyle, which is itself a risk factor for constipation. Clozapine causes constipation by slowing transit time through the gut. Mean transit times are four times longer than normal, and 80% of clozapine patients show reduced transit time.

Clozapine-induced constipation is much more common than blood dyscrasias, and mortality rates are also higher. When constipation is severe, the case fatality rate is around 20–30%. The most recent (and largest) study found an incidence of 37/10,000 cases of severe hypomotility and 7/10,000 constipation-related deaths. Case fatality was 18%. Enhanced monitoring of CIGH is clearly needed to reduce the likelihood of constipation-related fatality.

A gastrointestinal history and abdominal examination is recommended prior to starting treatment and, if the patient is constipated, clozapine should not be initiated until this has resolved. CIGH is most severe during the first 4 months of treatment but may occur at any time. Adopting the Rome III criteria at routine FBCs might be a successful strategy to combat preventable deaths due to CIGH.

Opinions differ on the relationship between clozapine dose and constipation, and between clozapine plasma level and constipation. However, patients who died as a result of CIGH had higher than average daily doses (mean 535 mg/day). Median duration of clozapine treatment at the time of death is 2.5 years.

The risk factors for developing clozapine-induced constipation are summarised in Box 1.6.

---

**Box 1.6 Risk factors for developing clozapine-induced constipation**

- Increasing age
- Female sex
- Anticholinergic medication
- Higher clozapine dose/plasma level (consider the effect of interacting drugs or stopping smoking)
- Hypercalcaemia
- Gastrointestinal disease
- Obesity
- Diaphoresis
- Low-fibre diet
- Poor bowel habit
- Dehydration (exacerbated by hypersalivation)
- Diabetes
- Hypothyroidism
- Parkinson’s disease
- Multiple sclerosis
Prevention and simple management of CIGH

A slow clozapine titration may reduce the risk of developing constipation, with dose increments not exceeding 25 mg/day or 100 mg/week. Increasing dietary fibre intake to at least 20–25 g/day can increase stool weight and decrease gut transit time. If fibre intake is increased it is important that adequate fluid intake (1.5–2 L/day) is also maintained to avoid intestinal obstruction. Daily food and fluid charts would be ideal to monitor fibre and fluid intake, especially during the titration phase of clozapine. Regular exercise (150 minutes/week) in addition to a high-fibre diet and increased fluid intake also assist in the prevention of CIGH.

Patients often do not self-report even life-threatening constipation. Use of stool charts daily for the first 4 weeks, and weekly or monthly thereafter is recommended. If there is a change from usual baseline bowel habit or fewer than three bowel movements per week an abdominal examination is indicated. Where this excludes intestinal obstruction, both a stimulant and stool-softening laxative should be started (e.g. senna and docusate). Bulk-forming laxatives are not effective in slow-transit constipation and therefore should be avoided. There is some evidence that lactulose and polyethylene glycol (e.g. Movicol) are effective and could be considered as second-line options or in addition to the stimulant and softener combination. Choice of laxative should also be guided by the patient’s previous response to certain agents in association with the required speed of action. It would not be appropriate for example to start lactulose treatment (takes up to 72 hours of regular use to work) for someone in need of urgent treatment. Stimulant laxatives are usually the fastest acting (6–10 hours).

Management of suspected acute CIGH

Signs and symptoms that warrant immediate medical attention are abdominal pain, distension, vomiting, overflow diarrhoea, absent bowel sounds, acute abdomen, feculent vomitus and symptoms of sepsis. There have been case reports of fatalities occurring only hours after first symptoms present, and this emphasises the urgency for prompt assessment and management. There should therefore be a low threshold for referral to a gastroenterologist and/or A&E when conservative management fails or constipation is severe and acute.

Clozapine re-challenge following severe constipation

Some patients have been successfully re-challenged following severe cases of CIGH. However, this process does not come without risk. Prophylactic measures should therefore be considered for those with a history of CIGH or who are deemed at high risk of developing CIGH. Where conventional laxatives have not been tried in regular and adequate doses, this should be done. However, when this approach has previously failed, a number of more experimental options are available. Prescribers must familiarise themselves with the literature (at the very least by reading the SPC) before using any of these treatments.

The prostaglandin E1 analogue lubiprostone is licensed in the UK for the treatment of chronic idiopathic constipation and associated symptoms in adults, when response
to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate. The recommended dose for the licensed indication is 24 µg twice daily for a maximum of 2 weeks’ duration. Lubiprostone has been reported to be effective in obviating the need for other laxatives in a clozapine re-challenge following a severe case of CIGH and is used in some centres for this indication.

**Orlistat**, a drug used to aid weight loss, is also known to have a laxative effect, particularly when a high-fat diet is consumed. It was reported as being successfully used for three patients with severe constipation associated with opioid use (hypomotility-induced constipation). A small, randomised, placebo-controlled study of orlistat for clozapine-induced constipation found a statistically significant favourable difference at study endpoint (week 16) for the prevalence of constipation, diarrhoea and normal stools for orlistat compared with placebo, although 47 of the 54 participants required conventional laxatives. Note also that orlistat is known to reduce the absorption of some drugs from the gastrointestinal tract. It is therefore important to monitor plasma clozapine levels if starting treatment with orlistat. Orlistat may be particularly difficult to use outside clinical study settings as without adherence to a strict low-fat diet, gastric adverse effects can be unpleasant (specifically, oily rectal leakage).

**Bethanechol**, a cholinergic agonist, has been described as being effective in reducing the amount of laxatives and enemas required to maintain regular bowel movements for a patient diagnosed with clozapine-related CIGH. Bethanechol in this case was used at a dose of 10mg tds. Bethanechol should only ever be initiated after other options have failed and then in consultation with a gastroenterologist.

**References**

Clozapine, neutropenia and lithium

Risk of clozapine-induced neutropenia and agranulocytosis

Around 2.7% of patients treated with clozapine develop neutropenia. Of these, half do so within the first 18 weeks of treatment and three-quarters by the end of the first year. Risk factors include being Afro-Caribbean, younger age and having a low baseline white cell count (WCC). Risk is not dose-related. The mechanism of clozapine-induced neutropenia/agranulocytosis is unclear; both immune-mediated and direct cytotoxic effects may be important. Furthermore, the mechanism may differ between individuals and also between mild and severe forms of marrow suppression. One-third of patients who stop clozapine because they have developed neutropenia or agranulocytosis will develop a blood dyscrasia on re-challenge. Where the index dyscrasia was agranulocytosis, the second blood dyscrasia invariably occurs more rapidly and can be more severe and last longer, although this is not necessarily the case where the index dyscrasia was neutropenia.

Confusion arises because of the various possible reasons for a low neutrophil count in people taking clozapine. A single low count might just be a coincidental finding of no clinical relevance, as is common with all drugs. Several low counts (consecutive or intermittent) might be seen in people with benign ethnic neutropenia (BEN) or as a result of clozapine-associated bone marrow suppression (especially if consecutive and progressively falling). Full-blown agranulocytosis can probably always be interpreted as a result of severe bone marrow suppression caused by clozapine. The pattern of the results can be important. In non-BEN patients, agranulocytosis is normally preceded by normal neutrophil counts which are then followed by a precipitous fall in neutrophils (usually over a week or less) and a prolonged period of counts near to zero (assuming that it has not been treated). Neutrophil counts that do not follow this characteristic pattern are difficult to interpret. An Icelandic study found no difference in the risk of severe neutropenia between clozapine and non-clozapine antipsychotics, suggesting that many cases of neutropenia during clozapine treatment are probably not caused by clozapine.

At least 0.8% of clozapine-treated patients develop agranulocytosis, which is potentially fatal. Over 80% of cases of agranulocytosis develop within the first 18 weeks of treatment. Risk factors include increasing age and Asian ethnicity. Some patients may be genetically predisposed. Although the timescale and individual risk factors for the development of agranulocytosis are different from those associated with neutropenia, it is impossible to be certain in any given patient that neutropenia is not a precursor to agranulocytosis.

Haematological monitoring is mandatory to mitigate the haematological risk. However, worldwide, there are marked variations in the recommendations for monitoring frequency and the threshold for clozapine cessation, reflecting, perhaps, the weak evidence on which they are based. In October 2015, the US FDA introduced changes to the clozapine monitoring system making only the absolute neutrophil count (ANC) mandatory and effectively lowering the threshold for cessation of clozapine treatment. It is recommended that treatment with clozapine be stopped when neutrophils fall below 1000/mm³ (compared with UK recommendations for cessation if ANC is <1500/mm³).

There is evidence that clozapine is grossly under-utilised worldwide, with very wide variation in prescribing frequency from one country to another. This may be explained
at least in part by the stringent blood monitoring requirements. The new FDA regulations will undoubtedly improve clozapine use in the USA and may have implications internationally.

**Benign ethnic neutropenia**

Benign ethnic neutropenia (BEN) is a widely recognised hereditary condition in which the neutrophil count is relatively low. People of African or Middle Eastern descent have a higher prevalence. BEN is characterised by low WCCs which may frequently fall below the lower limit of normal. This pattern may be observed before, during and after the use of clozapine and very probably accounts for a proportion of observed or apparent clozapine-associated neutropenias and treatment cessation. Many countries allow registration of BEN status whereby different (lower) limits are set for neutrophil counts in these patients. While true clozapine-induced neutropenia can occur in the context of BEN, the current evidence suggests that BEN does not pose an increased risk of dyscrasias during clozapine treatment.10,11

**Concurrent medications**

Different classes of medicines associated with haematological adverse effects are co-prescribed with clozapine. These include other antipsychotics, anticonvulsants such as sodium valproate and carbamazepine, antibacterials and gastrointestinal agents such as proton-pump inhibitors. Many patients develop neutropenia on clozapine but not all cases are clozapine-related or even pathological. The possible contributory role of these agents should always be considered and these agents discontinued if clozapine re-challenge is attempted.12

**Management options**

Before treatment initiation, it is important to evaluate baseline haematological values. If a patient is suspected of having BEN, there should be a referral to a haematologist for confirmation.13

Distinguishing between true clozapine toxicity and neutropenia unrelated to clozapine is not possible with certainty but some factors are important. Consultation with a haematologist is advisable regarding BEN and to exclude any other co-prescribed medication that may be responsible. The use of iatrogenic agents to elevate WCC in patients with clear prior clozapine-induced neutropenia (i.e. certainty that clozapine was the cause) is not recommended. Lithium or other medicines should only be used to elevate WCC where it is strongly felt that prior neutropenic episodes were unrelated to clozapine. Patients who have had a previous episode of agranulocytosis that is attributable to clozapine should not be re-challenged.

**Lithium**

Lithium increases the neutrophil count and total WCC both acutely and chronically. The magnitude of this effect is poorly quantified, but a mean neutrophil count of $11.9 \times 10^9$/L has been reported in lithium-treated patients and a mean rise in neutrophil
count of $2 \times 10^9/L$ was seen in clozapine-treated patients after the addition of lithium. This effect does not seem to be clearly dose-related although a minimum lithium serum level of 0.4 mmol/L may be required. The mechanism is not completely understood.\textsuperscript{14}

Lithium has been used to increase the WCC in patients who have developed neutropenia while taking clozapine, allowing clozapine treatment to continue. Several case reports in adults\textsuperscript{15–19} and in children\textsuperscript{20,21} have been published. Almost all patients had serum lithium levels of $>0.6$ mmol/L. In a case series (n=25) of patients who had stopped clozapine because of a blood dyscrasia and were re-challenged in the presence of lithium, only one developed a subsequent dyscrasia.\textsuperscript{22} If considering lithium, discuss with the medical advisor at the relevant monitoring service to determine the optimum pharmacological strategy for the particular patient.

Lithium does not seem to protect against true clozapine-induced agranulocytosis: one case of fatal agranulocytosis has occurred with this combination\textsuperscript{23} and a second case of agranulocytosis has been reported where the bone marrow was resistant to treatment with granulocyte colony-stimulating factor (G-CSF).\textsuperscript{24}

**Granulocyte colony-stimulating factor (G-CSF)**

The use of G-CSF to facilitate uninterrupted clozapine therapy in patients with previous neutropenia is a strategy that is attracting increasing interest but is somewhat controversial. There are both successful\textsuperscript{24–26} and unsuccessful\textsuperscript{26,27} case reports of patients receiving regular long-term G-CSF to enable clozapine therapy. As well as the commonly reported adverse effects of bone pain\textsuperscript{28} and neutrophil dysplasia,\textsuperscript{29} the administration of G-CSF in the face of a low or declining neutrophil count may mask an impending neutropenia or agranulocytosis, leading to dire consequences. The long-term safety of G-CSF has not been determined; bone density and spleen size should probably be monitored.

‘When required’ G-CSF, to be administered if neutrophils drop below a defined threshold, may allow re-challenge with clozapine of patients in whom lithium is insufficient to prevent ‘dipping’ of WCC below the normal range. Again, this strategy risks masking a severe neutropenia or agranulocytosis. It is also likely to be practically difficult to manage outside a specialist unit, as frequent blood testing (twice to three times a week) is required, as well as immediate access to medical review and the G-CSF itself.

Consultation with a haematologist and discussion with the medical adviser at the clozapine monitoring service is essential before considering the use of G-CSF. A patient’s individual clinical circumstances should be considered. In particular, patients should be considered to be very high risk for re-challenge with clozapine if the first episode of dyscrasias fulfilled any of the following criteria, all of which suggest that the low counts are clozapine-related:

- inconsistent with previous WCCs (i.e. not part of a pattern of repeated low WCCs)
- occurred within the first 18 weeks of treatment
- severe (neutrophils $<0.5 \times 10^9/L$), or
- prolonged.

While G-CSF has been reported as allowing successful re-challenge with clozapine in some people with previous episodes of clozapine-induced neutropenia,\textsuperscript{30} the available evidence excludes this course of action for someone with a true clozapine-related agranulocytosis.\textsuperscript{31}
Management of patients with either of the following conditions is outlined in Figure 1.7.

- Low initial WCC (<4 x 10^9/L) or neutrophils (<2.5 x 10^9/L).
- Leucopenia (WCC <3 x 10^9/L) or neutropenia (neutrophils <1.5 x 10^9/L) thought to be linked to BEN. Such patients may be of African or Middle Eastern descent, have no history of susceptibility to infection and have morphologically normal white blood cells.32
References

CHAPTER 1

Clozapine and chemotherapy

The use of clozapine with agents that cause neutropenia is formally contraindicated. Most chemotherapy treatments cause significant bone marrow suppression. When the WCC drops below $3.0 \times 10^9/L$, clozapine is usually discontinued; this is an important safety precaution outlined in the formal licence/labelling. In many regimens it can be predicted that chemotherapy will reduce the WCC below this level, irrespective of the use of clozapine.

Where possible, clozapine should be discontinued before chemotherapy. However, this will place most patients at high risk of relapse or deterioration, which may then affect their capacity to consent to chemotherapy. This poses a therapeutic dilemma in patients prescribed clozapine and requiring chemotherapy. In practice, many patients, perhaps even a majority, continue clozapine during chemotherapy.

There are a number of case reports supporting continuing clozapine during chemotherapy, but interpretation of this literature should take account of possible publication bias. Before initiating chemotherapy in a patient receiving clozapine it is essential to put in place a treatment plan that is agreed with all relevant health-care staff involved and, of course, the patient and family members/carers; this will include the oncologist/physician, psychiatrist, pharmacist and the clozapine monitoring service. Plans should be made in advance for the action that should be taken when the WCC drops below the normally accepted minimum. This plan should cover the frequency of haematological monitoring, increased vigilance regarding the clinical consequences of neutropenia/agranulocytosis, if and when clozapine should be stopped, and the place of ‘antidote’ medication such as lithium and G-CSF.

In the UK, the clozapine monitoring service will normally ask for the psychiatrist to sign an ‘unlicensed use’ form and will request additional blood monitoring. Complications appear to be rare but there is one case report of neutropenia persisting for 6 months after doxorubicin, radiotherapy and clozapine. G-CSF has been used to treat agranulocytosis associated with chemotherapy and clozapine in combination. Risks of life-threatening blood dyscrasias are probably lowest in those who have received clozapine for longer than a year, in whom clozapine-induced neutropenia would be highly unusual.

Summary

- If possible, clozapine should be discontinued before starting chemotherapy. However, for most patients withdrawal is not possible or sensible.
- The risk of relapse or deterioration must be considered before discontinuing clozapine.
- If the patient’s mental state deteriorates they may retract their consent for chemotherapy.
- When clozapine is continued during chemotherapy a collaborative approach between the oncologist, psychiatrist, pharmacy, patient and clozapine monitoring service is strongly recommended.
References
