Chapter 1

Schizophrenia and related psychoses

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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 effects, 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 extrapyramidal side effects (EPSEs) 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 EPSEs and its failure in animal-based antipsychotic screening tests. Its remarketing in 1990 signalled the beginning of a series of new medications, all of which were introduced with claims (to varying degrees of accuracy) of 'atypicality'. Of these medications, perhaps only clozapine, and possibly quetiapine, is completely atypical, seemingly having a

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very low or zero liability for extrapyramidal symptoms (EPS). Others show dose-related effects, although, unlike with typical drugs, therapeutic activity can usually be achieved without EPSEs. 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 that is effective but does not cause EPSEs (for example, compare haloperidol with olanzapine).

The typical/atypical dichotomy does not lend itself well to classification of antipsychotics in the middle ground of EPSE 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 16mg/day, 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 usually worse with risperidone, paliperidone and amisulpride than with typical drugs). Lastly, some more recently introduced agents (e.g. pimavanserin, xanomeline) have antipsychotic activity and do not cause EPS but have almost nothing in common with other atypicals in respect to chemistry, pharmacology or adverse-effect profile.

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 *Maudsley Prescribing 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

In the UK, the National Institute for Health and Care Excellence (NICE) guideline for medicines adherence[2] 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 healthcare, 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, and, 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

After the publication of the independent CATIE[4] and CUtLASS[5] studies, the World Psychiatric Association reviewed the evidence relating to the relative efficacy of 51 FGAs and 11 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 for EPS and tardive dyskinesia (TD),[7] but this was 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 later 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, summary data suggest that olanzapine is marginally more effective than aripiprazole, risperidone, quetiapine and ziprasidone, and that risperidone has a minor advantage over quetiapine and ziprasidone.[10] 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)[13] and must be weighed against the very different adverse effect profiles associated with individual antipsychotics. A 2019 network meta-analysis of 32 antipsychotics[14] ranked amisulpride as the most effective drug for positive symptoms and clozapine as the best for both negative symptoms and overall symptom improvement. Olanzapine and risperidone were also highly ranked for positive symptom response. The greatest (beneficial) effect on depressive symptoms was seen with sulpiride, clozapine, amisulpride, olanzapine and the dopamine partial agonists, perhaps reflecting the relative absence of neuroleptic-induced dysphoria common to most FGAs.[15] In the longer term, olanzapine may have advantages over some other antipsychotics.[16] There was a tendency for more recently introduced drugs to have a lower estimated efficacy – a phenomenon that derives from the substantial increase in placebo response since 1970.[17]

Clozapine is clearly the drug of choice in refractory schizophrenia,[18] although bizarrely, this is not a universal finding,[19] probably because of the biased nature and quality of many active–comparator trials.[20,21]

Both FGAs and SGAs are associated with a number of adverse effects. These include weight gain, dyslipidaemia, increases in plasma glucose/diabetes,[22,23] hyperprolactinaemia, hip fracture,[24] sexual dysfunction, EPS including neuroleptic malignant syndrome,[25] anticholinergic effects, venous thromboembolism (VTE),[26] sedation and postural hypotension. The exact profile is drug specific (see individual sections on

specific adverse effects), although comparative data are not robust[27] (see large-scale meta-analyses[13,28] for rankings of some adverse-effect risks).

Adverse effects are a common reason for treatment discontinuation,[29] particularly when efficacy is poor.[13] Patients do not always spontaneously report adverse effects, however,[30] and psychiatrists' views of the prevalence and importance of adverse effects differ markedly from patient experience.[31] Systematic enquiry, together 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)[32] can be a useful first step in this process. The clinician-completed Antipsychotic Non-Neurological Side-Effects Rating Scale facilitates more detailed and comprehensive assessment.[33]

Non-adherence to antipsychotic treatment is common and here the guaranteed medication delivery associated with depot/long-acting injectable antipsychotic preparations (LAIs) is unequivocally advantageous. In comparison with oral antipsychotics, there is strong evidence that depots are associated with a reduced risk of relapse and rehospitalisation,[34–36] although randomised controlled trials (RCTs) do not always reflect this difference.[37] Any logical assessment of the benefits of LAIs and the damage caused by relapse would conclude that LAIs should be first-line treatments, rather than reserved for those who have already relapsed on oral medication. Moreover, the wider use of SGA LAIs 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 300mg or 400mg/month, with flupentixol, which has a licensed dose in the UK of 50mg every 4 weeks to 400mg/week). The optimal dose of flupentixol is around 40mg every 2 weeks[28] – just 5% of the maximum allowed.

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.[38–40] Its use in these circumstances is recommended by NICE[3] and probably every schizophrenia guideline besides. The biological basis for the superior efficacy of clozapine is uncertain.[41] Olanzapine should probably be one of the two drugs used before clozapine.[10,42] A case might also be made for a trial of amisulpride: it has a uniformly high ranking in meta-analyses and one trial found continuation with amisulpride to be as effective as switching to olanzapine.[43] This same trial also suggested clozapine might be best placed as the second drug used, given that switching provided no benefit over continuing with the first prescribed drug.

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.

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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 1–2 weeks of assessment, during which the patient is clearly showing poor or no response.
- With regular dosing of LAIs, plasma levels rise for at least 6–12 weeks after initiation, even without a change in dose (see section on depot 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 the oral drug in LAI form. Where this is not possible, the target dose of LAI for an individual should be the dose established to be optimal in clinical trials (although such data are not always available for older LAIs).
- Antipsychotic LAIs provide better relapse protection than oral treatment. LAIs should be used as first-line treatment aimed at preventing relapse. They should not be reserved only for those who have already relapsed on oral treatment.
- Clozapine should be offered as soon as treatment resistance is apparent. The sooner clozapine is prescribed, the more effective it will be.
- For the large majority of patients, the use of a single antipsychotic (with or without additional mood stabiliser or sedatives) is recommended. Apart from some exceptional circumstances (e.g. clozapine augmentation or adjunctive aripiprazole for prolactin elevation) antipsychotic polypharmacy should generally be avoided because of the increased adverse-effect burden and risks associated with QT prolongation and sudden cardiac death (see section on antipsychotic polypharmacy 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 on 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 'when necessary' sedatives. Time-limited prescriptions of benzodiazepines or general sedatives (e.g. promethazine) are preferred (see section on rapid tranquillisation in this chapter).
- Response to antipsychotic drug treatment should be assessed using recognised rating scales and outcomes documented in patients' records.
- Those receiving antipsychotics should undergo close monitoring of physical health (including blood pressure, pulse, ECG, plasma glucose and plasma lipids; see appropriate sections in this chapter).
- When withdrawing antipsychotics, reduce the dose slowly in a hyperbolic regimen, which minimises the risks of withdrawal symptoms and rebound psychosis.

Note – this section is not referenced. Please see relevant individual sections in this chapter for detailed and referenced guidance.

Antipsychotics – minimum effective doses

Table 1.1 suggests the minimum dose of individual antipsychotics 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 some consensus opinion has also been used. Only oral treatment with commonly used drugs is covered.

Table 1.1 Minimum effective dose/day – antipsychotics

Drug	First episode	Multi-episode
First-generation		
Chlorpromazine[1]	200mg*	300mg
Haloperidol[2–6]	2mg	4mg
Sulpiride[7]	400mg*	800mg
Trifluoperazine[8,9]	10mg*	15mg
Second-generation		
Amisulpride[10,11]	300mg*	400mg*
Aripiprazole[6,12–16]	10mg	10mg
Asenapine[6,16,17]	5mg*	10mg
Blonanserin[18]	Not known	8mg
Brexpiprazole[19,20]	2mg*	4mg
Cariprazine[21,22]	1.5mg*	1.5mg
Clotiapine[23,24]	Not known	120mg
Iloperidone[6,16,25]	4mg*	8mg
Lumateperone[26]	Not known	42mg*
Lurasidone[6,27]	40mg HCl/37mg base*	40mg HCl/37mg base
Olanzapine[6,28–31]	5mg	7.5mg
Paliperidone[16]	3mg*	3mg
Pimavanserin[32–34]	Not known	34mg**
Quetiapine[35,36]	150mg* (but higher doses often used[37])	300mg IR 500mg MR[38]
Risperidone[3,6,39–42]	2mg	4mg
Xanomeline[43,44]	200mg*	200mg*
Ziprasidone[6,15,45–47]	40mg*	80mg

* Estimate – too few data available.
** US Food and Drug Administration-approved for Parkinson's disease psychosis; dose in schizophrenia not clear.

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Quick reference for licensed maximum doses

Table 1.2 lists the licensed maximum doses of antipsychotics according to the European Medicines Agency, as of January 2025.[1]

Table 1.2 Maximum doses of antipsychotics according to European Medicines Agency labelling.[1]

Drug	Maximum dose
FGAs – oral	
Chlorpromazine	1000mg/day
Flupentixol	18mg/day
Haloperidol	20mg/day
Levomepromazine	1200mg/day
Pericyazine	300mg/day
Perphenazine	24mg/day (64mg/day hospitalised patients)
Pimozide	20mg/day
Sulpiride	2400mg/day
Trifluoperazine	20mg/day (maximum dose not formally specified)
Zuclopenthixol	150mg/day
SGAs – oral	
Amisulpride	1200mg/day
Aripiprazole	30mg/day
Asenapine	20mg/day (sublingual)
Cariprazine	6mg/day
Clozapine	900mg/day
Lurasidone	160mg (HCl)/148mg (base)/day
Olanzapine	20mg/day
Paliperidone	12mg/day
Quetiapine	750mg/day schizophrenia (800mg/day MR)
	800mg/day bipolar disorder
Risperidone	16mg/day
Sertindole	24mg/day
Long-acting injections	
Aripiprazole 1-monthly	400mg/month (SPC implies 'every 4 weeks')
Aripiprazole 2-monthly	960mg/2 months (SPC states 'every 56 days')
Flupentixol decanoate	400mg/week
Haloperidol decanoate	300mg/4 weeks
Olanzapine pamoate	300mg/2 weeks
Paliperidone palmitate 1-monthly	150mg/month
Paliperidone palmitate 3-monthly	525mg/3 months

(*Continued*)

Table 1.2 (*Continued*)

Drug	Maximum dose
Paliperidone depot 6-monthly	1000mg/6 months
Risperidone (Consta®)	50mg/2 weeks
Risperidone (Okedi®)	100mg/4 weeks
Zuclopenthixol decanote	600mg/week

Table 1.3 lists the licensed maximum doses of antipsychotics available outside the EU, according to the US Food and Drug Administration, where available (as of December 2024).[2]

Table 1.3 Licensed maximum doses of antipsychotics, according to US Food and Drug Administration labelling, where available.[2]

Drug	Maximum dose
FGAs – oral	
Fluphenazine	40mg/day
Thiothixene	60mg/day
SGAs – oral	
Blonanserin*	24mg/day[3]
Brexpiprazole	4mg/day
Iloperidone	24mg/day
Lumateperone	42mg/day
Molindone	225mg/day
Perospirone**	48mg/day
Pimavanserin	34mg/day
Xanomeline and trospium chloride	250mg/60mg/day
Ziprasidone	160mg/day
Long-acting injections	
Aripiprazole lauroxil (Aristada Initio®)†	675mg
Aripiprazole lauroxil (Aristada®)	882mg/month or 1064mg/2 months
Fluphenazine decanoate	100mg/14 days
Risperidone (Uzedy®)	125mg/month or 250mg/2 months
Risperidone (Rykindo®)	50mg/2 weeks
Transdermal patch	
Asenapine	7.6mg/24hr
Blonanserin*	80mg/24hr patch[4]

* Available only in China, Japan and South Korea at the time of writing.
** Available only in Japan at the time of writing.
† Used to initiate treatment with Aristada, not for repeat dosing.

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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 (using various methods) and any dopamine binding studies available.

Table 1.4 provides approximate equivalent doses for FGAs.[1–3] 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 better defined, evidence-based licensed dose ranges. There are several different ways of calculating equivalence based on, for example, defined daily dose,[4] minimum effective dose[5,6] and average dose.[7] These methods give different estimates of equivalence. A very rough guide to equivalent SGA daily dosages is given in Table 1.5.[3,6–10] There is considerable disagreement about exact equivalencies, even among the references cited here. Clozapine is not included because this has a distinct initial titration schedule and a high dose–plasma level variability and because it probably has a different mechanism of action.

Comparing potencies of FGAs with SGAs introduces yet more uncertainty in respect to dose equivalence. Very approximately, 100mg chlorpromazine is equivalent to 1.5mg risperidone.[3] An online calculator is available from the American Association of Psychiatric Pharmacists.[11]

Table 1.4 Equivalent doses of first-generation antipsychotic medications.

Drug	Equivalent dose (consensus)	Range of values in literature
FGAs – oral		
Chlorpromazine	100mg/day	Reference
Flupentixol	3mg/day	2–3mg/day
Fluphenazine	2mg/day	1–5mg/day
Haloperidol	2mg/day	1.5–5mg/day
Pericyazine	10mg/day	10mg/day
Perphenazine	10mg/day	5–10mg/day
Pimozide	2mg/day	1.33–2mg/day
Sulpiride	200mg/day	133–300mg/day
Trifluoperazine	5mg/day	2.5–5mg/day
Zuclopenthixol	25mg/day	25–60mg/day
FGAs – long-acting injections		
Flupentixol decanoate	10mg/week	10–20mg/week
Fluphenazine decanoate	5mg/week	1–12.5mg/week
Haloperidol decanoate	15mg/week	5–25mg/week
Zuclopenthixol decanoate	100mg/week	40–100mg/week

Table 1.5 Second-generation antipsychotics – approximate equivalent doses.[3–10]

Drug	Approximate equivalent dose
SGAs – oral	
Amisulpride	400mg
Aripiprazole	15mg
Asenapine	10mg
Blonanserin	~
Brexpiprazole	2mg
Cariprazine	1.5mg
Clotiapine	100mg
Iloperidone	12mg
Lumateperone	21mg*
Lurasidone	80mg (74mg base)
Melperone	300mg
Molindone	50mg
Olanzapine	10mg
Pimavaserin	17mg*
Quetiapine	400mg
Risperidone	4mg
Sertindole	10mg*
Xanomeline	~
Ziprasidone	80mg
SGAs – long-acting injections	
Aripiprazole 1-monthly	300mg/month
Aripiprazole lauroxil	441mg every 2 months
Olanzapine pamoate	405mg/4 weeks
Paliperidone palmitate	100mg/month
Risperidone (Consta)	50mg/2 weeks
Risperidone (Okedi)	100mg/4 weeks
Risperidone (Uzedy)	100mg/month or 200mg every 2 months
Transdermal patch	
Asenapine	5.7mg/24 hr

~ Unknown equivalence at time of writing.
* Expert consensus recommendation.

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High-dose antipsychotic medication: 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, results 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 tranquillisation, relapse prevention, persistent aggression and the management of acute psychotic episodes.[1] Nevertheless, the prescription of high-dose antipsychotic medication remains relatively common in clinical practice.[4–6] In the UK, the national audit of schizophrenia in 2013, reporting on prescribing practice for over 5,000 predominantly community-based patients, found that, overall, 10% were prescribed a high dose of antipsychotic medication.[7] A 2022 audit of adult inpatients in mental health services[8] found that in over 4,000 patients on acute adult wards, just under 10% were prescribed high-dose antipsychotic medication, and for over 2,000 patients on forensic wards, the respective figure was 13%. In both settings, a high-dose prescription was predominantly a consequence of combined antipsychotic medications.

Examination 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.[9,10] Efficacy appears to be optimal at relatively low doses, such as 4mg/day risperidone,[11] 300mg/day quetiapine,[12] and olanzapine 10mg.[13,14] Similarly, treatment with LAI risperidone at a dose of 100mg 2-weekly offers no benefits over 50mg 2-weekly,[15] and 320mg/day ziprasidone[16] is no better than 160mg/day. All currently available antipsychotic medications (with the possible exception of clozapine) exert their antipsychotic effect primarily through antagonism (or partial agonism) at postsynaptic dopamine receptors. But there is increasing evidence that refractory symptoms in some patients with treatment-resistant schizophrenia may not be driven by dysfunction of dopamine pathways,[17–20] so prescribing a higher dosage to increase dopamine blockade in such patients would seem to be of uncertain value.

Dold and colleagues[21] conducted a meta-analysis of 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. In a study of patients with first-episode schizophrenia, increasing the dose of olanzapine up to 30mg/day and the dose of risperidone up to 10mg/day in those cases where the illness was non-responsive to treatment with standard doses yielded only a 4% absolute increase in overall response rate. Switching to an alternative antipsychotic, including clozapine, was considerably more successful.[22]

A small number of RCTs have examined the efficacy of high versus standard dosage in patients with treatment-resistant schizophrenia (TRS).[1] Some have demonstrated benefit[23] 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 10g chlorpromazine. One small (n = 12) open study of high-dose quetiapine (up to 1400mg/day) in refractory schizophrenia found modest benefits in a third of patients[24] but other, larger studies of quetiapine for such patients have shown no benefit for higher doses.[22,23] A further RCT of high-dose olanzapine (up to 45mg/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.[25] Subsequent systematic reviews of relevant studies addressing high-dose olanzapine for TRS have similarly concluded that while such a regimen may be superior to other, non-clozapine antipsychotic medications, it may be seen as a safe and effective alternative for refractory illness only when clozapine use is not appropriate.[26,27]

Perhaps the most comprehensive systematic analysis of dose–response[28] largely confirmed the observation that the dose–response curve reaches a plateau above a certain dose for nearly all antipsychotic medications, with the possible exceptions of olanzapine and lurasidone. (With these two medications there is some evidence that doses at the upper end of the licensed range are somewhat more effective than lower doses.)[14,29] This systematic review also suggested that the doses above which no additional benefit was likely (e.g. risperidone 6.3mg/day; quetiapine 482mg/day) were somewhat higher than the doses of optimal efficacy previously determined (see above). Importantly, however, there was no evidence to support the use of doses of any antipsychotic medication above its licensed dose range.

Consensus panel recommendations are broadly in line with clinical trial outcomes. A 2023 international consensus study[30] suggested maximum effective doses exceeded licensed doses in only two cases: olanzapine (30mg/day) and quetiapine (800mg/day).

A 2023 systematic review of dose–response relationships[31] found that the effect of all antipsychotics reached a plateau within the licensed dose range, with the possible exceptions of lumateperone, olanzapine and lurasidone.

Adverse effects

The majority of adverse effects associated with antipsychotic treatment are dose-related.[32] These include EPS,[31] weight gain,[33] sedation, postural hypotension, anticholinergic effects, QTc prolongation[34] and coronary heart disease mortality.[35–38] High-dose antipsychotic treatment is clearly associated with a greater adverse-effect burden.[16,35,39–41] There is some evidence that antipsychotic dose reduction from a very high (mean 2253mg chlorpromazine equivalents per day) to a high (mean 1315mg chlorpromazine equivalents per day) dose can lead to improvements in cognition and negative symptoms.[42]

Recommendations

- The use of high-dose antipsychotic medication should be an exceptional clinical practice and only ever employed when adequate trials of such medication (including clozapine) at standard dosage have failed.
- If high-dose antipsychotic medication is prescribed, it should be standard practice to review and document the target symptoms, therapeutic response and adverse effects, ideally using validated rating scales, so that there is ongoing consideration of the risk–benefit balance 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 'time to response').
- There have been adequate trials of at least two different antipsychotic medications (including, if possible, olanzapine), conducted sequentially.
- Clozapine has failed or not been tolerated because of agranulocytosis or other serious adverse effects. Most other adverse effects can be managed. A small proportion of patients may also decline to take clozapine.

The decision to prescribe high doses should:

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

Process

- Rule out contraindications (e.g. 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, together with a description of the 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'.
- All patients on high doses should have regular ECGs (at 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.

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Combined antipsychotics (antipsychotic polypharmacy)

In psychiatric practice, prescriptions for combined antipsychotic medications are common[1–3] and often long term.[4] The medications combined are likely to include LAI antipsychotic preparations,[5,6] quetiapine[7] and FGAs,[8] the last of these perhaps reflecting the frequent use of haloperidol and chlorpromazine as prn medications.

Poor response to antipsychotic monotherapy

A national clinical audit conducted in the UK in 2022[9] found that by far the most common reason recorded for prescribing regular, combined antipsychotic medications was an insufficient response to antipsychotic monotherapy. The use of combined antipsychotic medications has been found to be associated with younger patient age, male gender, increased illness severity, complexity and chronicity, as well as poorer functioning, inpatient status and a diagnosis of schizophrenia.[2,7,10–12] These associations largely reinforce the notion that antipsychotic polypharmacy is used where schizophrenia has proved to be refractory to trials of antipsychotic monotherapy.[10,13–15]

Importantly, there is a lack of robust evidence that the efficacy of combined antipsychotic medications is superior to treatment with a single antipsychotic.[16,17] A meta-analysis of 16 RCTs in schizophrenia, comparing augmentation with a second antipsychotic with continued antipsychotic monotherapy, found that combining antipsychotic medications lacked double-blind/high-quality evidence of efficacy.[18] In addition, in patients with schizophrenia, the effects of a change back from antipsychotic polypharmacy to monotherapy, even when carefully conducted, are uncertain. 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,[19,20] and an open-label trial in institutionalised patients with chronic psychotic disorders found that such a switch did not increase the likelihood of relapse.[21] However, an RCT in outpatients with schizophrenia reported greater increases in symptoms 6 months after a switch from two co-prescribed antipsychotic medications to one,[22] although the expectation is that such exacerbations can be successfully managed.[19]

Long-term antipsychotic treatment

A non-interventional, population-based study in Hungary sought to compare the effectiveness of antipsychotic monotherapy with the use of combined antipsychotic medications over a 1-year observation period.

While the results provided evidence for the superiority of monotherapy over polypharmacy for SGAs in terms of all-cause treatment discontinuation in schizophrenia, polypharmacy was associated with a lower likelihood of mortality and psychiatric hospitalisations.[23] Similarly, a 20-year observational study in Finland reported on the risk of rehospitalisation in a cohort of 62,250 hospital-treated patients with schizophrenia. To minimise selection bias, the investigators used within-individual analyses, with each patient used as their own control. The main finding was that antipsychotic combinations, particularly those including clozapine and LAI antipsychotic medications, were associated with a slightly lower risk of psychiatric rehospitalisation than

monotherapy.[24] Although the interpretation of such real-world findings is hindered by the issue of confounding by indication,[25] there are perhaps several plausible explanations for improved efficacy with polypharmacy. It may be that combining antipsychotic medications with different receptor profiles can be more effective and lead to better therapeutic efficacy and/or a lower adverse-effect burden and therefore better outcomes. It may be also that co-prescribing two antipsychotic medications improves medication adherence in that it increases the likelihood that a patient may use at least one of them.[24] Notably, clozapine and LAI antipsychotic preparations appear to be the most effective monotherapies for relapse prevention in schizophrenia.[26] Thus, adding a second antipsychotic medication to clozapine or an LAI antipsychotic medication in an attempt to mitigate metabolic adverse effects (e.g. by adding aripiprazole) or manage symptoms of agitation, anxiety or sleep disturbance (e.g. by adding olanzapine or quetiapine) might enhance a patient's engagement in their treatment and improve adherence to the effective antipsychotic treatment that has been augmented.

Adverse effects

Evidence for possible harm with combined antipsychotic medications is perhaps more convincing. Clinically significant adverse effects have been associated with combined antipsychotic medications, which may partly reflect that polypharmacy regimens are commonly a high-dose prescription.[8,27] There is an increased prevalence and severity of EPS,[28,29] increased metabolic adverse effects and diabetes,[22,30,31] sexual dysfunction,[32] an increased risk of hip fracture,[33] paralytic ileus,[34] grand mal seizures,[35] prolonged QTc,[36] hypertension[37] and arrhythmias.[13] Switching from antipsychotic polypharmacy to monotherapy has been shown to lead to worthwhile improvements in cognitive functioning.[20]

The evidence relating to an increased mortality with a continuing antipsychotic polypharmacy regimen is inconsistent. Two large case–control studies and a database study[38–40] found no increased mortality in patients with schizophrenia receiving antipsychotic polypharmacy compared with antipsychotic monotherapy. However, a 10-year prospective study of a cohort of 88 patients with schizophrenia found that receiving more than one antipsychotic medication concurrently was associated with substantially increased mortality.[18,41] These investigators explored the possibility that the use of combined antipsychotic medications might be a proxy for greater severity/increased refractoriness of psychiatric illness but found no association between mortality and any measured index of illness severity, although these measures focused on negative symptoms and cognitive deficits. Further, analysis of data from a large anonymised mental healthcare database (2007–2014) of 10,945 adult patients with serious mental illness who had been prescribed a single antipsychotic or polypharmacy for 6 months or more revealed a weak association between regular, long-term antipsychotic polypharmacy and all-cause mortality and natural causes of death.[42] However, the authors concluded that the evidence for the association was limited, even after controlling for the effect of dose. Another study, involving 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.[43] These authors also considered the possibility of indication bias influencing the findings, speculating that combined antipsychotic medication might be more likely to be prescribed for the most severe schizophrenia.

Given the association between combined antipsychotic medication and a greater adverse-effect burden,[15,44] it follows that it should be standard practice to document in the clinical records the rationale for prescribing combined antipsychotics in individual cases, together with a clear account of the benefits and adverse effects of an individual trial of the strategy. Medicolegally, this would seem to be prudent, although in practice it is not always done.[45]

The use of combined antipsychotic medications in clinical practice

There are myriad possible antipsychotic medication combinations but very limited data on their relative risk–benefit profiles in relation to overall therapeutic response or target symptom clusters. The clinical disadvantages of antipsychotic polypharmacy include an increased adverse-effect burden, higher total dosage, increased risk of drug–drug interactions, poorer medication adherence related to the complexity of the treatment and difficulties in the attribution of any response to one or more of the individual antipsychotic medications prescribed, leading to difficulty in determining the implications for an optimal longer-term regimen.[6]

Despite the limited supportive evidence base, the use of antipsychotic polypharmacy is an established custom and practice in many countries.[46–48] Further, 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.[6,12,13,49–51] However, a trial of clozapine augmentation with a second antipsychotic medication to enhance efficacy is a potentially supportable practice[52–56] (see section on optimising clozapine treatment in this chapter). Other antipsychotic polypharmacy strategies with potentially valid rationales are the addition of aripiprazole to reduce body weight in patients receiving clozapine.[57,58] Adjunctive aripiprazole can also normalise prolactin levels, although, while the study findings on resolving hyperprolactinaemia are generally positive, they are not entirely consistent.[59–64] Such polypharmacy with aripiprazole may be seen as worthwhile, evidence-based practice, albeit in the absence of regulatory trials demonstrating safety. In some cases, the use of aripiprazole alone might be a more logical choice.

Conclusion

Prescribing more than one antipsychotic medication may improve efficacy and very probably increases medical morbidity.[65,66] Nevertheless, based on evidence currently available relating to efficacy and the potential for serious adverse effects, the routine use of combined, non-clozapine, antipsychotic medications is probably best avoided.

Summary

- There is a dearth of robust evidence supporting the superiority of combined, non-clozapine, antipsychotic medications over antipsychotic monotherapy.
- There is more substantial evidence supporting the potential for harm and so the use of combined antipsychotic medications, which is commonly a high-dose prescription, should generally be avoided.

- Combined antipsychotic medications are commonly prescribed and this practice seems to be relatively resistant to change.
- As a minimum requirement, all patients who are prescribed combined antipsychotic medications should be systematically monitored for adverse effects (including an ECG) and any beneficial effect on the symptoms of psychotic illness carefully documented.
- Some antipsychotic polypharmacy strategies (e.g. combinations with aripiprazole) show clear benefits for tolerability but not efficacy.

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Antipsychotic prophylaxis

First episode of psychosis

Antipsychotics provide effective protection against relapse, at least in the short to medium term,[1] and the introduction of antipsychotics in the 1950s seems to have improved outcomes overall.[2] A meta-analysis of placebo-controlled trials found that 26% of patients with first-episode schizophrenia on maintenance antipsychotic relapsed after 6–12 months compared with 61% on placebo.[3] Although the current consensus is that antipsychotics should be prescribed for 1–2 years after a first episode of schizophrenia,[4,5] one study[6] found that withdrawing antipsychotic treatment in line with this view led to a relapse rate of almost 80% after 1 year medication-free and 98% after 2 years. A 2019 Swedish population study revealed that the longer the treatment with antipsychotics, the lower the risk of hospitalisation (e.g. those with 5 years' treatment had half the hospitalisation rate of those treated for less than 6 months).[7]

Other studies in first-episode schizophrenia confirmed that only a small minority of patients who discontinue remain well 1–2 years later[8–11] (e.g. a small study found 94% of patients with first-episode schizophrenia relapsed within 2 years of stopping risperidone long-acting injection; 97% at three years).[12] A 2018 meta-analysis of eight RCTs was rather more optimistic and found relapse rates averaged 35% (treated) and 61% (discontinued) at 18–24 months.[13]

A 5-year follow-up of a 2-year RCT, during which patients either received 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.[14] There are numerous interpretations of these outcomes but the most that can be concluded is that dose reduction is a possible option in first-episode psychosis. The study has been heavily criticised[15] and there are certainly other studies showing disastrous outcomes from antipsychotic discontinuation,[16] albeit over shorter periods with fewer patients. Nonetheless, some patients with first-episode psychosis will not need long-term antipsychotics to stay well – figures as high as 18–30% have been put forward.[17]

There are no reliable patient factors linked to outcome following discontinuation of antipsychotics in patients with first-episode psychosis (other than cannabis use)[18] and there remains more evidence in favour of continuing antipsychotics than for stopping them.[19] There are indications that very prolonged discontinuation regimens using hyperbolic tapering (see section on stopping antipsychotics in this chapter) may offer the best chance of successfully withdrawing from antipsychotic treatment.[20,21]

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 patients with first-episode non-refractory schizophrenia.[22] However, in a large naturalistic study of patients with

a first admission for schizophrenia, clozapine and olanzapine fared better with respect to preventing readmission than other oral antipsychotics.[23] 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).[23] Later studies show a huge advantage for long-acting risperidone over oral risperidone in the first episode[24] and a smaller but substantial benefit for paliperidone LAI over oral antipsychotics in 'recently diagnosed schizophrenia'.[25] In a later study, amisulpride was shown to give good outcomes and staying on amisulpride after not initially reaching remission was as successful as switching to olanzapine.[26]

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 one year.[27] Ideally, patients should have their dose reduced very gradually and all relevant family members and healthcare 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 keyworkers 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.[28]

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.[29] With each subsequent episode, the baseline level of functioning deteriorates[30] 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.[3,31] Those who receive targeted antipsychotics (i.e. only when symptoms re-emerge) seem to have a worse outcome than those who receive prophylactic antipsychotics[32,33] and the risk of TD may also be higher. Similarly, low-dose antipsychotics are less effective than standard doses.[34] The optimal dose to prevent relapse is 5mg/day risperidone equivalents.[35] Higher doses offer no benefit and ensure poorer tolerability.

Depot preparations may have an advantage over oral in maintenance treatment, most likely because of guaranteed medication delivery (or at least guaranteed awareness of medication delivery). Meta-analyses of clinical trials have shown that the relative and absolute risks of relapse with depot maintenance treatment were 30% and 10% lower, respectively, than with oral treatment.[3,36] Long-acting preparations of antipsychotics may thus be preferred by both prescribers and patients.

Summary

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

A large meta-analysis concluded that the risk of relapse with newer SGAs is similar to that associated with older drugs.[3] (Note that lack of relapse is not the same as good functioning.[37]) The proportion of patients with multi-episode schizophrenia who achieve remission is small and may differ between antipsychotic drugs. The CATIE study[38] 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. The advantage seen here for olanzapine is consistent with that seen in an acute efficacy network meta-analysis,[39] and in two recent meta-analyses of long-term efficacy.[40,41]

Adherence to antipsychotic treatment

Among people with schizophrenia, non-adherence to 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.[42] Not only does non-adherence increase the risk of relapse, it may also increase the severity of relapse and the duration of hospitalisation.[42] The risk of suicide attempts also increases four-fold[42] (see section on working towards adherence in Chapter 14). Given these low rates of adherence and the near certainty of relapse if antipsychotics are not taken, the use of oral antipsychotics is difficult to justify.

Dose for prophylaxis

Many patients probably receive higher doses than necessary (particularly of the older drugs) when acutely psychotic.[43,44] In the longer term, a balance needs to be made between effectiveness and adverse effects. Lower doses of the older drugs (8mg haloperidol/day or equivalent) are, when compared with higher doses, associated with less severe adverse effects,[45] better subjective state and better community adjustment.[46] Very low doses increase the risk of psychotic relapse.[43,47,48] The largest meta-analysis showed very clearly that prophylactic efficacy begins to be lost at doses below around 5mg/day risperidone equivalents.[35]

Doses that are acutely effective should generally be continued as prophylaxis,[49,50] although an exception to this is prophylaxis after a first episode, where very careful dose reduction is probably supportable. There is some recent support for dose reduction in multi-episode schizophrenia.[51] The concept of guided antipsychotic dose reduction has gained attention in the past few years, following the apparent success of the famous Wunderink study.[14] Later studies have suggested that guided dose reduction is associated with a substantially greater risk of relapse compared with continuation.[52,53] However (and perhaps most importantly), guided dose reduction or stopping treatment does not result in relapse in everyone, at least over the time periods examined.[54] So some people (probably a small minority) appear to be able to stop antipsychotic treatment without relapsing.

How and when to stop[55]

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).[56] 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.[57] 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.[58]

The following factors should be considered:[55]

- 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 patients having their first episode, patients, carers and keyworkers 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.[10] Those with a history of aggressive behaviour or serious suicide attempts and those with residual psychotic symptoms should be considered for life-long treatment.

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.[59] This phenomenon might explain better outcomes seen in patients with first-episode schizophrenia who receive lower doses of antipsychotics, but it also suggests the possibility that the use of antipsychotics might ultimately worsen outcomes. It might also explain the poor outcomes seen with abrupt discontinuation of antipsychotics.[56] This observation in turn leads some to question the validity of long-term studies in which active and successful treatment is abruptly stopped, since rebound phenomena and withdrawal reactions may account for at least some of the observed high relapse rates.[60]

The concept of 'super-sensitivity psychosis' was much discussed decades ago[61,62] and has more recently seen a resurgence.[59,63] It is striking that dopamine antagonists used for non-psychiatric conditions can induce withdrawal psychosis.[64–66] While 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).[67] Clinicians should remain open-minded about the possibility that long-term antipsychotics may worsen, or at least not improve, outcomes in some people with schizophrenia.

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Negative symptoms

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 and verbal expressiveness, and flattened or blunted affect, which is 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] While there is some consensus around this two-dimensional model, five-factor models of negative symptoms have also been propounded.[3,4]

Persistent negative symptoms are held to account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.[5–8] 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 constitute 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 adverse medication effects, such as dysphoria and bradykinesia as part of drug-induced parkinsonism.[7,9] Other sources of secondary negative symptoms may include chronic substance or alcohol use, high-dose antipsychotic medication, social deprivation, lack of stimulation and hospitalisation.[10] Secondary negative symptoms may be best tackled by treating the relevant underlying cause. In people with established schizophrenia, prominent, clinically relevant negative symptoms are seen in around 60%, with up to 20% judged to have persistent, primary negative symptoms.[11–13]

The literature pertaining to the pharmacological treatment of negative symptoms partly comprises sub-analyses of acute efficacy studies, correlational analyses and path analyses.[14] There is often no reliable distinction between primary and secondary negative symptoms or between the two subdomains of expressive deficits and avolition/amotivation, and relatively few studies specifically recruit patients with persistent or predominant negative symptoms. While the evidence suggests short- and medium-term efficacy for a few interventions, there is no widely accepted evidence for an effective treatment for persistent primary negative symptoms.

Pharmacological treatment of negative symptoms

- In first-episode psychosis, the presence of negative symptoms is related to poor outcome in terms of recovery and level of social functioning.[6,11] 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.[15–17] However, when interpreting such data, it should be borne in mind that an early clinical picture characterised by negative symptoms, being a less socially disruptive and more subtle signal 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 has mainly been shown in secondary negative symptoms in acute psychotic episodes.[18] Against expectations, there is no consistent evidence for the superiority of SGAs over FGAs in the treatment of negative symptoms.[19–23] Similarly, early analyses found no consistent evidence for the superiority of any individual SGA.[24] A 2015 meta-analysis of 38 RCTs found a statistically significant reduction in negative symptoms with SGAs, but the effect size did not reach a threshold for 'minimally detectable clinical improvement over time'.[25]
- There are some relatively robust data suggesting superior efficacy for negative symptoms with certain antipsychotics, such as **cariprazine**,[26–28] **aripiprazole** and **amisulpride**, and single trials suggesting that **olanzapine** and **quetiapine** may be more effective than risperidone.[26,29–37] A 2023 review included **amisulpride** and **cariprazine** among the medications considered to have the most promise as treatments for primary negative symptoms.[38]
- While **clozapine** remains the only medication with convincing superiority for TRS, whether or not it has superior efficacy for negative symptoms in such cases, at least in the short term, remains uncertain.[39–41] One potential confound in studies of clozapine for negative symptoms is that the medication has a low liability for parkinsonian adverse effects, including bradykinesia. These are symptoms which have a phenomenological overlap with negative symptoms, particularly the subdomain of expressive deficits. There is some evidence to suggest that for patients being treated with clozapine who have residual negative symptoms, the addition of cariprazine may help.[42,43]
- With respect to the effect of decreasing glutamate transmission on negative symptoms, three meta-analyses have suggested a beneficial response with add-on **memantine**[44–46] but there have been inconsistent meta-analysis findings for lamotrigine augmentation of clozapine.[47,48] Adding **minocycline**, an antibiotic and inflammatory drug, initially showed promise[46,49,50] but a relatively large RCT of adjunctive minocycline found it was not efficacious in treating negative symptoms.[51] Further, the BeneMin study,[49] which was designed to determine whether adjunctive minocycline, administered early in the course of schizophrenia, protected against the development of negative symptoms over a year, also failed to find any evidence of clinical benefit. The glutamate antagonist **topiramate** may have some efficacy for symptom reduction in schizophrenia spectrum disorders, including negative symptoms.[52]
- A 2006 Cochrane review concluded that **antidepressant augmentation** of an antipsychotic for negative symptoms may be an effective strategy for reducing affective flattening, alogia and avolition.[53] RCTs and meta-analyses addressing antidepressant augmentation of antipsychotic medication have yielded somewhat inconsistent evidence of modest efficacy.[54–59] One meta-analysis of placebo-controlled studies in people with established schizophrenia found that adjunctive antidepressant treatment was associated with a limited reduction in negative symptoms, and only when added to treatment with FGAs.[58] Another review of meta-analyses concluded that the evidence suggested a beneficial effect for some SSRIs, such as **fluvoxamine**, **citalopram**, and the α_2 receptor antagonists **mirtazapine** and **mianserin**.[18] **Reboxetine** (a noradrenaline reuptake inhibitor) may also have some activity.[60]
- A host of other augmentation agents have been tested.[46,61,62] For example, meta-analyses provide some support for adjunctive treatment with **Ginkgo biloba**[63] and a **COX-2** (cyclooxygenase-2) **inhibitor** (albeit with a small effect size),[64] while small

RCTs have demonstrated some benefit for **selegiline**,[65,66] **pramiprexole**,[67] **topical testosterone**,[68] **ondansetron**,[69] **granisetron**,[70] **palmitoylethanolamide** (an endogenous analogue of anandamide, an endocannabinoid) added to risperidone[71] and **pimavanserin**, a potent 5-HT_{2A} inverse agonist and antagonist.[72,73] The $5HT_2$ antagonist **roluperidone** may also be effective.[74,75]

- Other experimental treatments for which promising data exist include **pregnenolone**,[76] **raloxifene** (in women),[77] **levetiracetam**,[78] **clonidine**,[79] **nanocurcumin**,[80] **xanomeline** (as Cobenfy)[81] and the anti-inflammatory drugs **berberine**[82] and **fingolimod.**[61]
- The findings from studies of repetitive transcranial magnetic stimulation (**rTMS**) are mixed but promising.[83] Transcranial direct current stimulation (**tDCS**) may also have some potential as a treatment for negative symptoms, but the evidence thus far is limited and rather inconsistent.[18,84–87]

Patients who misuse psychoactive substances may experience less severe negative symptoms than patients who do not.[88] 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.[89,90]

Summary and recommendations

These recommendations are derived from the British Association for Psychopharmacology (BAP) schizophrenia guideline (2020),[91] Galderisi et al. (2021),[87] Veerman et al. (2017),[10] Aleman et al. (2017)[18] and Howes et al. (2023).[38]

- 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 that 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 or an antipsychotic, 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.

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Monitoring

Table 1.6 summarises suggested monitoring for those receiving antipsychotic medication.[1] Monitoring of people taking antipsychotics is very poor in most countries.[2–5] The guidance given here is strongly recommended to ensure safer use of these drugs. Other sections in this chapter provide further background information and relevant references. This table is a summary; see the individual sections for details and discussion.

Table 1.6 Suggested monitoring for people receiving antipsychotic medication.

Parameter/test	Suggested frequency	Action to be taken if results outside reference range	Medications with special precautions	Medications for which monitoring is not required
Urea and electrolytes (including creatinine or eGFR)	Baseline, then yearly as part of a routine physical health check	Investigate all abnormalities detected	Amisulpride and sulpiride renally excreted – consider reducing dose if eGFR reduced	None
Full blood count[6–8]	Baseline, then yearly as part of a routine physical health check and to detect chronic bone marrow suppression (small risk associated with some antipsychotic medications)	Stop suspect medication if neutrophils fall below 1.5×10^9/L (unless diagnosed with BEN). Refer to specialist medical care if neutrophils below 0.5×10^9/L.	Clozapine FBC weekly for 18 weeks, then 2-weekly up to 1 year, then monthly (schedule varies from country to country)	None
Blood lipids[9,10] (cholesterol, triglycerides; fasting sample, if possible)	Baseline, at 3 months, then yearly to detect antipsychotic-induced changes and to generally monitor physical health	Offer lifestyle advice. Consider changing antipsychotic medication and/or initiating statin therapy.	Clozapine, olanzapine: 3-monthly for first year, then yearly	Some antipsychotic medications (e.g. aripiprazole, brexpiprazole cariprazine,[11] lurasidone) not clearly associated with dyslipidaemia but prevalence is high in this patient group[12–14] so all patients should be monitored
Weight[9,10,14] (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 medication 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 strongly recommended
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 HbA_{1c}. Refer to GP or specialist.	Clozapine, olanzapine, chlorpromazine – test at baseline, one month, then 4–6 monthly	Some antipsychotic medications not clearly associated with IFG but prevalence is high,[15,16] so all patients should be monitored

(*Continued*)

Table 1.6 (*Continued*)

Parameter/test	Suggested frequency	Action to be taken if results outside reference range	Medications with special precautions	Medications for which monitoring is not required
ECG[17,18]	Baseline, when the target dose is reached (ECG changes are rare in practice),[19] on admission to hospital, if there are cardiac symptoms, or when medication is changed (e.g. to high-dose or combined antipsychotic medications)[17]	Discuss with/refer to cardiologist if abnormality detected	Haloperidol, pimozide, sertindole – ECG mandatory Ziprasidone – ECG mandatory in some situations Pimavanserin – ECG strongly recommended	Risk of sudden cardiac death increased with most antipsychotic medications.[20] Ideally, all patients should be offered an ECG at least yearly.
Blood pressure	Baseline and then frequently during dose titration and after dosage changes	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 national guidelines.	Clozapine, chlorpromazine and quetiapine most likely to be associated with postural hypotension	Amisulpride, aripiprazole, brexpiprazole, cariprazine, lumateperone, lurasidone, trifluoperazine, sulpiride
Prolactin	Baseline, at 6 months, then yearly	Switch medications if hyperprolactinaemia confirmed and symptomatic. Consider tests of bone mineral density (e.g. DEXA) for those with chronically raised prolactin.	Amisulpride, sulpiride, risperidone and paliperidone particularly associated with hyperprolactinaemia	Asenapine, aripiprazole, brexpiprazole, cariprazine, clozapine, lumateperone, lurasidone, quetiapine, olanzapine (low dose), xanomeline and ziprasidone do not usually elevate plasma prolactin, but measure if symptoms arise
Liver function tests[21–23]	Baseline, then yearly as part of a routine physical health check	Stop suspect medication if LFTs indicate hepatitis (transaminases × 3 normal) or functional damage (PT/albumin change)	Clozapine and chlorpromazine associated with hepatic failure	Amisulpride, sulpiride
Creatinine phosphokinase	Baseline, then if NMS suspected	See section on NMS in this chapter	NMS most likely with high-potency FGAs but can occur with any dopamine antagonist or partial agonist	None
Other tests	Patients on clozapine may benefit from an **EEG**[24,25] as this may help determine the need for antiseizure treatment (although interpretation is obviously complex). Those on quetiapine should have **thyroid** function tests yearly, although the risk of abnormality is very small.[26,27]			

BEN, benign ethnic neutropenia; BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FGA, first-generation antipsychotic; HbA_{1c}, glycated haemoglobin; IFG, impaired fasting glucose; NMS, neuroleptic malignant syndrome; PT, prothrombin time.

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Relative adverse effects – a rough guide

Table 1.7 provides approximate estimates of relative incidence and severity of adverse effects. It serves as a rough guide and does not replace the detailed and referenced sections included elsewhere. For further details, refer to the dedicated sections in this chapter. Other adverse effects not mentioned in this table also occur.

Table 1.7 Approximate estimates of relative incidence and severity of adverse effects.

Drug	Sedation	Weight gain	Akathisia	Parkinsonism	Anticholinergic	Hypotension	Prolactin elevation	Prolonged QT interval
Amisulpride	–	+	+	+	–	–	+++	++
Aripiprazole	–	+	+	–	–	–	–	–
Asenapine	+	+	+	+	–	–	+	–
Benperidol	+	+	+	+++	+	+	+++	+
Blonanserin	–	–	+	–	–	–	+	–
Brexpiprazole	–	+	+	–	–	–	–	–
Cariprazine	–	+	+	–	–	–	–	–
Chlorpromazine	+++	++	+	++	++	+++	++	++
Clozapine	+++	+++	–	–	+++	+++	–	+++
Flupentixol	+	++	++	++	++	+	+++	–
Fluphenazine	+	+	++	+++	+	+	+++	+
Haloperidol	+	+	+++	+++	–	+	+++	++
Iloperidone	–	++	+	+	–	+	–	++
Levomepromazine	+++	+	+	+	++	++	++	+
Lumateperone	++	–	–	–	–	–	–	–
Loxapine	++	+	+	++	+	++	+++	–
Lurasidone	+	+	+	+	–	–	–	–
Olanzapine	+++	+++	+	–	+	+	+	+
Paliperidone	+	++	++	+	–	++	+++	+
Penfluridol	–	++	++	++	++	+	+++	++
Perphenazine	+	+	++	+++	+	+	+++	+
Pimavanserin	–	–	–	–	–	–	–	++
Pimozide	+	++	++	+	++	+	+++	+++
Promazine	+++	++	+	+	++	++	+	++
Quetiapine	+++	++	+	–	+	++	–	++
Risperidone	+	++	++	+	–	++	+++	+
Sertindole	–	+	+	–	–	+++	–	+++
Sulpiride	–	+	+	+	–	–	+++	+

(*Continued*)

Table 1.7 (*Continued*)

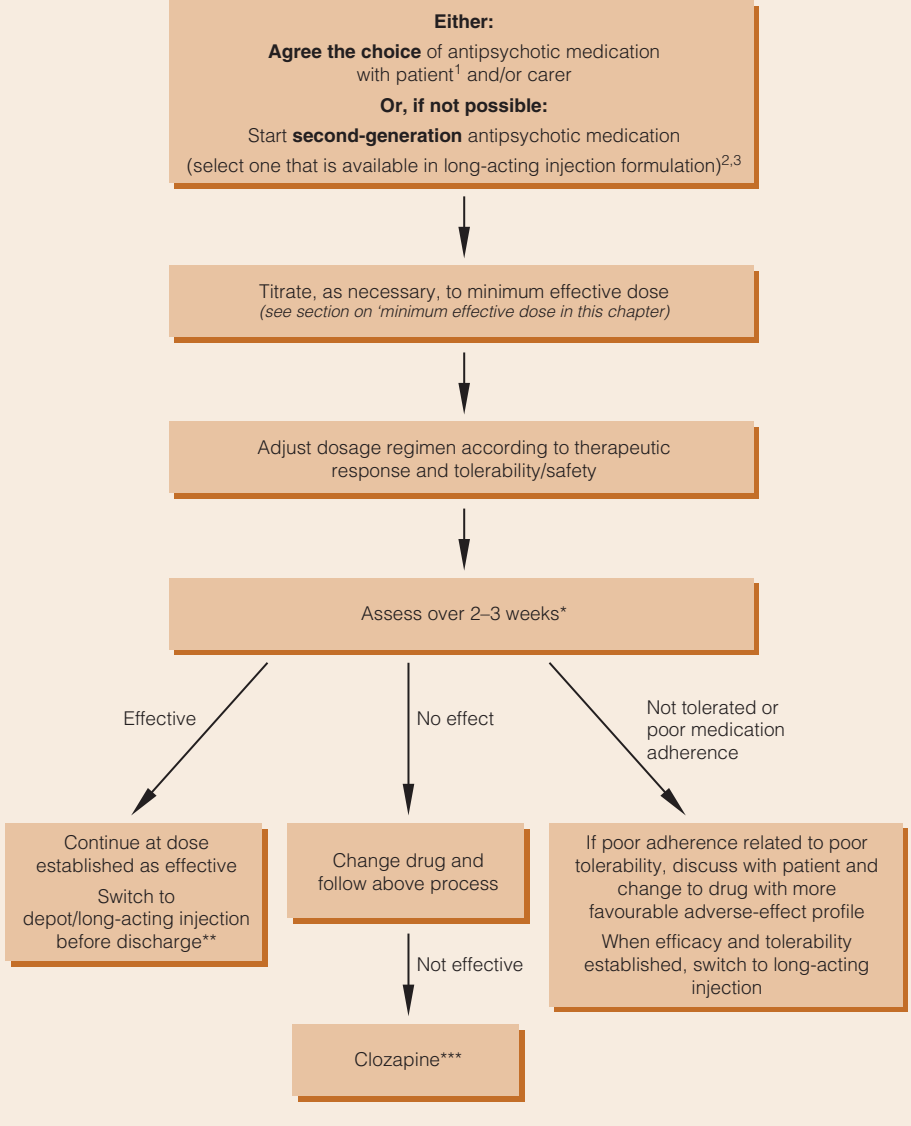
Drug	Sedation	Weight gain	Akathisia	Parkin-sonism	Anti-cholinergic	Hypotension	Prolactin elevation	Prolonged QT interval
Thiothixene	++	++	+	+	++	++	+	+
Trifluoperazine	+	+	+	+++	+	+	+++	?
Xanomeline	–	–	–	–	–	–	–	+
Ziprasidone	+	–	+	–	–	+	–	++
Zuclopenthixol	++	++	++	++	++	+	+++	+

Key: +++ high incidence/severity, ++ moderate, + low, – very low/zero.

Treatment algorithms for schizophrenia

First-episode schizophrenia

Treatment algorithm

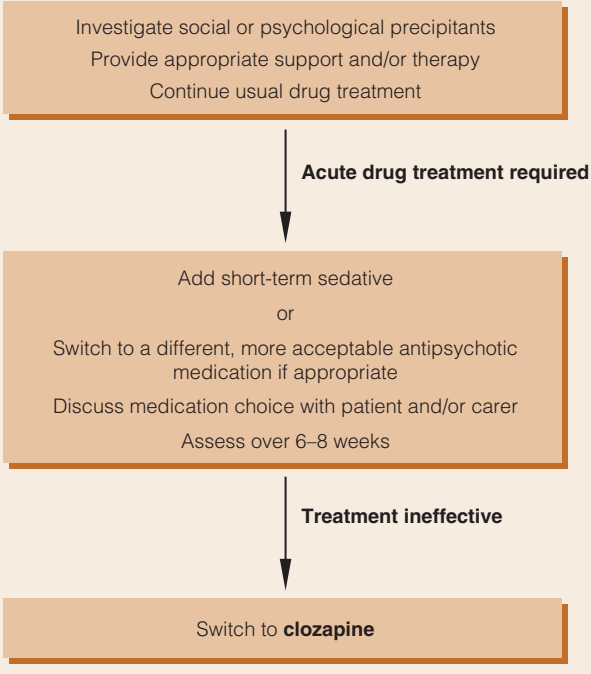


* Any improvement is likely to be apparent within 2–3 weeks of receiving an effective dose.[4] Most improvement occurs during this period.[5] If *no* effect by 2–3 weeks, increase the dose or change the drug. If some response detected, continue for a total of 10 weeks before abandoning treatment.[6]
** Relapse and readmission rates are vastly reduced by early use of depot/long-acting injections in this patient group.[7–9] Patients with first-episode schizophrenia will accept long-acting injections.[10]
*** Early use of clozapine much more likely than anything else to be successful.[6,11] Reluctance to use clozapine is associated with poor outcomes.[12] Delaying the use of clozapine diminishes response to clozapine.[13]

Relapse or acute exacerbation of schizophrenia

(full adherence to medication confirmed)*

Treatment algorithm



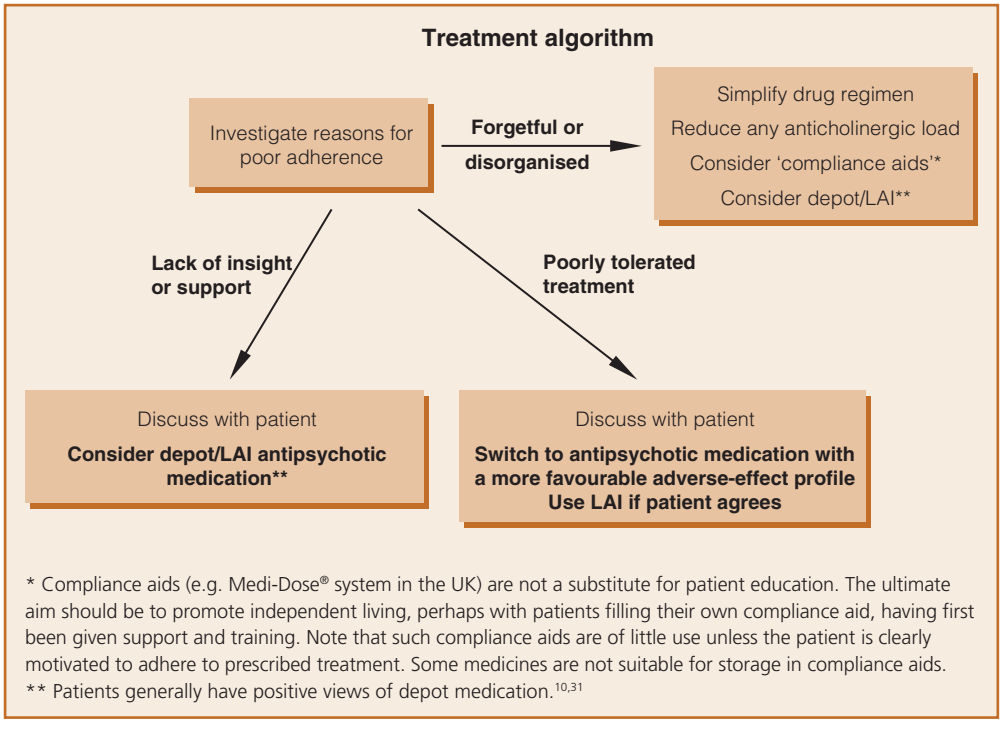
Notes

- First-generation drugs may be slightly less efficacious than some SGAs.[14,15] FGAs should probably be reserved for second- or third-line use (or not used at all) because of the possibility of poorer outcome compared with SGAs and the higher risk of movement disorder, particularly TD.[16,17]
- Choice should be based largely on comparative adverse-effect profile and relative toxicity. Patients seem able to make informed choices based on these factors,[18,19] although in practice they are rarely involved in drug choice.[20] Allowing patients informed choice seems to improve outcomes.[1]
- Where there is prior treatment failure (but not confirmed treatment refractoriness), olanzapine or risperidone may be better options than quetiapine.[21] Olanzapine, because of the wealth of evidence suggesting slight superiority over other antipsychotics, should probably be tried before clozapine unless contraindicated.[22–25] However, one RCT[6] found that continuing with amisulpride was as effective as switching to olanzapine.
- 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,[21,26] and apparent treatment resistance may simply be a result of inadequate treatment.[27]
- Time to response is increased and total response decreased in exacerbations of multi-episode schizophrenia.[28]
- 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.[29,30]

* In patients taking oral antipsychotics, non-compliance often goes undetected.[26] Absolute non-compliance (blood levels of zero) is surprisingly common.[27]

Relapse or acute exacerbation of schizophrenia

(adherence doubtful or known to be poor)



* Compliance aids (e.g. Medi-Dose® system in the UK) are not a substitute for patient education. The ultimate aim should be to promote independent living, perhaps with patients filling their own compliance aid, having first been given support and training. Note that such compliance aids are of little use unless the patient is clearly motivated to adhere to prescribed treatment. Some medicines are not suitable for storage in compliance aids.
** Patients generally have positive views of depot medication.[10,31]

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First-generation antipsychotics – place in therapy

Nomenclature

First-generation ('typical') and second-generation ('atypical') antipsychotic medications are not categorically differentiated. Drugs in both groups differ substantially in pharmacological and adverse-effect profiles and there is some overlap between the two groups in pharmacological characteristics. FGA medications were introduced before 1990 and tend to be associated with acute EPS, hyperprolactinaemia and, in the longer term, TD. It might be expected that these adverse effects are less likely or absent with SGA medications (introduced after 1990), although in practice most SGAs show dose-related EPS, some induce hyperprolactinaemia (some to a greater extent than FGAs) and all will give rise to TD, albeit at a lower incidence than FGAs. SGA medications tend to be associated with metabolic and cardiac complications,[1–3] although this is *not* true of all SGAs and it *is* true of some FGAs. To complicate matters further, it has been suggested that the therapeutic and adverse effects of FGAs can be separated by careful dosing.[4] That is, FGAs can be indistinguishable from SGAs if used in small enough doses (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 range of doses at which it is effective but does not cause EPSEs (perhaps 4.0–4.5mg/day) whereas olanzapine has a wide range of therapeutic doses (5–40mg/day) at which it does not generally cause such adverse effects.

The use of NbN[1,2] (for which there is a free application for smartphones and other devices) obviates the need for classification into an FGA or SGA and describes individual drug by their pharmacological activity. NbN is certainly a useful alternative to standard classifications, but one possible limitation is that it preselects specific pharmacological features to create categories while ignoring others, based on the opinion of experts that these features are essential to drug action (despite exact mechanisms of action being unknown). In 2023, a different approach based on in vitro binding profiles was proposed.[3] Four clusters of effects were identified, one with high affinity for muscarinic receptors (e.g. olanzapine and quetiapine), one with relatively low antagonism of the dopamine D2 receptor (e.g. the partial agonists and lurasidone), one with serotonergic antagonism (e.g. risperidone) and one with relatively pure dopaminergic antagonism (e.g. amisulpride). These clusters mapped to adverse-effect profiles with greater accuracy than the other classification systems. One possible disadvantage of this so-called data-driven approach is that all receptors are assigned an equal level of importance regardless of their magnitude of impact in producing clinically relevant effects. The wider use of NbN or the data-driven approach 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, haloperidol is a frequent choice for 'when necessary' medication and depot preparations of haloperidol, zuclopenthixol and flupentixol are still commonly prescribed. FGAs can offer a valid

alternative to SGAs where SGAs 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 slightly more efficacious)[4,5] but any differences in therapeutic efficacy seem to be modest. Two large, independent and pragmatic studies, CATIE[6] and CUtLASS,[7] found few important differences between SGAs and FGAs (mainly perphenazine and sulpiride, respectively).

The main drawbacks of FGAs are acute EPS, hyperprolactinaemia and TD. Hyperprolactinaemia is probably unavoidable in practice because the dose that achieves efficacy is too close to the dose that causes hyperprolactinaemia. Even when not symptomatic, hyperprolactinaemia may grossly affect hypothalamic function.[8] Raised prolactin is also associated with sexual dysfunction,[9] as are the autonomic effects of some SGAs.[10] Notably, some SGAs (risperidone, paliperidone, amisulpride) increase prolactin to a greater extent than FGAs.[11]

All FGAs are potent dopamine antagonists, which are liable to induce dysphoria.[12] Perhaps as a consequence, some FGAs may produce smaller benefits in quality of life than some SGAs.[6]

Tardive dyskinesia very probably occurs more frequently with FGAs than SGAs[13–16] (notwithstanding difficulties in defining what is 'atypical'), although there remains some uncertainty[16–18] and the dose of FGA used is a crucial factor.[19] A complicating aspect is the occurrence of TD in untreated schizophrenia,[20] which may mean that antipsychotics do not necessarily cause TD but simply fail to suppress it to varying degrees. Among SGAs, partial agonists may have the lowest risk of TD.[21] Careful observation of patients and the prescribing of the lowest effective dose are essential to help reduce the risk of this serious adverse event.[22,23] Even with these precautions, the risk of TD with some FGAs may be unacceptably high.[24]

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.[25] Paliperidone produced more weight gain and prolactin change but haloperidol was associated with significantly more frequent akathisia and parkinsonism, and, numerically, a higher incidence of TD. Efficacy was identical.

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NICE guidelines for the treatment of schizophrenia[1]

The UK NICE guidelines[1] were published in February 2014 and last reviewed in September 2024 but have remained largely unchanged.

NICE guidelines – a summary

First-episode psychosis

For people with newly diagnosed schizophrenia, offer oral antipsychotic medication as well as psychological interventions (cognitive behavioural therapy [CBT] or family intervention). 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 healthcare professional together, considering:

- the relative potential of individual antipsychotic drugs to cause extrapyramidal adverse effects (EPSEs; including akathisia), cardiovascular adverse effects, metabolic adverse effects (including weight gain), hormonal adverse effects (including raised prolactin levels) and other adverse effects (including unpleasant subjective experiences)
- the views of the carer where the service user agrees.

Before starting antipsychotic medication, undertake a thorough assessment of physical health and offer an ECG if specified in the summary of product characteristics (SPC) or clinically indicated.

Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial and the following should be considered:

- Recording of 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 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 (e.g. 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, HbA_{1c} 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.
- Discuss the use of alcohol, tobacco, prescription and non-prescription medication, as well as the use of illicit drugs, with the service user and carer if appropriate. Discuss their potential interactions with the prescribed therapy and psychological treatments.
- Do not use a loading dose of antipsychotic medication (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 (e.g. when changing medication).

Subsequent episodes of psychosis/maintenance treatment of schizophrenia

- Consider the clinical response and adverse effects of the service user's current and previous medication.
- Consider offering depot/LAI antipsychotic medication to people with schizophrenia:
  - who would prefer such treatment after an acute episode
  - known to be non-adherent to oral treatment and/or those who prefer this method of administration.

GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is first transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia.

Treatment-resistant schizophrenia

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. The misuse of illicit substances (including alcohol) and the use of other prescribed medication or physical illness should be excluded. At least one of the drugs should be a non-clozapine SGA (see section on treatment algorithms for schizophrenia in this chapter – 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, healthcare 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. Choose a drug that does not compound the common adverse effects of clozapine.

There are some notable differences with some more recently published guidelines. In first-episode psychosis, NICE makes no specific antipsychotic recommendation, whereas the Royal Australian and New Zealand College of Psychiatrists (RANZCP)[2] guidelines recommend atypical antipsychotics. They also explicitly suggest or at least

allow the use of long-acting agents, as do the BAP guidelines.[3] The duration of antipsychotic treatment in first episode is not clearly defined in the NICE guidelines. The Canadian Psychiatric Association guidelines[4] recommend at least 18 months, the BAP at least 2 years, and RANZCP 2–5 years. There is scant mention of the treatment of negative symptoms in any of the guidelines. UK NICE guidelines recommend psychological approaches while RANZCP tentatively recommends rTMS. Reflecting the paucity of evidence in clozapine-resistant schizophrenia there is little detail or difference in guideline recommendations – all suggest adding a second antipsychotic.

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

For any clinician actively involved in the care of people with schizophrenia, perhaps the single most common clinical dilemma is what to do when treatment with the current antipsychotic medication seems to be suboptimal (symptoms are well controlled but adverse effects are problematic or the therapeutic response is inadequate). Fortunately, with regard to poor tolerability, the diversity of the available antipsychotic medications means that it is usually possible to find one that has an adverse-effect profile that is more appropriate and more tolerable. With regard to inadequate symptom response, what to do next is a more difficult question. If the illness has not shown sufficient improvement despite serial adequate trials, in terms of dosage, duration and adherence, of at least two antipsychotic medications, then a trial of clozapine should be considered. However, should the person be reluctant to try clozapine, the clinician has four main options: to increase the dose of the current medication, to switch to another antipsychotic medication, to add an adjunctive medication, or just to monitor the illness in the hope that changing external factors will allow recovery. Unfortunately, the evidence base supporting these management options is limited.[1–3]

Optimal dosage

While the optimal doses for FGAs were always a matter of debate, the recommended doses of the SGAs are generally based on careful and extensive (fixed-dose) clinical trials. Despite this, the consensus on optimal SGA dosages has changed over time. For example, when risperidone was first introduced it was suggested that the optimal dose was 6mg or more for all patients. However, subsequently clinical practice moved towards the use of lower doses.[4] On the other hand, when quetiapine was introduced, 300mg was considered the optimal dose. The overall consensus now is towards higher doses,[5] although RCT and other evidence does not consistently support this shift.[5,6] Nonetheless, most clinicians feel comfortable in navigating within the recommended clinical dose ranges for the SGAs. The more critical question is what should be done if the upper limit of the dose range has been reached and, while the individual is tolerating the medication well, there is only limited benefit.

High dosage

For antipsychotic medications, the dose–response relationships for the treatment of schizophrenia are not that well defined. Davis and Chen[7] performed the first comprehensive systematic meta-analysis of relevant dose–response data available up to 2004 and concluded that the average dose that produces maximal benefit was 4mg for risperidone, 16mg olanzapine, 120mg ziprasidone and 10–15mg aripiprazole (they could not determine such a dose for quetiapine using their method). In 2020, Leucht and colleagues[8] carried out a similar meta-analysis of dose–response in acute schizophrenia and concluded that doses higher than standard doses were not more efficacious. However, they did suggest that for a few medications (such as olanzapine, lurasidone, ziprasidone) with clearly increasing dose curves (i.e. did not plateau), it might be worth testing higher-than-licensed doses in clinical trials. For example, the findings of a

network meta-analysis of the dose–response effects of lurasidone in acute schizophrenia suggested that 160mg/day might be the most effective and acceptable dose.[9]

Several trials have tried to compare high-dose antipsychotic medication with standard dosage. For example, one study[10] explored the dose–response relationship of olanzapine in a randomised, double-blind, 8-week, fixed-dose study, comparing doses of 10mg, 20mg and 40mg. While no additional benefit was found with the higher doses (i.e. 40mg was no better than 10mg), there was clear evidence of a greater adverse-effect burden (weight gain and raised plasma prolactin level). Similarly, early studies of risperidone[11] compared the usual daily doses of 2mg and 6mg with higher doses, up to 16mg. There was no additional benefit with the higher doses but a clear signal for a greater risk of adverse effects (EPS and raised plasma prolactin). The findings of these studies are in accord with older studies involving fixed doses of haloperidol,[12] where 8mg/day is clearly the dose above which no additional benefit is seen.[13] Interestingly, the likelihood of inducing EPSEs is not constrained by dose in the same way – the frequency of EPS continues to increase at doses well beyond standard or even high doses.[14]

Despite the lack of evidence for the benefit of higher doses, 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. In 1993, Kinon and colleagues[15] examined patients who failed to respond to the (then) standard dose of fluphenazine (20mg) and tested three strategies: increasing the dose to 80mg, 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 (within the standard ranges) and found that such decisions were only weakly associated with clinical measures.[16] A later trial of lurasidone[17] for early, non-responsive schizophrenia showed that after 2 weeks on lurasidone 80mg/day, a dose increase to 160mg/day was associated with significant symptom improvement compared with continuing on lurasidone 80mg/day. However, the clinical implications of these findings are uncertain, given the limitations of the trial: it lasted only 4 weeks, and there was no testing of the intermediate dose of 120mg/day.

A 2018 Cochrane systematic review of relevant studies concluded that there was no good-quality evidence that for illness not responding to initial antipsychotic treatment there was any difference between increasing the antipsychotic dose and continuing antipsychotic treatment at the same dose.[1] A similar meta-analysis in 2023[3] concluded that, for early non-responsive schizophrenia, the evidence for treatment strategies such as dose escalation or switching antipsychotic medication was too limited to allow for any strong clinical recommendations.

Plasma level variations

There are significant inter-individual variations in plasma drug levels in patients treated with antipsychotic medication. Patients may be encountered who, when receiving medication at the higher end of the dose range (say 6mg of risperidone or 20mg of olanzapine),

have plasma drug levels that are well below the range expected for 2mg risperidone or 10mg olanzapine, and these levels may not reach the threshold required for a therapeutic effect. 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 into the optimal range for the particular medication. Genetic analysis is helpful in identifying ultrafast metabolisers of aripiprazole, risperidone[18] and clozapine.[19]

Treatment options for schizophrenia that is poorly responsive to standard antipsychotic treatment

So what are the treatment possibilities when a lack of therapeutic response is encountered despite a patient's adherence to their medication regimen, the prescription of a dosage at the top of the recommended range, and apparently sufficient plasma drug levels? There are essentially three options: a trial of clozapine, switching to another antipsychotic medication or adding another (non-clozapine) antipsychotic medication. If the patient meets the criteria for clozapine treatment, this is undoubtedly the preferred option. Yet, in a clinical audit of community (not inpatient) practice in the UK, covering some 5,000 patients in 60 different NHS trusts, it was found that 40% of the patients whose illnesses met the criteria for TRS had not received clozapine. For the vast majority (85%) of those who had started clozapine, this had been delayed after the failure of two serial trials of antipsychotic medication for much longer than is advised in most guidelines.[20] Significant delay in the commencement of clozapine treatment has also been found in early intervention in psychosis services.[21] However, when reflecting on the findings suggesting delay or underuse of clozapine, it should be borne in mind that among those patients with a diagnosis of treatment-resistant illness who have not had a trial of clozapine, there will be some who have declined this treatment, some who have yet to be persuaded, and some for whom the prescribing clinician considers, perhaps because of factors such as comorbid physical illness, substance use or adverse social circumstances, that another intervention has a more favourable risk–benefit balance.[22]

Some patients may be averse to the mandatory regular blood testing, the adverse effects and the regular appointments required as part of the clozapine regimen. In such patients, the options are switching to another antipsychotic medication or adding one. 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 addressing preferred medication switches (e.g. if risperidone fails – what next? Olanzapine, quetiapine, aripiprazole or ziprasidone?). If one looks at only the switching trials which have been sponsored by the drug companies it leads to a rather confusing picture, with the trial results being very closely linked to the sponsors' interest (see 'Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics').[23] Further, switching can be associated with destabilisation of the illness and the emergence of adverse effects, which may be a consequence of stopping the original antipsychotic medication and/or a response to the subsequent medication and/or differences between the pharmacological profiles of the two medications. The extent to which the management of a switch can minimise such problems is not entirely clear, but a gradual cross-tapering approach is usually recommended.[24–26]

CATIE, the major US-based publicly funded comparative trial, examined participants whose illness had failed to respond to a first SGA and were then randomly assigned to a different second one.[27] Participants 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.[28] Further, the findings of a meta-analysis comparing SGAs among themselves suggested that olanzapine and risperidone (in that order) may be modestly more effective than the others.[29] Thus, if olanzapine or risperidone have not yet been tried, it would be a reasonable decision to switch to these medications, provided the risk–benefit balance was considered likely to be favourable for the particular patient. Comparing these two medications, the data are somewhat limited. However, a number of controlled and open-label studies do show an asymmetrical advantage, with a switch to olanzapine being more effective than to risperidone.[30,31] Such findings have been reinforced recently: a systematic review[32] found high-dose olanzapine to be superior to other commonly used FGAs and SGAs, including risperidone, for TRS, while a network meta-analysis[33] confirmed olanzapine as the second most effective antipsychotic, behind clozapine, for such illness.

The best medication regimen (aside from clozapine) to choose for a patient whose illness has failed trials of olanzapine and risperidone remains unclear. Should one switch to, say, aripiprazole or ziprasidone or even an older FGA, or should another antipsychotic medication be added? Interestingly, studies that have switched patients to aripiprazole for reasons of tolerability (weight gain, etc.) find either no loss of efficacy[34,35] or an improvement in symptom severity.[24,36]

After switching, adding another antipsychotic is probably the most common clinical strategy chosen. A 2022 clinical audit in the UK[37] found that of 4,156 people on acute adult psychiatric wards, 14% were prescribed more than one antipsychotic medication. By far the most common reason for such a prescription was an insufficient response of symptoms and/or behavioural disturbance with antipsychotic monotherapy at standard dosage. A second antipsychotic may also be added for additional properties (e.g. quetiapine for sedation or aripiprazole to decrease plasma prolactin – these matters are discussed elsewhere) but here we are concerned solely with the use of combined antipsychotic medications to increase efficacy. From a theoretical point of view, since all currently available antipsychotic medications (with xanomeline and pimavanserin as exceptions) block D_2 receptors (unlike, say, antihypertensive drugs which use different mechanisms) there is a limited rationale for addition. Studies of add-ons have often chosen combinations on the basis of convenience or clinical lore and perhaps the most systematic evidence is available for the addition of a second antipsychotic to clozapine,[38–40] a strategy that may be supported by the rationale that since clozapine has relatively low D_2 occupancy, increasing its D_2 occupancy may yield additional benefits.[41] However, a meta-analysis of RCTs comparing augmentation with a second antipsychotic with continuing monotherapy in schizophrenia[42] found a lack of double-blind/high-quality evidence for efficacy, in terms of treatment response and symptom improvement, for a range of antipsychotic combinations. 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.[43,44] Nonetheless, at a population level, antipsychotic polypharmacy does not appear to result in increased rates of hospitalisation for either physical or specifically cardiovascular illness.[45]

While augmentation with another antipsychotic medication 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,[46–48] although this is not a universal finding.[49] Essock and co-workers[48] conducted a 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 participants in whom it was tested. And 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, switching to another antipsychotic medication or augmentation with a second antipsychotic medication, is the clear winner in all situations. But increasing the dose if plasma drug levels are low, switching to olanzapine if this has not been tried, or augmentation if there is insufficient response to clozapine may be beneficial in some cases. Given the limited efficacy of these manoeuvres perhaps an equally important call by the treating doctor is when 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 with the current medication regimen may often do less harm than aimless switching and dosage increments.

Summary

When treatment fails

- If the dose of antipsychotic medication has been optimised, consider watchful waiting.
- Consider increasing the antipsychotic dose according to tolerability and plasma levels (little supporting evidence for most drugs).[2,50]
- 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).

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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. This section deals with behavioural disturbance in the context of severe mental illness. Agitated states caused by illicit substance misuse are dealt with in Chapter 9.

The clinical practice of rapid tranquillisation 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 rapid tranquillisation (RT) are often too disturbed to give informed consent and therefore participate in 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. A comprehensive and up-to-date consensus guideline was published in 2018[1] and, more recently, a systematic review and meta-analysis.[2] A network meta-analysis of RT in the emergency department has also been published.[3]

Oral/inhaled treatment

Several studies supporting the efficacy of oral SGAs have been conducted.[4–7] The level of behavioural disturbance exhibited by the patients in these studies was moderate at most, and all participants accepted oral treatment (this degree of compliance would be unusual in clinical practice). Patients recruited to these studies received the SGA as antipsychotic monotherapy. The efficacy and safety of adding a second antipsychotic as a 'when necessary' treatment have not been explicitly tested in formal RCTs.

A single-dose RCT showed sublingual asenapine to be more effective than placebo for acute agitation.[8] The efficacy of inhaled loxapine in behavioural disturbance that is moderate in severity is also supported by RCTs.[9–11] The use of this preparation is now restricted in many countries owing to the risk of bronchospasm.

Dexmedetomidine, an α_2 receptor agonist used in anaesthesia, has been developed as a sublingual film. It seems to be rapidly effective in acute agitation.[12]

Parenteral treatment

Large, placebo-controlled RCTs support the efficacy of 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, which itself is more effective than ziprasidone.[2,13,14] The level of behavioural disturbance in these studies was moderate at most and differences between treatments small.

A large observational study supported the efficacy and tolerability of IM olanzapine in clinical emergencies (where disturbance was severe).[15] 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.[16]

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

- Compared with 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.[17]
- IM midazolam 7.5–15mg was more rapidly sedating than a combination of haloperidol 5–10mg and promethazine 50mg (TREC 1).[18]
- Olanzapine 10mg was as effective as a combination of haloperidol 10mg and promethazine 25–50mg in the short term, but the effect did not last as long (TREC 4).[19]
- A combination of haloperidol 5–10mg and promethazine 50mg was more effective and better tolerated than haloperidol 5–10mg alone; 6% of patients had an acute dystonic reaction (TREC 3).[20]
- A combination of haloperidol 10mg and promethazine 25–50mg was more effective than lorazepam 4mg (TREC 2).[21]
- A combination of IM chlorpromazine 100mg, haloperidol 5mg and promethazine 25mg was no better than IM haloperidol 5mg plus promethazine 25mg (TREC Lebanon).[22]
- 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.[23]
- 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.[24]
- IM midazolam 5mg was faster acting and more effective than olanzapine 10mg, ziprasidone 20mg and both 5 and 10mg haloperidol in a large (n = 737) emergency room study.[25]
- In an open-label study, the combination of IM haloperidol and IM lorazepam was found to be similar in efficacy to IM olanzapine.[26]
- IM droperidol and IM haloperidol were equally effective.[27]
- IM droperidol with IM midazolam was more effective than IM haloperidol with IM lorazepam.[28]

Nearly 10 years ago, Cochrane 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.[29,30] However NICE considers the evidence relating to the use of promethazine for this purpose to be inconclusive.[31] The authors also stated that 'haloperidol used on its own without something to offset its frequent and serious adverse effects is difficult to justify'.[32]

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 EPSEs.[33] Cochrane suggests that droperidol is effective and may be used to control disturbed and aggressive behaviours caused by psychosis.[34] Droperidol has seen a resurgence in use in some countries having become available again (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 performing considerably better.[35] Acute EPSEs may adversely affect longer-term compliance.[36] In addition, the formal prescribing information in most countries for haloperidol calls for a pretreatment ECG[37,38] and recommends that concomitant antipsychotics are not prescribed. The mean increase in QTc after 10mg IM haloperidol can be up to 15ms but the range is wide.[39]

Promethazine may inhibit the metabolism of haloperidol;[40] 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 1,009 patients administered parenteral droperidol, only 13 patients (1.28%) had an abnormal QT after dose administration. In seven of these cases, another contributory factor was identified. There were no cases of torsades de pointes (TdP).[27] In all RT studies of IM droperidol, the overall rate of QTc measurements greater than 500ms was less than 2%.[2]

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.[41] 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,[42] 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 patients and supplemental oxygen was used in 20.4%. Six patients required intubation (two of these because of olanzapine treatment). In the other study,[43] 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 10mg of haloperidol, droperidol or midazolam) was not more effective than lower doses but was associated with more adverse effects (hypotension and oxygen desaturation).[44] 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.[45] These data broadly support the use of standard doses in clinical emergencies but the need for further physical restraint after lower doses needs to be considered.

A small observational study supported the effectiveness of buccal midazolam in a PICU setting.[46] Parenteral administration of midazolam, particularly in higher doses, may cause over-sedation accompanied by respiratory depression.[47] Lorazepam IM is an established treatment and TREC 2[21] supports its efficacy, although combining all results from the TREC studies suggests that midazolam 7.5–15mg is probably more effective. More recent studies have used 5mg IM midazolam and found it to be rapidly effective.[28,48] 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 while adding a benzodiazepine to another drug may not be clearly advantageous it may lead to unnecessary adverse effects.[49]

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 5mg and lorazepam 2mg) was more effective and reduced the need for subsequent sedation than either drug given alone.[50] 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 consumption showed that haloperidol was effective and well tolerated (one case each of mild hypotension and mild hypoxia).[51] A section on the treatment of behavioural disturbance caused by substance misuse is included in Chapter 9.

Ketamine is widely used for agitation in hospital emergency departments. In a systematic review of 18 studies of ketamine,[52] a mean dose of 315mg IM ketamine achieved adequate sedation in an average of 7.2 minutes. Over 30% of 650 patients were eventually intubated and more than 1% experienced laryngospasm. Ketamine is not suitable for RT where facilities for intubation are not available, although it may be the most effective treatment.[3]

Overall, the current broad consensus is that midazolam and droperidol are the fastest-acting single-drug, intramuscular treatments[53] and that haloperidol alone should be avoided and perhaps abandoned completely even in combination.[54] Second-line treatments are combinations of benzodiazepines and antipsychotics and third line would probably be intravenous benzodiazepines and then ketamine (2–5mg/kg IM), assuming intubation facilities are available.

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),[55] increased nursing levels, transfer of the patient to a psychiatric intensive care unit 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. RT is often, of course, viewed as punitive by patients. There is little research into the patient experience of RT. The aims of RT are threefold:

- 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 regimens 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 in Europe, and is best known by its trade name Acuphase®. Zuclopenthixol itself is a thioxanthene dopamine antagonist first introduced in the early 1960s. ZA is not a rapidly tranquillising agent. 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 proportional 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 carbon atoms fewer) would be expected to provide relatively prompt release but with an intermediate duration of action. The intention of the manufacturers was that 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'.[56] 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 one-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[57] 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.[58,59] The first UK study was reported in 1990.[60] 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[61] 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.[62] Participants were given either ZA or haloperidol IM

and assessed over 3 days. Changes in Brief Psychiatric Rating Scale and Clinical Global Impression scores were near identical on each daily assessment. However, only 1 of 23 patients taking ZA required a second injection, whereas 7 of 21 required a repeat dose of haloperidol. Speed of onset was not examined. Similar findings were reported by Thai researchers comparing the same treatments[63] and in three other studies of moderate size (n = 44,[64] n = 40,[65] n = 50[66]). In each study, the timing of assessments was such that time to onset of effect could not be determined.

Overall, the utility of ZA in rapid tranquillisation 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 rapid tranquillisation.

Guidelines for the use of zuclopenthixol acetate (Acuphase)

- ZA is not a rapidly tranquillising agent. It should be used only after an acutely psychotic patient has required (or is likely to require) ***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 for rapid tranquillisation (the onset of effect is too slow) or to a patient who is physically resistant (risk of intravasation and oil embolus) or to neuroleptic-naïve patients (risk of prolonged EPSEs).

Rapid tranquillisation summary

In an emergency situation: Assess whether there may be a medical cause.[67] Optimise regular prescription. The aim of pharmacological treatment is to calm the patient but not to over-sedate. Note that 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 protocol).

Step intervention

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

2 Offer oral treatment

If patient is prescribed a regular antipsychotic:
Lorazepam 1–2mg
Promethazine 25–50mg
Monotherapy with **buccal midazolam** may avoid the need for IM treatment
Dose: 10mg
Note that this preparation is unlicensed

If patient is not already taking a regular oral or LAI antipsychotic:
- **Olanzapine** 10mg or
- **Risperidone** 1–2mg or
- **Quetiapine** 50–100mg or
- **Haloperidol** 5mg (with promethazine 25mg). ECG is required in UK/EU

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 2mg[ab]	Have flumazenil to hand in case of benzodiazepine-induced respiratory depression
Promethazine 50mg	IM promethazine is a useful option in a benzodiazepine-tolerant patient
Olanzapine 10mg[d]	IM olanzapine should not be combined with an IM benzodiazepine, particularly if alcohol has been consumed[68]
Aripiprazole 9.75mg	Less hypotension than olanzapine, but less effective[6,13,69]
Haloperidol 5mg	**Haloperidol should be the last drug considered.** The incidence of acute dystonia is high; combine with IM promethazine and ensure IM procyclidine is available. Pretreatment ECG required

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 10mg over at least 2 minutes[be]
Repeat after 5–10 minutes if insufficient effect (up to 3 times)
Have flumazenil to hand

5 Seek expert advice[f]
Consider transfer to medical unit for administration of **IM ketamine**

Notes

a. Carefully check administration and dilution instructions, which differ between manufacturers. Many centres use 4mg. An alternative is IM midazolam 5–15mg. 5mg is usually sufficient. The risk of respiratory depression is dose-related with both drugs 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.[70]

(*Continued*)

Rapid tranquillisation summary (*Continued*)

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 100mg/day. Wait 1–2 hours after injection to assess response. Note that promethazine alone has been reported, albeit very rarely, to cause NMS,[71] although it is an extremely weak dopamine antagonist. Note also 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 diazepam to avoid injection site reactions. Lorazepam can also be given IV. 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. IV doses can be repeated after only 5–10 minutes if no effect is observed. Midazolam can also be used IV but respiratory depression is common.[1]

f. Options at this point are limited, although the wider use of IM ketamine has improved the range of options available. IM amylobarbitone and IM paraldehyde have been used in the past but are used now only extremely rarely and are generally not easy to obtain. IV olanzapine, IV droperidol and IV haloperidol are possible but adverse effects are fairly common. ECT is also an option.

Rapid tranquillisation – physical monitoring

After any parenteral drug administration, monitor as follows:

- **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, over-sedation and general physical well-being.

All patients should be continuously observed ('in sight') for at least 1 hour and until clearly ambulatory.

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.[72,73] Hypokalaemia, stress and agitation place the patient at risk of cardiac arrhythmia[74] (see section on 'QT prolongation'). ECG monitoring is formally recommended for all patients who receive haloperidol.

Remedial measures in rapid tranquillisation

Problem	Remedial measures
Acute dystonia (including oculogyric crises)	Give **procyclidine** 5–10mg IM or IV
Reduced respiratory rate (<10/minute) or oxygen saturation (<90%)	Give oxygen, raise legs, ensure patient is not lying face down Give **flumazenil** if benzodiazepine-induced respiratory depression suspected (see protocol) If induced by any other sedative agent: **transfer to a medical bed and ventilate mechanically**
Irregular or slow (<50/minute) **pulse**	**Refer** to specialist medical care immediately
Fall in blood pressure (>30mmHg orthostatic drop or <50mmHg diastolic)	**Have patient lie flat**, tilt bed towards head Monitor closely
Increased temperature	Risk of NMS and perhaps arrhythmia; check creatine kinase urgently

Guidelines for the use of flumazenil

Indication for use	If, after the administration of lorazepam, midazolam or diazepam, respiratory rate falls below 10/minute
Contraindications	Patients with epilepsy who have been receiving long-term benzodiazepines
Caution	Dose should be carefully titrated in hepatic impairment
Dose and route of administration	***Initial:*** 200mcg ***intravenously*** over 15 seconds if required level of consciousness not achieved after 60 seconds, then ***Subsequent dose:*** 100mcg over 15 seconds
Time before dose can be repeated	60 seconds
Maximum dose	1mg in 24 hours (one initial dose and eight subsequent doses)
Adverse effects[75]	Patients may become agitated, anxious or fearful on awakening. Seizures may occur in regular benzodiazepine users. Cardiac arrhythmia (supraventricular tachycardia)
Management	Adverse effects usually subside
Monitoring:	
■ **What to monitor?**	Respiratory rate
■ **How often?**	Continuously until respiratory rate returns to baseline level Flumazenil has a short half-life (much shorter than diazepam) and respiratory function may recover and then deteriorate again

Note: If respiratory rate does not return to normal or patient is not alert after initial doses given, assume that sedation is from some other cause

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Antipsychotic depots/long-acting injections

Long-acting injectable preparations of antipsychotic medication are commonly prescribed in clinical practice, especially in the UK, Australasia and the EU. Real-world, observational studies of patients with schizophrenia have confirmed that continued treatment with such medication is associated with fewer relapses and readmissions to hospital compared with oral antipsychotic treatment,[1–5] although there are confounding factors in such studies, such as indication bias.

A 2020 Cochrane systematic review of RCTs comparing antipsychotic maintenance treatment with placebo for people with schizophrenia found that LAI antipsychotic medications (in particular, LAI haloperidol and LAI fluphenazine) were more effective than oral antipsychotic medications.[6] However, the authors noted that only head-to-head comparisons of LAI and oral antipsychotic medications can determine whether the former are more effective. The findings of such RCTs have generally failed to show the superiority of LAI antipsychotic medications that is apparent in real-world studies,[7–9] and it has been postulated that this is partly related to study design and methodology issues.[2] Specifically, double-blind RCTs are generally relatively short term and the study samples will tend to be biased towards patients with rather less severe illness, fewer comorbid conditions and better adherence to medication.[10,11] Nevertheless, a 2021 systematic review and meta-analysis of RCTs, observational cohort studies and pre–post (mirror-image) studies comparing LAIs with oral antipsychotic medications found that LAIs were associated with a lower risk of hospitalisation or relapse, across all the study designs.[12] There are also hints from meta-analyses of relevant RCTs that some adverse effects are less frequent with LAIs than with their oral counterparts.[8,13]

While it is generally accepted that treatment with LAI antipsychotic medication reduces the risk of relapse, the findings of studies of all designs suggest that treatment with LAIs does not confer complete protection against relapse.[14] In clinical practice, relapse is strongly linked to delayed or missed doses of LAIs. Two UK studies showed that patients receiving 10 doses a year (or fewer) of monthly paliperidone palmitate were at a substantially higher risk of relapse than those receiving 11 or 12 doses.[15,16] Very long-acting injections given consistently on time may offer better protection against relapse.[17–19]

LAI antipsychotic medication is recommended for all patients, but especially where a patient has expressed a preference for such a formulation because of its convenience or where avoidance of covert non-adherence is considered a clinical priority.[10,20,21] While LAI medication does not ensure adherence, it does ensure clinical awareness of adherence, unlike the use of oral medication. Thus, failure to adhere, which may be a sign of relapse or a potential cause, will be signalled by delayed attendance for, or refusal of, an injection, allowing the clinical team to intervene promptly. Another advantage for LAI antipsychotic medication is that its use may help clarify whether an unsatisfactory therapeutic response to antipsychotic medication is because of adherence problems or treatment resistance. Patients with an apparently refractory illness may simply be non-adherent to their oral medication, sometimes completely so.[22] Further, an LAI antipsychotic regimen provides the opportunity for regular scrutiny of a patient's mental state and adverse effects.[23]

The proportion of patients with schizophrenia prescribed LAI antipsychotic medications varies between and across countries, suggesting that the use of such medication is influenced by factors beyond the extent of poor adherence. Greater

understanding of these factors might allow for possible barriers to the optimal implementation of this treatment to be identified.[24–26] A study in the USA found that patients with first-episode schizophrenia were largely willing to accept long-acting treatment.[27] This suggests that the relatively low usage of LAIs in the USA might be partly a result of reluctance on the part of clinicians, rather than resistance from patients.[28,29]

Advice on prescribing LAIs

- **Test doses**
  Because of its long half-life, any adverse effects that result from the administration of LAI antipsychotic medication are likely to be long lived. Therefore, such treatment 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 LAI 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 of the patient's sensitivity to EPS and of any sensitivity to the base oil. For LAI SGAs, test doses may not be required (there is a lower propensity to cause EPS and the aqueous base is not known to be allergenic), although they could be considered appropriate where a patient is suspected of being non-adherent to oral antipsychotic medication and the LAI preparation will be the first exposure to guaranteed antipsychotic medication delivery. For both LAI FGAs and SGAs, prior treatment with the equivalent oral formulation, establishing the optimally effective and tolerated dose, is advised,[30] but may not be necessary from a pharmacokinetic viewpoint. Most LAI SGAs can be used as sole treatment from the outset, although loading doses are usually necessary (e.g. for paliperidone and aripiprazole).
- **Begin with the lowest therapeutic dose**
  For LAI FGA medications, there is limited evidence for a clear dose–response effect and a near absence of data on optimal dosing. However, low doses (within the licensed range) may be at least as effective as higher ones.[31–34] For the LAI antipsychotic medications that are commonly used, it remains uncertain that the dosages and frequency of injections achieve the optimal benefit–risk balance.[35–37]
- **Administer at the longest possible licensed interval**
  All LAI antipsychotic medications 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, less frequent administration may be desirable, as the IM injection site can be a cause of discomfort and pain; these reactions may be more common with LAIs that have oil-based formulations.[38,39]

  Although there are reports of illness deterioration in some patients in the days before their next injection is due, plasma drug concentrations may continue to fall for some hours (or even days with some preparations) after each injection. In this context, a patient's apparent recovery soon after the injection makes little sense. More importantly, at steady state, trough plasma levels (immediately before and after the dose) are usually substantially above the threshold concentration required for therapeutic effect.[30,40,41]

- **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 LAI antipsychotic medications, compared with oral antipsychotics. Doses may be *reduced* if adverse effects occur but should only be increased after careful assessment over at least 1 month, and preferably longer. Note that with most LAI antipsychotic preparations, at the start of treatment, plasma drug levels increase over several weeks to months without any increase in the dosage. This is due to accumulation: steady state is only achieved after at least 6–8 weeks. Dose increases during this initial period are therefore illogical and impossible to evaluate properly. With continued LAI antipsychotic treatment, the monitoring and recording of therapeutic efficacy, adverse effects and any impact on physical health are recommended, although in clinical practice there seems to be a relatively low frequency of assessment of adverse effects.[42]

  Table 1.8 gives doses and frequencies for LAI antipsychotic medications for adults.
- **Adding an oral antipsychotic medication risks a high-dose prescription**
  The regular prescription of an oral antipsychotic medication in addition to an LAI antipsychotic preparation was once common with LAI FGAs.[22,43] While this may be a possible strategy for the control of breakthrough symptoms and may offer greater flexibility in dosage titration, the safety and tolerability of such a combination are uncertain, particularly over the longer term.[44] The co-prescription of an LAI and oral antipsychotic medication may well result in a possibly inadvertent high-dose prescription, with an increased adverse effect burden and implications for physical health monitoring.[10,23]

Differences between LAIs

A 2021 network meta-analysis of 86 RCTs[45] comparing LAIs with each other, with placebo or with oral antipsychotic medication concluded that the LAI formulations of paliperidone (3-month formulation), aripiprazole, olanzapine and paliperidone (1-month formulation) had the largest effect sizes and greater certainty of evidence for both relapse prevention and acceptability. The LAI SGAs, aripiprazole, paliperidone, risperidone and olanzapine, have generally been reported to have comparable efficacy, although they vary in their liability for particular adverse effects, such as weight gain, metabolic effects, EPS and raised plasma prolactin.[46–49] For example, LAI paliperidone is associated with substantial increases in serum prolactin[48] and LAI olanzapine can cause significant weight gain and is associated with a post-injection delirium/sedation syndrome, assumed to be caused by unintended partial intravascular injection or blood vessel injury.[50,51] Details on dosing of individual SGAs are given elsewhere in this chapter.

Table 1.8 Long-acting injectable antipsychotic medications – doses and frequencies.*

Drug	UK trade name	Licensed injection site	Test dose (mg)	Dose range (mg/day or week or month)	Dosing interval (weeks)	Comments
Aripiprazole	Abilify Maintena	Buttock	Not required**	300–400mg monthly	Monthly	Does not increase prolactin
Aripiprazole	Abilify Asimtufil	Gluteal	Not required**	720–960mg every 2 months	8	Can be started after oral loading or as continuation of monthly injections
Aripiprazole	Aristada Initio	Deltoid or gluteal	Not required**	675mg	Single dose, not for repeat dosing	Given together with 30mg dose of oral aripiprazole. The first Aristata injection can be given on the same day or up to 10 days after Aristada Initio.
Aripiprazole	Aristada	Deltoid† or gluteal	Not required**	441mg, 662mg monthly, 882mg every 4–6 weeks and 1062mg every 2 months	4–8	Can be given with 30mg dose of oral aripiprazole and 675mg Aristada Initio ***or*** continue with oral aripiprazole for 21 consecutive days
Flupentixol decanoate	Depixol	Buttock or thigh	20	50mg every 4 weeks to 400mg a week	2–4	Maximum licensed dose is high relative to other LAIs
Fluphenazine decanoate	Modecate	Gluteal region	12.5	12.5mg every 2 weeks to 100mg every 2 weeks	2–5	High risk of EPS
Haloperidol decanoate	Haldol	Gluteal region	25††	50–300mg every 4 weeks	4	High risk of EPS
Olanzapine pamoate	ZypAdhera	Gluteal	Not required**	150mg every 4 weeks to 300mg every 2 weeks	2–4	Risk of post-injection syndrome
Paliperidone palmitate (monthly)	Xeplion	Deltoid or gluteal	Not required**	50–150mg monthly	Monthly	Loading dose required at treatment initiation
Paliperidone palmitate (3-monthly)	Trevicta	Deltoid or gluteal	Not required‡	175–525mg every 3 months	3 months	Not suitable for acutely agitated patients
Paliperidone palmitate (6-monthly)	Byannli	Gluteal region	Not required§	700–1000mg every 6 months	6 months	Contraindicated in mild renal impairment (creatinine clearance ≥50 to ≤80 mL/minute)

(*Continued*)

Table 1.8 (*Continued*)

Drug	UK trade name	Licensed injection site	Test dose (mg)	Dose range (mg/day or week or month)	Dosing interval (weeks)	Comments
Pipothiazine palmitate	Piportil	Gluteal region	25	50–200mg every 4 weeks	4	Lower incidence of EPS (relative to other FGAs)
Risperidone microspheres	Risperidal Consta	Deltoid or gluteal	Not required**	25–50mg every 2 weeks	2	Drug release delayed for 2–3 weeks – oral therapy required
Risperidone	Perseris	Abdomen	Not required**	90–120mg every month	4	Given subcutaneously in the abdomen
Risperidone	Okedi	Deltoid or gluteal	Not required**	75–100mg every 28 days	4	Loading dose not required at treatment initiation
Zuclopenthixol decanoate	Clopixol	Buttock or thigh	100	200mg every 3 weeks to 600mg/week	2–4	High risk of EPS

* Refer to manufacturer's official documentation for full details.
** 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.
† Aripiprazole 441mg dose only.
†† Test dose not stated by manufacturer.
‡ May not be started until the completion of 4 months' treatment with monthly LAI.
§ For patients stabilised on 100mg or 150mg of monthly LAI for at least 4 months or for patients given at least one injection of 350mg or 525mg of 3-monthly LAI.
EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; LAI, long-acting injection.
Notes:
The doses in this 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 500mg every week is licensed whereas 1000mg every 2 weeks is not (more than the licensed maximum of 600mg is administered). Always check official manufacturer's information.

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Depot antipsychotics – summary of pharmacokinetics

Table 1.9 provides a summary of the pharmacokinetics of depot antipsychotic medications.

Table 1.9 Depot antipsychotics – summary of pharmacokinetics.

Drug	UK trade name	Time to peak (days)*	Plasma half-life (days)	Time to steady state (weeks or months)**
Aripiprazole[1–3]	Abilify Maintena	Deltoid: 4 Gluteal: 5–7	27	~20 weeks
Aripiprazole 2-monthly injection[3–6]	Abilify Maintena	28	~29	~6 months
Aripiprazole lauroxil[2]	Aristada in USA	44–50	~54–57	~4 months
Aripiprazole lauroxil nanocrystal[2,7†]	Aristada Initio in USA	4	~15–18	
Flupentixol decanoate[8,9]	Depixol	4–7	8–17	~8–12 weeks
Fluphenazine decanoate[2,10–12]	Modecate	8–12d††	7–10	~8 weeks
Haloperidol decanoate[2]	Haldol	3–9	21	~14 weeks
Olanzapine pamoate[2,13]	ZypAdhera	2–6	30	~12 weeks
Paliperidone palmitate[2] (monthly)	Xeplion	13	25–49	~20 weeks
Paliperidone palmitate[14,15] (3-monthly)	Trevicta	25	Deltoid: 84–95 Gluteal: 118–139	~52 weeks
Paliperidone palmitate (6-monthly)[16]	Byannli	700mg: 29 1000mg: 32	700mg: 148 1000mg: 159	Not known
Pipotiazine palmitate[17,18]	Piportil	7–14	15	~9 weeks
RBP-7000[2,19] (risperidone SC monthly)	Perseris in USA	1st peak ~1 2nd peak ~11	~8–9	~8 weeks
Risperidone extended-release injectable suspension[20,21]	Rykindo in USA	25mg: 14 50mg: 17	3–6	~4 weeks
Risperidone in situ microimplants (ISM)[22,23]	Okedi	1st peak: 1–2 2nd peak: 18–25	7–9	~4 weeks
Risperidone microspheres[2]	Risperidal Consta	~28	3–6	~8 weeks
TV-46000[24] (risperidone SC)	Uzedy in USA	8–14	14–22	~2 months
Zuclopenthixol decanoate[2,8,17,25]	Clopixol	4–7	19	~12 weeks

* 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 attaining peak levels. For low (test) doses, the initial peak level may be subtherapeutic.

** Attainment of steady state (SS) follows logarithmic, not linear characteristics: nearly 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. SS is not the same as the concentration required for therapeutic effect. For most depots, SS concentrations during the dosing interval are some way above the concentration needed to give a therapeutic response.

† Used to initiate treatment with Aristada, IM injection with one 30mg oral dose of aripiprazole; not designed for repeat dosing.

†† Some estimates suggest peak concentrations after only a few hours.[25,26] 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.

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Management of patients on long-term treatment with long-acting injectable antipsychotic medication

For people with multi-episode schizophrenia prescribed maintenance LAI antipsychotic treatment, long-term follow-up is essential. Treatment and progress should be reviewed at least once a year (ideally more frequently) by the responsible psychiatrist, including a systematic assessment of the efficacy, tolerability and safety of the medication. The assessment of adverse effects should include cardiovascular and metabolic adverse effects, and EPS (principally parkinsonism, akathisia and TD).[1–3] Whether LAI antipsychotic medications are more or less likely to be associated with TD than oral antipsychotic medications remains uncertain,[4–7] but the risk of TD does not appear to be different when the LAI and oral formulations of the same antipsychotic medication are compared.[8,9]

Any reduction in dosage should be cautious and closely monitored, given the increased risk of relapse and rehospitalisation with lower than standard doses,[2,10,11] particularly in the longer term.[12–15] In a 2022 naturalistic study[16] of the risk of rehospitalisation associated with maintenance treatment with a range of antipsychotic medications, both oral and LAI formulations, in a nationwide cohort (n = 61,889), the risk of severe relapse was lowest with continuing standard dose LAI, two exceptions being better outcomes for high-dose olanzapine LAI and relatively low-dose oral perphenazine.

There is no simple formula for deciding when or whether to reduce the dose of continuing LAI antipsychotic treatment, so a risk–benefit analysis must be carried out for every patient. Many patients, it should be noted, prefer LAI antipsychotic preparations to oral medication.[9,17] When considering dose reduction, the patient's individual circumstances should be considered, including the severity of the illness, the risk of relapse and its possible consequences, their response to treatment and their social situation:[1,2]

- Is the patient symptom-free and, if so, for how long?
- How severe, tolerable, distressing and disabling are the current adverse effects?
- 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 should stressful life events be 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 their own symptoms? If so, will they seek appropriate help?

If, after consideration of the above, the decision is taken to reduce the medication dose, the patient's family should be involved, and a clear explanation given of what should be done if and when symptoms return or worsen.

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 4 weeks before starting to decrease the dose given each time.
- The dose should be reduced by no more than a third of the previous dose at any one time.
- Decrements should, if possible, be made no more frequently than every 3 months, preferably every 6 months or more.

- Discontinuation of medication should not be seen as the ultimate aim of the above process although it sometimes results.
- Because of their longer half-lives, relapse following discontinuation of LAI antipsychotic formulations may be delayed compared with their oral equivalents and shorter-acting LAIs, probably because of longer exposure and prolonged dopamine receptor blockade following discontinuation.[18]
- While an intermittent, targeted (i.e. symptom-triggered) treatment approach with antipsychotic medication is not as effective as continuous treatment, it may be preferable to no treatment.[2,19,20]
- If a patient becomes symptomatic following antipsychotic dose reduction, this should be seen as information relevant to the determination of the minimum effective dose for that patient.
- Complex hyperbolic tapering regimens have been proposed[21] and these may offer protection against relapse.

For more discussion, see the section on antipsychotic prophylaxis in this chapter.

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Aripiprazole long-acting injection

Aripiprazole 1-monthly

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 in the treatment of schizophrenia.[1] In the USA, aripiprazole long-acting injection (ALAI) is approved for maintenance monotherapy in bipolar I disorder in adults.[2] In the UK and some other countries, the use of aripiprazole LAI in bipolar is off-label.

Oral aripiprazole 10–20mg/day should be given for 14 days to establish tolerability and response. This oral run-in is also a vital part of the loading process.[3] In patients switching from another oral antipsychotic to ALAI, aripiprazole should have been effective and tolerated in the past. The current antipsychotic should be continued for the first 14 days following the initial ALAI administration.[2]

One of the following two regimens may be followed for administering the starting dose of aripiprazole LAI.[4]

One-injection start

On the day of initiation, administer one injection of 400mg aripiprazole LAI and continue treatment with 10–20mg/day oral aripiprazole for 14 consecutive days (i.e. 28 days in total) to maintain therapeutic aripiprazole concentrations during initiation. In the absence of the 14-day oral overlap, plasma levels may not be sufficient to afford a therapeutic effect.[3]

Two-injection start

On the day of initiation, administer two separate injections of 400mg aripiprazole LAI at separate injection sites in two different muscles (separate gluteal, separate deltoid or gluteal and deltoid injection sites), together with one 20mg dose of oral aripiprazole. Oral therapy should not continue after this point. The necessity for the single oral dose is doubtful, given it represents only 2.5% of the total dose given.

One month after the day of initiation, begin a regimen of 400mg each month (the manufacturer appears to define 'monthly' as every 28 days).[4] A monthly dose of 400mg aripiprazole is equivalent to 15–20mg of daily aripiprazole.[5]

After the one-injection plus oral starting regimen, peak plasma levels are reached 7 days post-injection, with trough levels occurring at 4 weeks.[6] After two-injection start, peak plasma concentration is observed at 5–7 days when administered in the gluteal muscle and at 4 days for the deltoid muscle.[7] Steady-state plasma levels are achieved after the fourth IM injection for both administration sites (see Table 1.10 for missed doses).[7]

A lower dose of 300mg a month can be used in those not tolerating 400mg or for those who are poor metabolisers via CYP2D6. A dose of 200mg/month may only be used for those patients receiving particular enzyme-inhibiting drugs. Most common adverse events are increased weight, akathisia, insomnia and injection site pain.[4,7]

Table 1.10 Delayed doses of aripiprazole long-acting injection.[4]

ALAI dose missed	Regimen
2nd or 3rd ALAI dose is missed and time since last injection is >4 weeks and <5 weeks	Administer as soon as possible
2nd or 3rd ALAI is missed and time since last injection is >5 weeks	Give oral aripiprazole for 14 days and one dose of ALAI *or* Give two ALAI injections at different sites + single dose 20mg aripiprazole
If ≥4th ALAI is missed and time since last injection is >4 weeks and <6 weeks	Administer as soon as possible
If ≥4th ALAI is missed and time since last injection is >6 weeks	Give oral aripiprazole for 14 days and one dose of ALAI *or* Give two ALAI injections at different sites + single dose 20mg aripiprazole

ALAI, aripiprazole long-acting injection.

While there are no official guidelines for switching to aripiprazole, the recommendations in Table 1.11 are based on our interpretation of existing pharmacokinetic data.

Table 1.11 Switching to 1-monthly aripiprazole long-acting injection.

Switching from	Aripiprazole LAI regimen
Oral antipsychotics	Cross-taper antipsychotic with oral aripiprazole* over 2 weeks **One-injection start** Start aripiprazole LAI, continue aripiprazole oral for another 2 weeks then stop **Two-injection start** Start aripiprazole LAI as indicated above after 2 weeks of oral aripiprazole, then stop oral treatment**
Depot antipsychotics (not Risperidone Consta)	Start oral aripiprazole* on day the last depot injection was due **One-injection start** Start aripiprazole LAI after 2 weeks then stop oral aripiprazole 2 weeks later **Two-injection start** Start aripiprazole LAI as indicated above after 2 weeks of oral aripiprazole, then stop oral treatment**
Risperidone Consta	Start oral aripiprazole* 4–5 weeks after the last risperidone injection **One-injection start** Start aripiprazole LAI 2 weeks later; discontinue oral aripiprazole 2 weeks after that **Two-injection start** Start aripiprazole LAI as indicated above after 2 weeks of oral aripiprazole, then stop oral treatment**

* If prior response and tolerability to aripiprazole are known, pre-injection oral aripiprazole may not be strictly required. However, attainment of effective aripiprazole plasma levels is dependent upon 4 weeks of oral supplementation for the one-injection start regimen. Similarly, for the two-injection start regimen, the pharmacokinetic modelling study was based on plasma levels from oral aripiprazole being at (therapeutic) steady state on the day of initiation. It may be sufficient to start aripiprazole LAI in the absence of prior oral aripiprazole where the prior antipsychotic is at a therapeutic level. Continuation for 14 days is presumably also required.
** If oral aripiprazole cannot be given at all (e.g. patient refusal) always use the two-injection starting regimen. This 800mg dose is likely to afford sustained therapeutic plasma concentrations even in the absence of prior oral treatment.
LAI, long-acting injection.

Aripiprazole 2-monthly[8,9]

Two-monthly ALAI (Aripiprazole 2-Month Ready-to-Use 960mg [Ari2MRTU]) is indicated for maintenance treatment of schizophrenia (in the USA it is also licensed for maintenance monotherapy treatment of bipolar-1 disorder[9]). It is available as 720mg and 960mg formulations and should only be administered into the gluteal muscle. The 960mg dose is equivalent to 10–20mg daily of oral aripiprazole. The initiation regimen is shown in Table 1.12.

The maintenance dose of Ari 2MRTU should be administered into the gluteal muscle every 56 days (this seems to be the manufacturer's definition of '2-monthly'). It may be given up to 2 weeks before or 2 weeks after the scheduled injection due date.[8] Table 1.13 gives recommendations in the event of a missed or delayed maintenance dose of Ari 2MRTU.

In the event of an adverse reaction, reduce the maintenance dose to 720mg every 2 months. For patients on concomitant treatment with CYP2D6 or CYP3A4 inhibitors or those who are confirmed CYP2D6 poor metabolisers, the 720mg dose is considered more appropriate.[9] Ari 2MRTU 960 is generally well tolerated, with safety, tolerability, efficacy and pharmacokinetic profiles similar to those of the 1-monthly ALAI (400mg).[10–13]

Table 1.12 Aripiprazole 2-month ready-to-use initiation regimen.[8]

Switching from	Initiation regimen
Oral antipsychotics	Establish tolerability with aripiprazole before initiating ALAI treatment
	One-injection start Administer one 960mg injection + give 10–20mg oral aripiprazole for 14 consecutive days
	Two-injection start Administer one 960mg injection and one 400mg injection at two different injection sites + give one 20mg dose of oral aripiprazole
400mg ALAI	Initiate 960mg no sooner than 26 days after the last 400mg ALAI

Table 1.13 Recommendations for delayed maintenance dose of Ari 2MRTU.

Missed maintenance dose[8]	Recommendations
>8weeks and <14 weeks since last injection	Administer 960mg or 720mg as soon as possible
>14 weeks since last injection	Administer 960mg or 720mg + oral aripiprazole for 14 days
	or
	Maintenance dose 960mg: Administer 960mg + 400mg + one dose of 20mg oral aripiprazole
	Maintenance dose 720mg: Administer 720mg + 300mg + one dose of 20mg oral aripiprazole
	Resume 2-monthly dosing schedule

Other LAI aripiprazole brands

Another two long-acting formulations of aripiprazole lauroxil (Aristada Initio and Aristada) are approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia.[14] Aristada Initio is given as a single 675mg IM injection to initiate treatment (Table 1.14). Aristada is administered at 1-monthly, 6-weekly or 2-monthly intervals by IM injection into the deltoid or gluteal muscle, depending on the dose (Table 1.15).[15,16] It is available in four strengths (441mg, 662mg, 882mg and 1064mg doses to deliver 300mg, 450mg, 600mg and 724mg of aripiprazole, respectively).[17] The most commonly reported adverse reaction is akathisia.[14]

The 1-day initiation regimen with 1064mg Aristada did not demonstrate any new safety or tolerability concerns and its adverse-effect profile was comparable to that of paliperidone palmitate 1-monthly injection.[13,18] Most adverse reactions occurred within the first 4 weeks of treatment (injection-site pain, akathisia, increased weight).[18]

Aristada 1064mg and Ari 2MRTU both give therapeutic plasma levels over the entire 2-month dosing interval.[19] The key differences between the two formulations lie in their dosing and the licensed indications. Aristada 1064mg corresponds to 15mg daily oral aripiprazole, while Ari 2MRTU is claimed to be suitable for patients taking 10–20mg of oral aripiprazole daily. While both formulations are licensed for the treatment of schizophrenia, Ari 2MRTU is also approved for the maintenance treatment of bipolar I disorder in the USA.

Table 1.14 Starting treatment with Aristada.[17]

1-day initiation regimen	Second option
Establish tolerability with oral aripiprazole before initiating treatment	Establish tolerability with oral aripiprazole before initiating treatment
Give single dose of 675mg IM Aristada Initio* into the gluteal muscle	Give IM Aristada on day one** and continue oral aripiprazole for 21 days
Give single dose of 30mg aripiprazole	
Give IM Aristada on the same day or up to 10 days after initiation**	

* Avoid giving Aristada Initio and Aristada into the same muscle.
** Only the 441mg dose can be given in the deltoid muscle; 662mg, 882mg and 1064mg must be given into the gluteal muscle.

Table 1.15 Equivalent doses and sites of administration for Aristada.[17]

Aripiprazole oral (mg/day)	Aripiprazole lauroxil dose (mg)	Dosing interval	Site of IM administration
10	441	Monthly	Deltoid or gluteal
15	662	Monthly	Gluteal
≥20	882	Monthly	Gluteal
15	882	Every 6 weeks	Gluteal
15	1064	Every 2 months	Gluteal

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Olanzapine long-acting injection

Olanzapine pamoate (embonate, in some countries) is a very poorly water-soluble salt ester of olanzapine. An aqueous suspension of olanzapine pamoate, when injected deep in the gluteal muscle, affords both prompt and sustained release of olanzapine. Peak plasma levels are seen within 1 week of injection (in most people within 2–4 days)[1,2] and efficacy can be demonstrated after only 3 days.[3] Only gluteal injection is licensed – deltoid injection is less effective.[2] Olanzapine LAI is effective when given every 4 weeks, with 2-weekly administrations only required when the highest dose is prescribed. Half-life is 30 days.[1,4] Olanzapine has not been compared with other LAIs in RCTs, but naturalistic data suggest similar effectiveness to paliperidone LAI.[5,6] Loading doses are recommended in some dose regimens (Table 1.16). The manufacturer recommends that patients be given oral olanzapine first to assess response and tolerability. Oral supplementation after the first depot injection is not necessary.

Table 1.16 Dosing regimen for olanzapine.

Oral olanzapine (mg/day)	Starting dose	Maintenance dose (given 8 weeks after the first dose)
10	210mg every 2 weeks or 405mg every 4 weeks	300mg/4 weeks (or 150mg every 2 weeks)
15	300mg every 2 weeks	405mg/4 weeks (or 210mg every 2 weeks)
20	300mg every 2 weeks	300mg every 2 weeks

Switching

Direct switching to olanzapine LAI, ideally following an oral trial, is usually possible. When switching from another LAI, 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. When switching from risperidone Consta, olanzapine should be started, we suggest, 2 weeks after the last Consta injection was due. That is, 4 weeks after the last Consta injection (peak risperidone plasma levels occur 4–5 weeks after the last injection).

Stopping

Clinicians should consider the gradual release of olanzapine from the pamoate salt when discontinuing treatment. There are various methods of ensuring a linear reduction in drug activity.[7] Olanzapine may remain detectable in the bloodstream for up to 8 months following the last dose.[4]

Post-injection delirium sedation syndrome

Although the precise mechanism of post-injection delirium sedation syndrome (PDSS) remains unclear, it is thought to occur when the pamoate salt of olanzapine is inadvertently exposed to a large volume of blood or plasma, such as through IV injection or a blood vessel injury.[8,9] This exposure can cause the salt to dissolve more rapidly and release a large amount of olanzapine into the circulation.[8] Olanzapine plasma levels may reach over 800mcg/L and confusion, delirium and somnolence result.[10,11] Treatment is supportive and outcomes invariably good.[9] The incidence of PDSS is less than 0.1% of injections and almost all reactions (86%) occur within 1 hour of injection (mean time is 30 minutes)[12] and fully resolve within 72 hours.[8,9,13] One study suggested an incidence of 0.044% of injections (less than 1 in 2,000) with 91% of reactions being apparent within 1 hour.[14] There are very rare reports of events occurring after 3 hours, including one case where the reaction occurred 12 hours after the injection.[15]

In most countries, olanzapine LAI may only be given in healthcare facilities under 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 in Australia, New Zealand[16,17] and some other countries). Shorter monitoring periods were also employed during the COVID-19 pandemic.[18] However, it is worth emphasising that PDSS may occur at any time and has no clear predictive risk factors,[8] even after several uses in the same patient. That is to say, prior safe use of olanzapine LAI in an individual does not imply low risk of PDSS. The risk may be reduced in patients on 1-monthly injection intervals,[8,19] presumably because they receive relatively fewer injections.

In the EU and UK, the exact wording of the SPC[4] is as follows:

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.

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.

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 has undoubtedly adversely affected the popularity of olanzapine LAI. Interestingly some patients continue treatment even after an episode of post-injection syndrome.[20]

As stated, no patient or medical factor has been identified which definitively predicts PDSS,[10] except perhaps that those experiencing the syndrome are somewhat more likely to have previously had an injection site-related adverse effect.[21] Male gender and higher doses have also been suggested to be risk factors for PDSS.[12,14]

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Paliperidone palmitate long-acting injection

Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone. Paliperidone palmitate is the ester prodrug of paliperidone. It is available as a monthly, 3-monthly and 6-monthly LAI. The ester is an aqueous nanosuspension, which is hydrolysed to paliperidone after IM administration and slowly absorbed into the circulatory system.[1,2]

Paliperidone long-acting injection 1-monthly

After the recommended initial loading dose of paliperidone LAI 1-monthly (PP1M), active paliperidone plasma levels are seen within a few days, so co-administration of oral paliperidone or risperidone during initiation is not required from a pharmacokinetic viewpoint but some patients may benefit from gradual withdrawal.[3] Dosing consists of two initiation doses (deltoid) followed by monthly maintenance doses (deltoid or gluteal). Administering a single IM dose to the deltoid muscle results in an average 28% higher peak concentration compared with IM injection to the gluteal muscle.[3] Therefore, the two deltoid muscle injections on days 1 and 8 help to attain therapeutic drug concentration quickly. Improvement in psychotic symptoms has been observed as early as day 4.[3] Table 1.17 gives information on dose and administration of PP1M. Table 1.19, later in this section, provides guidance on how to switch to PP1M.[3]

Table 1.17 Paliperidone dose and administration information.[3]

	Dose	Route
Initiation		
Day 1	150mg IM	Deltoid only
Day 8 (±4 days)	100mg IM	Deltoid only
Maintenance		
Every month (±7 days) thereafter	50–150mg IM*	Deltoid or gluteal**

* 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 (Table 1.18). Pre-treatment with oral risperidone is helpful in establishing efficacy and tolerability of a given dose.
** Continuation with deltoid injections for the first 6 months may be considered in some patients who switch from higher doses of oral paliperidone or risperidone.[3]

The second initiation dose may be given 4 days before or after day 8 (after the first initiation dose on day 1).[3] 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 to minimise the number of missed doses. See the manufacturer's information for full recommendations regarding missed doses.[3]

Points to note

- No test dose is necessary for paliperidone palmitate. However, patients should ideally be stabilised on or have previously responded to oral paliperidone or risperidone.
- After a single IM injection, paliperidone is continuously released into the systemic circulation from day 1 for at least 4 months.[3]

- The median time to maximum plasma concentration is 13 days,[3] and half-life ranges from 25 to 49 days.
- Patients receiving fewer than 12 injections a year have an increased risk of relapse – correct dosing is critical to the effectiveness of paliperidone monthly.[4,5]

Table 1.18 Approximate dose equivalence for paliperidone and risperidone.[3,6]

Risperidone oral (mg/day) (bioavailability = 70%)[7]	Paliperidone oral (mg/day) (bioavailability = 28%)[8]	Risperidone LAI (Consta) (mg/2 weeks)	Paliperidone palmitate (mg/monthly) (bioavailability = 100%)[3]
2	3	25	50
3	6	37.5	75
4	9	50	100
6	12	–	150

Paliperidone LAI has been compared with haloperidol depot given in a loading dose schedule matching that of paliperidone.[9] 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 tardive dyskinesia. The average dose of haloperidol was around 75mg a month, a dose rarely used in practice.

There are two studies comparing monthly paliperidone LAI with aripiprazole LAI. The first was a 28-week randomised head-to-head trial that found aripiprazole monthly injection superior in the improvement of quality of life and functioning in the short term, although the aripiprazole group included more younger patients.[10] The second study compared the two LAIs in patients with psychosis and comorbid substance use disorder. Improvement in quality of life and reduced substance cravings were seen with both LAIs, although aripiprazole fared better. Overall, there was no clear clinically meaningful superiority for aripiprazole over paliperidone in either of these studies.[11]

Table 1.19 Switching to paliperidone palmitate 1-monthly.[3]

Switching from	Recommended method of switching	Comments
No treatment	Give the two initiation doses: 150mg IM deltoid on day 1 and 100mg IM deltoid on day 8	The manufacturer recommends a dose of 75mg monthly for the general adult population.[12] This is approximately equivalent to 3mg/day oral risperidone (Table 1.18). In practice, the modal dose is 100mg/month.[13]
	Maintenance dose starts 1 month later	Maintenance dose adjustments should be made monthly. However, the full effect of the dose adjustment may not be apparent for several months.[3]
Oral paliperidone/ risperidone	Give the two initiation doses followed by the maintenance dose (see Table 1.18 and prescribe equivalent dose)	Oral paliperidone/risperidone can be discontinued at the time of initiation; some patients may benefit from a gradual withdrawal

(*Continued*)

Table 1.19 (*Continued*)

Switching from	Recommended method of switching	Comments
Oral antipsychotics	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.	
Depot antipsychotic	Start paliperidone (at the maintenance dose) when the next injection is due	Doses of paliperidone palmitate IM are difficult to predict from the dose of FGA depots. The manufacturer recommends a dose of 75mg monthly for the general adult population but in practice 100mg and 150mg are more often prescribed.[13,14] If switching from risperidone LAI see Table 1.18 and prescribe equivalent dose.
	NB No initiation doses are required	Maintenance dose adjustments should be made monthly. However, the full effect of the dose adjustment may not be apparent for several months.[3]
Antipsychotic polypharmacy with depot	Start paliperidone (at the maintenance dose) when the next injection is due NB No initiation doses are required	Aim to treat the patient with paliperidone palmitate IM as the sole antipsychotic
	Reduce the dose of the oral antipsychotic over 1–2 weeks following the first injection of paliperidone	The maintenance dose should be governed as far as possible by the total dose of oral and injectable antipsychotic (see section on dose equivalence in this chapter)

Paliperidone long-acting injection 3-monthly

Paliperidone LAI 3-monthly (PP3M) is indicated for patients who are clinically stable on PP1M and do not require dose adjustment.[15] It is recommended that before switching to PP3M, patients be treated for 4 months or more with PP1M and that the last two doses of PP1M are the same.

PP3M is generally well tolerated, with a tolerability and safety profile similar to the 1-monthly preparation.[16,17] PP3M has a lower risk of hospitalisations and emergency department visits compared with PP1M.[18]

Patient and family perspective of PP3M have been systematically examined.[19] In this study, PP3M was reported to be as effective, or even more effective, than PP1M and had similar or fewer adverse effects. The majority of patients preferred PP3M over PP1M. The advantages for the patients included less frequent and painful injections, less travelling and fewer moments of experiencing shame. The switch did not influence the frequency of their interaction with healthcare professionals.

Practical experience suggests that contacts with healthcare staff are reduced when LAIs are used. Healthcare workers should probably work towards ensuring that contact with patients is not reduced just because there are fewer antipsychotic administrations.

When initiating PP3M, give the first dose in place of the next scheduled dose of PP1M (±7 days). The dose of PP3M should be based on the previous PP1M dose

(Table 1.20). Dose adjustments should not be necessary but may be made at 3-monthly intervals thereafter; however, the full response to the new dose may not be apparent for several months.[15]

The administration process is important for avoiding incomplete administration of the suspension. This requires shaking vigorously the prefilled syringe with the cap and a loose wrist, in a vertical motion for at least 15 seconds to ensure an evenly distributed suspension.[15]

Table 1.20 Dosing of paliperidone long-acting injection 3-monthly.[15]

Dose of PP1M	Dose of PP3M
50mg	175mg
75mg	263mg
100mg	350mg
150mg	525mg

Points to note

- Patients should be on a stable and effective therapeutic dose of PP1M before changing to PP3M to ensure optimal dosing and avoid relapse and hospital admissions.[14,20–22]
- PP3M should be given in place of the next PP1M injection at an equivalent dose.
- The median time to maximum plasma concentration is 30–33 days.[15]
- The median half-life for deltoid injection is 84–95 days and for gluteal injection is 118–139 days.
- After IM injection of PP3M into the deltoid muscle, there was an average increase of 11–12% maximum concentration in plasma compared with gluteal injection.

Paliperidone LAI 6-monthly (PP6M)

PP6M is indicated for patients on maintenance treatment with 100mg or 150mg of PP1M (ideally for 4 months or more, same dose for the last two injections) or patients who have had at least one injection of 350mg or 525mg of PP3M and do not require any dose changes. It is designed to be given once every 6 months into the gluteal muscle. It should not be administered via any other route. There are no corresponding PP6M doses for 25mg, 50mg, 75mg of PP1M or for 263mg and 350mg of PP3M.[23] Table 1.21 gives equivalent doses for paliperidone LAI.

Table 1.21 Paliperidone long-acting injection – equivalent doses.

Dose of PP1M (mg)	Dose of PP3M (mg)	Dose of PP6M (mg)
100	350	700
150	525	1000

PP6M is generally well tolerated and has a tolerability profile similar to PP3M and PP1M.[24] The most common adverse effect in one phase 3 trial was the injection site pain (which can be attributed to the large injection volume: 3.5mL or 5mL), followed by weight gain.[24] Patients and clinicians seem to prefer PP6M over PP3M.[25] Table 1.22 gives the regimen for switching to PP6M.

Table 1.22 Switching to paliperidone 6-monthly.[23]

Switching from	Recommended method of switching	Comments
100mg PP1M	Give 700mg of PP6M in place of the next scheduled dose of 100mg PP1M	PP6M can be initiated ±7 days of the PP1M due date
150mg PP1M	Give 1000mg of PP6M in place of the next scheduled dose of 150mg PP1M	
350mg PP3M	Give 700mg of PP6M in place of the next scheduled dose of 350mg PP3M	PP6M can be initiated ±14 days of the PP3M due date
525mg PP3M	Give 1000mg of PP6M in place of the next scheduled dose of 525mg PP3M	

Dose adjustments should not be needed but can be made every 6 months based on patient response and tolerability. Any dose change may not be apparent in respect to clinical effects for several months owing to the long-acting nature of PP6M and the time needed for a new steady-state level to be reached.[23]

Points to note

- PP6M is suitable for patients who are stable in their mental state and do not require any dose adjustments.
- PP6M should be given only into the upper-outer quadrant of the gluteal muscle.
- Before IM administration, the vial requires extensive and rapid shaking for a minimum of 30 seconds.
- The median half-life is 148–159 days or longer.[23,24]

See the manufacturer's information for full information on missed doses and re-initiation regimens.

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Risperidone long-acting injection

In this section we give brief details on the range of risperidone LAIs (RLAIs) available around the world in 2024. We have done our best to identify each formulation by some unique property and by a trade name. These trade names do vary somewhat by country. Readers are directed to formal product information for full details of each formulation.

Risperidone intramuscular long-acting injections

Risperdal Consta – risperidone 2-weekly long-acting injection

RLAI is now very rarely initiated in practice and here we give no information on starting doses or its therapeutic uses. It has been superseded by longer-acting risperidone and paliperidone injections with less complex pharmacokinetic profiles. Here we provide information on stopping RLAI and on switching to other formulations. In doing this, we have relied upon the following assumptions:[1]

Timescale of plasma concentrations after last dose of RLAI	
4–5 weeks	Peak plasma concentration from last dose reached
6 weeks	Plasma levels fall below threshold for therapeutic effect
7–8 weeks	Plasma concentrations approach zero

Switching from RLAI is complicated because, in regular dosing, plasma concentrations remain therapeutic for around 6 weeks following the last injection. Two weeks after the last injection (i.e. the time of the first missed injection) plasma levels are yet to peak and will in fact reach a peak on two occasions after this time (Figure 1.1).

Figure 1.1 Blood levels following discontinuation of treatment with 25mg every 2 weeks: last injection at week 4. Source: reproduced with permission from Wilson (2004).[2]

Table 1.23 provides general recommendations when switching from RLAI. These suggestions are aimed at ensuring that, when switching someone who is responsive to RLAI, a therapeutic plasma concentration of the new antipsychotic is established before risperidone concentrations become subtherapeutic. A further aim is to ensure that therapeutic levels of the new drug will be maintained during the first dosing interval.

Table 1.23 Switching from risperidone long-acting injections.[3,4]

Switching to	Recommended method of switching	Comments
Oral risperidone	Start oral tablets 4–5 weeks after the last RLAI injection	25mg/2 weeks = 2mg/day 37.5mg/2 weeks = 3mg/day 50mg/2 weeks = 4 mg/day[5]
Oral antipsychotic (not risperidone)	Start oral antipsychotic 4–5 weeks after the last RLAI injection	Monitor for adverse effects
Paliperidone LAI[6]	Initiate the equivalent dose of the paliperidone LAI in place of the next scheduled dose of RLAI, then continue monthly administration (a second loading dose is not required and should not be given)	25mg/2 weeks = 50mg/monthly 37.5mg/2 weeks = 75mg/monthly 50mg/2 weeks = 100mg/monthly
Risperidone ISM®* (Okedi, Risvan, and others)[7]	Initiate the equivalent dose of risperidone ISM in place of the next scheduled dose of RLAI and continue risperidone ISM at 28-day intervals	37.5mg/2 weeks = 75mg/28 days 50mg/2 weeks = 100mg/28 days
Aripiprazole LAI	Start oral aripiprazole 4–5 weeks after the last RLAI dose. Initiate ALAI 2 weeks after starting oral aripiprazole.	Note that aripiprazole LAI can be initiated in two ways. For more information refer to the relevant section of this book and manufacturer's advice.
Antipsychotic LAI (not paliperidone or risperidone ISM)	Start the new LAI 4–5 weeks after the last RLAI	For some LAIs, oral trial and/or test dose may be required to establish response and tolerability

* Formal recommendations recommend giving risperidone ISM in place of the next RLAI injection; i.e. 2 weeks after the last injection. A 4-week interval makes more sense because risperidone ISM will then be given shortly before the time of peak plasma levels from the last RLAI injection.

Rykindo®

Rykindo is a 2-weekly injectable suspension of risperidone given in the gluteal muscle to patients who have previously responded and tolerated risperidone.[8] After IM injection risperidone blood concentration peaks at 14 days and reaches steady state after two administrations. Oral supplementation is required for the first 7 days of treatment. The recommended starting dose is 25mg every 2 weeks, with a maximum dose of 50mg every 2 weeks. Dose adjustments can be made every 4 weeks.

Patients on Consta can switch directly to Rykindo without needing oral supplementation. The first IM injection should be given 4–5 weeks after the last Consta administration (refer to Table 1.25 later in this section for equivalent doses). Like Consta, Rykindo must be stored in the refrigerator and allowed to sit at room temperature for at least 30 minutes before reconstitution. The reconstitution process is similar to that for Consta. Please refer to manufacturer's advice for further details.

Risperidone ISM® (Risvan, Okedi)

Risperidone ISM is an injectable suspension of risperidone suitable for stable patients who have previously responded and tolerated risperidone.[7] Risperidone ISM employs in situ microparticle technology (ISM) to provide effective plasma levels as early as 2 hours following IM administration without requiring a loading dose or oral supplementation. An initial peak in plasma concentration is seen within 24–48 hours of administration with a second peak appearing between days 18 and 25. The delayed appearance of the second peak should be noted when assessing clinical efficacy, tolerability and when making changes to dose.[7] The dosing interval for the injection is every 28 days (Table 1.24).

Table 1.24 Initiation of risperidone ISM.

	Dose	Route
Initiation		
Day 1*	75mg or 100mg IM	Deltoid or gluteal
Maintenance		
Every 28 days (±3 days) thereafter	75mg IM or 100mg** IM	Deltoid or gluteal

* No loading dose is required but response and tolerability to oral risperidone must be assured by prior oral supplementation for at least 14 days.
** 75mg risperidone ISM is recommended as maintenance treatment by the manufacturer. It seems likely that 100mg will be required by most people (equivalent to 4mg/day oral risperidone).

Risperidone ISM is effective both as an acute[9] and maintenance[10] treatment and is generally well tolerated, although increased prolactin is common, as with all risperidone formulations.[9] An indirect comparison with other SGA LAIs suggested somewhat better tolerability for risperidone ISM, but this study was authored by researchers linked to risperidone ISM's manufacturers.[11] Its main advantages are the absence of a loading dose requirement and the 28-day administration interval. The main disadvantages of risperidone ISM are that it is not suitable for patients requiring 2mg or 6mg/day of oral risperidone and that it may not be given to patients with a creatinine clearance of less than 60mL/minute.

Risperidone subcutaneous long-acting injections

Perseris®

RBP-7000 (Perseris) is SC risperidone LAI that is available in 90mg and 120mg dosage forms. It is given every 28 days. The lower dose is equivalent to 3mg/day oral risperidone and the higher dose 4mg/day.[12] There are no specific formulations corresponding to 2mg or 6mg/day of oral risperidone. However, two SC injections of 90mg RBP-7000 can be given to afford a similar plasma concentration to 6mg oral risperidone.[13]

RBP-7000 is suitable for SC administration in the abdominal region or back of the upper arm.[14] It has a biphasic release pattern, with the first peak occurring 4–6 hours after administration and the second at 10–14 days post-dose.[15] The active metabolite, paliperidone, has its first peak at 4–48 hours post-injection and the second at 7–11 days. Steady state is achieved after the second SC injection.[16]

The injection is acutely effective at both licensed doses (although 120mg may be better than 90mg), without the need for oral pre-treatment or oral supplementation, although tolerability with oral risperidone should be established before commencing treatment.[17,18] In the longer term, monthly doses of 120mg are effective in maintaining response.[19,20]

RBP-7000 is rapidly active, achieving therapeutic plasma concentration on the first day.[21] Disadvantages include the need for refrigerated storage and a complex multi-step injection procedure. The complexity of preparation and subcutaneous administration are new to psychiatry and failure to follow the instructions might result in dosage errors.[14,21,22] RBP-7000 appears to be well tolerated and has a safety profile similar to that of oral risperidone. In clinical trials, the most commonly reported adverse effects were injection site pain and weight gain.[16,19] See manufacturer's advice on how to initiate RBP-7000.[21]

Uzedy® (TV-46000)

Uzedy is a risperidone extended-release injectable suspension licensed for SC administration in the abdominal region or upper arm. It is available as a 1- or 2-monthly injection (see Table 1.25 for equivalent doses).[23] Uzedy does not require oral supplementation or loading doses but response and tolerability to oral risperidone should be established before initiating treatment. The pre-filled syringe must be stored in the fridge and allowed to sit at room temperature for at least 30 minutes before administration. The syringe content is solid at refrigerated temperatures and converts to liquid at 20–25°C.

Steady-state plasma level of Uzedy is reached after two SC injections. Therapeutic concentrations are seen on day one. Like other risperidone injections, Uzedy has a biphasic release pattern with two peak levels.

In clinical trials,[24–26] Uzedy was effective both acutely and as relapse prevention. One-monthly administration afforded numerically better protection against relapse than two-monthly injections.[27] The most commonly reported adverse effects were injection site pain, injection site nodules, weight gain and EPSEs. Most participants had an F20 diagnosis for 20 years and were stabilised on oral risperidone for at least 12 weeks before trial entry.

Table 1.25 Equivalent doses – risperidone-based long-acting injections.[6,7,28–33]

Risperidone oral (mg/day) (bioavailability = 70%)	Paliperidone oral (mg/day) (bioavailability = 28%)	Risperidone LAI							
		(Consta)* (mg/2weeks)	Rykindo* (mg/2 weeks)	Risperidone ISM˜† (mg/28 days)	RBP-7000* (mg/28 days)	Uzedy* (mg/ monthly)	Uzedy* (mg/2 monthly)	Paliperidone palmitate** (mg/monthly)	Paliperidone palmitate** (mg/3-monthly)
1	–	–	12.5***	–	–	–	–	–	–
2	3	25	25	–	–	50	100	50	175
3	6	37.5	37.5	75	90	75	150	75	263
4	9	50	50	100	120	100	200	100	350
6	12	–	–	–	–††	125	250	150	525

* Bioavailability assumed to be 100%.

** Bioavailability has been confirmed to be 100%.

˜Initiate risperidone ISM 24 hours after the last oral dose of risperidone.

†Recommended starting dose for patients with renal or hepatic impairment[8] or poor antipsychotic tolerability, not studied in clinical trials.[34]

†† 180mg (two SC injections of 90mg) of RBP-7000 is equivalent to 6mg daily risperidone dose.

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Penfluridol weekly

Background

Penfluridol is a diphenylbutylpiperidine FGA available in countries such as Brazil, China, India, Israel and the Netherlands and can be imported to other countries.

Penfluridol is unusual in having a very long plasma half-life – at least 60 hours.[1] After oral administration, peak levels are reached within 12 hours and drug can still be detected 168 hours after a single oral dose.[2] Its long duration of action seems to be a result of rapid distribution into fat tissue which acts as a drug reservoir.[3] This property allows penfluridol to be used as a once-weekly oral therapy for supervised ingestion – an alternative to long-acting injectable antipsychotics.

Clinical effectiveness

Several trials have examined the use of once-weekly oral penfluridol, in doses ranging from 5mg to 160mg per week.[4] When given in this manner it is at least as effective as depot FGAs[5,6] and may be better tolerated overall.[4] A Dutch retrospective cohort study (n = 8,257) found that discontinuation trends for oral penfluridol and depot formulations were similar.[7] In a small retrospective observational study of 19 patients (most of whom were treatment resistant), Dunnett and colleagues found just over half of the people prescribed penfluridol (n=9) continued taking it during a 1-year follow-up,[8] suggesting some efficacy in these patients.

Although the dose–response relationship remains unclear, a weekly dose of 30mg is thought to be adequately effective,[9] although a dose of 120mg a day (that is, a total of 840mg a week) has been used.[10] Steady-state levels and plasma elimination half-lives of people taking penfluridol can vary significantly, probably because of differences in adiposity.[3] An early study found that a loading dose regimen (first dose 80mg; a total of 200mg over the first week) is effective and well tolerated[11] but this regimen remains unlicensed and untested in larger studies. Penfluridol is probably underused considering the high rates of non-adherence with oral antipsychotics and the reluctance to prescribe depots.[12]

Adverse effects

Adverse effects include acute EPS, increased prolactin and TD, as might be expected.[8] It is usually not sedative. Like pimozide (another diphenylbutylpiperidine), penfluridol appears to prolong the QT interval.[13] Penfluridol is a cytotoxic agent which may have anticancer properties.[14]

Summary

- Penfluridol can be given orally once a week.
- Supervised weekly administration is at least as effective as long-acting injections.
- The usual dose is 20–40mg a week, but much higher doses have been used.
- Adverse effects are those common to FGAs and include QT prolongation.
- Sedation is minimal.

In practice, penfluridol is usually started at a dose of 20mg and increased to a maximum of 40mg after assessment. Steady-state levels are effectively reached after 2–3 weeks. Monitoring includes investigations of renal and hepatic function, changes in cardio-metabolic parameter such as lipids, blood glucose, ECG and general adverse effect screening.

Other antipsychotics which may be suitable for once-weekly oral administration include pimozide, aripiprazole and cariprazine.[12]

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Electroconvulsive therapy and psychosis

Evidence from prospective RCTs and retrospective studies suggests that ECT augmentation of antipsychotic medication can have a beneficial effect on persistent positive symptoms in schizophrenia, including medication-resistant schizophrenia.[1–7] However, there is a relative lack of data on long-term effectiveness and efficacy, cognitive deficits and quality of life.

A 2005 Cochrane systematic review[8] assessed RCTs that had compared ECT with placebo, sham ECT, non-pharmacological interventions and antipsychotic medication for patients with schizophrenia, schizoaffective disorder or chronic mental disorder. In studies where ECT was compared with placebo or sham ECT, more participants 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 are desired (for example, treating patients with a high risk of aggression or self-harm),[9] and where the illness has shown only a limited response to medication alone.

A naturalistic, mirror-image study compared 2,074 people with schizophrenia on antipsychotic medication who had received ECT with a control group of patients prescribed continuing antipsychotic medication.[10] The rate of psychiatric hospitalisation over a 1-year post-treatment period decreased in those treated with ECT, but not in the control group. The effectiveness of ECT was more pronounced among those treated with clozapine or a medium to high antipsychotic dosage.

Treatment-refractory schizophrenia

The benefits and harms of adding ECT to standard care for people with TRS were examined in a 2019 Cochrane systematic review.[6] The investigators were able to reach the limited conclusion that the moderate-quality RCT evidence available suggested a positive effect for ECT on medium-term clinical response. It was noted that further evidence of better quality was required before a stronger conclusion could be made.

Several studies have focused on ECT augmentation of antipsychotic medication for TRS.[1–3,11,12] For example, in a 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.[13] A 2016 meta-analysis of RCTs[3] in TRS that examined the efficacy of the combination of ECT and (non-clozapine) antipsychotic medication versus the same antipsychotic medication as monotherapy found that the combination proved to be superior in terms of symptom improvement, study-defined response and remission rate.

ECT augmentation of clozapine may be at least as effective as ECT augmentation of other antipsychotic medications, if not more so.[4,12,14–16] Response is probably unrelated to post-ECT changes in clozapine levels.[17] In a retrospective study[1] 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 Positive and Negative Syndrome Scale [PANSS] total score).[18] Follow-up data on a subsample of these patients over a mean of 30 months revealed that the majority had

maintained their symptomatic improvement or improved further. Another small retrospective study of ECT augmentation of clozapine reported an acute response (defined as improvement rated on the Clinical Global Impression Improvement scale)[19] in around three-quarters of the patient sample, and three-quarters of the responders remained out of hospital over a 1-year follow-up period.[20] In a randomised, single-blind study,[2] participants 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 (which included a 40% or greater reduction in the psychotic symptom subscale of the Brief Psychiatric Rating Scale)[21] was met by half the participants 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 2016 systematic review and meta-analysis[22] looking specifically at ECT augmentation of clozapine treatment found a paucity of controlled studies, although the authors acknowledged the methodological challenges of such investigations. They concluded that ECT may be an effective augmentation strategy for schizophrenia that has failed to respond to clozapine monotherapy, but that further research was required to determine the place of such a strategy in any TRS treatment algorithm. A subsequent meta-analysis of RCTs addressing ECT augmentation for clozapine-resistant schizophrenia noted the lack of studies with sham ECT as a control, but reached the conclusion that such a treatment strategy was effective and relatively safe.[23] In 2021, Chakrabarti[9] reinforced the point that such meta-analyses were based on limited and low-quality evidence and only addressed the short-term efficacy of ECT augmentation. Counter to the relatively encouraging conclusions of these meta-analyses, in a more recent, 10-week RCT[24] involving 40 participants with clozapine-resistant schizophrenia, augmentation with real ECT was not found to be superior to sham treatment in terms of symptom response. The primary outcome was a 50% reduction in PANSS total score, but this was achieved for only one participant (in the real ECT group). There is some provisional evidence that maintenance ECT may be effective when combined with clozapine.[25]

Adverse effects

Although ECT augmentation of continuing antipsychotic medication appears to be generally well tolerated, adverse effects such as transient retrograde and anterograde amnesia, drowsiness, headaches and nausea have been reported for a minority of cases[3,12,13,24,26] and there are reports of an increase in blood pressure after ECT and prolonged seizures.[1] The cognitive adverse effects are generally considered to be mild and transient.[20,23,27]

Summary

While the evidence remains rather inconclusive, it tends to support ECT augmentation of antipsychotic treatment, particularly clozapine, as a potentially efficacious and relatively safe augmentation strategy in TRS.[7,28–30] However, further, well-controlled trials are required to establish the clinical benefit–risk balance of such a treatment strategy in both the short and long term.

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Omega-3 fatty acid (fish oils) in schizophrenia

Fish oils contain the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexanoic 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.[1] Imaging studies suggest that the ratio between omega-6 and omega-3 may be relevant in the development of psychotic disorders.[2] One genetic study has suggested that people with schizophrenia may have difficulty converting short-chain fatty acids to long-chain polyunsaturated fatty acids.[3] High dietary intake of PUFAs may protect against psychosis[4] and antipsychotic treatment seems to normalise PUFA deficits.[5] Animal models suggest a protective effect for PUFAs.[6] They have been suggested as treatments for a variety of psychiatric illnesses.[7,8] In schizophrenia, case reports,[9–12] case series[13] and prospective trials originally suggested useful efficacy.[14–18]

Treatment

A 2012 meta-analysis of these RCTs[19] concluded that EPA had 'no beneficial effect in established schizophrenia'. Since then, an RCT comprising 71 patients with first-episode schizophrenia given 2.2g EPA + DHA daily for 6 months showed a reduction in symptom severity for patients in the active arm, finding a number needed to treat (NNT) of 4 to produce a 50% reduction in symptoms measured by PANSS.[20] However, a further RCT of 97 patients in acute psychosis showed no advantage for EPA 2g daily[21] and a relapse prevention study of EPA 2g + DHA 1g/day failed to demonstrate any value for PUFAs over placebo (relapse rate was 90% with PUFAs, 75% with placebo).[22] The limitations affecting the published data in this area (small sample sizes, heterogeneity of diagnosis and stage of illness, differences in intervention combinations and doses) mean that overall findings remain at best inconclusive.[23,24] A 2019 meta-review of published meta-analyses found no evidence for the use of PUFAs in the treatment of schizophrenia.[25]

On balance, evidence now suggests that EPA (2–3g daily) is unlikely to be a worthwhile option in schizophrenia when added to standard treatment. Omega-3 fatty acids are not recommended by the World Federation of Societies of Biological Psychiatry for use in schizophrenia.[26] Set against doubts over efficacy are the facts that fish oils are relatively cheap, well tolerated[27] (mild gastrointestinal [GI] symptoms may occur) and benefit physical health.[1,28–32] A few small RCTs suggest some benefit to neurocognition (social cognition),[33] verbal fluency and working memory[34] in recent-onset psychosis or young people at ultra-high risk of psychosis. Other studies have failed to show any benefit on aggressive behaviour.[35]

Prevention

The Vienna High Risk study (VHR) gave 700mg EPA + 480mg DHA to adolescents and young adults at high risk of psychosis, and showed that such treatment greatly reduced emergence of psychotic symptoms compared with placebo[36] (although a review described this study as 'very low quality evidence').[37] Since publication of this single-site study, the large, multi-site NEURAPRO trial[38] gave adult patients at high risk of psychosis 840mg EPA + 560mg DHA for 6 months and failed to find any evidence of efficacy either for

reduction in transition to psychosis or improvement in symptoms. From these RCTs, Cochrane concluded that omega-3 fatty acids 'may' prevent transition to psychosis in the prodromal phase, but that the evidence is of low quality and this conclusion unconfirmed.[39] The non-randomised North American Prodromal Longitudinal Studies (NAPLS)[40] found a positive correlation between functional improvement and frequency of dietary intake of EPA. The Program of Rehabilitation and Therapy (PORT) study[41] found that young people at ultra-high risk of psychosis who then developed the condition had lower dietary intake of omega-3 and higher consumption of omega-6 fatty acids compared with healthy controls. Taken together, these two RCTs (VHR and NEURAPRO) and two non-randomised trials (PORT and NAPLS) indicate a possible positive correlation between dietary omega-3 and functional status, but more studies are required before a clinical benefit can be confirmed.[42] A 2024 network meta-analysis concluded that omega-3 fatty acids are correlated with a lower risk of transition to psychosis compared with placebo, antipsychotics, mood stabilisers or antidepressants.[43] However, this result was derived from only two studies (VHR and NEURAPRO) and just 194 participants.

Overall

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.[25,44–46] If used, careful assessment of response is important and fish oils should be withdrawn if no effect is observed after 3 months' treatment, unless required for their beneficial metabolic effects.

Summary recommendations – fish oils (PUFAs)

- Patients at high risk of first-episode psychosis:
  - Not recommended. If used, suggest **EPA 700mg/day**.
- Residual symptoms of multi-episode schizophrenia (added to antipsychotic):
  - Not recommended. If used, suggest dose of **EPA 2g/day**.

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Alternative routes of administration

The main routes of administration for antipsychotics are oral or intramuscular. Preparations formulated for these routes of administration are readily available and discussed elsewhere in the *Guidelines*. There may be some rare circumstances where these routes of administration are unsuitable, for example due to medical illness or surgery affecting the GI tract and/or patient preference. Below and in Table 1.26 we list some alternative routes of administration and the drugs available in formulations suitable for these routes.

Table 1.26 Alternative formulations and routes of administration of antipsychotics.

Drug name and route	Dosing information	Manufacturer	Notes
Inhaled			
Loxapine inhaled (Adasuve)	9.1mg (10mg), can be repeated after 2 hours	Angelini Pharma (UK) Teva (USA)	■ Licensed for the rapid control of mild to moderate agitation in patients with schizophrenia or bipolar disorder in the UK and USA ■ Administration requires co-operation of the patient ■ Associated with increased risk of bronchospasms
Intranasal			
Droperidol IV	5–10mg (higher doses have been used)	Off-label, see notes	■ ECG monitoring is recommended
Haloperidol IV	5–10mg (higher doses have been used)	Off-label, see notes	■ Used off-label for acute disturbance, limited evidence ■ ECG monitoring is recommended ■ EPSEs reported in case studies
Olanzapine IV	1.25–30mg	Off-label, see notes	■ Used off-label for acute disturbance, limited evidence ■ Hypoxia, respiratory depression and bradycardia reported
Sublingual			
Asenapine sublingual (Sycrest, Saphris)	5mg twice daily, up to a maximum dose of 10mg twice daily	Organon Pharma (UK)	■ Licensed for moderate to severe manic episodes associated with bipolar disorder in the UK ■ Licensed for schizophrenia and bipolar disorder in the USA ■ Eating and drinking should be avoided for 10 minutes after administration

(*Continued*)

Table 1.26 (*Continued*)

Drug name and route	Dosing information	Manufacturer	Notes
Transdermal			
Asenapine transdermal patch (Secuado)	Starting dose 3.8mg/24 hr, may increase to 5.7mg/24 hr or 7.6mg/24 hr after 1 week	Noven Pharmaceuticals Inc (USA)	■ Licensed in the USA ■ Can be applied to upper arm, upper back, abdomen and hip ■ Patients may shower with the patch on. Avoid bathing or swimming.
Blonanserin transdermal patch (Lonasen)	Starting dose 40mg/24 hr up to 80mg/24 hr	Sumitomo Pharma	■ Licensed in China, Japan and South Korea ■ Can be applied to upper arm, upper back, abdomen and hip ■ Patients may shower with the patch on. However, avoid bathing or swimming.
Rectal			
Chlorpromazine rectal	100mg every 6–8 hr	Special order	■ 25mg and 100mg suppositories available. Limited information about this route for the treatment of psychosis.
Olanzapine rectal	2.5–10mg suppositories used	Suppositories have been manufactured by pharmacies	■ Has been used for delirium, nausea and vomiting in terminally ill patients rather than for psychosis
Prochlorperazine rectal	25mg every 12 hr	Suppositories available in some countries	■ Case report only

Inhaled

Loxapine is the only antipsychotic licensed as an inhalation powder. It is indicated for adults with mild to moderate agitation associated with schizophrenia and bipolar disorder in the hospital setting. It was licensed in Europe and the USA in 2013 but has since been discontinued in the UK. Inhaled loxapine remains available in the EU and USA but use is restricted. Onset of tranquillising effect is around 10 minutes. Administration requires co-operation with the patient, which may not be possible in medically unwell patients. It is not clear if repeated administration of inhaled loxapine has an antipsychotic effect.

Intranasal

There are no commercially available preparations designed for intranasal and clinical investigations in humans are limited.[1] Nanotechnology delivery systems have been developed for intranasal delivery of various antipsychotics, but this system remains clinically untested.[2–4] One small study compared the pharmacokinetics of intranasal and intramuscular haloperidol in healthy volunteers.[5] Using a compounded nasal spray, intranasal

haloperidol had a shorter time to peak levels (15 minutes) and a bioavailability comparable to oral routes of administration. Similar findings have been reported with droperidol.[6]

Intravenous

Intravenous haloperidol is often used off-label to manage acute behavioural disturbance or agitation and psychosis in patients with delirium in a general hospital setting. However, antipsychotics are probably not effective in delirium. A large clinical trial (n = 566) showed no evidence that either IV haloperidol or ziprasidone provided benefit over placebo in patients with delirium in intensive care.[7] Other studies have reported similar findings.[8]

In respect to toxicity, a systematic review found that IV haloperidol did not cause greater QT prolongation than placebo, but close ECG monitoring is officially advised for IV haloperidol.[9] Doses between 5 and 10mg are typically recommended but doses in the literature have ranged from 50 to 1500mg (over hours to days).[9] A review of observational studies reported effectiveness of off-label IV olanzapine.[10] Bolus doses from 2.5 to 10mg (maximum dose of 30mg/day) have apparently been safely administered. IV droperidol is used off-label to manage acute behavioural disturbance. Low-dose IV prochlorperazine (a piperazine phenothiazine)[11] has been used in migraine.[12]

Sublingual

Asenapine is the only commercially available antipsychotic designed for sublingual use. When used sublingually, the bioavailability of asenapine is 35%, compared with only 2% when taken orally.[13] Other drugs may be absorbed sublingually but this has not been investigated. Dexmedetomidine is used sublingually in acute agitation.[14,15]

Buccal

Buccally administered drugs are absorbed through the lining of the cheek. Compared with sublingual use, buccal administration results in somewhat slower absorption.[13] There are no commercially available preparations licensed for buccal use and there has been little clinical investigation into this route of administration for antipsychotics. Prochlorperazine is available in the UK as a buccal tablet[16] but it is indicated for the treatment of nausea and vomiting associated with migraines.[17] Prochlorperazine is now rarely used for psychiatric indications and the dose needed for an antipsychotic effect (75–100mg a day) is much greater than that used for nausea.

Transdermal

Asenapine is available in the USA as a daily transdermal patch (Secuado) for treatment of adults with schizophrenia. Blonanserin (Lonasen) is commercially available as a daily transdermal patch in China, Japan and South Korea. Transdermal drug delivery minimises fluctuations in plasma drug concentrations and allows for lower doses (by bypassing first-pass metabolism) and possibly reduced systemic adverse effects. At the time of writing, proof of concept clinical trials of once-weekly aripiprazole transdermal patch had been successfully conducted.[18] Chlorpromazine, haloperidol, olanzapine, prochlorperazine, quetiapine and risperidone have been developed as transdermal delivery systems but are not commercially available.[19,20]

Rectal

Chlorpromazine suppositories are available from specials manufacturers in the UK in 25mg and 100mg strengths.[21] The rectal route is not licensed in adults.[17] 100mg given rectally as a suppository is approximately equivalent to 20–25mg chlorpromazine hydrochloride given by IM injection or 40–50mg of chlorpromazine base or hydrochloride given orally.[17] Prochlorperazine suppositories were used successfully short term for the treatment of psychosis in one case report.[22] Olanzapine suppositories have been manufactured by a hospital pharmacy and administered for the treatment of delirium or nausea and vomiting in terminally ill patients.[23]

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Stopping antipsychotics

Antipsychotics are recommended for long-term treatment of schizophrenia because they reduce symptoms and lessen the risk of relapse.[1] However, antipsychotics have many adverse effects, including metabolic complications, TD, emotional blunting and anatomical brain changes.[2] There is some (hotly disputed) evidence that reducing or stopping antipsychotics may improve social functioning (relationships, education or employment, independent living) without worsening the rate of relapse or symptom burden in the medium term,[3] although it might increase risk of relapse in the short term.[4,5] Reducing antipsychotic burden may also improve cognitive functioning.[6]

It is also worth considering that much of the evidence for the relapse prevention properties of antipsychotics relies on discontinuation trials in which antipsychotics are stopped quickly (over a matter of weeks), and that process may have elevated the apparent rate of relapse in the discontinuation group, so exaggerating the relapse prevention properties of antipsychotics.[7] Patients often ask to reduce or stop medication and, in light of the above, this may be a reasonable course of action. Cautious deprescribing should be a component of high-quality prescribing practice, depending on the condition being treated. More than half of antipsychotic prescriptions in the UK are given to patients without a psychotic or manic disorder and instead are prescribed for insomnia, anxiety, personality disorders and symptoms of dementia.[8] In the UK, NICE strongly cautions against medium- or long-term use of antipsychotics in personality disorder,[9] and only limited use in dementia.[10] The principles for deprescribing outlined below also apply to these patients.

Withdrawal effects of antipsychotics

Stopping or reducing the dose of an antipsychotic can cause a variety of withdrawal symptoms reflecting their various actions (blocking dopamine, histamine, acetylcholine, serotonin and noradrenaline receptors).[11,12] Symptoms are listed in Figure 1.2.[11–15]

Importantly, withdrawal/discontinuation symptoms from antipsychotics can include psychotic symptoms.[12,16] This is suggested by a number of case studies in which people without a psychotic disorder treated with dopamine antagonists for reasons such as nausea or lactation difficulties develop psychotic symptoms when these medications are abruptly stopped.[17–19] Non-psychotic withdrawal effects (e.g. insomnia, agitation and anxiety) may also precipitate genuine relapse that would not have occurred in the absence of antipsychotic dose reduction (perhaps clumsily named withdrawal-associated relapse).[20]

In patients with psychotic disorders, relapse often occurs when antipsychotics are withdrawn. This has been widely thought to represent an unmasking of the underlying chronic illness, but the nature of the process of withdrawing antipsychotics may itself be causally related to relapse.[7] This suggestion is supported by the marked preponderance of relapses soon after abrupt antipsychotic cessation in patients with schizophrenia. In one analysis 60% of all relapses over 4 years occurred within 3 months of drug cessation,[21] the time most likely for withdrawal effects to be evident. The idea that speed of stopping is an influence on relapse is also supported by evidence that slower tapering can reduce the rate of relapse.[22,23] Withdrawal effects can be delayed in onset for weeks and sometimes months, for reasons that are poorly understood.[20]

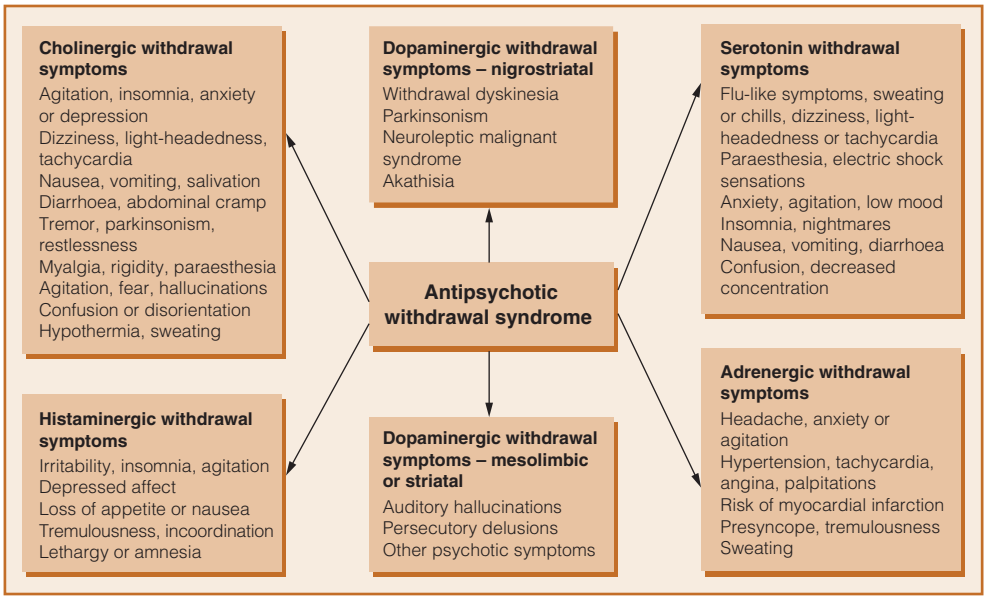

Figure 1.2 Antipsychotic withdrawal symptoms. Source: adapted from Chouinard et al. (2017).[12]

Neurobiology of withdrawal

Withdrawal-associated relapse has been attributed to neural adaptations to long-term antipsychotic treatment (dopaminergic hypersensitivity, among other effects) that persist after antipsychotic cessation.[24] Indeed, molecular imaging studies in schizophrenia have found increased D_2/D_3 receptor availability in those patients who had been exposed to antipsychotic medication but not in antipsychotic-naïve patients.[25] This hypersensitivity to dopamine may render patients more susceptible to psychotic relapse when D_2 blockade is diminished by antipsychotic dose reduction.[11,24]

There are converging lines of evidence that suggest that the neuroadaptive effects of antipsychotics can persist for months or years after stopping. Dopaminergic hypersensitivity in animals persists for the equivalent of a human year after treatment is stopped.[26,27] TD – widely attributed to dopaminergic hypersensitivity – can persist for years after antipsychotic medication has been ceased.[28] There is also evidence that patients who have discontinued antipsychotics have increased rates of relapse for 3 years compared with people maintained on their antipsychotics, after which relapse rates converge,[1] perhaps suggesting that adaptations may have resolved by this point. Persisting dopaminergic hypersensitivity may lower the threshold for precipitating relapse from other triggers for as long as they persist (which may be months or years).[20]

It follows that the risk of relapse on cessation of antipsychotics might be minimised by more gradual dose tapering because these neuroadaptations would then have time to resolve during the tapering process and the rate of decline of receptor antagonism is more modest.[20] Studies in which antipsychotics are tapered over months or years show reduced rates of relapse compared with relatively faster tapers,[23,29,30] with one study finding that reducing dose over a year reduced the hazard rate of relapse by 3.5-fold compared with reducing over days.[29]

Pattern of tapering

Positron emission tomography demonstrates a hyperbolic relationship between dose of antipsychotic and D_2 receptor occupancy.[31] This hyperbolic relationship applies to other receptor targets of antipsychotics as well (including histaminergic, cholinergic and serotonergic receptors) because it arises from the law of mass action (whereby each additional molecule of a drug has incrementally less effect as receptor targets become saturated).[32] The nature of this relationship is often obscured by the habit of plotting dose–response curves on semi-logarithmic axes.[32] A hyperbolic relationship between dose of antipsychotic and its therapeutic effects (as measured by symptoms scales) has also been shown,[33] suggesting that clinical response mirrors the neurobiological pattern of effects.

This brings into question the rationale for a linear reduction of antipsychotic dose – for example, a reduction from 20 to 15 to 10 to 5 to 0mg of olanzapine. Although this regimen appears logical, the hyperbolic relationship between dose and effect on D_2 blockade dictates that these linear dose decreases will produce increasingly larger reductions of D_2 blockade (and there may be clinical consequences of this; Figure 1.3a). Indeed, the reduction of dose from 5 to 0mg will produce a reduction in D_2 blockade (52.6%) that is larger than that produced by the reduction from 40 to 5mg of olanzapine (37.3%). These increasingly large reductions in D_2 blockade are more likely to provoke relapse.[34,35]

Linear or 'evenly spaced' reductions in D_2 blockade require hyperbolically reducing doses of antipsychotic (Figure 1.3b).[36] These hyperbolic reductions are approximated by sequential halving of dose: for example, olanzapine doses of 20mg, 10mg, 5mg, 2.5mg, 1.25mg, 0.6mg, 0.3mg, 0mg produce roughly 15 percentage point reductions in D_2 blockade. This pattern of reduction may be less likely to provoke relapse because it avoids large increases in dopaminergic signalling. Example regimens are shown in Table 1.27 and Box 1.1. Preliminary support for this approach comes from a study in which antipsychotics were reduced hyperbolically by on average 40% in people with chronic psychotic disorders, with no difference in relapse rates from the maintenance group but improved clinical outcomes.[30]

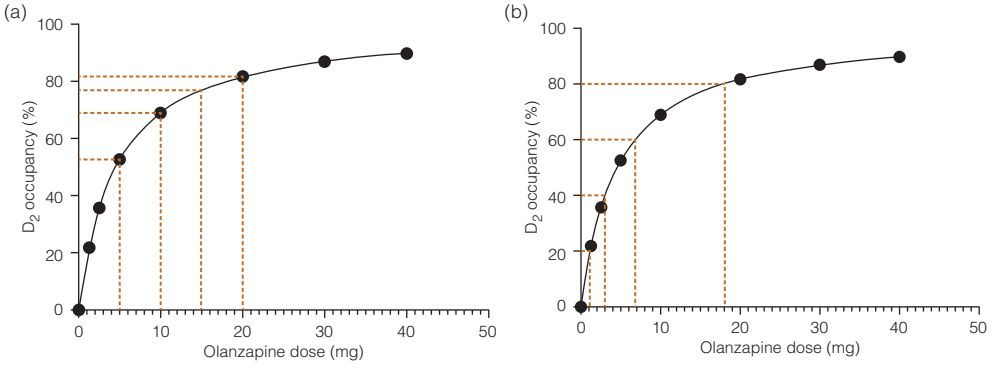

Figure 1.3 (a) Linear dose reductions of olanzapine cause increasingly large reductions in D_2 dopaminergic receptor blockade. The relationship between dose of olanzapine and D_2 blockade is derived from the line of best fit from meta-analysis of positron emission tomography studies.[31] (b) Linear reductions of D_2 dopaminergic occupancy (in this case 20% reductions) correspond to hyperbolically decreasing doses of olanzapine. The doses in this case correspond to 6.9mg (80% D_2 occupancy), 2.0mg (60% D_2 occupancy), 0.82 mg (40% D_2 occupancy) and 0.30mg (20% D_2 occupancy). Approximations to this regimen that correspond to available formulations are given in the text.

Table 1.27 Reductions of olanzapine dose by up to 5 percentage points of D_2 occupancy at each step, adjusted to allow use of quarter tablets. Liquid versions of drug will be needed for smaller doses.

Period	Olanzapine dose (mg)	D_2 occupancy (%)	Period	Olanzapine dose (mg)	D_2 occupancy (%)
1	**20**	72.9	11	**4.375**	37.5
2	**17.5**	70.9	12	**3.75**	34.0
3	**15**	66.9	13	**3.125**	30.4
4	**12.5**	62.8	14	**2.5**	26.3
5	**10**	58.8	15	**2**	22.3
6	**8.75**	54.7	16	**1.5**	17.3
7	**7.5**	50.7	17	**1.1**	13.1
8	**6.25**	46.6	18	**0.7**	9.1
9	**5.625**	43.5	19	**0.35**	4.0
10	**5**	40.5	20	**0**	0

Box 1.1 A summary of a slow hyperbolic reduction schedule for olanzapine

Reduce olanzapine by 5–10mg every 1–3 months until reaching 20mg per day, *then*
Reduce dose by 2.5–5mg every 1–3 months until reaching 10mg per day, *then*
Reduce dose by 1.25–2.5mg every 1–3 months until reaching 5mg per day, *then*
Reduce dose by 0.6–1.25mg every 1–3 months until reaching 2.5mg per day, *then*
Reduce dose by 0.3–0.6mg every 1–3 months until reaching 1.25mg per day, *then*
Reduce dose by 0.15–0.3mg every 1–3 months until reaching 0.6mg per day, *then*
Reduce dose by 0.07–0.15mg every 1–3 months until olanzapine is **completely stopped**.

This process could take 12–48 months, depending on how the patient tolerates the reductions. Liquid versions of drug or other options will be required for smaller doses.

Exponentially reducing regimens (reducing by a fixed proportion of the most recent dose, e.g. 10%) will produce roughly linear reductions at all receptor targets of antipsychotics, making it applicable to a wide range of antipsychotic medication.

Tapering in practice

All patients should be informed of the risk of withdrawal symptoms on stopping or reducing the dose of any antipsychotic, including insomnia and a potential increase in psychotic symptoms.

Patients should be warned not to stop antipsychotics abruptly or too quickly, because this is the method thought to be most likely to precipitate a relapse and severe withdrawal effects.

When to attempt discontinuation

Longstanding or lifelong antipsychotic treatment is something of a modern-day phenomenon. In the 1960s, discontinuation of antipsychotics was usually attempted after acute response. There are currently no evidence-based recommendations for antipsychotic withdrawal but we suggest that it only be considered in patients who have been in remission for 6 months (first episode) or 1 year (multi-episode). Relapse rates using fast linear tapers generally exceed 90% for both groups of patients. This might suggest that abrupt tapering always precipitates relapse or that relapse is inevitable when antipsychotics are withdrawn. Certainly, some people (probably the majority with a schizophrenia diagnosis) will relapse no matter how the antipsychotic is stopped.

A cautious approach to antipsychotic reduction is recommended, especially in long-term users, where a test reduction of 5–10% of dose might be a sensible starting point. In people who have been on medication for shorter periods (e.g. <1 year) a reduction as large as 25% might be feasible.

The patient should then be monitored for several weeks following this reduction for any withdrawal symptoms or worsening of psychotic symptoms. These symptoms may be transitory withdrawal effects rather than signs of inevitable relapse necessitating reinstatement of the regular dose of medication.[20] If a patient tolerates this reduction with no significant effect on their overall mental state (or perhaps only mild symptoms) then further reductions could be made at the same rate (for example, a reduction of 10–25% of the dose every 2–3 months). Patients may require increased psychosocial support during this period of withdrawal.

If a patient experiences significant withdrawal symptoms or worsening of psychotic symptoms then an increase in dose back one or two steps or back to the original dose may be necessary.[20] This does not preclude further attempts at reduction, but these attempts should be delayed until stability is established and should be performed more gradually than previously attempted (some long-term users can only tolerate <5% dose reductions per month).

Final doses before complete cessation may need to be very small to prevent a large decrease in D_2 blockade. This may need to be as small as 1/80th the original therapeutic dose (for example, 0.25mg of olanzapine) or smaller. Delivery of these small doses will require splitting tablets or using liquid formulations of the medications. Use of adjunctive medication to manage withdrawal symptoms may lead to accumulation of further medications and so pausing or slowing the taper is generally more advisable.[20] Every-other-day dosing of antipsychotics with half-lives of less than 24 hours leads to fluctuating plasma levels, which can precipitate withdrawal effects and so should generally be avoided.

Reducing depot medication may facilitate gradual tapering because of the longer half-lives of elimination. However, depots cannot be said to be 'self-tapering' for long-term users because the time taken for elimination may be shorter than the time required for many patients to adapt to lower blood levels of medication, and will require switching from the lowest depot dose to oral medication in order to continue a gradual taper.[37,38] Example reducing regimens are presented in Table 1.27 and Box 1.1.

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ANTIPSYCHOTIC ADVERSE EFFECTS

Extrapyramidal symptoms

The EPS associated with antipsychotic medication can be stigmatising, distressing, potentially disabling and act as a disincentive to taking medication.[1,2] EPS are commonly overlooked and underdiagnosed or misdiagnosed in clinical practice.[3,4] These movement disorders tend to be dose-related and are less likely to occur with SGAs, particularly clozapine, olanzapine, quetiapine and aripiprazole,[2,5] compared with FGAs such as haloperidol. Generally it is agreed that the greater use of SGAs has led to a reduction in the frequency of EPS,[6] although the prevalence of EPS of any description in community samples may exceed 30%.[7] The incidence of EPS is often steeply dose-related for most drugs (clozapine and quetiapine are possible exceptions) and this relationship extends beyond the licensed dose range for some drugs.[8]

Patients who experience one type of EPS may be more vulnerable to developing others.[9] Substance misuse increases the risk of dystonia, akathisia and TD,[10,11] and there is some evidence for an association between alcohol use and akathisia.[12,13] Vulnerability to EPS may be partly genetically determined.[14–16]

Establishing the prevalence of antipsychotic-induced EPS is problematic, given that similar movement disorders may be seen in never-medicated patients with schizophrenia.[17–19] In one study of such patients at first episode, 1% had dystonia, 8% parkinsonian symptoms and 11% akathisia.[19] Parkinsonian symptoms and other motor abnormalities in this context may be associated with cognitive impairment[19,20] and poor long-term psychosocial functioning.[21] In another study of never-treated patients with established psychotic illness, 9% exhibited spontaneous dyskinesias and 17% parkinsonian symptoms.[22] Table 1.28 details the most common EPSEs.

Table 1.28 Most common extrapyramidal side effects.

	Dystonia *(uncontrolled muscular spasm)*	**Pseudoparkinsonism *(bradykinesia, tremor, muscle rigidity, etc.)***	**Akathisia *(restlessness)*[23]**	**Tardive dyskinesia (TD) (abnormal involuntary movements)**

Signs and symptoms[24]	■ Muscle spasm in any part of the body, e.g.
	  ■ eyes rolling upwards (oculogyric spasm)
	  ■ head and neck twisted to the side (torticollis)
	■ The patient may be unable to swallow or speak clearly. In extreme cases, the back may arch or the jaw dislocate.
	■ Acute dystonia can be both painful and very frightening
		■ Tremor and/or rigidity
		■ Bradykinesia (decreased facial expression, flat monotone voice, slow body movements, inability to initiate movement)
		■ Bradyphrenia (slowed thinking)
		■ Salivation
		■ Pseudoparkinsonism can be mistaken for depression or negative symptoms of schizophrenia
			■ A subjectively unpleasant state of inner restlessness with a desire or compulsion to move[23,25]
			■ Foot stamping when seated
			■ Constantly crossing/uncrossing legs
			■ Rocking from foot to foot when standing
			■ Constantly pacing up and down
			■ Akathisia can be mistaken for psychotic agitation and has been linked with suicidal ideation[26] and aggression towards others[27]
				■ A wide variety of movements can occur,[28] such as:
				  ■ lip smacking or chewing
				  ■ tongue protrusion (‘fly catching’)
				  ■ choreiform hand movements (‘piano playing’)
				  ■ dystonic and choreoathetoid movements of the limbs
				■ Severe orofacial movements can lead to difficulty speaking, eating or breathing. Movements are worse when under stress.

Rating scales (see Martino et al. 2023)[29]	■ No specific scale ■ Small component of general EPS scales	■ Simpson–Angus EPS Rating Scale[30]	■ Barnes Akathisia Rating Scale[3,31]	■ Abnormal Involuntary Movement Scale[32,33]

Prevalence	■ Approximately 10%[34] but more common:[35]
	  ■ in young males
	  ■ in those who are antipsychotic-naïve
	  ■ with high-potency medications (e.g. haloperidol)
	■ Dystonic reactions are rare in the elderly
		■ Approximately 20%[36] but more common in:
		  ■ elderly females
		  ■ those with pre-existing neurological damage (head injury, stroke, etc.)
			■ Wide variation but approximately 25%[37] for acute akathisia with FGAs, lower with SGAs
			■ The relative liability of individual antipsychotic medications for akathisia is uncertain,[2] but there is consensus that the incidence is lowest for olanzapine, quetiapine and clozapine[38,39]
				■ 5% of patients per year of antipsychotic exposure.[40] More common in respect to:[41]
				  ■ age
				  ■ affective illness
				  ■ schizophrenia
				  ■ higher doses
				  ■ acute EPS early in treatment
				■ Lower incidence in those on SGAs.[42,43] TD may be associated with neurocognitive deficits.[44]

(*Continued*)

Table 1.28 (*Continued*)

	Dystonia ***(uncontrolled muscular spasm)***	**Pseudoparkinsonism** ***(bradykinesia, tremor, muscle rigidity, etc.)***	**Akathisia** ***(restlessness)***[23]	**Tardive dyskinesia (TD) (abnormal involuntary movements)**
Time taken to develop	■ Acute dystonia can occur within hours of starting antipsychotic medication (minutes if the IM or IV route is used) ■ TD occurs after months to years of antipsychotic treatment	■ Days to weeks after the start of antipsychotic medication or an increase in dose	■ Acute akathisia occurs within hours to weeks of starting antipsychotic medication or increasing the dose ■ 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.[23]	■ Months to years ■ The proportion of cases showing reversibility on cessation of antipsychotic medication is unclear and may partly depend on age[28]
Treatment	■ Anticholinergic drugs given orally, IM or IV depending on the severity of symptoms[35] ■ Remember the patient may be unable to swallow ■ Response to IV administration will be seen within 5 minutes ■ Response to IM administration takes around 20 minutes ■ TD may respond to ECT[45,46] ■ Where severe symptoms do not respond to simpler measures including switching to an antipsychotic with a low propensity for EPS, botulinum toxin may be effective[47,48]	■ Several options are available depending on the clinical circumstances: ■ Reduce the antipsychotic dose ■ Change to an antipsychotic medication with a lower propensity for pseudoparkinsonism (see section on relative liability of antipsychotic medications for adverse effects) ■ 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).	■ Reduce the antipsychotic dose ■ Change to an antipsychotic drug with lower propensity for akathisia (see sections on akathisia and relative liability of antipsychotic medications for adverse effects) ■ A reduction in symptoms may be seen with[25,49,50] low-dose propranolol, 30–80mg/day; clonazepam (low dose); $5HT_2$ antagonists such as cyproheptadine,[46] mirtazapine,[49] trazodone,[51,52] mianserin[53] and cyproheptadine[46] may help, as may possibly diphenhydramine[54] ■ Note that all of the above medications are unlicensed for this indication ■ Anticholinergics are generally unhelpful unless possibly if akathisia is part of a general EPS spectrum[55,56]	■ Stop anticholinergic if prescribed ■ Reduce dose of antipsychotic medication ■ Change to an antipsychotic with lower propensity for TD;[57–60] note that data are conflicting[61,62] ■ Clozapine is the antipsychotic most likely to be associated with resolution of symptoms.[63,64] Quetiapine may also be useful in this regard.[65] ■ Both valbenazine[66] and deutetrabenazine[67–69] have a positive risk–benefit balance as add-on treatments.[67,70] There is also some evidence for tetrabenazine and Ginkgo biloba[71] as add-on treatments. For other treatment options,[72,73] see the review by the American Academy of Neurology[74] and the section on treatment of TD in this chapter.

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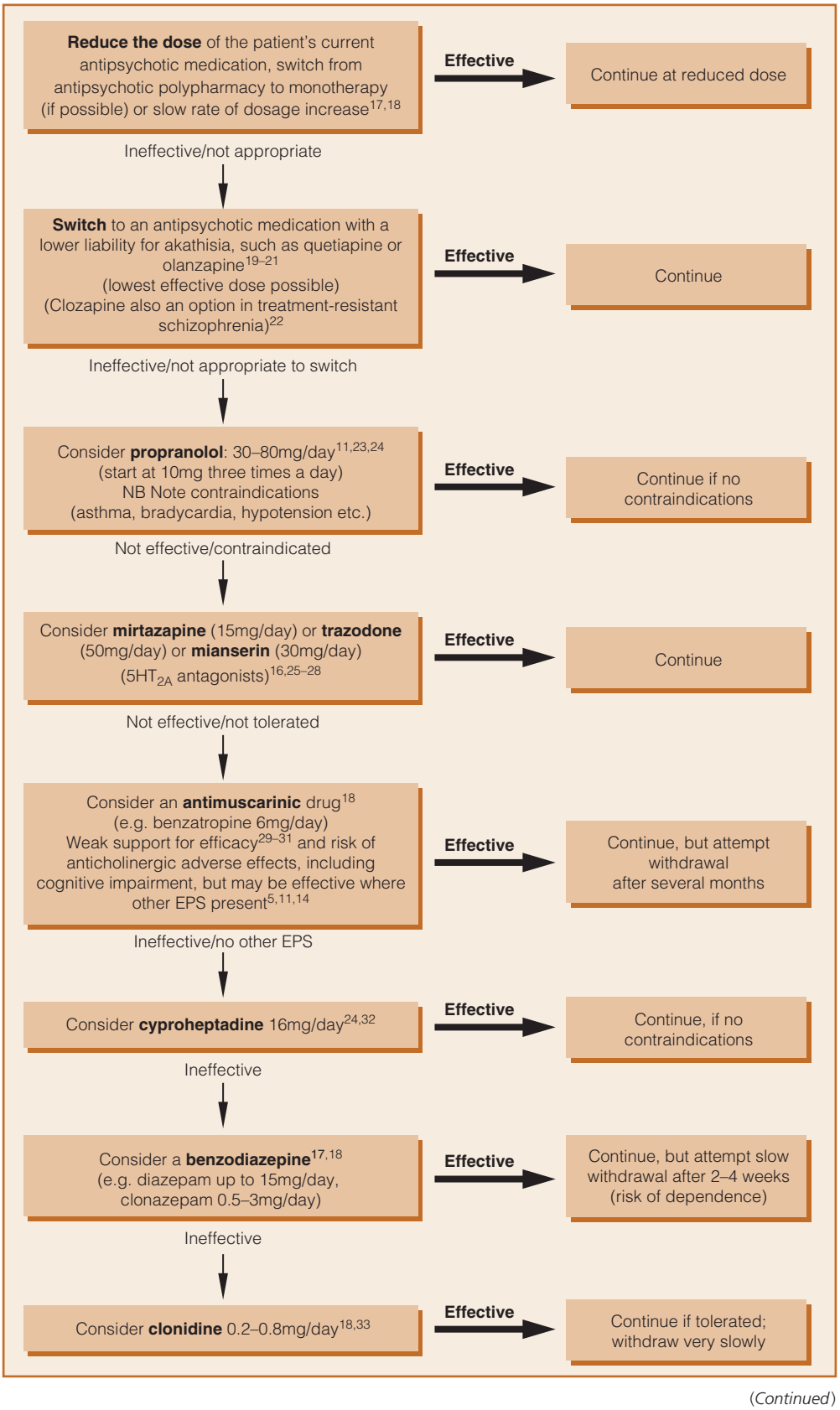
Akathisia

Akathisia is a fairly common adverse effect of most antipsychotic medications, although the risk of developing akathisia varies markedly between such medications.[1–3] For example, a 2023 dose–response meta-analysis[4] investigating antipsychotic-induced akathisia with haloperidol and 16 SGAs (not including clozapine) found that the risk was minimal with sertindole and quetiapine but high with haloperidol and lurasidone. The risk of akathisia tended to increase with dose, but the dose–response curves differed between medications, plateauing at a certain dose with some medications, such as amisulpride, haloperidol and risperidone, but increasing beyond the licensed dose range with others, such as lurasidone and lumateperone. This meta-analysis[4] also confirmed the risk of akathisia with partial agonist to be greatest with cariprazine and lowest with brexpiprazole.

The core feature of akathisia is mental unease and dysphoria characterised by a sense of restlessness.[5,6] There is commonly a compulsion to move and a characteristic pattern of 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.[5,6] There is a phenomenological overlap between antipsychotic-induced akathisia and the restless legs syndrome and possibly an overlap in pathophysiology.[7,8] The subjective experience of akathisia can be discomfiting and distressing; an association with suicidal ideation has been postulated[9,10] but remains uncertain.

There is some evidence to suggest that the risk of akathisia may be mitigated by avoiding high-dose antipsychotic medication, antipsychotic polypharmacy and a rapid increase in dosage.[5,11–13] There is limited evidence on the benefit–risk balance for pharmacological treatments of antipsychotic-induced akathisia, even those most commonly used, such as switching to an antipsychotic medication with a lower risk of akathisia or adding a beta-adrenergic blocker, 5-HT_{2A} antagonist or anticholinergic agent.[14,15] Nevertheless, a 2024 systematic review and meta-analysis of adjunctive treatments identified 15 eligible studies of 10 treatments.[16] Mirtazapine, biperiden and vitamin B6 emerged as the most efficacious, with vitamin B6 judged to have the most favourable efficacy and tolerability profile. Trazodone, mianserin and propranolol were considered effective alternative treatments, albeit with a slightly less favourable risk–benefit balance. However, given the lack of robust evidence of efficacy for such adjunctive treatments, particularly in the medium to long term, it is probably prudent to initially consider reduction of the antipsychotic dose or switching to an antipsychotic medication with a lower liability for the condition.

The following diagram suggests a programme of treatment options for persistent, antipsychotic-induced akathisia.


Reduce the dose of the patient's current antipsychotic medication, switch from antipsychotic polypharmacy to monotherapy (if possible) or slow rate of dosage increase[17,18]
Effective
Continue at reduced dose
Ineffective/not appropriate
Switch to an antipsychotic medication with a lower liability for akathisia, such as quetiapine or olanzapine[19–21] (lowest effective dose possible) (Clozapine also an option in treatment-resistant schizophrenia)[22]
Effective
Continue
Ineffective/not appropriate to switch
Consider **propranolol**: 30–80mg/day[11,23,24] (start at 10mg three times a day) NB Note contraindications (asthma, bradycardia, hypotension etc.)
Effective
Continue if no contraindications
Not effective/contraindicated
Consider **mirtazapine** (15mg/day) or **trazodone** (50mg/day) or **mianserin** (30mg/day) ($5HT_{2A}$ antagonists)[16,25–28]
Effective
Continue
Not effective/not tolerated
Consider an **antimuscarinic** drug[18] (e.g. benzatropine 6mg/day) Weak support for efficacy[29–31] and risk of anticholinergic adverse effects, including cognitive impairment, but may be effective where other EPS present[5,11,14]
Effective
Continue, but attempt withdrawal after several months
Ineffective/no other EPS
Consider **cyproheptadine** 16mg/day[24,32]
Effective
Continue, if no contraindications
Ineffective
Consider a **benzodiazepine**[17,18] (e.g. diazepam up to 15mg/day, clonazepam 0.5–3mg/day)
Effective
Continue, but attempt slow withdrawal after 2–4 weeks (risk of dependence)
Ineffective
Consider **clonidine** 0.2–0.8mg/day[18,33]
Effective
Continue if tolerated; withdraw very slowly

(*Continued*)

(*Continued*)

Notes

- Akathisia can be difficult to diagnose with certainty and is commonly overlooked or misdiagnosed in clinical practice. Clinical physical examination schedules for EPS and akathisia have been proposed.[34,35]
- Evaluate the efficacy of each treatment option over at least 1 month if possible. 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 add-on akathisia treatments before starting the next option in the algorithm.
- Combinations of treatments may be considered for refractory cases, if carefully monitored.
- Other possible treatments for acute akathisia that have been investigated include vitamin B6,[16,36,37] pregabalin,[38] diphenhydramine,[39] trazodone[25,40] and zolmitriptan.[41,42] Always read the primary literature before considering any of the treatment options.
- Parenteral midazolam (1.5mg) has been successfully used to prevent akathisia associated with IV metoclopramide,[43] suggesting a specific therapeutic effect for midazolam against akathisia and perhaps benzodiazepines more generally.
- In some cases where agitation/akathisia are recognised as short-lived effects of antipsychotic medication when initiated (e.g. with aripiprazole, cariprazine), prophylactic or rescue benzodiazepines may be prescribed for a limited period. Clinical experience suggests this practice can be effective.

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Treatment of tardive dyskinesia

Tardive dyskinesia is a somewhat less commonly encountered problem now than in previous decades,[1,2] probably because of the more widespread use of SGAs,[3–6] which generally have a lower risk for the condition than FGAs. Treatment of established TD is often unsuccessful, so prevention, early detection and early remedial action are essential.[7,8] There is evidence to suggest that TD is associated with greater cognitive impairment,[7,9] more severe psychopathology[10,11] and higher mortality.[12,13] While the majority of patients seem to be unaware of the involuntary movements, the condition can still impose a substantial burden on physical, psychological and social well-being.[14–16]

While SGAs are less likely to cause TD,[17–23] the condition still occurs with these medications. An extensive meta-analysis of relevant studies found the annualised incidence of TD across all FGA treatment groups was 6.5%, while the respective figure for SGA treatment groups was 2.6%.[24] However, there is a significant variation in liability between individual SGA medications.[24–28] The risk of developing TD may be related to the extent of D2 receptor occupancy (greater occupancy, higher risk) with a medication,[29] although data from the meta-analysis mentioned above did not support the notion that the lower risk of TD with SGAs is a consequence of the use of relatively high equivalent doses of FGAs.[24] There is a hint that dopamine partial agonists (or, at least, aripiprazole) may have the lowest liability for TD.[24] Whether the risk of TD differs between LAI FGA and LAI SGA preparations is unclear[30] but there is one report suggesting that the risk of TD with LAI SGAs is lower than with the equivalent oral SGA preparations.[31]

TD can occur even with low doses of haloperidol (and in the absence of prior acute movement disorder)[32] and with the use of other dopamine antagonists such as metoclopramide.[33] The characteristic abnormal involuntary movements of TD have also been observed in never-medicated patients with both first-episode[34,35] and established[36] schizophrenia. This suggests that the use of antipsychotic medication adds to an inherent risk of TD that is present in people with a diagnosis of schizophrenia.

Treatment – first steps

Most authorities recommend the withdrawal of any co-prescribed anticholinergic agents and a reduction in the dose of antipsychotic medication (which may initially worsen TD) as initial steps in those with early signs of TD,[37,38] although there is a lack of robust evidence to support such a strategy.[14,39–41] Nevertheless, it is common practice to withdraw the antipsychotic prescribed when TD is first observed and to substitute it with an antipsychotic medication that is perceived to have a lower liability for the condition. However, the evidence for a beneficial effect on TD when switching to any particular SGA is limited.[42] Changing to clozapine[37,43] is probably best supported,[37,43–45] but quetiapine, another weak striatal dopamine antagonist, may also be effective.[46–52] Olanzapine[39–42,53,54] and aripiprazole[55] are also potential options.

Treatment – additional agents

Given that there is insufficient evidence to recommend dose reduction as a treatment for TD, and that switching or withdrawing antipsychotic medication is not always effective or advisable, add-on agents are often considered. Evidence-based, pharmacological treatment algorithms for TD have been published.[41,56] A 2020 meta-analysis[57] concluded that vesicular monoamine transporter 2 (VMAT-2) inhibitors (such as deutetrabenazine and valbenazine), vitamin E, amantadine and vitamin B6 (pyridoxine) are probably effective treatments. VMAT-2 inhibitors are considered agents of first choice, given the body of evidence supporting their use[58–60] and their additional antipsychotic action.[61] Table 1.29 describes the most frequently prescribed add-on medications for TD.

Table 1.29 First-choice agents prescribed for tardive dyskinesia (alphabetical order; no preference implied).

Drug	Comments
Amantadine[56,57,62–64]	Rarely used and evidence for efficacy is limited. Dose is 100–300mg/day.
Benzodiazepines[37,38]	Widely used for TD, but a Cochrane review considered that the limited evidence for efficacy was inconclusive.[65] Intermittent use may be necessary to avoid tolerance to effects. Most commonly used are clonazepam 1–4mg/day and diazepam 6–25mg/day, with better supporting evidence for clonazepam.[42,66]
Deutetrabenazine[8,56,58,60,67,68]	Deutetrabenazine (a VMAT-2 inhibitor) is effective as a treatment for TD. Licensed for TD in the USA.[69] Better supporting evidence than for tetrabenazine. Longer half-life than tetrabenazine but still needs to be taken twice a day (a once daily slow-release tablet is in development).[70] Low incidence of psychiatric and neurological effects. Dose is 12–48mg/day.
Ginkgo biloba[56,71,72]	Well tolerated. A Cochrane review concluded that while Ginkgo biloba could reduce TD symptoms, the available evidence did not justify its routine use as a treatment.[73] A meta-analysis of three Chinese RCTs showed a good effect with 240mg/day.[74]
Pyridoxine[75]	Supported by a Cochrane review[76] and a 2020 meta-analysis.[57] Dose is up to 400mg/day.
Tetrabenazine[77,78]	The only licensed treatment for moderate to severe TD in UK. Depression, drowsiness, parkinsonism and akathisia may occur.[66,79] Dose is 25–200mg/day. Reserpine (similar mode of action) also effective but rarely, if ever, used.
Valbenazine[8,59,67,73,80]	Evidence supports a favourable benefit–risk ratio for valbenazine (VMAT-2 inhibitor) as a treatment for TD. Licensed for TD in the USA.[81] A dose of 80mg once daily is effective. It has a benign cardiovascular profile and a low incidence of depression and akathisia.
Vitamin E[57,82]	Numerous studies but efficacy remains to be conclusively established. A Cochrane review suggested that there is evidence only for slowing the deterioration of TD,[8,83] but a 2022 meta-analysis also suggested a treatment effect.[84] Dose is in the range 400–1600 IU/day.

Treatment – other possible options

The large number of proposed treatments for TD undoubtedly reflects the somewhat limited effectiveness of standard remedies, at least before the introduction of valbenazine and deutetrabenazine.[14] Table 1.30 lists some of these putative treatments, most of which have a low level of evidence.[8,62]

Table 1.30 Other options for the treatment of tardive dyskinesia (in alphabetical order).

Drug	Comments
Amino acids[85]	Use is supported by a small randomised, placebo-controlled trial. Low risk of toxicity.
Botulinum toxin[86–89]	Case reports of success for localised dyskinesia. Probably now treatment of choice for disabling or distressing focal symptoms.
Calcium antagonists[90]	A few published studies but not widely used. A Cochrane review is dismissive.[91] A 2020 meta-analysis found no effect.[57]
DBS[8,92,93]	Reports refer most commonly to stimulation of the globus pallidus internus. The evidence is limited but DBS may potentially have a role when TD symptoms are severe and distressing and unresponsive to pharmacological treatment.
Donepezil[94–96]	Supported by a single open study and a case series. One very small, negative RCT. Dose is 10mg/day. No clear evidence of efficacy for rivastigmine or galantamine.[97]
Fish oils[98,99]	Very limited support for use of EPA at dose of 2g/day
Fluvoxamine[100]	Three case reports. Dose is 100mg/day. Beware interactions.
Gabapentin[101]	Adds weight to the theory that GABAergic mechanisms improve TD. Dose is 900–1200mg/day. Inconclusive data on other GABA agonists.[102]
Levetiracetam[103–106]	Three published case studies. One RCT. Dose up to 3000mg/day.
Melatonin[107]	Use is supported by a meta-analysis of four trials.[108] Usually well tolerated. Dose is 10mg/day. Some evidence that melatonin receptor genotype determines risk of TD.[109]
Naltrexone[110]	May be effective when added to benzodiazepines. Well tolerated. Dose is 200mg/day.
Ondansetron[111,112]	Limited evidence but low toxicity. Dose is up to 12mg/day.
Propranolol[113–115]	Formerly a relatively widely used treatment. Open-label studies only but a prospective randomised trial is probably warranted. Dose is 40–120mg/day. Beware contraindications, such as asthma, bradycardia and hypotension.
Quercetin[116]	Plant compound which is thought to be an antioxidant. Some promising case reports.[116–118]
Sodium oxybate[119]	One case report. Dose was 8g/day.
rTMS[120,121]	RCT data on patients with 'tardive syndromes' suggest that bilateral hemispheric high-frequency rTMS has the potential to be a feasible treatment where TD is unresponsive to 'first-line' pharmacological treatment[120]
Zolpidem[122]	Three case reports. Dose is 10–30mg a day.

DBS, deep brain stimulation; EPA, eicosapentaenoic acid; GABA, gamma-aminobutyric acid; rTMS, repetitive transcranial magnetic stimulation.

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Antipsychotic-induced weight gain

Weight gain is a common adverse effect of antipsychotic medication.[1] This may reflect interference with the homeostatic control of appetite and metabolism, leading to increased food intake and reduced energy expenditure, although the various mechanisms involved are not well understood.[2–4] Factors such as $5HT_{2C}$ antagonism, H_1 antagonism, D_2 antagonism and increased serum leptin (leading to leptin desensitisation)[5–7] are commonly implicated, as well as, possibly, effects on gut microbiota.[8–11]

The risk of weight gain appears to be related to clinical response[12,13] (although the association may be too small to be clinically important)[14] and may have a genetic basis.[15] Weight gain may be more pronounced in antipsychotic-naïve patients and during the early stages of the treatment of psychotic illness[16–18] and women may be at greater risk than men.[19,20]

Almost all available antipsychotic medications have been associated with weight gain,[16] although the mean gain in body weight varies substantially between the medications. There is also marked inter-individual variation among those treated, with some losing weight, some gaining no weight and some gaining a great deal of weight. Thus, knowledge of the mean increase in weight reported for a particular medication may not be a helpful predictor of how much weight an individual might gain. Assessment of the relative liability for weight gain of different antipsychotic medications is based largely on short-term studies. Notwithstanding these limitations, the results of indirect and direct meta-analyses suggest that these medications can be clustered into three groups based on their relative risk of weight gain (Table 1.31).[21,22]

Table 1.31 Risk/extent of antipsychotic-induced weight gain (drugs in alphabetical order).[23–26]

Risk/extent of weight gain	Drug
High	Clozapine
	Olanzapine
Moderate	Chlorpromazine
	FGAs*
	Iloperidone
	Haloperidol
	Quetiapine
	Paliperidone
	Risperidone
	Sertindole

(*Continued*)

Table 1.31 (*Continued*)

Risk/extent of weight gain	Drug
Low	Amisulpride
	Aripiprazole
	Asenapine
	Brexpiprazole
	Cariprazine
	Lumateperone
	Lurasidone
	Sulpiride
	Trifluoperazine
	Ziprasidone

* Data on individual FGAs other than chlorpromazine and haloperidol are scarce but one comprehensive analysis showed that FGAs (not including haloperidol) had a moderate risk of weight gain: 20–30% of people gained more than 7% of original body weight in the medium term.[16] Individual FGAs are likely to vary in their propensity for weight gain. Traditionally low-potency FGAs (e.g. chlorpromazine) were considered to have a higher risk of weight gain.

Time course

Antipsychotic-induced weight gain occurs primarily in the first few months of treatment but continues for many months or even years afterwards. In a 10-year study of patients with first-episode schizophrenia, the mean weight gain was 15kg. Most of this (9kg) was gained in the first year.[27] In those gaining the most weight, increase in weight continues at the same rate for at least 2 years.[28]

Dose–response

The relationship between dose and weight gain is complex and varies from one antipsychotic medication to another.[22,29] Two broad patterns have emerged: an increase in weight gained over a lower dose range, which then reaches a plateau (e.g. risperidone, haloperidol and quetiapine), and an increasing risk of weight gain up to and beyond the maximum dose (e.g. clozapine and olanzapine). Both patterns suggest that dose reduction might reverse or mitigate weight gain and there is some evidence that this is possible.[30] However, the dose–response relationships identified indicate that the risk of weight gain emerges at doses that are subtherapeutic for psychosis, meaning that there is no effective dose that does not carry a risk of weight gain.

See following section for advice on the treatment of antipsychotic-induced weight gain.

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Treatment of antipsychotic-induced weight gain

Weight gain is an important adverse effect of nearly all antipsychotic medications.[1,2] Women may be at greater risk than men.[3] An increase in body weight has obvious consequences for self-image, morbidity and mortality, so prevention and treatment are matters of some clinical urgency.

Monitoring

Patients starting antipsychotic treatment or changing medication should, as an absolute minimum, have their body weight recorded in their clinical records. Ideally, BMI and waist circumference should also be recorded.[4,5] Early in treatment, monitoring of body weight every week or two is recommended, for at least the first 6 months.[5,6] Rapid weight gain in early treatment (e.g. an increase of ≥5% above baseline after a month of treatment) strongly predicts long-term weight gain and should prompt consideration of preventative or remedial measures.[7–10] With continuing antipsychotic treatment, annual measurement of body weight is recommended as a minimum.[5,6,11]

In clinical practice, the monitoring of body weight and other metabolic adverse effects in people on continuing antipsychotic medication is inconsistent and limited, falling short of recommended best practice.[12–16]

Treatment and prevention

Most of the relevant literature in this area addresses attempts to reduce body weight gained during treatment with medication, although there are useful data suggesting that early interventions can prevent or mitigate weight gain.[17,18]

When weight gain occurs, initial options involve switching a patient's antipsychotic medication or instituting behavioural programmes (or both). Switching always presents a risk of relapse and treatment discontinuation,[19] but there is fairly strong support for switching to aripiprazole,[20] ziprasidone[21] or lurasidone as a method for reversing weight gain.[20,22,23] Another option is adjunctive aripiprazole:[5] weight loss has been observed when aripiprazole has been added to antipsychotic medications such as clozapine and olanzapine.[18,24]

Stopping antipsychotic treatment altogether can be associated with weight loss[25,26] but this course of action would not be clinically appropriate for the vast 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.[27] Additional lifestyle interventions are often required if BMI is to remain within or move towards the normal range.

A variety of lifestyle interventions have been proposed and evaluated with generally good results.[5,17,28–31] Interventions do vary, but they are mainly 'behavioural lifestyle programmes' aimed at improving diet and increasing physical activity. Meta-analyses of RCTs have generally found a positive effect for both prevention and intervention with these non-pharmacological interventions.[17,29,32,33]

Pharmacological methods should be considered only where behavioural treatment strategies or switching to a medication with a lower liability for weight gain have failed

or where obesity presents a clear, immediate physical risk to the patient. Some drug treatment options for antipsychotic-induced weight gain are listed in Table 1.32.

Metformin is now probably considered to be the drug of choice for the prevention and treatment of antipsychotic-induced weight gain, although glucagon-like peptide-1 (GLP-1) agonists may ultimately prove to be more effective and better tolerated.[34] Bariatric surgery may have a role in a few rare, severe cases where all else has failed.[35] However, the efficacy of bariatric surgery for drug-induced weight gain is not known.[5]

Table 1.32 Drug treatment of antipsychotic-induced weight gain (alphabetical order).

Drug	Comments
Alpha-lipoic acid[36–38] (1200mg/day)	Supplementation may lead to a small, short-term, weight loss. Limited data for antipsychotic-induced weight gain. Not recommended.
Amantadine[39,40] (100–300mg/day)	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 recommend.[5]
Aripiprazole augmentation[18,31,41] (5–15mg/day)	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 antipsychotic medications.
Betahistine[42,43] (48mg/day)	May attenuate olanzapine-induced weight gain. Limited data. Not recommended.
Bupropion[44,45] (formerly amfebutamone)	Seems to be effective in obesity when combined with calorie-restricted diets. Appears to not exacerbate psychosis symptoms, at least when used for smoking cessation.[46] One small (positive) RCT in antipsychotic-related weight gain.[47]
Bupropion + naltrexone (Contrave/Mysimba)[48]	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.
Fluvoxamine[49–51] (50mg/day)	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.
Liraglutide[52–54] (3mg/day via SC injection)	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 (3mg/day) is higher than the dose used for diabetes (≤1.8mg). Limited data in drug-induced weight gain. One RCT shows significant weight loss in overweight pre-diabetic patients stable on olanzapine or clozapine.[52] Beneficial effects on other metabolic parameters. Well tolerated but can cause GI disturbances. Recommended option in pre-diabetic/diabetic patients and clozapine-induced weight gain. Other GLP-1 agonists are currently only approved for diabetes and have a more limited dose range. Exenatide LA (a once-weekly GLP-1 agonist) may be effective for weight loss in clozapine-treated patients[55] but perhaps not with other antipsychotics.[56]

(*Continued*)

Table 1.32 (*Continued*)

Drug	Comments
Melatonin[57–59] (up to 5mg at night)	One small RCT showing attenuation of olanzapine-induced weight gain. Other studies show negative results. Effect, if any, is small.
Metformin[5,31,60–62] (500–2000mg/day)	There is a substantial database (in non-diabetic patients) supporting the use of metformin in both reducing and reversing weight gain caused by antipsychotic medications (mainly olanzapine). A Cochrane review in 2022 concluded that there was 'low-certainty evidence to suggest that metformin may be effective in preventing weight gain' in people with schizophrenia.[62] There may also be beneficial effects on other metabolic parameters. A later cohort study[63] showed that metformin prevented weight gain with clozapine. One positive RCT[64] and extension study[65] in children and adolescents with autism spectrum disorder. May be ideal for those with weight gain and diabetes or polycystic ovary syndrome. Note that metformin treatment increases the risk of vitamin B12 deficiency.[66]
Modafinil[67,68] (up to 300mg/day)	Limited positive data and one negative RCT for clozapine-induced weight gain. Not recommended.
Naltrexone[69,70] (25–50mg/day)	Some positive results but evidence is limited to two small pilot RCTs. Not recommended.
Orlistat[71–76] (120mg shortly before or after each meal). Official maximum is three times daily.	Reliable effect in obesity, especially when combined with calorie restriction. Few published data in medication-induced weight gain but widely used in practice with some success. In trials for clozapine or olanzapine-induced weight gain effect was only seen in men.[75,76] When used without calorie restriction in psychiatric patients, the effects are very limited. Failure to adhere to a low-fat diet will result in fatty diarrhoea and possible malabsorption of orally administered medication. Overall, a good choice for clozapine-induced weight gain where it reduces both weight and the incidence of constipation.[77]
Reboxetine[18] (4–8mg/day)	Attenuates olanzapine-induced weight gain. Reverses some metabolic changes.[78] Effective when combined with betahistine.
Samidorphan (μ–opioid receptor antagonist)[79–85]	There is good evidence from RCTs that the combination of samidorphan and olanzapine can mitigate olanzapine-associated weight gain. But these findings need to be confirmed 'through further high-quality research'.[83] The combination was approved by the US FDA in 2021 for indications including the treatment of schizophrenia and bipolar I disorder.
Semaglutide (weekly injectable, glucagon–like peptide-1RA)[86,87]	A small case series suggested that semaglutide, up to 2mg/week, might reduce antipsychotic-associated weight gain that had not responded to metformin.
Topiramate[31,58,88,89] (up to 300mg/day)	Reliably reduces weight even when medication induced. Meta-analyses of RCTs suggest a greater effect for prevention rather than treatment. Problems may arise because of topiramate's propensity for causing sedation, confusion and cognitive impairment. May have antipsychotic properties.
Zonisamide[90] (100–600mg/day)	Antiepileptic drug with weight-reducing properties. An RCT of 150mg/day showed significant weight reduction in people receiving SGAs. Another RCT (up to 600mg/day) shows attenuated olanzapine-induced weight gain. Sedation, diarrhoea and cognitive impairment are the most common problems. Not recommended.

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Neuroleptic malignant syndrome

NMS occurs as a rare but potentially serious or even fatal adverse effect of antipsychotics and other dopamine antagonists (Table 1.33).[1,2] It is an acute disorder of thermoregulation and neuromotor control, characterised by muscular rigidity, hyperthermia, altered consciousness and autonomic dysfunction, although there is considerable heterogeneity in the clinical presentation.[1,3–5] In many cases, the presentation is atypical, lacking key signs and symptoms such as hyperthermia and muscle rigidity.[6–8] Asymptomatic rises in plasma creatine kinase (CK) seem to be fairly common and so CK cannot be used as a diagnostic marker of NMS.[9]

Table 1.33 Neuroleptic malignant syndrome.

Signs and symptoms[10–13] (presentation varies considerably)[14]	Fever, diaphoresis, muscle rigidity, confusion, fluctuating level of consciousness, labile or high BP, tachycardia
	Elevated CK, often >1000 units/L,[2,15] leukocytosis, altered LFTs
Risk factors[12,13,16–21]	High-potency FGAs, recent or rapid dose increase, rapid dose reduction, abrupt withdrawal of anticholinergic agents, antipsychotic polypharmacy
	Psychosis, organic brain disease, alcoholism, Parkinson's disease, hyperthyroidism, psychomotor agitation, cognitive impairment
	Male gender, younger age
	Agitation, dehydration
Treatments[10,12,22–25] (note that guideline recommendations for NMS vary widely and are based on limited evidence)[26]	**In the psychiatric unit:** withdraw antipsychotic medication, monitor temperature, pulse, BP. Consider benzodiazepines if not already prescribed – IM lorazepam has been used.[27]
	In the medical/emergency unit: rehydration, bromocriptine + dantrolene, sedation with benzodiazepines, artificial ventilation if required
	L-dopa, apomorphine and carbamazepine have also been used, among many other drugs. ECT may be effective for NMS, even after pharmacotherapy has failed.[28–30]
Restarting antipsychotics[12,22,31,32]	Antipsychotic treatment will be required in most instances and rechallenge is associated with acceptable risk
	Stop antipsychotic medication for at least 5 days, preferably longer. Allow time for symptoms and signs of NMS to resolve completely
	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.[13,33] Close monitoring of physical and biochemical parameters is effective in reducing progression to 'full-blown' NMS.[34,35]
	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[36] but it has a long plasma half-life and has been linked to an increased risk of NMS.[17]
	Avoid depot/LAI antipsychotic preparations (of any kind) and high-potency FGAs

CK, creatine kinase; FGA, first-generation antipsychotic.

Risk factors for developing NMS include being male, dehydration, exhaustion and confusion/agitation.[4,37] Although NMS has commonly been reported to occur at standard doses of antipsychotics, there is some evidence that higher dosage or combined antipsychotic medications may also be risk factors.[2] Young adult males seem to be particularly at risk, while the condition is more likely to be lethal in older people.[4,16,38,39] Other predictors of mortality with NMS are the presence of respiratory difficulties, the severity of hyperthermia, and failing to stop antipsychotic medication.[39]

The incidence and mortality rate of NMS are difficult to establish and probably vary as medication regimens change and recognition of NMS waxes and wanes. The incidence of NMS has been estimated at 0.02–0.03%, with a mortality rate of 5.6%.[25] However, data from a drug safety programme from 1993 to 2015 yielded an overall incidence of 0.16%,[10] while a similar study, covering the period 2004 to 2017, reported an incidence of 0.11%.[40] High-potency FGAs seem to be associated with the greatest incidence, while SGAs and low-potency FGAs seem to have a lower incidence.[3,10,17]

Most available antipsychotic medications have been reported to be associated with NMS,[41–45] including more recently introduced SGAs such as lurasidone,[46] ziprasidone,[47,48] iloperidone,[49] aripiprazole,[6,50,52] paliperidone[53] (including paliperidone palmitate),[54] asenapine[55] and risperidone injection.[56] Mortality is probably lower with SGAs than with FGAs,[3,57–59] although the clinical picture is essentially similar[58] except that rigidity and fever may be less common.[3,58] In 2020, NMS had yet to be associated with pimavanserin, cariprazine, brexpiprazole or lumateperone,[60] and we could find no reports of NMS being linked to these drugs in mid-2024.

NMS is also sometimes seen with other medications, such as antidepressants,[61–64] valproate,[65,66] phenytoin[31] and lithium.[67,68] The co-prescription of SSRIs[69] or cholinesterase inhibitors[70,71] with antipsychotic medication may increase the risk of NMS. NMS-type syndromes induced by combinations of SGA and SSRI medications may share their symptoms and pathogenesis with the serotonin syndrome.[72,73] Benzodiazepines are a recommended treatment for NMS,[26] but an association between their use and NMS has been reported, possibly confounded by diagnosis or explained by the occurrence of NMS-like symptoms during benzodiazepine withdrawal.[17,18,74] NMS is also occasionally seen in people given non-psychotropic dopamine antagonists such as metoclopramide[75] and prochlorperazine.[76,77]

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Catatonia

Catatonia is a neuropsychiatric disorder that presents with a wide range of signs and symptoms, covering focal and generalised motor activity, speech, affect, complex behaviour and autonomic function.[1] A comprehensive meta-analysis of international data from 74 studies, conducted between 1935 and 2017 and involving 107,304 individuals, found an overall pooled, mean prevalence of catatonia of just over 9% in patients diagnosed with a range of psychiatric and medical conditions.[2]

Three main catatonia subtypes are recognised: a **retarded** or **stuporous** form with decreased psychomotor behaviour; an **excited** form, characterised by agitation, combativeness, impulsivity and apparently purposeless overactivity; and **malignant catatonia**, a life-threatening state that presents as catatonia with clinically significant autonomic abnormalities, including raised blood pressure and body temperature, and change in heart rate and respiratory rate.[1,3–5]

The retarded form tends to present as stupor – the key features include mutism, rigidity, marked psychomotor retardation, negativism, posturing, waxy flexibility and catalepsy. While historically associated with schizophrenia, stupor is also seen in other psychiatric conditions such as depression and, less commonly, mania,[6–11] alcohol[12] or benzodiazepine withdrawal,[13] and conversion disorder.[6,7,14–20] If psychiatric stupor is left untreated, physical health complications are unavoidable and develop rapidly. Prompt treatment is crucial to prevent serious complications such as dehydration, venous thrombosis, pulmonary embolism, pneumonia and, ultimately, death.[21]

A catatonic syndrome is most commonly associated with psychiatric conditions such as bipolar disorder, schizophrenia and major depressive disorder,[1,2] but may also be seen in patients with postpartum psychosis,[22–24] post-traumatic stress disorder,[25,26] developmental disorders such as autism spectrum disorder, neurodegenerative conditions,[27,28] and a range of underlying medical conditions, including:

- subarachnoid haemorrhages
- basal ganglia disorders
- non-convulsive status epilepticus
- locked-in and akinetic mutism states
- endocrine and metabolic disorders (e.g. Wilson's)[29]
- Prader–Willi syndrome
- antiphospholipid syndrome[30]
- autoimmune encephalitis, such as anti-NMDAR encephalitis[1,31–33]
- systemic lupus erythematosus[34,35]
- infections (especially CNS infections)
- dementia
- drug withdrawal and toxic drug states (e.g. after abrupt withdrawal of clozapine and withdrawal of zolpidem, benzodiazepines[36] and many non-psychotropic medications, including medicines used in oncology).

Treatment

The treatment of stupor in the context of catatonia is somewhat dependent on its cause but should usually include benzodiazepines. Benzodiazepine monotherapy is the treatment of choice for stupor occurring in the context of affective and conversion

disorders.[8,9,37] It is postulated that benzodiazepines may act by increasing gamma-aminobutyric acid (GABA)ergic transmission or reducing levels of brain-derived neurotropic factor.[38]

There is most clinical experience with lorazepam.[32,39] Many patients will respond to standard doses (up to 4mg/day) but repeated and higher doses (between 8 and 24mg per day) may be needed.[40] One small, observational study of patients with catatonic stupor in the context of a mood disorder[8] (either major depressive disorder or bipolar I disorder) used a lorazepam–diazepam treatment protocol and reported a response in 10 of the 12 patients with intramuscular lorazepam 2–4mg. In another study, which followed a very similar protocol, relief of symptoms was achieved in 18 of 21 patients with catatonia caused by general medical conditions or substance misuse.[41] Where benzodiazepines are effective, onset effect is rapid. A test dose of zolpidem (10mg) may predict response to benzodiazepines[42] and frequent dosing of zolpidem may provide effective treatment.[43,44] IV lorazepam has also been used to predict response.[45]

Catatonia in schizophrenia may be somewhat less likely to respond to benzodiazepines alone, with a response in 40–50%[46] of cases. A double-blind, placebo-controlled, crossover trial with lorazepam up to 6mg/day demonstrated no effect on chronic catatonic symptoms in patients with established schizophrenia,[47] similar to the poor effect of lorazepam seen in a non-randomised trial.[48] A Cochrane review[49] searched for RCTs in which people with schizophrenia or other similar severe mental illness had received benzodiazepines or another relevant treatment for catatonia. Only one study was eligible, which involved 17 participants treated with lorazepam or oxazepam; there was no clear difference in effect. The authors noted that no data were available for benzodiazepines compared with either placebo or standard care.

A further complication in schizophrenia is that of differential diagnosis, which includes EPSEs and the NMS. Debate continues regarding the similarities and differences between catatonic stupor in psychosis and NMS.[50–53] Malignant catatonia[5] may not be distinguishable from NMS, either clinically or by laboratory testing, which has prompted the view that NMS may be a variant form of malignant catatonia.[54] However, NMS can probably be ruled out in the absence of any prior or recent administration of a dopamine antagonist.

The vast majority of evidence published recently and over previous decades suggests that prompt ECT remains the most successful treatment for catatonia.[39,45,48,55–71] ECT-responsive catatonia has been recognised in the context of NMS, delirious mania, autism spectrum disorder and limbic encephalitis.[53,72] While it has been suggested that response to ECT may be lower in patients with schizophrenia (or in those who have been treated with antipsychotic medication) than in patients with mood disorders,[73] ECT is still considered the treatment of choice for catatonic schizophrenia that has failed to respond to an adequate trial of benzodiazepines.[1,74] In malignant catatonia, every effort should be made to maximise the effect of ECT by using liberal stimulus dosing to induce well-generalised seizures.[75] Physical health needs should be prioritised, with inpatient medical care being provided, when necessary, especially for those showing autonomic instability and those for whom dietary intake cannot be managed in psychiatric care. A 2024 systematic review[76] of studies of 'non-invasive brain stimulation' techniques for catatonia reinforced ECT as an effective treatment and suggested that it may be considered as first-line therapy in certain cases, but also identified rTMS and

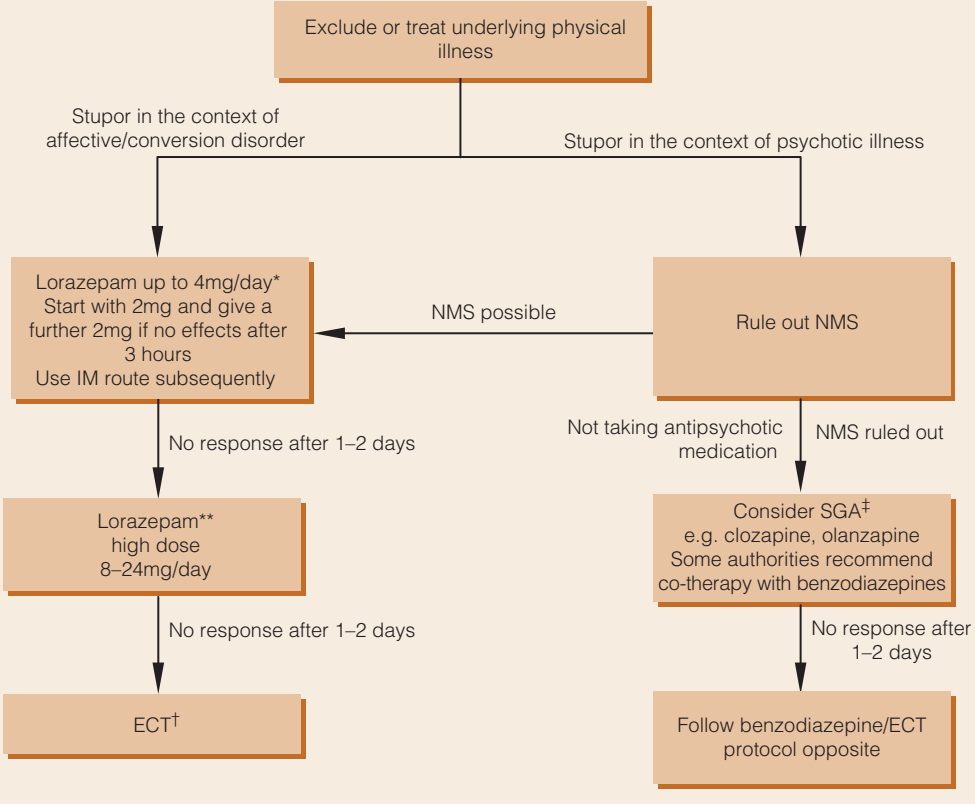
tDCS as promising treatments, although high-quality RCTs are required to establish efficacy.[76,77]

The use of antipsychotic medication should be carefully considered. Some authors recommend that such treatment should be avoided altogether in patients with catatonia, although there are reports of successful treatment of catatonia with clozapine,[78] as well as other SGAs, such as olanzapine, aripiprazole, risperidone and ziprasidone[1,79–85] (particularly in cases of catatonic schizophrenia).[86] There are also case reports of combination treatment with antipsychotic and benzodiazepine medication proving effective when each has failed individually.[87,88]

When considering the use of antipsychotic medication, account should be taken of the patient's history, their psychiatric diagnosis and previous response to antipsychotic treatment. If stupor develops in a patient on antipsychotic medication, any treatment with antipsychotic medication should be avoided if there are any signs or symptoms of NMS. 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, with consideration of adjunctive benzodiazepines. This may be particularly relevant when catatonic symptoms have occurred following discontinuation of clozapine.[36,89] Catatonia has also been reported after withdrawal of long-term benzodiazepine treatment.[36]

When physical health conditions, as in the examples listed earlier this section, are associated with a catatonia-like clinical picture, treatment of the underlying medical condition (e.g. lupus)[90] is warranted.

A treatment algorithm for catatonic stupor[91] is provided in Figure 1.4. The 2023 British Association for Psychopharmacology consensus guideline for the management of catatonia[1] includes a more detailed referenced algorithm for the management of the condition. Medications other than benzodiazepines reported as treatments for catatonia/stupor are listed in Table 1.34.



*Lorazepam is absorbed sublingually and is tasteless. This route may be preferred in non-cooperative patients or those who cannot swallow.
**Intravenous diazepam or lorazepam may be considered here.
†Do not wait to give ECT if there is significant danger to life.
‡There is considerable uncertainty about the use of antipsychotic medication for catatonic stupor. Antipsychotics can induce catatonia[92] and risk of NMS in catatonic schizophrenia is much higher than with non-catatonic schizophrenia.[93] An alternative approach is to use antipsychotic medication either once catatonia has resolved or when benzodiazepines or ECT have failed and there is clear evidence of a psychotic illness.[91]

Figure 1.4 Algorithm for treating catatonic stupor.[91]

Table 1.34 Medications other than benzodiazepines reported as treatments for catatonia/stupor (listed in alphabetical order – no ranking or judgement is implied by the order).

Antipsychotic medications[1,78–84,94–97]	aripiprazole clozapine olanzapine risperidone ziprasidone
Experimental treatments*[9,10,43,44,64,98–103]	amantadine amitriptyline carbamazepine fluoxetine fluvoxamine lithium memantine methylphenidate mirtazapine tramadol valproate zolpidem

* Always read the primary literature before using any of the medications listed in this section.

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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 TdP, which is sometimes fatal.[1]

Case–control studies have suggested that the use of most antipsychotics is associated with an increase in the rate of sudden cardiac death.[2–8] This risk is probably a result of the arrhythmogenic potential of antipsychotics,[9,10] although schizophrenia itself may be associated with QT prolongation,[11] QT interval is longer in patients with schizophrenia than in controls (e.g. 418ms vs 393ms in one study)[12] and in one study prolonged QTc was identified in 7.6% of psychiatric in-patients who had an ECG.[13] A more recent systematic review[14] suggested that 4% of people with schizophrenia and receiving an antipsychotic had a prolonged QTc.

Antipsychotic-related 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.[9] One report of cases gathered by a national database put the risk of TdP at between 0 and 19.2 cases per 100,000 patient years, depending on the individual antipsychotic and age of patients.[15] The effect of antipsychotic polypharmacy on QT is somewhat uncertain,[16] but the extent of QT prolongation is probably a function of overall dose.[17]

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 20ms.[18] Self-reading, computerised ECG devices are now widely available and compensate for some lack of expertise, but different models use different algorithms and different correction formulae.[19] ECG machines may not be as readily available as they are in general medicine. Also, there may be insufficient time for ECG determination in many areas (e.g. outpatients). Lastly, ECG determination may be difficult to perform in acutely disturbed, physically uncooperative patients.

ECG monitoring is nonetheless 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)[20] 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 TdP and of increased cardiac mortality.[21] Different correction factors and methods may give markedly different values.[22] The most widely used formula is Bazett's. This tends to overestimate QT length, especially when heart rate is increased.[23]
- 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 after-depolarisations, which may provoke ventricular extrasystole and TdP. Measures have been developed (QT dispersion ratio, dispersion transmural repolarisation time) which may better predict arrhythmia.[12]

- 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 (440ms for men; 470ms for women), although there are well-known exceptions which appear to disprove this theory[24] (some drugs prolong QT without increasing dispersion). Rather stronger evidence links QTc values over 500ms to a clearly increased risk of arrhythmia.[25] QT intervals of >650ms may be more likely than not to induce torsades.[26] Overall, 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 an important aspect of QT prolongation associated with sudden cardiac deaths;[27] T-wave peak to end interval may also be predictive of arrhythmia.[12]
- QTc measurements and evaluation are complicated by:
  - difficulty in determining the end of the T wave, particularly where U waves are present (this applies to both manual and self-reading ECG machines)[25]
  - normal physiological variation in QTc interval: QT varies with gender, time of day, food intake, alcohol intake, menstrual cycle, ECG lead, etc.[22,24]
  - 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.[22,24]

Other ECG changes

Other reported antipsychotic-induced changes include atrial fibrillation, giant P waves, T-wave changes and heart block.[24]

Quantifying risk

Drugs are categorised here according to data available on their effects on the cardiac QTc interval as reported, mostly using Bazett's correction formula (Table 1.35). '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 (<10ms) have been observed at clinical doses. 'Moderate-effect' drugs are those which have been observed to prolong QTc by >10ms 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 there is extensive average QTc prolongation (usually >20ms at normal clinical doses).

As outlined above, effect on QTc may not necessarily equate directly to risk of TdP or sudden death,[28] although this is often assumed.[29] (A good example here is ziprasidone – a drug with a moderate effect on QTc but with minimal evidence of cardiac toxicity.[30]) Also, 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.[31]

Outside these guidelines, readers are directed to the RISQ-PATH study,[32] 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.[33]

Table 1.35 Antipsychotics – effect on QTc.[12,22,24,34–59]

Effect on QTc	Drug
No effect	Brexpiprazole Cariprazine Lurasidone Lumateperone*
Low effect	Aripiprazole** Asenapine Clozapine Flupentixol Fluphenazine Perphenazine Prochlorperazine Olanzapine† Paliperidone Risperidone Sulpiride Zuclopenthixol
Moderate effect	Amisulpride‡ Chlorpromazine Haloperidol Iloperidone Levomepromazine Melperone Pimavanserin Quetiapine Ziprasidone
High effect	Pimozide Sertindole
Unknown effect	Loxapine Pipotiazine Trifluoperazine

* Limited clinical experience (association with QT prolongation may emerge).

** One case of TdP reported,[60] two cases of QT prolongation[61,62] and an association with TdP found in database studies.[63,64] Healthy volunteer data suggest aripiprazole causes QTc prolongation of around 8ms.[65] Aripiprazole may increase QT dispersion.[66] Low-dose aripiprazole has no effect on QT when added to another antipsychotic.[67]

† Isolated cases of QTc prolongation[38,68] and has effects on cardiac ion channel, IKr.[69] Other data suggest no effect on QTC.[24,36,37,70]

‡ TdP common in overdose,[26,71] strong association with TdP in clinical doses.[63]

Aripiprazole remains in the low-effect group having previously been firmly placed in 'no effect'. Data are rather contradictory, with most studies showing a decrease in QTc associated with aripiprazole use,[51] even in children and adolescents.[72] However, later data[60,61,63,65,73] cast doubt on assumptions of cardiac safety. Nonetheless, a 2020 paper analysing reports of events in >400,000 in-patients over 20 years found aripiprazole had the lowest rate of cardiac events (0.06%) of all antipsychotics.[74]

Lurasidone remains in the 'no-effect' group,[51] although one study mentioned in the US labelling[75] reports a QT lengthening of 7.5ms in people receiving 120mg (111mg) a day. Those receiving 600mg (555mg) daily showed a lower change (+4.6ms). These findings are in some contrast with those from studies in patients which uniformly suggest no or minimal effect.[76–78] This disparity is probably explained by the use of different correction factors and by random change, as often seen in placebo-treated patients[78] and as suggested by the apparent lack of dose-related effect. One case of QTc >500ms has been reported with lurasidone in which lurasidone was judged the 'probable' cause.[79]

Brexpiprazole remains in the 'no-effect' group although one study of 16 patients found an increase in QTc (Hodges' formula) of 10.1ms and an important increase in dispersion transmural repolarisation time.[12] All other data suggest no effect.

Other risk factors

A number of physiological, pathological and genetic[80] factors are associated with an increased risk of QT changes and of arrhythmia (Table 1.36) and many non-psychotropic drugs are linked to QT prolongation (Table 1.37).[25] These additional risk factors seem almost always to be present in cases of antipsychotic-induced TdP.[81]

Table 1.36 Physiological risk factors for QTc prolongation and arrhythmia.

Cardiac	Long QT syndrome Bradycardia 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 may be more susceptible to QT changes Female gender

Note: Hypokalaemia-related QTc prolongation is more commonly observed in acute psychotic admissions.[82] There are a number of physical and genetic factors (related to cardiac potassium channels or CYP enzyme function),[80] which may not be discovered on routine examination but which probably predispose patients to arrhythmia.[83,84]

Table 1.37 Non-psychotropics associated with QT prolongation (see Crediblemeds.org for latest information; this is not a complete list).

Antibiotics	Erythromycin Clarithromycin Ampicillin Co-trimoxazole Pentamidine (Some 4 quinolones affect QTc – see manufacturers' literature)
Antimalarials	Chloroquine Mefloquine Quinine
Antiarrhythmics	Quinidine Disopyramide Procainamide Sotalol Amiodarone Bretylium
Others	Amantadine Cyclosporin Diphenhydramine Hydroxyzine Methadone Nicardipine Tamoxifen

Note: β_2 agonists and sympathomimetics may provoke TdP in patients with prolonged QTc.

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. Management of QT prolongation in patients receiving antipsychotic drugs is detailed in Table 1.38.

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.

Table 1.38 Management of QT prolongation in patients receiving antipsychotic drugs.

QTc	Action	Refer to cardiologist
<440ms (men) or <470ms (women)	None unless abnormal T-wave morphology	Consider if in doubt
>440ms (men) or >470ms (women) but <500ms	Consider reducing dose or switching to drug of lower effect; repeat ECG	Consider
>500ms	Repeat ECG. Stop suspected causative drug(s) and switch to drug of lower effect.	Immediately
Abnormal T-wave morphology	Review treatment. Consider reducing dose or switching to drug of lower effect.	Immediately

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 the relevant sections for discussion of these problems.

Summary

- In the absence of conclusive data, assume that 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.

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Effects of antipsychotic medications on plasma lipids

Morbidity and mortality from cardiovascular disease are higher in people with schizophrenia than in the general population.[1–3] Dyslipidaemia is an established risk factor for cardiovascular disease, together with obesity, hypertension, smoking, diabetes and sedentary lifestyle. Specifically, reduced high-density lipoprotein (HDL) cholesterol and raised triglyceride levels are included in the definition of the metabolic syndrome.[4] The majority of patients with schizophrenia have several of these cardiometabolic 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.[5] 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).

Effect of antipsychotic medications on lipids

Antipsychotic medications show a marked variation in their effects on total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol and triglycerides.[6,7] Regarding FGAs, phenothiazines are known to be associated with increases in triglycerides and LDL cholesterol and decreases in HDL[8] cholesterol, but the magnitude of these effects is poorly quantified.[9] Haloperidol seems to have minimal effect on lipid profiles.[8] 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 such medications directly. While cholesterol levels can rise, the most profound effect of antipsychotic medications seems to be on triglycerides. Raised triglycerides are, in general, associated with obesity and diabetes. From the available data, clozapine and olanzapine[6,10] would seem to have the greatest propensity to increase lipids, while quetiapine and risperidone have a moderate propensity.[11,12] Aripiprazole, lurasidone and ziprasidone appear to have minimal adverse effect on blood lipids[6,10,13–18] and may even modestly reverse dyslipidaemias associated with previous antipsychotics.[17,19,20] For cariprazine and brexpiprazole, the effects on plasma lipids would also appear to be relatively limited.[6,21–24] Iloperidone causes some weight gain but may not have an equivalent impact on cholesterol or triglycerides.[6,25,26] Early RCT data suggest that lumateperone is not associated with any significant effects on plasma cholesterol or triglycerides in the short term, compared with placebo.[27]

Olanzapine

In people with schizophrenia, olanzapine has a relatively high propensity to induce dyslipidaemia,[6,7] which is characterised by elevated levels of plasma triglyceride, total cholesterol and LDL cholesterol and can occur in the first 4 weeks of treatment.[28] Triglyceride levels have been shown to increase by 40% over the short (12 weeks) and medium (16 months) term.[29,30] Levels may continue to rise for up to a year.[31] Up to two-thirds of patients treated with olanzapine have raised triglycerides[32] and just under 10% may develop severe hypertriglyceridaemia.[33] While weight gain with olanzapine is generally associated with increases in both cholesterol[30,34] and triglycerides,[33] severe hypertriglyceridaemia can occur independently of weight gain.[33] In one study, patients

treated with olanzapine or risperidone gained a similar amount of weight, but with olanzapine, serum triglyceride levels increased by four times as much (105mg/dL) as for risperidone (32 mg/dL).[35] Quetiapine[36] seems to have more modest effects than olanzapine, although the data are conflicting.[37]

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 hyperlipidaemia than those with no antipsychotic exposure and three times more likely to develop hyperlipidaemia than patients receiving FGAs.[38] Risperidone treatment was not associated with an increased likelihood of hyperlipidaemia compared with no antipsychotic exposure or treatment with an FGA.

Clozapine

Clozapine also has a relatively high propensity to induce dyslipidaemia.[6,7] Mean triglyceride levels have been shown to double and cholesterol levels to increase by at least 10% after 5 years of treatment with clozapine.[39] Patients treated with clozapine have triglyceride levels that are almost double those of patients who are treated with FGA medications.[40,41] Cholesterol levels are also increased.[10]

Particular care should be taken before prescribing clozapine or olanzapine for patients who are obese, diabetic or known to have pre-existing hyperlipidaemia.[42]

Screening and monitoring

In patients with schizophrenia treated with antipsychotic medication, the monitoring of plasma lipids by mental health services and in primary care is generally insufficient,[43–47] falling short of recommended practice.[48,49] All patients should have their lipids measured at baseline, 3 months after starting treatment with a new antipsychotic medication 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.[50] In practice, dyslipidaemia is widespread in patients on long-term antipsychotic treatment irrespective of the medication prescribed or of diagnosis.[51–53]

Severe hypertriglyceridaemia (fasting level of >5mmol/L) is a risk factor for pancreatitis. Note that antipsychotic-induced dyslipidaemia can occur independent of weight gain.[54]

Clinical management of dyslipidaemia

Patients with raised cholesterol may benefit from dietary advice, lifestyle changes and/or treatment with statins.[49,55] Statins seem to be effective in this patient group, although pharmacokinetic and pharmacodynamic interactions are possible.[56,57] The outline of a systematic approach to the diagnosis and management of hypercholesterolaemia is available,[58] based on NICE guidance in the UK.[59] Further, risk tables and treatment guidelines can be found in the BNF. Evidence supports the treatment of cholesterol concentrations as low as 4mmol/L in high-risk patients[60] and this is the highest level

recommended by NICE for secondary prevention of cardiovascular events.[61] 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.[61] Coronary heart disease and stroke risk can be reduced by a third by reducing cholesterol to as low as 3.5mmol/L. When triglycerides alone are raised, diets low in saturated fats and the taking of fish oil and fibrates are effective treatments,[31,62,63] although there is no proof that mortality is reduced. Such patients should be screened for impaired glucose tolerance and diabetes.

If moderate to severe hyperlipidaemia develops during antipsychotic treatment, a switch to another antipsychotic medication 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.[64] This may hold true with other switching regimens but data are scarce.[65] Aripiprazole and other D2 partial agonists seem to be the treatments of choice in those with prior antipsychotic-induced dyslipidaemia (lumateperone and ziprasidone are options outside the UK).[20,66] There is evidence to suggest that adjunctive aripiprazole may have beneficial effects on measures of plasma cholesterol and triglycerides when combined with clozapine or olanzapine[19,49,67] and that metformin added to antipsychotic medication may improve total cholesterol and triglyceride levels[49,68] (see Buzea et al. 2022[57] and the 'BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment'[49] for discussion of the potential risks and benefits of these two strategies).

Summary of monitoring

Medication	Suggested monitoring schedule
Clozapine	Fasting lipids at baseline then every 3 months for a year, then annually
Olanzapine	
Other antipsychotic medications	Fasting lipids at baseline, 3 months, and then annually[66]

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Diabetes and impaired glucose tolerance

Schizophrenia

Schizophrenia is associated with relatively high rates of insulin resistance and type 2 diabetes[1,2] – an observation that predates the discovery and widespread use of antipsychotic medication.[3–5] Lifestyle interventions (healthy diet, losing weight, regular physical activity) are effective in preventing diabetes[6,7] and should be considered for all people with a diagnosis of schizophrenia.

Antipsychotic medications

The data relating to diabetes and the use of antipsychotic medication are numerous but less than perfect.[8–12] The main problem is that while incidence and prevalence studies assume full or uniform screening for diabetes, this is unlikely to be occurring in clinical practice.[13] Many studies do not account for other factors affecting the risk of developing diabetes.[14] Small differences between medications 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 medication. This risk is fairly strongly linked to increased diabetes-related mortality.[11]

The mechanisms involved in the development of antipsychotic-related diabetes are unclear, but may include $5HT_{2A}$/$5HT_{2C}$ antagonism, increased plasma lipids, weight gain and leptin resistance.[15] Pancreatic insulin secretion is controlled by dopamine[16] and this may explain why so many antipsychotics cause impaired glucose tolerance.[17] Insulin resistance may occur in the absence of weight gain.[18]

First-generation antipsychotic medications

Phenothiazine derivatives have long been associated with impaired glucose tolerance and diabetes.[19] Diabetes prevalence was reported to have substantially increased following the introduction and widespread use of FGA medications.[20] The prevalence of impaired glucose tolerance seems to be higher with the aliphatic phenothiazines than with fluphenazine or haloperidol.[21] Hyperglycaemia has also been reported with other FGAs, such as loxapine,[22] and other data confirm an association with haloperidol.[23] Some studies have suggested that FGAs are no different from SGAs in their propensity to cause diabetes,[24,25] whereas others suggest a modest but statistically significant excess incidence of diabetes with SGAs.[26]

Second-generation antipsychotic medications

Clozapine

Clozapine is strongly linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis.[27] The risk of diabetes appears to be higher with clozapine than with other SGAs or FGAs, especially in younger patients,[28–31] although this is not a consistent finding.[32,33]

As many as a third of patients on continuing treatment with clozapine might develop diabetes after 5 years.[34] Many cases of diabetes occur in the first 6 months of treatment,

some within a month,[35] and some only after many years.[33] Death from ketoacidosis has also been reported.[35] Diabetes associated with clozapine is not necessarily linked to obesity or to family history of diabetes,[27,36] although these factors greatly increase the risk of developing diabetes on this medication.[37]

Clozapine appears to increase plasma levels of insulin in a clozapine level-dependent fashion.[38,39] It has been shown to be more likely than FGAs to increase plasma glucose and insulin following oral glucose challenge.[40] Testing for diabetes is essential, given the high prevalence of the condition in people receiving clozapine.[41,42]

Olanzapine

As with clozapine, olanzapine has been strongly linked to impaired glucose tolerance, diabetes and diabetic ketoacidosis.[43] Olanzapine and clozapine appear to directly induce insulin resistance.[44,45] Risk of diabetes has also been reported to be higher with olanzapine than with FGA drugs,[46] again with a particular risk in younger patients.[29] 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.[27,36] Olanzapine is probably more diabetogenic than risperidone.[47–51] Olanzapine is also associated with plasma levels of glucose and insulin higher than those seen with FGAs (after oral glucose load).[40,52]

Risperidone

Risperidone has been linked, mainly in case reports, to impaired glucose tolerance,[53] diabetes[54] and ketoacidosis.[55] The number of reports of such adverse effects is substantially smaller than with either clozapine or olanzapine.[56] At least one study has suggested that changes in fasting glucose are significantly less common with risperidone than with olanzapine,[47] but other studies have detected no difference.[57]

Risperidone seems no more likely than FGA drugs to be associated with diabetes,[29,46,48] although there may be an increased risk in patients under 40 years of age.[29] Risperidone has, however, been observed to adversely affect fasting glucose and plasma glucose (following glucose challenge) compared with the levels seen in healthy volunteers (but not compared with patients taking FGAs).[40]

Quetiapine

Like risperidone, quetiapine has been linked to cases of new-onset diabetes and ketoacidosis,[58–60] and associated with an increased risk of diabetes.[61,62] Two studies showed quetiapine to be equal to olanzapine in the incidence of diabetes.[57,63] The risk with quetiapine may be dose related, with daily doses of 400mg or more being clearly linked to changes in HbA_{1C}.[64]

Other SGAs

Amisulpride appears not to elevate plasma glucose,[65] although there is one reported case of ketoacidosis occurring in a patient given the closely related medication sulpiride.[66] Data for **aripiprazole**[67–70] and **ziprasidone**[71,72] suggest that neither drug alters

glucose homeostasis. Aripiprazole may even reverse diabetes caused by other drugs[73] (although ketoacidosis has been reported with aripiprazole).[74–76] Further, studies have not found amisulpride or aripiprazole to be associated with a significantly greater risk of diabetes.[61,77,78] So, 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 antipsychotic medications known to be diabetogenic.

Data suggest that neither **lurasidone**[79,80] nor **asenapine**[81,82] has any effect on glucose homeostasis. Likewise, early data on **brexpiprazole**[83,84] and **cariprazine**[85–87] suggest minimal effects on glucose tolerance. Thus, for patients developing prediabetes or diabetes who are being treated with clozapine, olanzapine or quetiapine, switching to antipsychotic medications with a lower cardiometabolic risk, such as aripiprazole, brexpiprazole, cariprazine, lurasidone or ziprasidone, has been recommended.[88] **Lumateperone** appears to have no effect on glucose parameters[89] but clinical experience is limited.

Predicting antipsychotic-related diabetes

The risk of diabetes is increased to a much greater extent in younger adults than in the elderly[90,91] (for whom antipsychotic medication may show no increased risk).[92] Patients with first-episode schizophrenia seem particularly prone to the development of diabetes with a variety of antipsychotic medications.[93–95] During treatment, rapid weight gain and a rise in plasma triglycerides seem to be predictive of the development of diabetes.[96,97] Monitoring of abnormal glucose metabolism is particularly warranted in those with obesity or hypertriglyceridaemia.[42]

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.[98,99] Diabetes markedly increases cardiovascular mortality, largely as a consequence of atherosclerosis.[100] Likewise, the use of antipsychotic medication also increases cardiovascular mortality.[101–103] Intervention to reduce plasma glucose levels and minimise other risk factors (obesity, hypercholesterolaemia) is therefore essential.[104]

There is no clear consensus on diabetes monitoring practice for those receiving antipsychotic medication,[105] and the recommendations in formal guidelines vary considerably.[106] Given the previous known parlous state of testing for diabetes in the UK[13,107–109] and elsewhere,[110] 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.

Ideally, though, all patients should have oral glucose tolerance tests (OGTT) performed as this is the most sensitive method of detection.[111,112] Fasting plasma glucose (FPG) tests are less sensitive but recommended.[113] 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 glycated haemoglobin (HbA_{1c}) may also be used (fasting not required). HbA_{1C} is recognised as a useful tool in detecting and monitoring diabetes.[7] In the UK, NICE[114] recommendations for monitoring people with a psychotic disorder, treated with antipsychotic medication, include the measurement of plasma glucose or HbA_{1C} 3 months after starting treatment and then annually (Table 1.39).

Table 1.39 Recommended monitoring for diabetes in patients receiving antipsychotic drugs.

	Recommended monitoring	
Treatment stage	**Ideally**	**Minimum**
At baseline	OGTT or FPG. HbA_{1C} if fasting not possible.	UG, RPG
Continuing	All antipsychotic medications: OGTT or FPG + HbA_{1C} at 4–6 months then every 12 months For clozapine and olanzapine or if other risk factors present: OGTT or FPG after 1 month, then every 4–6 months HbA_{1C} is a suitable test for monitoring. But note that this test is not suitable for detecting short-term change.	UG or RPG every 12 months, with symptom monitoring

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; OGTT, oral glucose tolerance tests; RPG, random plasma glucose; UG, urine glucose.

Frequency of monitoring should be determined by physical factors (e.g. weight gain) and known risk factors (e.g. family history of diabetes, lipid abnormalities, smoking status). 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 an antipsychotic medication with a lower cardiometabolic risk is often effective in reversing changes in glucose tolerance. In this respect, the most compelling evidence is for switching to aripiprazole,[115,116] but also to ziprasidone[116] and lurasidone.[80,117] Standard antidiabetic treatments are otherwise recommended.[88] Pioglitazone[118] may have particular benefit, but note the hepatotoxic potential of this drug. GLP-1 agonists such as liraglutide, exenatide and semaglutide are increasingly used.[119–121]

Summary: antipsychotic medications – risk of diabetes and impaired glucose tolerance

High risk	Clozapine, olanzapine
Moderate risk	Phenothiazines, quetiapine, risperidone
Low risk	High-potency FGAs (e.g. haloperidol)
Minimal risk	Aripiprazole, amisulpride, asenapine, brexpiprazole, cariprazine, lumateperone, lurasidone, ziprasidone

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Blood pressure changes with antipsychotics

Orthostatic hypotension

Orthostatic hypotension (postural 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 it can also be a chronic problem.[1] Symptoms include dizziness, light-headedness, asthenia, headache and visual disturbance. Patients may not be able to communicate the severity of these symptoms effectively and subjective reports of postural dizziness correlate only weakly with the magnitude of measured postural hypotension.[2]

Blood pressure monitoring is recommended in suspected cases to confirm orthostatic hypotension (usually defined as a ≥20mmHg fall in systolic blood pressure and/or a ≥10mmHg fall in diastolic blood pressure within 3 minutes of standing).[3] Orthostatic hypotension impairs quality of life and is associated with an increased risk of falls, cardiovascular disease, depression and death.[3] Risk factors are shown in Table 1.40.

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 side effect, preventing optimal treatment. Potential management strategies are shown in Table 1.41.

Table 1.40 Risk factors for orthostatic hypotension.[2]

Treatment factors	■ IM administration route (peak levels higher and achieved more rapidly) ■ Rapid dose increases ■ Antipsychotic polypharmacy ■ Drug interactions (e.g. tricyclic antidepressants, antihypertensive drugs – particularly alpha blockers, beta blockers and diuretics, although the number of antihypertensive drugs prescribed may be more predictive than the class)[3]
Patient factors	■ Old age (young patients may have sinus tachycardia with minimal change in blood pressure) ■ Disease states associated with autonomic dysfunction (e.g. Parkinson's disease) ■ Dehydration ■ Cardiovascular disease

Table 1.41 Management of antipsychotic-induced orthostatic hypotension.[2,4]

Minimise the risk of treatment	■ Limit initial doses and titrate slowly according to tolerability (most people develop a tolerance to the hypotensive effect) ■ Consider a temporary dose reduction if hypotension develops ■ Reduce peak plasma levels by using smaller and more frequent dosing or by using modified-release preparations
Non-pharmacological therapies	■ Advice to patients (e.g. sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position) ■ Abdominal binders and compression stockings can be used ■ Increasing fluid intake to 1.25–2.5L/day is advisable for all patients who are not fluid restricted

(*Continued*)

Table 1.41 (*Continued*)

Pharmacological therapies for patients with a compelling indication for treatment where alternatives are not suitable (e.g. clozapine) and management strategies have failed	■ Sodium chloride supplementation may help antidepressant-induced orthostatic hypotension ■ Fludrocortisone has been used to treat clozapine-induced orthostatic hypotension where other measures have failed (electrolyte and blood pressure monitoring essential). Long-term use is not recommended.[4] ■ Midodrine, an α1 receptor agonist, has been used in one small case series (including one patient on clozapine) to reduce symptom severity.[4] Of note, midodrine has been linked to acute dystonia when used alongside antipsychotics.[5] A review suggests that midodrine should be considered second line in clozapine-induced orthostatic hypotension or where fludrocortisone is contraindicated or poorly tolerated.[4] ■ Other sympathomimetic drugs have also been used to treat orthostatic hypotension, although for most there is an absence of evidence in the treatment of psychotropic-related cases. Etilefrine has shown benefit in psychotropic-induced hypotension but cannot be recommended owing to unfavourable risk–benefit profile.[4]

Antipsychotics with a high affinity for postsynaptic α_1-adrenergic receptors are most frequently implicated in postural hypotension. 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%).[2] There are limited quantitative data for FGAs,[6] but low-potency phenothiazines (e.g. chlorpromazine) are considered most likely to cause orthostatic hypotension.[7] All reported frequencies are somewhat dependent on titration schedules used. Please see the section on relative adverse effects – a rough guide in this chapter for a summary of the relative incidence and severity of hypotension with antipsychotics.

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 has been modelled using the Framingham data: for every 30 people who gain 4kg, one will develop hypertension over the next 10 years.[8] 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 (see section on antipsychotic-induced weight gain in this chapter).
- **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 mechanism for the rapid increase in blood pressure (i.e. that independent of obesity) is uncertain, so the risk of hypertension cannot be predicted from antipsychotic pharmacology. One review of the literature suggested a possible mechanism related to

dopamine receptor antagonism.[9] All five dopamine receptor subtypes ($D_{1–5}$) are known to be involved in renal sodium excretion and blood pressure regulation.[9] Antipsychotics vary in their affinity for these dopamine receptor subtypes, and the relative importance of each receptor subtype is unclear. Other suggested mechanisms include α_2 antagonism leading to prolonged noradrenaline release, hypertension through renal potassium loss, and sodium and fluid retention, possibly owing to D_4 receptor antagonism.[10]

Some antipsychotics are more commonly implicated than others, although individual patient factors are also likely to be important. Most case reports involve clozapine,[11,12] with some clearly describing normal blood pressure before clozapine was introduced, a sharp rise during treatment and return to normal when clozapine was discontinued or doses were decreased.[12] Blood pressure has also been reported to rise again on rechallenge and increased urinary catecholamines mimicking phaeochromocytoma have been noted in some cases. Clozapine can usually be continued with antihypertensive drugs.[12] Case reports also implicate aripiprazole,[13–16] sulpiride,[17,18] risperidone,[19] quetiapine[20] and ziprasidone.[21] Olanzapine has been linked to water retention and hypertension in a pregnant woman[22] and intracranial hypertension in an adolescent.[23]

Data available through the UK Medicines and Healthcare products Regulatory Authority yellow card system indicate that clozapine is the antipsychotic drug most associated with hypertension. There are substantially fewer reports with aripiprazole, olanzapine, quetiapine and risperidone.[24] The timing of the onset of hypertension in these reports with respect to antipsychotic initiation is unknown.

In long-term treatment, hypertension is seen in around 30–40% of patients regardless of antipsychotic prescribed.[25] A cross-sectional study found an increased risk of hypertension only for perphenazine,[26] 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 co-prescribed antipsychotic.[20] It is also theoretically possible that α_2 antagonism may be at least partially responsible for clozapine-induced tachycardia and nausea.[27]

Treatment of antipsychotic-associated hypertension should follow standard protocols. Switching to alternative antipsychotics with a lower cardiometabolic risk should be considered where possible. There is specific evidence for the efficacy of valsartan and telmisartan in antipsychotic-related hypertension.[28]

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Antipsychotic-associated 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 6–17%.[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 may be driven, at least in part, by an extreme compensatory response to the anticholinergic adverse effects of some antipsychotic drugs.[4] An alternative theory is that postsynaptic dopamine receptor antagonism results in receptor supersensitivity, increased presynaptic dopamine release, and elevated dopamine in the hypothalamus, driving thirst and polydipsia.[5] The fact that many reported cases occur in patients with long illness histories and treatment with antipsychotics with high D_2 receptor affinity (and that clozapine can improve polydipsia independent of improvement in psychosis) appears to support this suggestion.[5]
- **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 may be as high as 11% in acutely ill psychiatric patients.[6] Risk factors for antidepressant-induced SIADH (increasing age, female gender, medical comorbidity and polypharmacy) seem to be less relevant to the population of patients treated with antipsychotic drugs.[7] SIADH usually develops in the first few weeks of treatment with the offending drug[8] but can appear at a later time.[8] Case reports/series[7,9–30] implicate various phenothiazines, haloperidol, pimozide, risperidone, paliperidone, quetiapine, olanzapine, aripiprazole, cariprazine and clozapine. Systematic review[31] and case–control studies[32,33] suggest a clear increase in risk of hyponatraemia with antipsychotics. One large Swedish study found a stronger association for first-generation antipsychotics than for SGAs.[33] Analysis of pharmacovigilance reports appears to support this.[34] Another review[35] confirmed that drug-induced hyponatraemia is associated with concentrated urine and suggested that antipsychotic treatment 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%[36] and 26.1%.[37] It is assumed that the true figure is somewhere between these two widely different extremes. Desmopressin, when used for clozapine-induced enuresis, can also result in hyponatraemia.[38] Other drugs, including antidepressants and anticonvulsants (especially carbamazepine),[39] valbenazine[40] and many drugs for physical health conditions (diuretics, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin II receptor blockers, proton pump inhibitors), have also been implicated.[41] The risk of hyponatraemia is probably additive with concomitant prescriptions.[42–44]
- 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, particularly if several risk factors for hyponatraemia are present. A risk-scoring algorithm has been proposed.[45] Signs of confusion or lethargy should provoke thorough diagnostic analysis, including plasma sodium determination and urine osmolality (Table 1.42).

Tolvaptan,[46] a so-called vaptan (non-peptide arginine-vasopressin antagonist, also known as aquaretics because they induce a highly hypotonic diuresis),[47] shows promise in the treatment of hyponatraemia of various aetiologies, including that caused by drug-related SIADH and psychogenic polydipsia.[48]

Table 1.42 Treatment of hyponatraemia associated with antipsychotic treatment.[4,6]

Cause of hyponatraemia	Antipsychotic drugs implicated	Treatment
Water intoxication (serum and urine osmolality low)	Only very speculative evidence to support drugs as a cause. Core part of illness in a minority of patients (e.g. psychotic polydipsia)	■ **Fluid restriction** with careful monitoring of serum sodium, particularly diurnal variation (Na drops as the day progresses). Refer urgently to specialist medical care if Na <125 mmol/L. Note that over-rapid correction of sodium levels can cause irreversible osmotic demyelination syndrome.[49] ■ Consider treatment with **clozapine**, which has been shown to increase plasma osmolality into the normal range and increase urine osmolality.[50,51] These effects are consistent with reduced fluid intake but are not clearly related to improvements in mental state.[52] ■ There are both[7] positive and negative reports for olanzapine[53] and risperidone[54] and one positive case report for quetiapine.[55] Compared with clozapine, the evidence base is weak. ■ There is no evidence that either reducing or increasing the dose of an antipsychotic results in improvements in serum sodium in water-intoxicated patients[56] although reducing the number and dose of antipsychotics prescribed may decrease dopamine receptor supersensitivity and drug adverse effects[5] ■ **Demeclocyline** may be used[57,58] and it is included in some practice guidelines for psychogenic polydipsia.[59] However, it exerts its effect by interfering with alcohol dehydrogenase and increasing water excretion, which is already at capacity in these patients. Any rationale for its use in the absence of SIADH is therefore debatable (and some cases in the literature may have been complicated by undiagnosed SIADH).[60] A single small RCT showed no benefit.[61] ■ Many other drugs have been used (naloxone, enalapril, clonidine, naltrexone, acetazolamide, captopril, propranolol, losartan, carbamazepine, fluoxetine, bupropion, trazodone, mianserin) but data are limited.[62] Successful use of the carbonic anhydrase inhibitor acetazolamide has also been reported.[63,64]

(*Continued*)

Table 1.42 (*Continued*)

Cause of hyponatraemia	Antipsychotic drugs implicated	Treatment
SIADH (serum osmolality low; urine osmolality relatively high)	All antipsychotic drugs	■ If mild, **fluid restriction** with careful monitoring of serum sodium. Refer urgently to specialist medical care if Na <125mmol/L. ■ **Dose reduction** of the antipsychotic has been suggested[45] but evidence to support this strategy is lacking ■ **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 overall and the choice of drug unimportant). ■ Consider **demeclocycline** (see formal prescribing information for details) ■ Lithium may be effective[7] but is a potentially toxic drug (and hyponatraemia predisposes to lithium toxicity)

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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,[1] and for most antipsychotic medications the threshold activity (D_2 occupancy) for increased prolactin is very close to that of therapeutic efficacy.[2] Genetic differences may also play a part.[3] Table 1.43 groups individual antipsychotics according to their effect on prolactin concentrations.

Table 1.43 Effects of antipsychotic medication on prolactin concentration.[4–12]

Effect	Risk	Drug
Prolactin-sparing	Prolactin increase very rare	Aripiprazole Asenapine Brexpiprazole Cariprazine Clozapine Iloperidone Lumateperone Pimavanserin Quetiapine Xanomeline
Prolactin-elevating	Low risk, minor changes only	Lurasidone Olanzapine Ziprasidone
Prolactin-elevating	High risk; major changes	Amisulpride Paliperidone Risperidone Sulpiride First-generation antipsychotics

Hyperprolactinaemia is often superficially asymptomatic (that is, the patient does not spontaneously report problems) and there is some evidence that hyperprolactinaemia does not affect subjective quality of life.[13] Nonetheless, persistent elevation of plasma prolactin is associated with suppression of the hypothalamic–pituitary–gonadal axis.[14] Symptoms of this include sexual dysfunction[15] (but note that other pharmacological activities also give rise to sexual dysfunction),[16] menstrual disturbances,[4,17] breast growth and galactorrhoea,[17] and may include delusions of pregnancy.[18] Long-term adverse consequences are reductions in bone mineral density[19,20] and a possible increase in the risk of breast cancer.[21]

Prolactin can also be raised because of stress, pregnancy and lactation, seizures, renal impairment and other medical conditions,[7,22,23] including prolactinoma. When measuring prolactin, the sample should be taken early in the morning and stress during venepuncture should be minimised.[23]

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.

Management

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

Below, we suggest an algorithm for managing antipsychotic-induced hyperprolactinaemia (Figure 1.5). 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 of relapse.[24] An alternative is to add aripiprazole to existing treatment.[25] Aripiprazole lowers prolactin levels in a dose-dependent manner: 3mg/day is effective but 6mg/day more so. Higher doses appear unnecessary.[26] 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 D3 intake).[19,27]

For patients who need to remain on a prolactin-elevating antipsychotic medication and who cannot tolerate aripiprazole, dopamine agonists can be effective.[28–30] 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). High-dose vitamin B6 (600mg/day) seems to be effective in reducing antipsychotic-induced hyperprolactinaemia and is well tolerated.[31] A herbal remedy – Peony–Glycyrrhiza Decoction – has also been shown to improve prolactin-related symptoms,[32,33] but the data are limited. A reduction in prolactin levels was also achieved by taking high daily doses (2.5–3g) of metformin[34] in a study of women with diabetes on antipsychotic medication. A 2022 network meta-analysis of all the above treatments confirmed the efficacy of aripiprazole 5mg a day and of vitamin B6 600mg/day in patients whose baseline prolactin exceeded 50ng/mL.[35] Two other meta-analyses concluded that adjunctive aripiprazole was the most effective treatment.[36,37]

Summary of management

First-choice adjunct treatment	Aripiprazole 5mg/day
Second-choice adjunct	Vitamin B6 600mg/day
Third-choice adjunct (in no particular order)	DA agonists – cabergoline, bromocriptine, amantadine Peony–Glycyrrhiza Decoction Metformin 2.5–3g/day

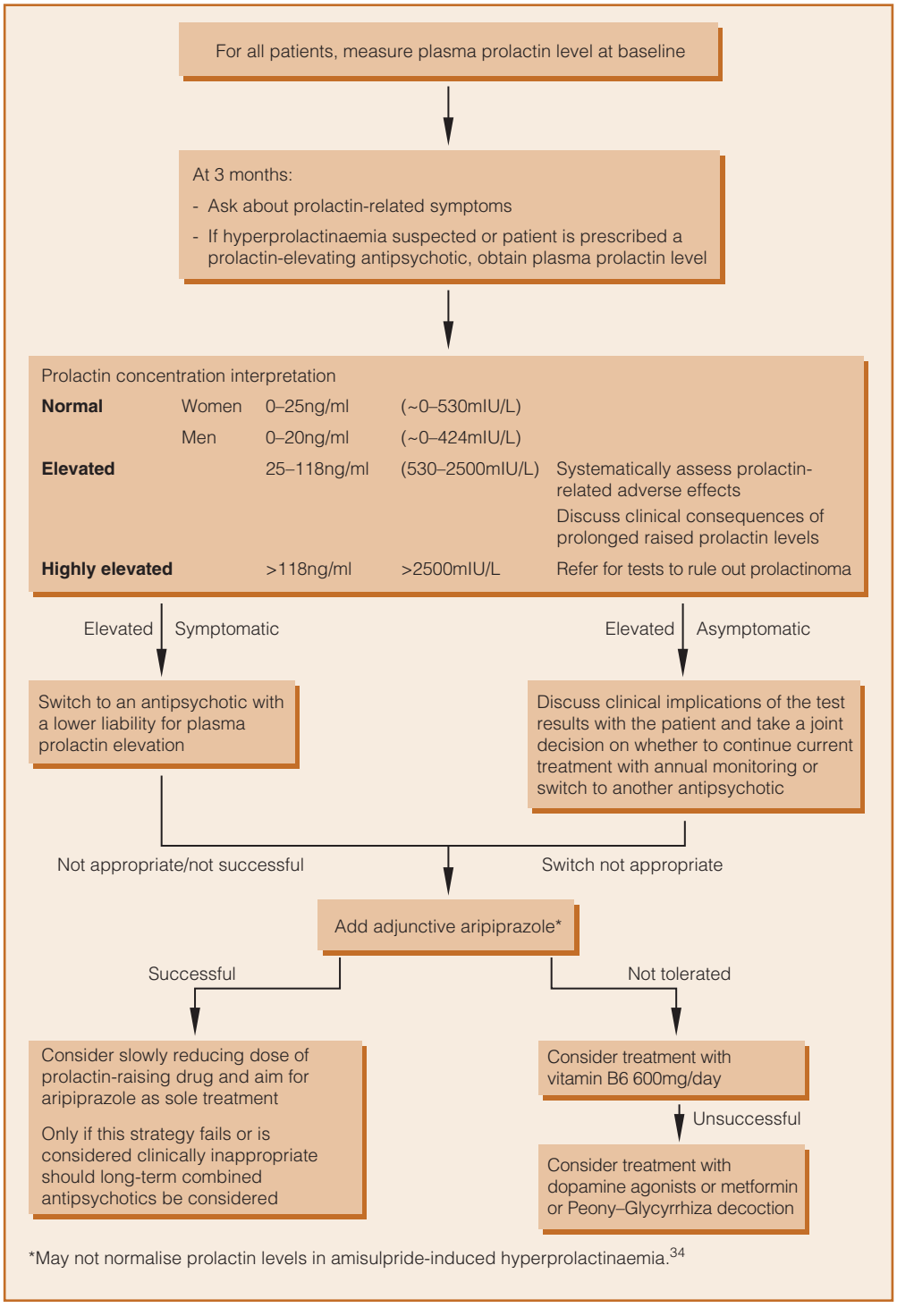

Figure 1.5 Management of antipsychotic-induced hyperprolactinaemia.[38]

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Sexual dysfunction and antipsychotics

A 2023 meta-analysis found the global prevalence of sexual dysfunction in people with schizophrenia to be 56% in men and 60% in women.[1] Problems are not always reported by patients. In one study of patients with psychosis, 37% spontaneously reported sexual problems but 46% were found to be experiencing difficulties when directly questioned.[2]

Baseline sexual functioning should be determined if possible (questionnaires may be useful) because sexual function can affect both quality of life[3] and compliance with medication (sexual dysfunction is one of the major causes of treatment dropout).[4,5] Complaints of sexual dysfunction may also indicate progression or inadequate treatment of underlying medical or psychiatric conditions.[6,7] Sexual problems may also be caused by drug treatment and are associated with early discontinuation of antipsychotics.[8] Intervention may greatly improve quality of life.[9]

The human sexual response

There are four phases of the human sexual response, as detailed in Table 1.44.[10–12]

Effects of psychosis

Sexual dysfunction is a well-established phenomenon in first-episode schizophrenia.[13,14] Up to 82% of men and 96% of women report problems, with associated reductions in quality of life.[3] Antipsychotic adverse effects are not solely responsible, because prevalence is also high (17–70%) in patients who are unmedicated.[15] Men complain of reduced desire,[16] inability to achieve an erection and premature ejaculation,[1] whereas women complain of lowered libido and orgasm dysfunction.[1] Women with psychosis also have reduced fertility.[17]

Table 1.44 The human sexual response.

Desire	■ Related to testosterone levels in men
	■ Possibly increased by dopamine and decreased by prolactin
	■ Psychosocial context and conditioning significantly affect desire
Arousal	■ Influenced by testosterone in men and oestrogen in women
	■ Other potential mechanisms include central dopamine stimulation, modulation of the cholinergic/adrenergic balance, peripheral α1 agonism and nitric oxide pathways
	■ Physical pathology such as hypertension or diabetes can have a significant effect
Orgasm	■ May be related to oxytocin
	■ Inhibition of orgasm may be caused by an increase in serotonin activity and raised prolactin, as well as α1 blockade
Resolution	■ Occurs passively after orgasm

Note: Many other hormones and neurotransmitters may interact in a complex way at each phase.

People with psychosis are less able to develop good psychosexual relationships and, for some, treatment with an antipsychotic can improve sexual functioning via an improvement in psychotic symptoms.[18] Assessment of sexual functioning can clearly be difficult in someone who is psychotic. The Arizona Sexual Experience Scale may be useful in this respect.[19]

Effects of antipsychotic drugs

Sexual dysfunction is an adverse effect of most antipsychotics. Individual susceptibility varies and effects are usually reversible. Psychosis, physical illness and drugs other than antipsychotics can also contribute to sexual dysfunction. Many studies do not control for these factors, making the prevalence of sexual dysfunction with different antipsychotics difficult to compare.[20]

Antipsychotics decrease dopaminergic transmission, which in itself can decrease libido but may also increase prolactin levels via negative feedback. Hyperprolactinaemia is a key factor in sexual dysfunction[21,22] but may only explain 40% of the sexual dysfunction that is associated with antipsychotic medication.[23] Hyperprolactinaemia can also cause amenorrhoea and infertility[24] in women, and breast enlargement and galactorrhoea in both men and women.[25] The overall propensity of an antipsychotic to cause sexual dysfunction is a function of the facility to raise prolactin (i.e. risperidone > haloperidol > olanzapine > quetiapine > aripiprazole).[6,20,26] Aripiprazole is relatively free of sexual adverse effects when used as monotherapy[27] and may improve symptoms in combination with another antipsychotic.[28,29] The same is probably true for brexpiprazole, and cariprazine is a theoretically appropriate alternative.[30]

Anticholinergic effects of drugs can cause disorders of arousal[31] and concomitant anticholinergics may thus contribute to sexual dysfunction.[32] Drugs that block peripheral α_1 receptors cause particular problems with erection and ejaculation in men.[9] Antipsychotic-induced sedation and weight gain may reduce sexual desire.[33] Table 1.45 gives details of the nature and frequency of sexual adverse effects caused by antipsychotics.

Table 1.45 Sexual adverse effects of antipsychotics.

Drug	Type of problem
Aripiprazole	■ No effect on prolactin or α_1 receptors. No reported adverse effects on sexual function. Improves sexual function in those switched from other antipsychotics[27,29,34–36] and when added as an adjunct.[37] Case reports of aripiprazole-induced hypersexuality have been published.[38,39]
Asenapine	■ Does not appear to significantly affect prolactin levels[40] ■ No reported cases of sexual dysfunction
Brexpiprazole	■ Similar mechanism of action to aripiprazole (5-HT_{1A} agonist, 5-HT_{2A} antagonist and partial D_2 agonist) ■ Causes negligible increases in prolactin[41] ■ No problems with sexual dysfunction reported in clinical trials[42]

(*Continued*)

Table 1.45 (*Continued*)

Drug	Type of problem
Cariprazine	■ Similar mechanism of action to aripiprazole (5-HT_{1A} agonist, 5-HT_{2A} antagonist and partial D_2 agonist) ■ Not associated with hyperprolactinaemia[43] ■ Very low rates of sexual dysfunction reported in clinical trials[44]
Clozapine	■ Significant α1 adrenergic blockade and anticholinergic effects.[45] No effect on prolactin.[46] ■ Probably fewer problems than with typical antipsychotics[47]
Haloperidol	■ Similar problems to phenothiazines[48] but anticholinergic effects reduced[49] ■ Prevalence of sexual dysfunction up to 70%[50]
Lurasidone	■ Does not appear to affect prolactin levels[51] ■ No reported cases of sexual dysfunction[52]
Olanzapine	■ Possibly less sexual dysfunction than drugs such as haloperidol owing to relative lack of prolactin-related effects[48] ■ Priapism reported rarely[53,54] ■ Prevalence of sexual dysfunction >50%[50]
Paliperidone	■ Similar prolactin elevations to risperidone ■ One small study[55] and one case report[56] showing reduction in sexual dysfunction following switching to paliperidone depot from risperidone oral or depot
Phenothiazines (e.g. chlorpromazine)	■ Hyperprolactinaemia and anticholinergic effects. May cause delayed orgasm at lower doses followed by normal orgasm but without ejaculation at higher doses.[57] ■ Priapism has been reported with thioridazine and chlorpromazine (probably due to α1 blockade)[49,58,59]
Quetiapine	■ No effect on prolactin[60] ■ Possibly associated with low risk of sexual dysfunction,[61–64] but studies are conflicting[65,66]
Risperidone	■ Potent elevator of serum prolactin ■ Less anticholinergic than some other antipsychotics (olanzapine, quetiapine) ■ Specific peripheral α1 adrenergic blockade leads to a moderately high reported incidence of ejaculatory problems such as retrograde ejaculation[67,68] ■ Priapism reported rarely[33] ■ Prevalence of sexual dysfunction 60–70%[50]
Sulpiride/amisulpride	■ Potent elevators of serum prolactin[69] but note that sulpiride was not associated with greater sexual dysfunction than SGAs in CUtLASS-1[18]
Thioxanthenes (e.g. flupentixol)	■ Arousal problems and anorgasmia[70]
Lumateperone	■ Does not appear to affect prolactin[71] ■ No sexual adverse effects reported in clinical trials[72]
Pimavanserin	■ Does not bind to dopamine receptors,[73] so has no effect on prolactin ■ May improve sexual function in patients with depression[74]
Iloperidone	■ Does not usually affect prolactin[75] ■ Some reports of sexual dysfunction in adverse event reporting databases,[76] case reports of retrograde ejaculation[77]

CUtLASS-1, Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study; SGA, second-generation antipsychotic.

Treatment of sexual dysfunction

Before attempting to treat sexual dysfunction, a thorough assessment is essential to determine the most likely cause. A large meta-analysis of 72 studies from 33 different countries found that for patients with schizophrenia spectrum disorders, concurrent antidepressant and mood stabiliser prescriptions were associated with *lower* rates of erection and ejaculation disorders.[1] This suggests that treating a comorbid depression or mood disorder is an important strategy to improve sexual health. Assuming that psychiatric comorbidity or physical pathology (diabetes, hypertension, cardiovascular disease, etc.) has been excluded or treated (e.g. obesity),[78] the following principles apply when considering the prescribing of antipsychotics:

- Spontaneous remission may occasionally occur[33] but may take 6 months to become apparent, if at all,[30] and may be more likely related to a reduction in severity of illness, rather than tolerance to the antipsychotic itself.
- When symptoms persist, the most obvious first step is to decrease the dose (although a correlation between dose and all types of sexual dysfunction has not been conclusively demonstrated)[79] 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 (Table 1.46). Another option is to add 5–10mg aripiprazole – this can normalise prolactin and improve sexual function.[37,80]
- If this fails or is not practicable, 'antidote' drugs can be tried: for example, cyproheptadine (a $5HT_2$ antagonist at doses of 4–16mg/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 $5HT_2$ antagonist as well as an α_2 antagonist) may relieve orgasmic dysfunction in patients treated with FGAs.[81] Amantadine, bupropion, buspirone, bethanechol and yohimbine have all been used with varying degrees of success but have several adverse effects and interactions with other drugs. Given that hyperprolactinaemia contributes to sexual dysfunction, selegiline, which enhances dopamine activity, has been investigated but was not effective.[82] Testosterone patches have been shown to increase libido in women, although breast cancer risk may be significantly increased.[83,84]

Table 1.46 lists remedial treatments for psychotropic-induced sexual dysfunction.

Table 1.46 Remedial treatments for psychotropic-induced sexual dysfunction.

Drug	Pharmacology	Potential treatment for	Adverse effects
Alprostadil[12,85]	Prostaglandin	Erectile dysfunction	Pain, fibrosis, hypotension, priapism
Amantadine[85,86,87]	Dopamine agonist	Prolactin-induced reduction in desire and arousal (dopamine increases libido and facilitates ejaculation)	Return of psychotic symptoms, GI effects, nervousness, insomnia, rash
Bethanechol[88]	Cholinergic or cholinergic potentiation of adrenergic neurotransmission	Anticholinergic-induced arousal problems and anorgasmia (from TCAs, antipsychotics, etc.)	Nausea and vomiting, colic, bradycardia, blurred vision, sweating
Bromocriptine[9]	Dopamine agonist	Prolactin-induced reduction in desire and arousal	Return of psychotic symptoms, GI effects
Bupropion[89,90]	Noradrenaline and dopamine reuptake inhibitor	SSRI-induced sexual dysfunction	Concentration problems, reduced sleep, tremor
Buspirone[91]	$5HT_{1a}$ partial agonist	SSRI-induced sexual dysfunction, particularly decreased libido and anorgasmia	Nausea, dizziness, headache
Cyproheptadine[85,91,92]	$5HT_2$ antagonist	Sexual dysfunction caused by increased serotonin transmission (e.g. SSRIs), particularly anorgasmia	Sedation and fatigue. Reversal of the therapeutic effect of antidepressants.
Flibanserin (licensed in USA)[93]	$5HT_{1A}$ agonist, $5HT_{2A}$ antagonist, dopamine antagonist	Lack or loss of sexual desire in premenopausal women. Appears to be safe in women taking antidepressants.[94]	Hypotension, syncope, sedation, dizziness, nausea, dry mouth
Sildenafil,[12,95–98] **tadalafil,**[99] **lodenafil,**[100] **vardenafil**[101]	Phosphodiesterase inhibitors	Erectile dysfunction of any aetiology. Anorgasmia in women. Effective even when prolactin raised.	Mild headaches, dizziness, nasal congestion
Yohimbine[12,85,102–104]	Central and peripheral α_2 adrenoceptor antagonist	SSRI-induced sexual dysfunction, particularly erectile dysfunction, decreased libido and anorgasmia	Anxiety, nausea, fine tremor, increased blood pressure, sweating, fatigue
Pimavanserin[74]	Inverse agonist at $5HT_{2A}$ and $5HT_{2C}$	Sexual dysfunction in depression with inadequate response to antidepressants. Improvement in sexual function independent of effect on depression unconfirmed.	Peripheral oedema, nausea, confusion
Bremelanotide[105]	Melanocortin receptor agonist	Hypoactive sexual desire in premenopausal women. No published data on use in patients with psychiatric diagnoses.	Flushing, nausea, headache

Note: The use of the drugs listed above should ideally be under the care or supervision of a specialist in sexual dysfunction.
GI, gastrointestinal; TCA, tricyclic antidepressant.

The evidence base supporting the use of 'antidotes' is often poor and specific to particular drug-induced problems.[33,106] The generalisability of results from positive trials is limited by small sample sizes, short trial durations and lack of controlling for confounding factors (age, concurrent medication, antipsychotic switches for reasons other than baseline sexual dysfunction).[106] Comparison of data between studies is further complicated by the use of varying assessment tools to measure outcomes.[107]

Drugs such as sildenafil (Viagra) or alprostadil (Caverject) are effective only in the treatment of erectile dysfunction (they have no effect on libido or central arousal). Psychological approaches used by sexual dysfunction clinics may be difficult for clients with mental health problems to engage in.[9]

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Pneumonia

Background

A 2018 meta-analysis of 14 observational studies (n = 206,899) reported that antipsychotic use was associated with a near doubling of pneumonia incidence compared with no use.[1] This same analysis found no difference in incidence of pneumonia between FGAs and SGAs and no increase in fatality rate. A later analysis of spontaneous reporting to the US FDA uncovered relatively greater incidence of pneumonia in people prescribed clozapine, olanzapine and antipsychotic polypharmacy (compared with haloperidol).[2] In 2024, a 20-year observational study (n = 61,889) in Finland found increased risk of hospitalisation with pneumonia in people prescribed antipsychotic monotherapy compared with no antipsychotic use.[3]

There is some dispute over the causal association between antipsychotic use and risk of pneumonia. One study looked at the incidence of pneumonia in over 8,000 people before and after starting various antipsychotics and found no change overall (or for any individual antipsychotic).[4] Another analysis, a case–control study, found that duration of antipsychotic use was just one of three factors linked to increased risk of pneumonia (the others being severity of illness and comorbidity index).[5] Schizophrenia itself seems to afford a higher risk of complications (e.g. admission to intensive care) in people diagnosed with pneumonia,[6] although neither diagnosis nor age appears to modify the effect of antipsychotic use on pneumonia.[7] Risk of antipsychotic-associated pneumonia is increased in patients with Alzheimer's disease and those without.[8] Factors associated with antipsychotic-induced pneumonia are listed in Table 1.47.

Table 1.47 Factors associated with antipsychotic-induced pneumonia.

Treatment factors	■ Antipsychotics with high anticholinergic effects (e.g. clozapine and olanzapine)[3,9] ■ High antipsychotic doses[10] ■ Antipsychotic polypharmacy*[11–13] ■ Concomitant benzodiazepines[14,15] ■ Concomitant mood stabilisers**
Patient factors	■ Decreased CYP2C19 and CYP1A2 activity[16] ■ Smoking[17] ■ Obesity[17] ■ Diagnosis of schizophrenia (especially TRS)[17]

* Not found in one study.[3]
** Lithium seems to have a protective effect.

The risk of pneumonia seems to be most pronounced in people prescribed antipsychotics with high anticholinergic effects (notably clozapine and high-dose olanzapine or quetiapine) and is probably dose dependent.[3,9] Among antipsychotics, clozapine is most often associated with pneumonia, with an estimated incidence of up to 30%[16] (although TRS itself increases risk of pneumonia by two-thirds).[18] In two studies, clozapine re-exposure was associated with a greater risk for recurrent pneumonia than the risk of baseline pneumonia with initial clozapine treatment.[16,19] Aripiprazole (and probably other

dopamine partial agonists) seem to have a lower risk of pneumonia than pure dopamine antagonists.[9] Another study found amisulpride (a dopamine antagonist with minimal anticholinergic activity) is not linked to pneumonia.[11]

Mechanisms

Although studies rarely distinguish between the various forms of pneumonia, cases of antipsychotic-induced aspiration, infective (viral and bacterial) and hypersensitivity pneumonia have been documented.[16] The mechanism by which antipsychotics increase the risk of such pneumonia is not known but is probably multifactorial. Proposed mechanisms are outlined in Box 1.2.

Box 1.2 Proposed mechanisms for antipsychotic-induced pneumonia

- Sedation
- Dystonia or dyskinesia
- Dry mouth
- General poor physical health
- Reduced immune response*
- Clozapine-specific: hypersalivation, constipation

* Clozapine is associated with antibody deficiency and greater use of antibiotics. This increased risk of infection is not related to neutrophil counts.[20]

An increased risk of pneumonia should probably be assumed for all patients taking any antipsychotic (but especially clozapine)[21] for any period. All patients should be very carefully monitored for signs of chest infection and effective treatment started promptly. Consideration should be given to using COVID-19, influenza and pneumococcal vaccines, although there is no direct evidence to support benefit for pneumonia prevention in this specific group of patients. Those patients prescribed clozapine should be proactively monitored and treated for hypersalivation. Pneumonia is likely to increase clozapine levels (see section on clozapine: common adverse effects in this chapter) so close monitoring is required. Slower-than-usual clozapine titration may prevent cases of hypersensitivity pneumonia.[14] Extra vigilance is required when re-exposing to patients with history of clozapine-induced pneumonia who are taking clozapine. With all cases, early referral to general medical services should be considered where there is any doubt about the severity or type of chest infection.

Summary

- Assume that the use of all antipsychotics increases the risk of pneumonia, but especially clozapine and high-dose olanzapine or quetiapine.
- Concomitant benzodiazepine use should be avoided, where possible.
- Monitor all patients for signs of chest infection and treat promptly.
- Offer vaccination against COVID-19, influenza and pneumococcus to all high-risk patients.

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Switching antipsychotics

Table 1.48 gives a summary of recommendations for switching antipsychotic medications because of poor tolerability.

Table 1.48 Switching antipsychotic medications because of poor tolerability – a summary of recommendations.

Adverse effect	Suggested medications	Alternative medications
Acute EPS[1–8] (dystonia, parkinsonism, bradykinesia)	Aripiprazole Brexpiprazole Cariprazine Olanzapine Quetiapine	Clozapine Lurasidone Ziprasidone
Akathisia[2,9,10]	Olanzapine Quetiapine	Clozapine Brexpiprazole
Dyslipidaemia[7,8,11–16]	Amisulpride Aripiprazole* Lurasidone Ziprasidone	Asenapine Brexpiprazole Cariprazine
Impaired glucose tolerance[7,8,15,17–21]	Amisulpride Aripiprazole* Lurasidone Ziprasidone	Brexpiprazole Cariprazine Haloperidol
Hyperprolactinaemia[7,8,15,22–29]	Aripiprazole* Brexpiprazole Cariprazine Lurasidone Quetiapine	Clozapine Olanzapine Ziprasidone
Postural hypotension[8,15,30]	Amisulpride Aripiprazole Brexpiprazole Cariprazine Lurasidone	Haloperidol Sulpiride Trifluoperazine
QT prolongation[27,31–38]	Brexpiprazole Cariprazine Lurasidone Paliperidone	Low-dose monotherapy of any drug not formally contraindicated in QT prolongation (with ECG monitoring)
Sedation[7,8,27]	Amisulpride Aripiprazole Brexpiprazole Cariprazine Risperidone Sulpiride	Haloperidol Trifuoperazine Ziprasidone
Sexual dysfunction[8,29,39–46]	Aripiprazole Brexpiprazole Cariprazine Lurasidone Quetiapine	Clozapine

(*Continued*)

Table 1.48 (*Continued*)

Adverse effect	Suggested medications	Alternative medications
Tardive dyskinesia[47–53]	Clozapine	Aripiprazole Olanzapine Quetiapine
Weight gain[16,36,38,54–65]	Amisulpride Aripiprazole* Brexpiprazole Cariprazine Lurasidone Ziprasidone	Asenapine Haloperidol Trifluoperazine

* There is evidence that both switching to and co-prescription of aripiprazole can be associated with reductions in body weight and plasma prolactin levels, better lipid profiles and a decrease in plasma glucose levels.[66–69]

Lumateperone and pimavanserin are not listed in the table because of their limited availability. Both drugs cause few or no EPSEs or akathisa, have no effect on prolactin or blood pressure and cause minimal weight gain and metabolic disturbance.[70,71] Pimvanserin prolongs QT,[72] whereas lumateperone seems to have no effect on the ECG.[73] To see the relative effect of all antipsychotics on these parameters, please see the Psymatik Treatment Optimizer.[74]

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Venous thromboembolism

Evidence of an association

Antipsychotic treatment was first linked to an increased risk of thromboembolism in 1965.[1] Over a 10-year observation period, 3.1% of 1,590 patients developed thromboembolism, of whom 9 (0.6%) died. However, the use of antipsychotic medication is a proxy for severe and enduring mental illness and so observed associations with antipsychotics may at least partly reflect inherent pathological processes in the conditions for which they are prescribed. To some extent, the relative contributions to the risk of thromboembolism of antipsychotic treatment and the conditions they treat remain to be clearly defined.

In a case–control study of nearly 30,000 patients,[2] risk of thromboembolism was greatly increased overall in people prescribed antipsychotics (odds ratio [OR] 7.1). The increased risk was driven by low-potency phenothiazines (thioridazine, chlorpromazine; OR 24.1) and was seen chiefly in the first few weeks of treatment. Absolute risk of VTE was low – it was seen in only 0.14% of patients (about 1 in every 714 people). A secondary analysis suggested no association with diagnosis, apparently ruling out an association with schizophrenia itself.

A later meta-analysis of seven case–control studies[3] confirmed an increased risk of thromboembolism with low-potency FGAs (OR 2.91) and suggested lower but significantly increased risks with all types of antipsychotics. Later, a meta-analysis of 17 studies[4] 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.[5–7] One study reported a risk for older people taking antipsychotics as 43 per 10,000 patient years.[7] Other noteworthy findings were a substantially increased association with thromboembolism for prochlorperazine – a drug not always (or even often) prescribed for psychotic disorders[5] – and an increased risk linked to antipsychotic dosage (risk was quadrupled in high-dose patients).[6] An association with prochlorperazine prescribing had previously been suggested by a UK study.[8] 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.[9,10] Several meta-analyses have been published in recent years. The findings of two studies are presented in Table 1.49.

Table 1.49 Findings of meta-analyses of the risk of pathological blood clotting.

		Relative risk vs no use			
Reference	**Number of studies included**	**FGAs (OR)**	**SGAs (OR)**	**All anti-psychotics (OR)**	**Comments**
Di et al, 2021[9]	22	1.83 VTE/PE	1.75 VTE 3.79 PE 2.06 VTE/PE	1.53 VTE 3.69 PE 1.60 VTE/PE	Highest risk in younger patients (<60 years). Low-potency FGAs highest risk.
Liu et al, 2021[10]	28	1.47 VTE/PE	1.62 VTE/PE	1.55 VTE 3.68 PE 2.01 VTE/PE	New users of antipsychotics had higher risk than continuing patients. Risk slightly elevated with higher doses vs low doses. Similar effect sizes for FGA vs SGA.

FGA, first-generation antipsychotic; OR, odds ratio; PE, pulmonary embolism; SGA, second-generation antipsychotic; VTE, venous thromboembolism.

Mechanisms

Several mechanisms have been suggested to explain the association between antipsychotics and thromboembolism. These proposed mechanisms are outlined in Box 1.3.

Box 1.3 Proposed mechanisms for antipsychotic-associated venous thromboembolism[11–15]

Sedation*
Obesity*
Hyperprolactinaemia*
Elevated phospholipid antibodies
Elevated platelet aggregation**
Elevated plasma homocysteine
Elevated tissue plasminogen activator
Elevated platelet count

* Some evidence that these factors are not the mechanism for antipsychotic-induced thromboembolism.[16]
** In vitro data suggest radically different effects on platelet aggregation for different antipsychotics.[12]

Outcomes

Increased risk of thromboembolism is reflected in numerous published reports of elevated incidence of pulmonary embolism,[17] stroke[18] and myocardial infarction.[19] A 2022 study suggested that antipsychotics increase the risk of fatal thromboembolism (OR 6.68),[17] although, again, the absolute risk remains low.

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.

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REFRACTORY SCHIZOPHRENIA AND CLOZAPINE

Clozapine initiation schedules

Clozapine dosing regimen

Many of the adverse effects of clozapine are dose dependent and linked to speed of titration. Adverse effects tend to be more common and severe at the beginning of treatment. Titration is required to allow tolerance to develop to the pharmacological effects of clozapine. The degree to which tolerance ultimately develops is evidenced by the fact that standard maintenance doses would be fatal in a clozapine-naïve person.[1]

To minimise adverse effects and maximise the chances of successful titration, it is clearly important to start treatment at a low dose and to increase dosage slowly. There are many different opinions on exactly how slowly clozapine should be titrated.

Titration schedules should certainly be individualised. This is something everyone agrees on. There are, however, competing imperatives: the need to establish an effective dose quickly, the need to allow time for the patient to gain tolerance to adverse effects, the need to minimise the risk of myocarditis and the need to account for very different rates of clozapine metabolism.

The aim of dose titration is to attain a minimum therapeutic plasma concentration of approximately 350mcg/L over the course of about 3 weeks. The average dose at which this plasma concentration is achieved varies according to sex, smoking status and genetic variability in cytochrome enzyme activity, such as lower CYP1A2 activity for people of Asian or Native American heritage.[2] Achieving a therapeutic concentration over a period of 2–3 weeks will require very different titration schedules for people with different metabolic capacities.

A dose that will achieve a plasma concentration of 350mcg/L for an individual patient can be estimated by extrapolation of concentrations reported for different populations. This method groups patients according to sex and smoking status to produce predictive models.[3–5] Results are summarised in Table 1.50.

Table 1.50 Clozapine dose (in mg/day) with the highest likelihood of providing a plasma concentration of 350mcg/L, estimated by extrapolation of concentrations reported for different populations.

			Reeves[5]		
Patient group	**Rostami-Hodjegan[3] (ethnicity not described)**	**Schoretsanitis[4] (White Europeans)**	**Asian**	**White**	**Afro-Caribbean**
Female non-smoker	265	236	175	225	250
Female smoker	435	357	25	300	325
Male non-smoker	325	256	225	275	300
Male smoker	525	368	250	375	400

Alternatively, an attempt can be made to include other factors into the predictive models, such as cytochrome enzyme metaboliser status, ancestry and concurrent medication to predict target dose and corresponding titration schedule.[2,6] The most accurate dose prediction is given by a genetic test that incorporates gene variant activity scores into a mathematical algorithm.[7] Results from this test can be used to select a titration schedule from the four provided here by choosing the schedule with the calculated target dose closest to the final dose in the schedule.

Clozapine should normally be started at a dose of 6.25mg – this is effectively a test dose for everyone. On subsequent days, the dose can be increased according to the selected schedule, provided the patient is tolerating clozapine. A flexible approach should be taken, altering schedules in response to adverse effects if needed (e.g. pausing titration, returning temporarily to a dose that was previously tolerated, or slowing the speed and/or reducing the magnitude of dose increases). Wherever possible, plasma concentration testing should be used in conjunction with adverse effect monitoring to inform dosing. Monitoring blood levels can help ensure that titration does not overshoot the target blood level. Use of point of care testing (delivering results within minutes) means this is possible without interrupting the dose regimen.[8,9] If results cannot be obtained rapidly then levels should be checked when titration is complete or if adverse effects cause problems during titration. The dose should be divided (usually into two daily doses) and, if sedation is a problem, the larger portion of the dose can be given at night.

The following tables outline four different starting regimens for clozapine. These are based on over 30 years' clinical experience and the published protocols described above. The concept behind the schedules is that every patient reaches, over 20 days, the lowest dose estimated to give a therapeutic blood concentration. The schedules should ensure that the rate of increase in clozapine plasma concentration is approximately the same for all people. This is important to note: the rate of *dose* increase may be very different in these schedules, but the rate of increase in *blood concentration* is the same. The reason we have moved away from providing a single titration schedule is because a single schedule has the opposite effect: the rate of change of plasma level will be vastly different for people with different metabolic capacities.

More rapid increases than those suggested here have been used, as has an extremely slow titration (the 'Laitman protocol' allows dose increases of only 25mg per week). Slower titration may be necessary where sedation or other dose-related side effects are severe, in the elderly, the very young, those who are physically compromised or those who have poorly tolerated other antipsychotics.

The target dose for patients with Asian ancestry should be around 65–75% of that given below. For older patients (>70 years), the target dose is around 50% of that given in the tables.

Faster titrations

The titration schedules listed here are aimed at maximising the likelihood of a successful titration – the aim is to establish the patient on a well-tolerated and therapeutic dose of clozapine. Faster titrations can be used and have been widely used in the past. The main risk with faster titrations, assuming the patient tolerates such a regimen, is myocarditis (see section on clozapine: serious cardiovascular adverse effects in this chapter). If tolerability is not assumed, the main risk is titration failure resulting from the patient's inability or unwillingness to tolerate rapid titration.

Female non-smoker – target dose 225mg/day.

Day	Morning dose (mg)	Evening dose (mg)	Total daily dose (mg)
1	–	6.25	6.25
2	–	6.25	6.25
3	6.25	6.25	12.5
4	6.25	12.5	18.75
5	12.5	12.5	25
6	12.5	12.5	25
7	25	25	50
8	25	25	50
9	25	50	75
10	25	50	75
11	50	50	100
12	50	50	100
13	50	75	125
14	50	75	125
15	75	75	150
16	75	75	150
17	75	100	175
18	75	100	175
19	100	100	200
20	100	100	225

Female smoker – target dose 300mg/day.

Day	Morning dose (mg)	Evening dose (mg)	Total daily dose (mg)
1	–	6.25	6.25
2	6.25	6.25	12.5
3	12.5	12.5	25
4	12.5	12.5	25
5	25	25	50
6	25	25	50
7	25	50	75
8	25	50	75
9	50	50	100
10	50	50	100
11	50	75	125

Day	Morning dose (mg)	Evening dose (mg)	Total daily dose (mg)
12	50	75	125
13	75	75	150
14	75	75	150
15	75	100	175
16	100	100	200
17	100	125	225
18	125	125	250
19	125	150	275
20	150	150	300

Male non-smoker – target dose 250mg/day.

Day	Morning dose (mg)	Evening dose (mg)	Total daily dose (mg)
1	–	6.25	6.25
2	–	6.25	6.25
3	6.25	6.25	12.5
4	6.25	12.5	18.75
5	12.5	12.5	25
6	12.5	12.5	25
7	25	25	50
8	25	25	50
9	25	50	75
10	25	50	75
11	50	50	100
12	50	50	100
13	50	75	125
14	50	75	125
15	75	75	150
16	75	75	150
17	75	100	175
18	100	100	200
19	100	125	225
20	125	125	250

Male smoker – target dose 375mg/day.

Day	Morning dose (mg)	Evening dose (mg)	Total daily dose (mg)
1	–	6.25	6.25
2	6.25	6.25	12.5
3	12.5	12.5	25
4	12.5	25	37.5
5	25	25	50
6	25	25	50
7	25	50	75
8	25	50	75
9	50	50	100
10	50	75	125
11	75	75	150
12	75	100	175
13	100	100	200
14	100	125	225
15	125	125	250
16	125	150	275
17	150	150	300
18	150	175	325
19	175	175	350
20	175	200	375

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Intramuscular clozapine

Intramuscular clozapine is a short-term intervention for patients with a treatment-refractory psychotic disorder who refuse oral medication. It is always used with a view to converting to oral clozapine once treatment is established.[1] IM clozapine has also been used for patients who are unable to take oral medication because of physical illness.[2] Although evidence is relatively limited, observational data indicate that initiating treatment with IM clozapine does not adversely affect long-term adherence to oral treatment.[1,3] IM clozapine is similar to oral clozapine in respect to short-term safety and tolerability.[4,5] The IM preparation is unlicensed in the UK and many other countries, so adequate precautions should be taken and patient or carer consent obtained.

General recommendations for prescribing intramuscular clozapine in adults are summarised in Table 1.51.

Table 1.51 General recommendations for prescribing intramuscular clozapine.

Strength	25mg/mL
Maximum dose*	100mg (4mL) per site
Oral equivalent dose	The oral bioavailability of clozapine is about half that of the IM injection (e.g. 50mg IM injection daily = 100mg tablets/oral solution daily)
Site of administration†	The manufacturer states deep intramuscular gluteal injection
Maximum treatment length‡	Before administering each injection, the patient should be offered oral clozapine. Clozapine injection should be used for the shortest duration possible (maximum 2 weeks consecutively).
Dosing frequency	To minimise the number of injections, once daily dosing is preferred
Monitoring	After each administration, patients should be observed every 15 minutes for the first 2 hours to check for excess sedation. Routine clozapine monitoring also applies.

* For doses >100mg, the dose may be divided and administered into two sites.
† Case series data report administration via lateral thigh or deltoid – note that the injection is painful[3] and the maximum volume for the deltoid route is 2mL (50mg).
‡ Case series data report use of intramuscular clozapine for up to 96 days.[3,4] Injection site reactions become common with longer-term treatment.
Note: Simultaneous injection of IM clozapine and parenteral benzodiazepines has not been studied. If IM benzodiazepines are required leave at least **1 hour** between administration of IM clozapine and IM benzodiapines.

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Optimising clozapine treatment

Using clozapine alone

Target dose (dose is best adjusted according to patient tolerability and plasma level)	■ Average dose in UK is around 450mg/day[1] ■ Response usually seen in the range 150–900mg/day[2] ■ Lower doses required in the elderly, females, people of Asian or Native American heritage, non-smokers, and those prescribed certain enzyme inhibitors[3,4] ■ Genetic testing of CYP enzymes accurately predicts therapeutic dose[5]
Plasma levels	■ Most studies indicate that threshold for response is in the range 350–420mcg/L.[6,7] Threshold in some may be as high as 500mcg/L.[8] One study suggests a minority of patients only respond at levels between 500 and 1000mcg/L.[9] ■ In male smokers who cannot achieve therapeutic plasma levels, metabolic inhibitors (fluvoxamine[10,11] or cimetidine,[12] for example) can be co-prescribed, but extreme caution is required[13] ■ Importance of norclozapine levels not established. Clozapine/norclozapine ratio is not a reliable indicator of partial adherence nor of clozapine metabolism.[14]

Clozapine augmentation

Clozapine augmentation has become common practice because inadequate response to clozapine on its own is a frequent clinical event. The evidence base supporting augmentation strategies is fairly large but, despite more than 50 reviews and meta-analyses on the subject, it remains insufficient to allow the development of any algorithm or schedule of treatment options.[15] 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.

Network meta-analyses examining pharmacological augmentation options often draw conclusions based on only a few studies of dubious merit and may come to different conclusions.[16–19] That mirtazapine augmentation has the largest effect size (and the addition of memantine, the second largest) is something most recent systematic reviews agree on[17–19] although, with both strategies, the supporting evidence was, at best, weak. Meta-analyses of antipsychotic augmentation of clozapine suggest either no effect,[20] a small effect in long-term studies,[21] a very small effect overall[22] or small effects in specific symptom domains.[23] Few high-quality studies in this area exist – when only large, high-quality studies are included, most meta-analyses report no benefit to pharmacological augmentation.[24] This is consistent with imaging studies – investigations into dopaminergic activity in refractory schizophrenia suggest there is no overproduction of dopamine.[25,26] Dopamine antagonists are thus unlikely to be effective.

All augmentation attempts should be carefully monitored and, if no clear benefit is forthcoming, abandoned after 3–6 months. The addition of another drug to clozapine treatment might be expected to worsen overall adverse effect burden, so continuing ineffective treatment is only likely to be detrimental. In some cases, however, the addition of an augmenting agent may reduce the severity of some adverse effects (e.g. weight gain, dyslipidaemia – see below) or allow a reduction in clozapine dose. The addition of aripiprazole to clozapine may be particularly effective in reversing metabolic effects.[27,28] International consensus guidelines recommend (after optimising plasma levels) tailoring augmentation agent choice to residual symptoms, and adding amisulpride or aripiprazole

for positive symptoms, antidepressants for negative symptoms, and mood stabilisers for suicidal ideation or aggression.[24] Recent data on cariprazine suggest particular benefit on negative symptoms unresponsive to clozapine.[29–32]

Table 1.52 shows suggested treatment options (in alphabetical order) where 3–6 months of optimised clozapine alone at maximum tolerated dose has provided unsatisfactory benefit.

Table 1.52 Suggested options for augmenting clozapine.

Option	Comment
Add amisulpride[33–40] (400–800mg/day)	Some evidence and experience suggest that amisulpride augmentation may be worthwhile. Five small RCTs (not all positive), the largest of which showed some benefit to positive symptoms and cognition, two of which found an increased adverse-effect burden, including cardiac adverse effects.[41,42] May allow clozapine dose reduction.[43]
Add antipsychotic long-acting injection[15,44–48]	Case series and observational studies suggest benefits to residual symptoms as well as number and length of hospitalisations. Appears to be well tolerated. Does not protect against relapse if clozapine is not taken.
Add aripiprazole[27,49–52] (15–30mg/day)	Very limited evidence of therapeutic benefit, although a meta-analysis suggests some effect.[53] Reduces weight and LDL cholesterol.[53] LAI has been used.[54,55]
Add cariprazine[56]	Three small case series and one pilot study suggest benefit, particularly for negative symptoms.[29–32] Two case reports of worsening psychosis.[57]
Add haloperidol[51,58,59] (2–3mg/day)	Modest evidence of benefit
Add lamotrigine[60–62] (25–300mg/day)	May be useful in partial or non-responders. May reduce alcohol consumption.[63] Several equivocal reports.[64–66] Some meta-analyses suggest moderate effect size[67] but this is largely influenced by two outlying studies.[68]
Add lurasidone[32,69]	One case series, one retrospective chart review and a case report. Appears to be well tolerated.
Add omega-3 triglycerides[70,71] (2–3g EPA daily)	Modest, and somewhat contested, evidence to support efficacy in non- or partial responders to antipsychotics, including clozapine
Add risperidone[72,73] (2–6mg/day)	Supported by an RCT but there are also two negative RCTs, each with minuscule response rates.[74,75] Small number of reports of increases in clozapine plasma levels. LAI also an option.[55,76] Paliperidone LAI has also been used.[48,55]
Add sodium valproate[68,77] (400–800mg/day)	Pooled effects from five Chinese RCTs[68] suggest improvement in positive symptoms, although studies are mostly of poor quality. Cochrane suggests benefit of adding valproate to antipsychotics in general, especially for excitement and aggression.[78]
Add sulpiride[79] (400mg/day)	May be useful in partial or non-responders. Supported by a single randomised trial in English and three in Chinese.[80] Overall effect modest.
Add topiramate[81–85] (50–300mg/day)	Two positive RCTs, two negative. Can worsen psychosis in some.[61,86] Two meta-analyses including hitherto unknown Chinese data[68,87] suggested robust effect on positive and negative symptoms, substantial weight loss but often with psychomotor slowing and attention difficulties.
Add ziprasidone[88–91] (80–160mg/day)	Supported by three RCTs.[91,92] Associated with QTc prolongation. Rarely used.

Note: consider the use of mood stabilisers and/or antidepressants especially where mood disturbance is thought to contribute to symptoms.[93–95]
EPA, eicosapentaenoic acid; LAI, long-acting injection; LDL, low-density lipoprotein.

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 supported[96] and likely to exacerbate metabolic adverse effects. Studies of pimozide[97,98] and sertindole[99] have shown no effect. One small RCT supports the use of Ginkgo biloba[100] and another two support the use of memantine.[101,102] Another study suggests possible benefit of augmentation with acetyl-L-carnitine[103] and a case study reports good outcome with thyroxine.[104] A single RCT describes successful use of sodium benzoate.[105] Minocycline is probably not effective.[77,106] Glycine may be effective for positive symptoms, but studies are of poor quality.[107] A small case series (n = 6) found benefit from adding pimavanserin.[108] N-acetylcysteine is probably of no benefit.[109–111]

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Alternatives to clozapine

Clozapine has the strongest evidence for efficacy for schizophrenia that has proved refractory to adequate trials of standard antipsychotic medication. About three-quarters of these patients are treatment resistant from the onset of illness.[1] Where treatment resistance has been established, clozapine treatment should not be delayed or withheld.[2,3] The practice of using successive antipsychotic medications (or the latest) instead of clozapine is widespread but not supported by any research. Where clozapine cannot be used because of toxicity or patient refusal or unwillingness to comply with the mandatory monitoring tests, other drugs or drug combinations may be tried (Table 1.53). In practice, outcome is usually disappointing and long-term data on efficacy and safety are generally lacking.

Available data do not allow any distinction between treatment regimens to be drawn, particularly choice of antipsychotic medication,[4,5] but it seems wise to use single drugs before trying polypharmacy options. Olanzapine is perhaps the most often used antipsychotic monotherapy, usually in doses 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.[6] In people who have stopped clozapine, clozapine reintroduction and olanzapine are the only effective treatments.[7] Among unconventional agents, minocycline and ondansetron have the advantage of low toxicity and good tolerability. With advances in the understanding of the neurobiology of TRS, non-dopaminergic treatments are an area of active research. Glutamatergic drugs such as evenamide[8] (although bitopertin is inactive),[9] $5HT_{2A}$ inverse agonists,[10] trace amine-associated receptor 1 (TAAR1) agonists and muscarinic receptor agonists such as xanomeline may hold some promise.[11]

Many of the treatments listed in Table 1.53 are somewhat experimental and some of the compounds difficult to obtain (e.g. glycine, D-serine, sarcosine, etc.). 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.

Table 1.53 Alternatives to clozapine (treatments are listed in alphabetical order – no preference is implied by position in table).

Treatment	Comments
Allopurinol 300–600mg/day (+ antipsychotic)[12–15]	Increases adenosinergic transmission, which may reduce effects of dopamine. Three positive RCTs.[12,13,15]
Amisulpride[16] (up to 1200mg/day)	Single, small open study
Antipsychotic polypharmacy	Various antipsychotics in combination have been used. Data are limited, mainly in the form of case reports, open and naturalistic studies. RCTs show no advantage for polypharmacy over monotherapy.[17]
Aripiprazole[18,19] (15–30mg/day)	Single RCT indicating moderate effect in patients resistant to risperidone or olanzapine (+ others). Higher doses (60mg/day) have been used.[20]

Table 1.53 (*Continued*)

Treatment	Comments
Asenapine (+ antipsychotic)[21]	A post-hoc analysis of a phase III extension study showed that add-on asenapine may be beneficial in some patients with TRS
Blonanserin (+ antipsychotic)[22]	Atypical antipsychotic licensed in Japan and Korea. A retrospective cohort study involving 69 patients showed improved PANSS scores with add-on blonanserin[23]
Cariprazine (+ antipsychotic)[24–26]	Case reports of successful use of cariprazine as monotherapy or as add-on
CBT[27]	Non-drug therapies should always be considered[28]
Deep brain stimulation	Effectiveness of nucleus accumbens and subgenual anterior cingulate cortex targeted deep brain stimulation demonstrated in 4 of 7 patients with TRS[29]
D–Alanine 100mg/kg/day (+ antipsychotic)[30]	Glycine (NMDA) agonist. One positive RCT.
D–Serine 30mg/kg/day (+ olanzapine)[31]	Glycine (NMDA) agonist. One positive RCT.
D–Serine up to 3g as monotherapy[32]	Improved negative symptoms in one RCT, but inferior to high-dose olanzapine for treatment of positive symptoms
ECT[33]	Open studies suggest moderate effect, as does a retrospective study.[34] Often reserved for last-line treatment in practice but can be successful in the short[35] and long[36] term. A 2024 RCT was negative.[37]
Estradiol 100–200mcg transdermal/day (+ antipsychotic)[38]	Oestrogens may be psychoprotective and/or antipsychotic in women of child-bearing age especially on positive symptoms, at higher doses.[39] Contraindications include being post-menopausal, history of VTE, stroke, breast cancer, migraine with aura. Unopposed estradiol increases risk of endometrial hyperplasia and malignancy – consult an endocrinologist. Evidence in men is lacking.
Famotidine 100mg bd + antipsychotic[40]	H_2 antagonist. One short (4-week) RCT suggested some benefit in overall PANSS and CGI scale scores.
Ginkgo biloba (+ antipsychotic)[41]	A systematic review of studies published in China showed improvements in total and negative symptoms
Lurasidone up to 240mg/day[42] (+ vortioxetine)	One RCT comparing standard with high-dose lurasidone produced comparable improvements in TRS when given up to 24 weeks.[43] Appears to be well tolerated. The addition of vortioxetine to lurasidone was effective in a small case series.[44]
Memantine 20mg/day (+ antipsychotic)[45–47]	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.
Minocycline 200mg/day (+ antipsychotic)[48,49]	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* = 52) of augmentation of clozapine showed improvement in some symptoms.[50] RCT evidence of neuroprotective effect in early psychosis.[51]
Mirtazapine 30mg/day (+ antipsychotic)[52–54]	Two RCTs, one negative,[53] one positive.[52] Effect seems to be mainly on positive symptoms.
N–acetylcysteine 2g/day (+ antipsychotic)[40]	One RCT suggests small benefits in negative symptoms and rates of akathisia. Another RCT showed benefits in chronic schizophrenia.[55] Case study of successful use of 600mg/day.[56] A large RCT failed to show any benefit when added to clozapine.[57]

(*Continued*)

Table 1.53 (*Continued*)

Treatment	Comments
Olanzapine[58–63] 5–25mg/day	Supported by some well-conducted trials but clinical experience disappointing. Some patients show moderate response.
Olanzapine 30–60mg/day	High-dose olanzapine is more effective than other non-clozapine antipsychotics.[64] High-dose olanzapine is not atypical[65] and can be poorly tolerated[66] with gross metabolic changes.[67]
Olanzapine + glycine[68] (0.8g/kg/day)	Small, double-blind crossover trial suggests clinically relevant improvement in negative symptoms
Olanzapine + lamotrigine[66,69] (up to 400mg/day)	Reports contradictory and rather unconvincing. Reasonable theoretical basis for adding lamotrigine which is usually well tolerated.
Ondansetron 8mg/day (+ antipsychotic)	A systematic review of RCTs showed improvements in negative symptoms and general psychopathology. Effect on cognition inconclusive.[70]
Paliperidone LAI	Improvement in endocrine and hepatic parameters and lower antipsychotic exposure in a small number of patients switched from clozapine to paliperidone 3-monthly. No data on clinical outcomes.[71]
Pimavanserin (+ antipsychotics)	Clinical improvement with pimavanserin alone or as adjunct to clozapine or other antipsychotics in 10 patients, 6 of whom had failed to respond to clozapine[72]
Propentofylline + risperidone[73] (900mg + 6mg/day)	One RCT suggests some activity against positive symptoms
Quetiapine[74–77]	Very limited evidence and clinical experience not encouraging. High doses (>1200mg/day) have been used but are no more effective.[78]
Raloxifene 60–120mg/day (+ antipsychotic)[39]	Selective oestrogen receptor modulator. May offer benefits of estradiol without long-term risks, but sexual dysfunction and weight gain may occur.[39] Data in non-treatment resistance are rather conflicting, with two overlapping positive trials[79,80] and one negative trial.[81] One positive RCT in refractory psychosis in women.[82] Evidence in men is lacking.
Riluzole 100mg/day + risperidone up to 6mg/day[83]	Glutamate modulating agent. One RCT demonstrated improvement in negative symptoms.
Risperidone[84–86] 4–8mg/day	Doubtful efficacy in true TRS but some supporting evidence. May also be tried in combination with glycine[68] or lamotrigine[60] or indeed with other SGAs.[87]
Risperidone LAI 50/100mg 2/52[88]	One RCT showing good response for both doses in refractory schizophrenia. Plasma levels for 100mg dose similar to 6–8mg/day oral risperidone.
Ritanserin + risperidone (12mg + 6mg/day)	$5HT_{2A/2C}$ antagonist. One RCT suggests small effect on negative symptoms.
Sarcosine (2g/day)[89,90] (+ antipsychotic)	Enhances glycine action. Supported by two RCTs. Benefits may be in patients with non-TRS.[91]
Sertindole[92] (12–24mg/day)	One large RCT (conducted in 1996–68 but published in 2011) suggested good effect and equivalence to risperidone. Around half of subjects responded. Another RCT[93] showed no effect at all when added to clozapine. Little experience in practice.
Topiramate (300mg/day) (+ antipsychotic)[94]	Small effect shown in single RCT. Induces weight loss. Cognitive adverse effects likely. Teratogenic.

(*Continued*)

Table 1.53 (*Continued*)

Treatment	Comments
Transcranial magnetic stimulation[95,96]	Conflicting results
Ursodeoxycholic acid[97]	Single case reports
Valproate[98]	Doubtful effect but may be useful where there is a clear affective component
Yokukansan (+ antipsychotic)[99]	Japanese herbal medicine, partial agonist at D_2 and $5HT_{1A}$, antagonist at $5HT_{2A}$ and glutamate receptors. Potential small benefit in excitement/hostility symptoms. Another 12-week double-blind placebo-controlled RCT showed modest symptomatic improvement.[100]
Ziprasidone 80–160mg/day[101–103]	Two good RCTs. One[103] suggests superior efficacy to chlorpromazine in refractory schizophrenia, the other[101] suggests equivalence to clozapine in subjects with treatment intolerance/resistance. Disappointing results in practice. Supratherapeutic doses offer no advantage.[104]
Zotepine 300mg/day+[105]	One study showed that some patients do not deteriorate when switched from clozapine to zotepine

CGI, Clinical Global Impression; LAI, long-acting injection; NMDA, N-methyl-D-aspartate; PANSS, Positive and Negative Syndrome Scale; TRS, treatment-resistant schizophrenia; VTE, venous thromboembolism.

Summary of alternatives to clozapine

Table 1.54 provides a summary of alternatives to clozapine in refractory schizophrenia.

Table 1.54 Summary of alternatives to clozapine in refractory schizophrenia.

Treatment	Examples	Comments	Strength of evidence
Monotherapy using non-clozapine antipsychotics in standard or high doses	Aripiprazole 15–30mg daily Olanzapine 25–60mg daily	Evidence of efficacy for any antipsychotic other than clozapine in refractory schizophrenia is controversial. Some data suggest efficacy for olanzapine above licensed doses but at the risk of metabolic adverse effects.	Weak +
Non-clozapine antipsychotic polypharmacy	Amisulpride + olanzapine, quetiapine + amisulpride, aripiprazole + olanzapine, and various other combinations	Polypharmacy is common in clinical practice. Evidence from controlled studies limited but open studies and real-world data suggest some effectiveness. Burden of adverse effects is increased.	Weak +
Anti-inflammatory agents as adjuncts to antipsychotics	N-acetylcysteine, NSAIDs, minocycline, oestrogens, aspirin, omega-3 fatty acids	A heterogeneous group of medicinal agents with inflammatory properties have been tried as adjuncts. Possible benefits in negative and cognitive symptoms but sample sizes have been small.	Very weak ±
NMDA receptor modulators as adjuncts	Memantine, glycine, D-serine and sarcosine	Rarely used in clinical practice. May have some benefit in negative symptoms.	Very weak ±

(*Continued*)

Table 1.54 (*Continued*)

Treatment	Examples	Comments	Strength of evidence
Physical treatments	ECT, rTMS, tDCS, DBS	Best evidence for ECT as adjunct to clozapine. Others still largely experimental.	Modest ++
Adjunctive antidepressants	Mirtazapine, vortioxetine, SSRIs	Limited data available suggest small benefits in negative and cognitive symptoms.	Weak +
Adjunctive anticonvulsants	Lamotrigine, topiramate, sodium valproate, carbamazepine	Data difficult to interpret	Weak +
Psychological therapies	CBT	Conflicting findings, effects small.	Very weak ±

CBT, cognitive behavioural therapy; DBS, deep brain stimulation; NSAIDs, non-steroidal anti-inflammatory drugs; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

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Restarting clozapine after a break in treatment

Interruptions in clozapine treatment are commonplace.[1] Patients prescribed clozapine should be advised to contact their prescriber if they stop taking the medication. This is partly because, if clozapine treatment is stopped abruptly, there is a need to monitor for symptoms of cholinergic rebound, such as nausea, vomiting, diarrhoea, sweating and headache,[2,3] as well as the possible emergence of dystonias, dyskinesias and catatonic symptoms.[4–7] If the last dose of clozapine was more than 48 hours ago, it should be re-introduced using a suitable dosage titration schedule.[8]

Depending on the time since clozapine was last taken, it may be feasible to re-titrate the dose to a therapeutic level more rapidly than is recommended for initial treatment. While there is some evidence to suggest that faster titrations may be safe in those patients naïve to clozapine[2] as well as those re-starting it,[3] there is the risk that such schedules could lead to drug discontinuation because of adverse effects. The risk of myocarditis, pneumonia, agranulocytosis and seizures, as well as the occurrence of adverse effects such as tachycardia and orthostatic hypotension, are probably reduced with slower initial titration schedules,[8,9] and the same may apply to restarting. More cautious dosage titration will be appropriate for certain patients, such as those who are elderly, people with Parkinson's disease and outpatients starting clozapine who are uncertain about the potential benefits of the medication.[10–12] Furthermore, there is some evidence that tolerance to the effects of clozapine is lost after only a few weeks,[13,14] so people who have missed clozapine treatment for more than a week should probably restart clozapine as if it were being initiated for the first time.

Restarting clozapine after gaps of various lengths should take account of the need to regain antipsychotic activity with clozapine while ensuring safety during titration. Examples of slow, fast and ultra-fast titration schedules are available[15] but it is probably best to individualise titration according to patient tolerability. A key element is flexibility: the dosage schedule prescribed for a patient will depend upon how previous dosages within the schedule are tolerated. In broad terms, this means starting with 12.5mg and increasing to 25mg for the next dose if the initial dose caused no adverse effects, such as sedation, increased heart rate or lowered blood pressure. If the 25mg dose is well tolerated then 50mg can be given for the next dose, and so on. In other words, the dose is doubled each time until the target daily dosage is reached (which is likely to be the dose the patient was taking before the break in medication).

Twice daily dosing allows for a faster rate of titration than once daily dosing. Some centres use three times daily dosing, which allows for even quicker titration but may increase the risk of adverse effects caused by accumulation. For example, if a patient were to receive 12.5mg, 25mg and 50mg doses of clozapine on the first day of re-titration, then each successive dose would be added to what remains of previous doses. Thus, the effect of the 50mg dose in this schedule would be greater than a single (i.e. stat) dose of 50mg. The same phenomenon occurs with twice daily dosing, but with 12 hours between doses the contribution of the prior dose is more limited.

Where a given dose in the titration schedule is not tolerated, the next dose should usually be delayed and not increased (or possibly decreased). Therefore, it is usually better to prescribe a series of single 'stat' doses, one at a time, rather than write up a complete schedule of doses that may then have to be changed.

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Initiation of clozapine in the community

While in-patient initiation remains the main method of starting clozapine, community initiation is fairly common in many countries. The likelihood of successful titration is similar for both methods (about 60%),[1] indicating that any risks associated with reduced monitoring frequency are offset by the relatively slower initiation schedules employed in the community.

Relative contraindications to community initiation

- History of uncontrolled seizures, significant cardiac disease, unstable diabetes, paralytic ileus, significant blood dyscrasia, neuroleptic malignant syndrome 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).

Essential criteria for suitability for community initiation

- Is the patient likely to be adherent with oral medication and to monitoring requirements or is there support for these?
- 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 weekly or more often 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)?
- Has the patient understood what needs to be done in the event of an abnormal blood test (e.g. daily monitoring of FBC until normalisation in the case of a RED result)?

Initial work-up

To screen for risk factors and provide a baseline:

- Physical examination, FBC (see below), liver function tests, urea and electrolytes, lipids, glucose/HbA_{1c}. Also, C-reactive protein (CRP), CK, troponin, beta-natriuretic peptide (BEN; as baseline for further tests).
- ECG: particularly to screen for evidence of past myocardial infarction or ventricular abnormality.

- Echocardiogram if clinically indicated.
- Consider work-up for BEN where baseline neutrophil counts are low (see section on clozapine, neutropenia and lithium in this chapter). Genetic testing for BEN is also available (see section on clozapine: genetic testing for clozapine treatment in this chapter).

Mandatory blood monitoring and registration

- Register with the relevant monitoring service.
- Perform baseline blood tests (white cell and differential counts) 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, of course, cause marked postural hypotension. The initial monitoring is partly aimed at detecting and managing this, partly at ensuring sedative effects are manageable.

There are two approaches to giving the first dose of clozapine in the community. One is to give the first dose in the morning in clinic and then monitor the patient for postural hypotension for at least 1 hour. If the dose is well tolerated, the patient is then allowed home with a dose to take before going to bed. The second approach involves giving the patient the first dose to take immediately before bed, thereby avoiding the need for close physical monitoring immediately after administration. All initiations should take place early in the week (e.g. on a Monday) so that adequate staffing and monitoring are assured. Unless there are significant concerns regarding tolerability (e.g. postural hypotension), the 1-hour monitoring for morning doses in clinic can be omitted.

Previous guidelines[2,3] recommended physical observations on 5 days/week during weeks one and two of community clozapine initiations, followed by 3 days/week for weeks three and four. A 2023 study showed that this frequency can be reduced when using a slower titration schedule.[4] Example titration schedules for these two protocols are shown in Table 1.55. These dose increase schedules are examples and may need to be adjusted based on tolerability and target dose. Additional reviews may be necessary to manage adverse effects. The low-frequency monitoring (on the left of the table) is suitable for most patients and even lower frequency of monitoring may be feasible in some patients (e.g. re-titration of clozapine where the patient tolerated it well previously). The standard monitoring frequency is recommended for patients who may be more sensitive to adverse effects (e.g. female non-smokers) or who may struggle to adhere to frequent dose adjustments. The two protocols do not differ in the frequency of physical monitoring after week four (i.e. both reduce to once a week). As with in-patient initiation, estimating the target dose for each individual patient is recommended before starting clozapine. This gives some idea of the likely duration of the titration schedule. Genetic testing appears to be the most accurate method of predicting an effective dose.[5]

Table 1.55 Suggested titration regimens for initiation of clozapine in the community.

Day	Low-frequency monitoring	Morning dose (mg)	Evening dose (mg)	Standard-frequency monitoring	Morning dose (mg)	Evening dose (mg)	Approximate percentage dose of previous antipsychotic
1	Mon #*	0	6.25	Mon #*	6.25	6.25	100
2	Tue	0	12.5	Tue #	6.25	12.5	
3	Wed #	6.25	12.5	Wed #	12.5	12.5	
4	Thu	6.25	25	Thu #	12.5	25	
5	Fri #	12.5	25	Fri #	25	25	
6	Sat	12.5	25	Sat	25	25	
7	Sun	12.5	37.5	Sun	25	50	
8	Mon #*	25	37.5	Mon #*	25	50	75
9	Tue	25	50	Tue #	50	50	
10	Wed #	25	62.5	Wed #	50	50	
11	Thu	25	75	Thu #	50	75	
12	Fri #	37.5	75	Fri #	50	75	
13	Sat	37.5	75	Sat	75	75	
14	Sun	37.5	87.5	Sun	75	75	
15	Mon #*	50	87.5	Mon #*	75	100	50
16	Tue	50	100	Tue	75	100	
17	Wed	50	125	Wed #	75	125	
18	Thu #	50	125	Thu	75	125	
19	Fri	50	125	Fri #	75	150	
20	Sat	50	125	Sat	75	150	
21	Sun	50	150	Sun	75	150	
22	Mon #*	50	150	Mon #*	75	175	25
23	Tue	50	150	Tue	75	175	
24	Wed	50	150	Wed	75	200	
25	Thu #	75	150	Thu #	75	200	
26	Fri	75	150	Fri	75	225	
27	Sat	75	150	Sat	75	225	
28	Sun	75	175	Sun	75	225	
29	Further increments should be 25–50mg/day (generally 25mg/day) until target dose is reached (use plasma levels). Beware of sudden increase in plasma levels due to saturation of first-pass metabolism (watch for increase in sedation/other adverse effects).						0

#Face-to-face assessments including physical observations (sitting and standing blood pressure, heart rate, oxygen saturation, temperature and respiratory rate), adverse effect and mental state review, actively manage adverse effects (e.g. behavioural advice, slow clozapine titration or reduce dose of other antipsychotic, start adjunctive treatments – see sections on clozapine adverse effects in this chapter).

*Full blood count; also consider C-reactive protein, CK, troponin, beta-natriuretic peptide.

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. Consider regular systematic assessment of adverse effects using a recognised scale such as the GASS for Clozapine.

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 >100bpm (also common and not, on its own, a reason for stopping, but may sometimes be linked to myocarditis)
- postural drop of >30mmHg
- patient is clearly over-sedated
- any signs of constipation (initiate laxatives early)
- flu-like symptoms (malaise, fatigue, etc.)
- chest pain, dyspnoea, tachypnoea
- any other adverse effect that is intolerable
- changes in smoking habit.

The patient should be reviewed at least once a week for the first month to assess mental and physical state.

Recommended additional monitoring

Baseline	1 month	3 months	4–6 months	12 months
Weight/BMI/waist	Weight/BMI/weight	Weight/BMI/waist	Weight/BMI/waist	Weight/BMI/waist
Plasma glucose and lipids	Plasma glucose and lipids		Plasma glucose and lipids	Plasma glucose and lipids
LFTs			LFTs	

Monitor CRP, CK, troponin weekly in the first four weeks of treatment or if temperature is above 38°C (see section on clozapine and myocarditis). CK, B-natriuretic peptide and echocardiogram should be used to confirm or rule out myocarditis if CRP and troponin are raised above thresholds.[6]

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).
- 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. (Pimozide and ziprasidone should be stopped before clozapine is started.)

Serious cardiac adverse effects

See section on clozapine: serious cardiovascular adverse effects in this chapter. Patients should be closely observed for signs or symptoms of myocarditis, particularly during the first month,[7] and advised to inform staff if they experience cardiac symptoms and to seek out-of-hours review if necessary. These symptoms include persistent tachycardia (although commonly benign), palpitations, shortness of breath, fever, arrhythmia, symptoms mimicking myocardial infarction, chest pain, unusually low blood pressure and other unexplained symptoms of heart failure. Myocarditis risk is probably lower when using the slow titrations used in the community.[8]

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CLOZAPINE ADVERSE EFFECTS

Clozapine: common adverse effects

This section provides a summary of management of the common adverse effects of clozapine.

Adverse effect	Time course	Action
Constipation	First 4 months are the highest risk.[1] Usually persists and so requires continuous monitoring and treatment.	Advise patients of the risks before starting, screen regularly, ensure adequate fibre, fluid and exercise. Consider early or even prophylactic laxatives. Stimulant laxatives (senna or bisacodyl) are first-line treatments, with emollients (docusate) and/or osmotics (macrogols).[2] Bulk-forming laxatives should be avoided. 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.[3,4] See section on clozapine-induced gastrointestinal hypomotility in this chapter.
Fever[5]	First 4 weeks[6]	Clozapine induces inflammatory response (increased CRP, interleukin-6 and eosinophils).[7–9] Give paracetamol but check FBC for neutropenia. Reduce rate of dose titration.[10] Concurrent valproate or quetiapine may increase risk.[11] This fever is not usually related to blood dyscrasias[12] but beware myocarditis, NMS, pneumonia and other rarer types of inflammatory organ damage (see section on clozapine: uncommon or unusual adverse effects in this chapter).
Gastro-esophageal reflux disease[13,14]	Any time	Proton pump inhibitors often prescribed but some are CYP1A2 inducers and possibly increase risk of neutropenia and agranulocytosis.[15,16] Reasons for GERD association unclear – clozapine is an H_2 antagonist.[17]
Hypersalivation	First few months. Usually persists but sometimes wears off. Often very troublesome at night.	Reduce dose if possible.[18] Many options available[19] (see section on clozapine-induced hypersalivation in this chapter). Systemic anticholinergic drugs worsen constipation and cognition and so should not be used first line.
Hypertension[20]	First 4 weeks, sometimes longer	Monitor closely and increase dose as slowly as is necessary. Hypotensive therapy is sometimes necessary.[21]
Hypotension	First 4 weeks	Advise patient to stand up in stages. Reduce dose or slow down rate of increase. Ensure fluid intake of >2L daily.[22] If severe, consider fludrocortisone 0.05–0.3mg daily first line (monitor fluid intake, potassium and sodium) or midodrine 2.5–5mg three times a day (maximum 30mg/day).[23] Other options include moclobemide and Bovril® in combination or etilefrine.[23]
Myoclonus[24–27]	During dose titration or plasma level increases	May precede full tonic-clonic seizure. May present as knee-buckling.[28] Reduce dose. Antiseizure drugs may help and will reduce the likelihood of progression to seizures. Valproate is first choice but has limited utility. Referral to neurology specialist is advised.
Nausea	First 6 weeks	May give anti-emetic. Avoid prochlorperazine if previous EPS. Avoid domperidone if underlying cardiac risk or QTc prolongation. Ondansetron is a good choice, but it may worsen constipation. Metoclopramide may help with hypersalivation. Nausea and vomiting can be the only presenting symptoms of myocarditis.[29]

(*Continued*)

(*Continued*)

Adverse effect	Time course	Action
Nocturnal enuresis	May occur at any time	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 spontaneously,[30] but may persist for months or years.[31] Seems to affect 1 in 5 people on clozapine.[32] Try aripiprazole (10–15mg daily) or desmopressin (10mcg/mL nasal spray into each nostril at night, or 200–400mcg orally at night).[33] Monitoring for hyponatraemia is essential. Other options include oxybutynin, trihexyphenidyl, imipramine, amitriptyline and verapamil.[33]
Pneumonia[34,35]	Usually early in treatment, but may be any time	May result from saliva aspiration (this may be why pneumonia appears to be dose related),[36,37] and very rarely from constipation.[38] Pneumonia is a common cause of death in people on clozapine.[39] Infections in general may be more common in those on clozapine[40] and use of antibiotics is also increased.[41] Obesity,[34] anticholinergic burden[35] and treatment-resistant schizophrenia itself may also contribute to risk.[34] Respiratory infections may give rise to elevated clozapine levels.[42,43–45] This may be an artefact: smoking usually ceases during an infection and inflammation itself causes a reduction in CYP1A2 activity.[46,47] Clozapine is often successfully continued after the pneumonia has resolved, but recurrence may be more likely.[48–50]
Sedation	First few months. May persist, but usually wears off to some extent.	Give smaller dose in the morning. Give evening dose earlier if morning waking is troublesome. Once daily dosing in the evening seems effective and well tolerated.[51,52] Case reports of successful use of psychostimulants (methylphenidate[53]) and betahistine.[54] Modafinil does not appear to be effective.[55] Aripiprazole may help.[56]
Seizures[57]	May occur at any time[58]	Related to dose, plasma level and rapid dose escalation.[25] There is no step-change in risk at a particular dose or level. Consider prophylactic, topiramate, lamotrigine, gabapentin or valproate* if there are risk factors for seizures and or plasma level is high (≥600mcg/L). Some suggest risk of seizures below 1300mcg/L is not enough to support primary prophylaxis.[59] After a seizure: withhold clozapine for one day; restart at half previous dose; give antiseizure medication.**
Tachycardia	First 4 weeks, but usually persists	Very common in early stages of treatment but usually benign. May be dose-related.[60] Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate myocarditis or pericarditis (see section on clozapine: serious cardiovascular adverse effects in this chapter). Referral to a cardiologist is advised. Benign sinus tachycardia can be treated with bisoprolol[61] or atenolol,[62] although evidence base is poor.[63,64] Ivabradine may be used if hypotension or contraindications limit the use of beta blockers.[65] Prolonged tachycardia can itself precipitate cardiomyopathy[66] or other cardiovascular consequences.[22]
Weight gain	Usually during the first year of treatment, but may continue	Dietary counselling is essential. Advice may be more effective if given before weight gain occurs. Weight gain is common and often profound (4.5kg in the first 10 weeks).[67] Many treatments available (see section on treatment of antipsychotic-induced weight gain in this chapter).

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

** Lamotrigine may be helpful 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] Valproate should be avoided in most cases because of the risks of neurodevelopmental disorders and birth defects if valproate is taken during pregnancy or prior to conception (in the case of men). EEG abnormalities are common in those on clozapine.[68,69]

CRP, C-reactive protein; EPS, extrapyramidal symptoms; GERD, gastro-esophageal reflux disease.

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Clozapine: uncommon or unusual adverse effects

Adverse effect	Time course	Comment
Agranulocytosis (delayed)[1–4]	Usually first 3 months but may occur at any time	Occasional reports of apparent clozapine-related blood dyscrasia even after 1 year of treatment. Some suggest risk may be elevated for up to 9 years.[5] It is very likely that clozapine is not the causative agent in most, if not all late cases[6,7] (see section on clozapine: serious haematological adverse effects in this chapter).
Colitis/gastrointestinal necrosis[8–15]	Usually within the first month but may be any time[16]	Growing body of case reports. Any severe or chronic diarrhoea should prompt specialist referral as there is a substantial risk of death. Use of drugs with anticholinergic effects probably increases risk of colitis and necrosis.[17]
Delirium[18–20]	Any time	Reported rates vary (0.1–10%)[18,21,22] but rarely seen in practice if dose is titrated slowly and plasma level determinations are used. Older age and medical comorbidity increase the risk of delirium. Ensure common causes of delirium are treated. Cholinergic rebound resulting from abrupt cessation of clozapine can cause delirium.
Eosinophilia[23–25]	First week,[26,27] but can be any time	Reasonably common but significance unclear. Eosinophilia may predict neutropenia but this is disputed. Usually benign but investigate for signs of inflammatory organ damage[28] (myocarditis,[29] interstitial nephritis,[27,30] interstitial lung disease, hepatitis, pancreatitis).[31] May be associated with colitis and related symptoms.[15,32] DRESS syndrome described in case reports.[33,34] Successful rechallenge is possible.[35] Concomitant antidepressants may increase risk.[36,37]
Heat stroke[38,39]	Any time	Two cases reported, both occurred during a heatwave. May be mistaken for NMS (CK was elevated in both cases).
Hepatic failure/enzyme abnormalities[40–46]	First few months	Benign changes in LFTs are common (up to 50% of patients) but worth monitoring because of the very small risk of fulminant hepatic failure.[47] Rash may be associated with clozapine-related hepatitis[48] (see section on hepatic impairment in Chapter 8).
Hypothermia[49]	Any time	A few case reports and events in pharmacovigilance databases. Can be fatal.
Interstitial nephritis[50,51]	Usually first 3 weeks, possibly up to 3 months[27]	A handful of reports implicating clozapine. Probably immune mediated. May occur after only a few doses. Symptoms include fever, tachycardia, nausea, vomiting, diarrhoea, raised creatinine, urinary difficulties and eosinophilia. The classic nephritis-associated rash may not be present.[27] There are no published cases of successful rechallenge.[27]
Interstitial lung disease	Usually first few months, possibly later in treatment	Six case reports.[52] May be caused by aspiration or an immune reaction. Symptoms are non-specific: shortness of breath, fever, cough, fatigue. Pneumonitis has also been reported.[53]
Knee-buckling[54,55]	Usually at the start of treatment	Several cases reported. May be mistaken for postural hypotension.
Ocular effects[56]	Any time	Single case report of ocular pigmentation,[57] five of periorbital oedema.[58] Clozapine may cause dry eye syndrome.[59]

(*Continued*)

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Adverse effect	Time course	Comment
Pancreatitis[60–69]	Usually first 6 weeks, possibly later in treatment[70]	Several reports of asymptomatic and symptomatic pancreatitis. Symptoms include fever, abdominal pain and distension, nausea and vomiting, raised CRP and raised lipase and/or amylase. Concomitant valproate may increase the risk.[27] The majority of attempts to rechallenge fail[63,71–74] but one successful case is reported.[75]
Parotid gland swelling[76–80]	Usually first few weeks, but may occur later[81]	Several case reports. Unclear mechanism, possibly immunological or thickening of saliva leading to calcium precipitation. Can be recurrent. May resolve spontaneously.[82] Terazosin in combination with benztropine may be helpful.
Pericarditis and pericardial effusion[69,83–90]	Any time	Several reports in the literature. Symptoms include fatigue, chest pain, dyspnoea, orthostatic hypotension and tachycardia, but may be asymptomatic.[91] Signs include raised inflammatory markers (specifically trop I) and pro-BNP levels.[91] Use echocardiogram to confirm/rule out effusion. Successful rechallenge possible.[92–94]
Stuttering[95,96]	Any time	Case reports only. Check plasma levels, consider dose reduction and/or antiseizure drugs – may be a warning sign for impending generalised seizures.[97]
Thrombocytopenia[98–101]	First 3 months	Few data but apparently fairly common (incidence over 1 year of 3[102]–8%[103]). Probably transient and clinically unimportant, but persistent in some cases[104,105] and recurrent on rechallenge in others.[106,107] Thrombocytosis also reported.[108]
Skin reactions[109]	Any time	Presence of skin diseases in general is higher in those with schizophrenia.[110] Four reports of vasculitis[111–114] in which patients developed confluent erythematous rash on lower limbs. One report of Stevens–Johnson syndrome,[115] two of pityriasis rosea,[116,117] one of a papular rash,[118] one of exanthematic pustulosis,[119] one of cholinergic urticaria[120] and two of Sweet's syndrome,[121] one fatal.[122] Rash is often reported in DRESS syndrome.[123]
Thromboembolism[124–126]	Any time[127]	Weight increase and sedation may contribute to risk. Mechanism may be increased platelet aggregation via $5HT_{2A}$ receptor activation.[128] Clozapine increases risk of pulmonary thromboembolism by 28 times compared with the general population.[129] The risk may be dose related[130] but cases are reported across the dose range.[131,132] Consider prophylactic antithrombotic treatment where additional risk factors are present (surgery, immobility). Continuation of therapy after embolism may be possible[133] but consult haematologist as without prophylactic antithrombotic treatment recurrence is likely[134,135] and may be fatal.[131,136]
Polyserositis	Usually first few weeks, but can occur at any time	Case reports describe a wide variety of symptoms related to inflammatory processes, including flu-like symptoms, fever, eosinophilia, diarrhoea, shortness of breath, tachycardia, thoracic pain.[137] Other inflammatory conditions may be present (hepatitis, pancreatitis, dermatosis). Suggested to be either IgE-mediated hypersensitivity or an immunomodulatory effect.[138] All reported cases have resolved on discontinuation of clozapine.[138]

CK, creatine kinase; CRP, C-reactive protein; DRESS, drug rash with eosinophilia and systemic symptoms; IgE, immunoglobulin E; NMS, neuroleptic malignant syndrome; pro-BNP, pro-brain natriuretic peptide.

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Clozapine: serious haematological adverse effects

Agranulocytosis

Clozapine is a somewhat toxic drug. Despite this, clozapine reduces overall mortality in schizophrenia,[1] in part owing to a reduction in the rate of suicide.[2–4] Non-clozapine antipsychotics also reduce natural-cause mortality,[5] possibly because of improved adherence to cardiometabolic medication.[6] Clozapine is more effective than any other antipsychotic in this regard.[6]

Clozapine can cause serious, life-threatening adverse effects, of which **agranulocytosis** is the best known, and which is seen in 0.4% of patients.[7] The incidence of death related to agranulocytosis following clozapine prescription is 0.013%, with a case fatality rate for agranulocytosis of 2.1%.[8] Risk is clearly well managed by the approved clozapine monitoring systems. The incidence of severe neutropenia declines to negligible levels after the first year of treatment.[8]

Successful rechallenge after neutropenia occurring during clozapine treatment may be possible,[9] but rechallenge should not be attempted after confirmed clozapine-related agranulocytosis.[10] Most neutropenia occurring in the context of clozapine treatment is coincidental to the use of clozapine.[11] Distinguishing between benign, clinically insignificant neutropenia and clozapine-related life-threatening agranulocytosis (CRLTA) is vital. CRLTA is usually characterised by a continuous and rapid neutrophil count decline to zero, or near zero, mostly within the first 18 weeks of clozapine treatment. A prolonged nadir and delayed recovery (range 4–16 days) follow[12] unless GCSF is given. Non-CRLTA episodes are more often brief, show a non-continuous and/or slow decline in neutrophils, or have an obvious cause that is not clozapine.[12,13] However, if clozapine is withdrawn very early, the typical catastrophic fall in neutrophil counts may not develop.[13] Distinguishing between non-clozapine-related neutropenia and CRLTA is difficult, but cases can usually reliably be classified as non-CRLTA, possible CRLTA and definite CRLTA.

The mandatory threshold-based method of detecting agranulocytosis has a very low specificity for CRLTA – the system creates a huge number of false positives. Pattern-based criteria based on the above factors are more specific without loss of sensitivity.[14] Misdiagnosing benign neutropenia as CRLTA has resulted in many thousands of patients being denied access to clozapine.[11] The most common reason for misdiagnosis is the failure to detect BEN.[15]

Summary

- Overall mortality is lower for those on clozapine than in schizophrenia as a whole.
- Risk of fatal agranulocytosis is less than 1 in 8,000 during standard monitoring.
- Real clozapine-related agranulocytosis usually follows a distinctive, catastrophic pattern.
- Pattern-based criteria are more specific for clozapine-related agranulocytosis than standard threshold-based monitoring.

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Clozapine: serious cardiovascular adverse effects

Thromboembolism

Over 30 years ago a possible association between clozapine and thromboembolism was first suggested.[1,2] Later, data from Sweden[3] suggested the risk of thromboembolism was 1 in 2,000 to 1 in 6,000 patients treated.

Thromboembolism may be related to clozapine's effects on antiphospholipid antibodies[4] and platelet aggregation.[5] It seems most likely to occur in the first 6 months of treatment[6] but can occur at any time. The risk may be independent of dose,[6] but some studies suggest a correlation with higher doses.[7] Other antipsychotics are also strongly linked to thromboembolism,[8] although clozapine may present the highest risk.[7,9]

With all drugs, the causes of thromboembolism are probably multifactorial.[10] Sedation may lead to a reduction in movement and consequent venous stasis. Obesity, hyperprolactinaemia and smoking are additional independent risk factors for thromboembolism.[11,12] Encouraging exercise and ensuring good hydration are essential precautionary measures.[13]

Myocarditis

Clozapine is associated with **myocarditis** and **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 reporting an incidence of 3%[14–16] and one finding a rate of 9.8%.[17] Studies conducted outside Australia[18–20] have suggested an incidence of 1% or less. The reason for such variation is unclear but it may be that a lack of robust monitoring leads to missed diagnoses in those countries reporting lower incidences.[21] Geography, environment and higher starting doses may also play a role.[17,22] A 2020 meta-analysis suggested an event rate of less than 1% – 7/1,000 patients.[23]

Myocarditis is potentially fatal (case fatality rate of 12.7%)[23] and is most likely to occur in the first 6–8 weeks of starting clozapine treatment (median 3 weeks),[24] but may occur at any time.

Despite uncertainty over incidence, all patients should be closely monitored for signs and symptoms of myocarditis especially in the first few months of treatment.[25] Symptoms include hypotension, tachycardia, fever, flu-like symptoms, fatigue, dyspnoea (with increased respiratory rate) and chest pain.[26] Signs include ECG changes (ST depression), enlarged heart on radiography/echo and eosinophilia. Many of these symptoms occur in patients on clozapine not developing myocarditis[27] and, conversely, their absence does not rule out myocarditis.[28,29] Nonetheless, signs of heart failure should provoke immediate cessation of clozapine and referral to a cardiologist.

Rechallenge has been successfully completed[29–36] (the use of beta blockers, ACE inhibitors and mineralocorticoid receptor antagonists may help)[37–39] but recurrence is also possible.[29,40–43] Published cases suggest a success rate of 62%.[44] Use of echocardiography, measurement of CRP and troponin are obviously absolutely essential in cases of rechallenge.[45–47] Effective treatment of comorbid metabolic syndrome and diabetes may also help.[23] Most cases of successful rechallenge employ a very slow rate of titration.[44] One proposed schedule is to limit dose increases to 6.25mg increments every

4 days until a daily dose of 75mg is reached.[22] Dose increases (of 6.25mg) can then be made every 3 days after this point, and every 2 days after reaching a daily dose of 150mg.

Autopsy findings suggest that fatal myocarditis can occur in the absence of clear cardiac symptoms, although tachycardia and fever are usually present.[48] A monitoring programme which is said to detect 100% of symptomatic cases of myocarditis[49] using measurement of troponin I or T and CRP has been developed (Table 1.56). The additional measuring of NT-proBNP (an indicator of cardiac failure) and continuing cardiac and blood marker monitoring for 8 weeks have also been suggested[50] (5-8% of cases occur in the second month of treatment,[50,51] almost all of these in weeks four to six).[52] 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 been questioned.[53] Baseline echocardiography may at least be useful to establish a comparator if concerns arise later, especially in those with known cardiac disease, structural abnormalities or other cardiac risk factors.[54] 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.[20]

Factors that may increase the risk of developing myocarditis include rapid titration, concurrent use of sodium valproate[55] and older age (31% increased risk for each additional decade).[56] Other psychotropics, including lithium, risperidone, haloperidol, chlorpromazine and fluphenazine, have also been associated with myocarditis.[57] 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[15] or family history of cardiac disease should provoke extra caution.

Cardiomyopathy

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.[21] Long-term clozapine seems to induce cardiac myocyte autophagy and structural remodelling of the heart.[58] Most incidence data originate from Australia and range from 0.02 to 5%.[16,59] Meta-analysis suggests an event rate of 6 per 1,000 patients, with a case fatality rate of 7.8%.[23] Cardiomyopathy occurs later in treatment than myocarditis (median 9 months)[24] but, as with myocarditis, it may occur at any time. 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[60,61] and is often asymptomatic in the early stages,[16] so any reported symptoms of palpitations, chest pain, syncope, sweating, decreased exercise capacity or breathing difficulties should be closely investigated. Successful rechallenge with rigorous cardiac monitoring (including ECHO) and instigation of disease-modifying cardiac medications may be possible,[39,62–66] including in cases of pre-existing cardiomyopathy or heart failure (as opposed to clozapine-induced cardiomyopathy).

Despite an overall reduction in mortality, younger patients may have an increased risk of sudden death,[67] perhaps because of clozapine-induced ECG changes.[68] There may, of course, be similar problems with other antipsychotics.[57,69,70]

Table 1.56 Suggested monitoring for myocarditis.[22,49,71,72]

Baseline*	Pulse, BP, temperature, respiratory rate
	FBC
	CRP
	Troponin
	Echocardiography (if available)
	ECG
Daily, if possible	Pulse, BP, temperature, respiratory rate
	Ask about: chest pain, fever, cough, shortness of breath, exercise capacity
On days 7, 14, 21, and 28	CRP
	Troponin
	FBC
	ECG if possible
If CRP >100mg/L or troponin > twice upper limit of normal	Stop clozapine; repeat echo
	NT-proBNP
If fever + tachycardia* + raised CRP or troponin (but not as above)	Daily CRP and troponin measures
	NT-proBNP

* Tachycardia is not a good indicator of myocarditis – almost all cases have tachycardia, but tachycardia is very common in people who do not have myocarditis.[52]
CRP, C-reactive protein; NT-proBNP, N-terminal pro b-type brain natriuretic peptide.

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Clozapine-induced hypersalivation

Clozapine is well known to be causally associated with hypersalivation (sialorrhoea):[1] excess salivary pooling in the mouth and drooling, particularly at night. Hypersalivation is dose-[2] and plasma concentration-related[3] but some degree of excess salvation may be seen in the vast majority of patients.[4] Clinical observation suggests that hypersalivation reduces in severity somewhat over time (usually several months) but normally persists to some extent.

Clozapine-induced hypersalivation is socially embarrassing and discomfiting, has a negative impact on quality of life[4] and is often a reason for patients stopping clozapine treatment.[5] Further, hypersalivation has been implicated as a contributory factor in the development of aspiration pneumonia and so is potentially life-threatening.[6–10] Effective treatment is a matter of some urgency.

The pharmacological basis of clozapine-related hypersalivation remains unclear.[11] Suggested mechanisms include muscarinic M_4 agonism, adrenergic α_2 antagonism, and inhibition of the swallowing reflex.[12,13] The last of these is supported by trials which suggest that saliva production is not increased in patients treated with clozapine,[14,15] although at least one study has observed marked increases in salivary flow in the first 3 weeks of treatment.[16]

Whatever the mechanism, medications that reduce saliva production might be expected to diminish the severity of clozapine-induced sialorrhoea. However, there are no medications licensed for this condition and many of the relevant published studies have limitations that preclude any confident treatment recommendations.[17] A 2023 network analysis of RCTs testing a range of pharmacological interventions for clozapine-induced sialorrhoea in adults[18] yielded 'low confidence' findings of efficacy, ranking metoclopramide highest, and decreasing through cyproheptadine, sulpiride, propantheline, diphenhydramine, benzhexol, doxepin, amisulpride, chlorpheniramine, to amitriptyline and atropine. Overall, the evidence, such as it is, seems to favour antimuscarinic agents, such as propantheline and diphenhydramine.[19,20] Use of antimuscarinic agents should take account of the risk of compounding clozapine's liability for serious, potentially life-threatening, gastrointestinal hypomotility.[21,22] Topical antimuscarinic treatment might be preferred. Several topical agents have been shown to be effective and a small RCT of sofpironium bromide gel in 2023 produced encouraging results.[23] In 2024, another small RCT[24] found topical atropine to be more effective than amitriptyline and ipratropium bromide nasal spray. Metoclopramide and other benzamide compounds are probably second-line treatments.[25]

Table 1.57 describes pharmacological treatments that have been examined. Non-drug treatments may be used if appropriate – these include chewing gum during the day, elevating pillows and placing a towel on the pillow to prevent soaking.[11] Nonetheless, problematic hypersalivation should not be considered an inevitable consequence of clozapine use and strenuous efforts should be made to minimise its severity.

Table 1.57 Clozapine-related hypersalivation – summary.

Treatment	Comments
Amisulpride 100–400mg/day[20,26,27]	Supported by a positive RCT compared with placebo, one other in which it was compared with moclobemide and numerous case studies.[28–32] May allow dose reduction of clozapine.
Amitriptyline 25–100 mg/day[33–36]	Limited literature support. Adverse effects may be troublesome. Worsens constipation.
Atropine given sublingually[37–41] or as solution (1mg/10mL) used as a mouthwash	Limited literature support and the benefit–risk balance is uncertain, although case reports suggest that it may be a relatively effective and tolerable treatment for some patients in clinical practice[41,42] and a 2024 RCT yielded positive findings.[24] But one meta-analysis[18] failed to find atropine superior to placebo for nocturnal sialorrhoea. Problems with administration have been reported.[43]
Benzhexol (trihexyphenidyl) 5–15mg/day[44]	Small, open study suggests useful activity. Used in some centres but may impair cognitive function. Lower doses (2mg) may be effective.[45]
Benztropine 2mg/day + terazosin 2mg/day[46]	Combination shown to be better than either drug alone. Terazosin is an α_1 antagonist so may cause hypotension.
Botulinum toxin[47–50] (Botox) bilateral parotid gland injections (150IU into each gland)	Effective in treating sialorrhoea associated with neurological disorders. Six cases of successful treatment of clozapine-related hypersalivation in the literature. Widely used in some US centres. Slow onset of effect. Some botulinum preparations are formally licensed for chronic sialorrhoea caused by neurological conditions in adults.
Bupropion 100–150mg/day[51]	Single case report. May lower seizure threshold.
Chlorphenamine[20]	Antihistamine and relatively weak antimuscarinic. One high-quality study.
Clonidine 0.1–0.2mg patch weekly or 0.1mg orally at night[52,53]	α_2 partial agonist. Limited literature support. May exacerbate psychosis, depression and cause hypotension.
Diphenhydramine[19,20]	Antihistamine and potent antimuscarinic. Few high-quality studies.
Glycopyrrolate 0.5–4mg bd[54–59]	One RCT showed glycopyrrolate to be more effective than biperiden without worsening cognitive function while another found significant clinical improvement of 'nocturnal sialorrhoea' with 2mg a day, compared with placebo. May worsen constipation.
Guanfacine 1mg/day[60]	α_2 agonist. Single case report. May cause hypotension.
Hyoscine 0.3mg tablet sucked or chewed up to three times daily or 1.5mg/72 hr patch[61–64]	Hyoscine hydrobromide is a peripheral and central anticholinergic that is commonly prescribed for clozapine-induced hypersalivation,[59] but in the UK is an unlicensed use.[65] There is one double-blind RCT.[53] May cause cognitive impairment, drowsiness and worsen constipation.
Ipratropium nasal spray (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%[66,67]	Limited literature support. The only placebo-controlled RCT conducted was negative.[68]
Lofexidine 0.2 mg twice daily[69]	α_2 agonist. Very few data. May exacerbate psychosis, depression and cause hypotension.

(*Continued*)

Table 1.57 (*Continued*)

Treatment	Comments
Metoclopramide Starting dose of 10mg/day[20,70,71]	Double-blind, RCT trial found metoclopramide was associated with a significant reduction in nocturnal hypersalivation and drooling. Described as an 'effective and tolerated' treatment in cases in clinical practice.[72]
Moclobemide 150–300mg/day[45]	Effective in 9 of 14 patients treated in one open study. Appears to be as effective as amisulpride (see above).
N–acetylcysteine[73]	An antioxidant that also modulates glutamatergic, neurotrophic and inflammatory pathways. Small case series reported with significant decrease in sialorrhea.
Oxybutynin 5mg up to twice daily[74]	Single case report
Pirenzepine 50–150mg/day[75–77]	Selective M_1, M_4 antagonist. Extensive clinical experience suggests efficacy in some but only randomised trial suggested no effect. Still widely used. Does not have a UK or US licence for any indication. May cause constipation.
Propantheline 7.5mg at night[19,20]	Peripheral anticholinergic. No central effects. Meta-analyses of relevant trials have found that propantheline outperforms placebo for the treatment of antipsychotic-induced sialorrhoea.[18–20] May worsen constipation.
Quetiapine[51]	May reduce hypersalivation by allowing lower doses of clozapine to be used
Sofpironium bromide 5% gel[23]	A small RCT reported a 40% reduction in saliva flow at 4 weeks. Very limited availability – Japan only.
Sulpiride 150–300mg/day[20,78–80]	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.

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Clozapine-induced gastrointestinal hypomotility

Constipation is a common adverse effect of clozapine treatment with a prevalence of more than 30%, three times that seen with other antipsychotics.[1] The mechanism of action is not completely understood but is thought to be a combination of the drug's anticholinergic[2,3] and antihistaminergic properties,[4] which are further complicated by antagonism at 5-HT_3 receptors.[2,3,5] In addition, clozapine-induced sedation can result in a sedentary lifestyle,[4] 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 patients taking clozapine show reduced transit time.[6]

Clozapine-induced GI hypomotility (CIGH) is a much greater risk to life than clozapine-related agranulocytosis.[4] When constipation is severe, the case fatality rate is around 20–30%.[4,7–9] One long-term study[10] found an incidence of 37/10,000 cases of severe hypomotility and 7/10,000 constipation-related deaths. Case fatality was 18%. Enhanced monitoring and effective treatment of CIGH are clearly needed to reduce the likelihood of constipation-related fatality.

A GI history and abdominal examination are recommended prior to starting treatment and, if the patient is constipated, clozapine should not be initiated until this has resolved.[8] CIGH is most severe during the first 4 months of treatment,[8] but may occur at any time. Adopting the Rome III criteria[11] at routine FBCs might be a successful strategy to combat preventable deaths due to CIGH, but even this does not guarantee identification of hypomotility.[12] A study that examined the diagnostic accuracy of constipation screening found self-reporting to have a sensitivity of just 18%. Adding the Rome criteria improved this to 50%, but this means half of cases were still missed.[13]

Opinions differ on the relationship between clozapine dose and constipation, and between clozapine plasma level and constipation.[8,14,15] However, most studies report that deaths that have occurred as a result of CIGH have higher than average daily doses.[8,9,16] Older age, male sex and higher daily doses have been proposed as possible risk factors for death based on case series review[16] and pharmacovigilance database studies (Box 1.4).[9]

Box 1.4 Risk factors for developing clozapine-induced constipation[8,17–20]

- Increasing age
- Female sex
- Anticholinergic medication
- Higher clozapine dose/plasma concentration
- Hypercalcaemia
- GI 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 25mg/day or 100mg/week.[21] Increasing dietary fibre intake to at least 20–25g/day can increase stool weight but can decrease gut transit time[20,22] (fibre decreases or increases transit time depending on the initial transit time).[23] If fibre intake is increased it is important that adequate fluid intake (1.5–2L/day) is also maintained to avoid intestinal obstruction.[8,20,24] 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)[25] in addition to a high-fibre diet and increased fluid intake also assists in the prevention of CIGH.[26,27]

Active monitoring of patients, including direct questioning, is essential. Patients often do not self-report even life-threatening constipation.[8] 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 a week,[11] an abdominal examination is indicated.[8] Where this excludes intestinal obstruction, both a stimulant and stool-softening laxative should be started, as suggested by the Porirua protocol[28] (for example senna 15mg at night and docusate 100mg three times daily).[8,28,29] Bulk-forming laxatives are not usually effective in slow-transit constipation[2,30] and therefore should be avoided. There is some evidence that lactulose and polyethylene glycol (for example Movicol®) are effective[2,31] and could be considered in addition to the stimulant and softener combination.[28] Most people with CIGH will need a stimulant laxative such as senna or bisacodyl, or both. These should not be withheld on the basis that long-term use of stimulants is usually proscribed. In addition to laxative treatment, a review of the anticholinergic burden of other prescribed medicines should be undertaken. Consideration may be made of reducing the clozapine dose, but this step alone cannot be considered treatment of CIGH – use of laxatives is still essential.

Choice of laxative should also be guided by the patient's previous response to certain agents in association with consideration of the required speed of action. Lactulose takes up to 72 hours of regular use to work,[32] so is of no use for urgent treatment. Stimulant laxatives are usually the fastest acting (6–10 hours). Laxative doses should be increased every 24 hours until resolution of symptoms (usual maximum daily dose of senna is 30mg, bisacodyl 20mg and docusate 500mg). Glycerin or bisacodyl suppositories can be used and are usually effective within 30 minutes but there are no data on their use in CIGH. In fact, published data supporting laxative choice for antipsychotic-related constipation are sparse and of poor quality.[12]

Management of suspected acute CIGH

Up to 30% of patients on long-term clozapine will suffer severe GI hypomotility unless preventative steps are taken.[33] 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.[7,8,21,34–38] There have been case reports of fatalities occurring only hours after first symptoms present,[39] and this emphasises the urgency for prompt assessment and management (including cessation of clozapine). There should therefore be a low threshold for referral to emergency medical services when conservative management fails or constipation is severe and acute.[8,40]

Clozapine rechallenge following severe constipation

Some patients have been successfully rechallenged following severe cases of CIGH, but this process does not come without risk. Prophylactic measures should be used for those with a history of CIGH or who are deemed high risk of developing CIGH. Minimise the use of other constipating drugs and ensure other modifiable risk factors are addressed (fibre and fluid intake, exercise). Conventional laxatives should be started in regular and adequate doses to prevent constipation from developing. 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 and involvement of gastrointestinal specialists is encouraged.

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).[41] A small, randomised placebo controlled study of orlistat for clozapine-induced constipation found a favourable difference at study endpoint (week 16) for the prevalence of constipation, diarrhoea and normal stools for orlistat compared with placebo,[42] although 47 of the 54 participants required conventional laxatives. Orlistat is known to reduce the absorption of some drugs from the GI tract. It is therefore important to monitor plasma clozapine levels if starting treatment with orlistat.

Bethanechol, a cholinergic agonist, was effective at 30mg/day in reducing the amount of laxatives and enemas required to maintain regular bowel movements for a patient diagnosed with clozapine-related CIGH.[43] Another case report described use in a patient with a gastrostomy, where up to 200mg/day bethanechol was given to reduce dilation of the bowel.[44] Bethanechol should only ever be initiated after other options have failed and in consultation with a gastroenterologist.[43]

Prucalopride is a $5HT_4$ agonist which increases gut motility and is licensed for chronic constipation where laxatives have failed to provide adequate relief. Case reports of successful use for clozapine-induced constipation have been described,[45,46] and superior efficacy to lactulose for this indication was demonstrated in an open-label study.[47]

Linaclotide (licensed in the UK for constipation in irritable bowel syndrome) and **plecanatide** (available in the USA for chronic idiopathic constipation) are oral guanylate cyclase C agonists. Neither has any published data to date supporting use in antipsychotic-induced constipation, beyond a single case report for linaclotide.[44]

Key message

- Prevent clozapine-related constipation by aggressive use of stimulant laxatives.

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Clozapine, neutropenia and lithium

Mild neutropenia

Around 3.8% of patients treated with clozapine develop neutropenia.[1] Most of these cases are unrelated to clozapine treatment, and clozapine in fact may not cause neutropenia per se.[2] The risk of neutropenia (<1.5×10^9/L) in patients treated with clozapine is broadly similar to the cross-sectional prevalence of neutropenia in otherwise healthy individuals (0.4–4.5% depending on ethnicity).[3] Indeed, a meta-analysis comparing the risk of neutropenia between clozapine and other antipsychotics found that clozapine did not have a stronger association with neutropenia than other antipsychotic medications.[4]

Most people developing mild neutropenia will not develop severe neutropenia or agranulocytosis. Risk factors for neutropenia include being Afro-Caribbean, younger age and having a low baseline white cell count (WCC).[5] The vast majority of patients who stop clozapine because they have developed neutropenia can be successfully rechallenged.[6] Adopting the US monitoring criteria would eliminate the requirement to discontinue clozapine treatment in cases of mild neutropenia (absolute neutrophil count [ANC] between 1 and 1.5×10^9/L).

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 BEN (see below) 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 being the result of severe bone marrow suppression caused by clozapine.

Severe neutropenia or agranulocytosis

The risk of agranulocytosis during clozapine treatment is 1 in 250 (0.4%),[7] lower than previously thought, and risk of death resulting from this is 0.05% – a rare event. Most cases of agranulocytosis develop within the first 18 weeks of treatment. Thereafter, the risk diminishes steeply.[8] The mechanism of clozapine-induced agranulocytosis is not fully understood but is thought to be immune mediated, given the significant association with certain human leucocyte antigen variants.[9]

Identifying with certainty whether an episode of severe neutropenia is clozapine-related may be difficult. However, the pattern of neutrophil count change is important. A single episode of a below-threshold ANC <0.5×10^9/L may be unrelated to clozapine but would normally promptly lead to treatment cessation. In patients without BEN, agranulocytosis is generally 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).[10] Neutrophil counts that do not follow this characteristic pattern are difficult to interpret.

The Netherlands Clozapine Collaboration Group[11] considers the risk of agranulocytosis so low that a mentally competent patient may stop routine haematological monitoring after 6 months of treatment. The group still nevertheless recommends low-frequency testing (for example four times a year if routine monitoring is stopped).

Risk factors for agranulocytosis include increasing age and Asian race.[5] Unlike neutropenia, risk of agranulocytosis appears to be higher in people of European ancestry than in those of African descent.[12] Some patients may be genetically predisposed[13] (see section on clozapine: genetic testing for clozapine treatment in this chapter). Although the timescale and individual risk factors for the development of agranulocytosis are different from those associated with neutropenia/coincidental low neutrophil counts, it is difficult to be certain in any given patient that neutropenia is not a precursor to agranulocytosis. However, it is notable that only 30% of confirmed cases of agranulocytosis pass through a neutropenia phase during the precipitous fall in counts.[12]

Haematological monitoring is mandatory to mitigate haematological risk. However, worldwide, there are marked variations in the recommendations for monitoring frequency and the threshold for clozapine cessation,[14] reflecting, perhaps, the weak evidence on which they are based. In 2015, the US FDA introduced changes to the clozapine monitoring system making only the ANC mandatory and effectively lowering the threshold for cessation of clozapine treatment.[15] It is recommended that treatment with clozapine be stopped when neutrophils fall below 1000/mm[16] (compared with UK recommendations for cessation if ANC <1500/mm).[16]

There is evidence that clozapine is grossly under-used worldwide, with very wide variation in prescribing frequency from one country to another.[17] This may be explained at least in part by the stringent blood monitoring requirements. The worldwide outbreak of COVID-19 in 2020 prompted a re-evaluation of clozapine haematological monitoring, with a group proposing a reduction from monthly to 3-monthly for patients who have received clozapine for more than 1 year without a history of neutropenia.[18] Implementation of the extended 3-monthly monitoring found no difference in the rates of severe neutropenia compared with monthly monitoring.[19] In addition to this, when considering that the development of true agranulocytosis occurs over 10 days or less, the value of monthly monitoring is clearly questionable, especially in patients for whom the overall risk of agranulocytosis is near to zero.

Benign ethnic neutropenia

BEN is a widely recognised hereditary condition in which the neutrophil count is relatively low – there is a left shift in the normal distribution of counts. People of African or Middle Eastern descent have a high prevalence. BEN is characterised by low WCC, 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, evidence suggests that BEN does not pose an increased risk of dyscrasias during clozapine treatment.[20,21] The use of genetic testing to identify BEN may be useful in reducing the risk of unnecessary termination of treatment and is strongly recommended for all patients starting clozapine, regardless of ethnicity.[22,23]

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 GI agents such as proton-pump inhibitors. Many patients develop neutropenia on clozapine but not all are clozapine-related or even pathological. The possible contributory role of these agents should always be considered and these drugs discontinued if clozapine rechallenge is attempted.[24]

Management options

Before treatment initiation, it is important to evaluate baseline haematological values. All patients should be genetically tested for BEN.[25]

In those already taking clozapine, there are three distinct patient groups: those with normal neutrophil counts, those with neutropenia unrelated to clozapine, and those with clozapine-related agranulocytosis. Here, we discuss options for the middle group – those with mild neutropenia unrelated to clozapine. The use of iatrogenic agents to elevate WCC in patients with clear prior clozapine-induced severe neutropenia or agranulocytosis (i.e. there is 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 rechallenged either with or without lithium.

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 11.9×10^9/L has been reported in patients treated with lithium, and a mean rise in neutrophil count of 2×10^9/L was seen in patients treated with clozapine after the addition of lithium. This effect does not seem to be clearly dose-related, although a minimum lithium serum level of at least 0.4mmol/L may be required. The mechanism is not completely understood.[26]

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[27–31] and in children[32,33] have been published. Almost all patients had plasma lithium levels of >0.6mmol/L. In a case series (n = 25) of patients who had stopped clozapine because of an apparent blood dyscrasia and were rechallenged in the presence of lithium, only one developed a subsequent dyscrasia.[34]

If considering lithium, discuss with the medical adviser at the relevant monitoring service to determine the optimum pharmacological strategy for the particular patient. Increased risk of neurological adverse effects such as myoclonus, ataxia and seizures should be considered when using the combination.[35] Where there are valid concerns regarding neurotoxic effect, it may be prudent to use clozapine alone (off-licence) with US monitoring criteria (Figure 1.6).[36]

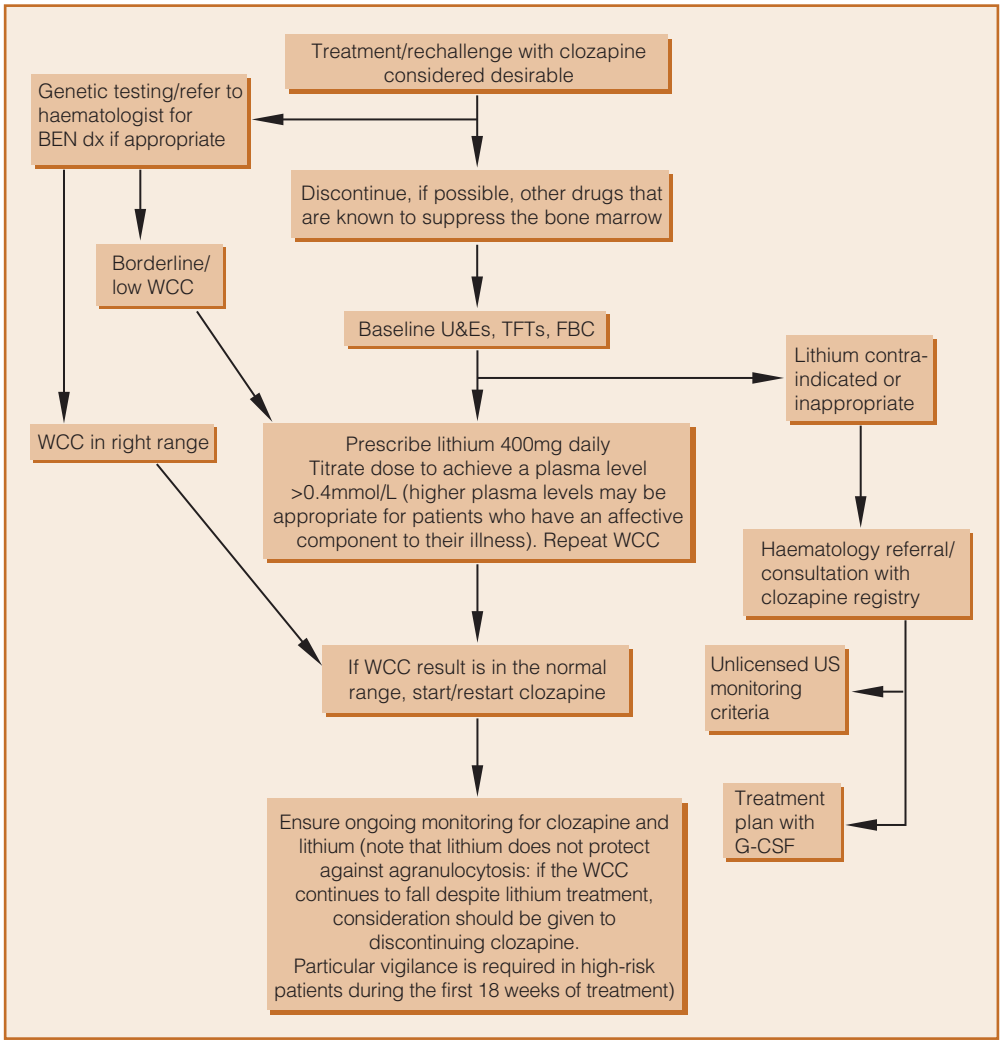

Figure 1.6 The use of lithium with clozapine.

Lithium does not protect against true clozapine-induced agranulocytosis. One case of fatal agranulocytosis has occurred with this combination[25] and a second case of agranulocytosis has been reported with the combination with subsequent resistant to treatment with granulocyte colony-stimulating factor (G-CSF).[37]

Granulocyte colony-stimulating factor

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. In one study, clozapine was successfully rechallenged using G-CSF in 76% of patients for an average follow-up period of 1.9 years.[38] As well as the commonly reported adverse effects of bone pain[39] and neutrophil dysplasia,[40] 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 but 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 rechallenge 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/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 are 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 rechallenge with clozapine if the first episode of dyscrasia 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 $<0.5\times10^9$/L) or
- prolonged.

While G-CSF has been reported as allowing successful rechallenge with clozapine in some people with previous episodes of clozapine-induced neutropenia,[41] the available evidence should exclude this course of action for someone with a true clozapine-related agranulocytosis.[42]

Lithium is indicated in the management of patients with:

- low initial WCC ($<4\times10^9$/L) or neutrophils ($< 2.5\times10^9$/L)
- leucopenia (WCC $<3\times10^9$/L) or neutropenia (neutrophils $<1.5\times10^9$/L) thought to be linked to benign ethnic neutropenia. Such patients may be of African or Middle Eastern descent, have no history of susceptibility to infection and have morphologically normal white blood cells[3]
- recurrent 'amber' results during clozapine treatment
- a 'red' result probably unrelated to clozapine.

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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 white blood cell count drops below 3.0×10^9/L clozapine is usually discontinued. This is an important safety precaution outlined in the formal licence/labelling. For many regimens it can be predicted that chemotherapy will reduce the white blood cell (WBC) count below this level, irrespective of the use of clozapine.

The use of chemotherapy may be more likely in people taking clozapine because of its association with malignancy.[1,2] Ideally, clozapine should be discontinued before chemotherapy starts. However, this will place most patients at high risk of relapse or at least significant deterioration of their psychotic illness, which may then affect their capacity to consent to chemotherapy. This poses a therapeutic dilemma in patients prescribed clozapine and requiring chemotherapy. In practice, most patients do continue on clozapine treatment during chemotherapy.

Liaison with regulatory bodies is essential in ensuring continuity of clozapine treatment for patients who are also receiving chemotherapy. Severe clozapine-induced neutropenia is very rare in people taking clozapine for longer than a year, while neutropenia is a known adverse effect of many chemotherapy regimens. Chemotherapy has a predictable effect on neutrophil counts, both in terms of magnitude of effect and the timing, so knowledge of these factors should help determine the cause of any neutropenia that develops.

There are a number of case reports supporting continuing clozapine during chemotherapy,[3–18] but interpretation of this literature should take account of possible publication bias.[3] Before initiating chemotherapy for a patient receiving clozapine, it is essential to put in place a treatment plan that is agreed with all relevant healthcare staff involved and, of course, the patient and family members/carers. This will include the oncologist/physician, psychiatrist, haematologist, pharmacist and the clozapine monitoring service. Plans should be made in advance for the action that should be taken when the WBC count 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 medication such as lithium and G-CSF[19,20] to try and support the maintenance of normal neutrophil counts.

In the UK, the clozapine monitoring service will normally ask 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.[6] G-CSF has been used to treat agranulocytosis associated with chemotherapy and clozapine in combination.[7,8,21] As discussed above, the risks of life-threatening blood dyscrasia are probably lowest in those who have received clozapine for longer than a year, in whom a clozapine-induced severe neutropenia would be highly unusual.

Summary

- If possible, clozapine should be discontinued before starting chemotherapy but, for almost all people, the risk–benefit analysis will be judged to be in favour of continuing clozapine.

- The likelihood of relapse or deterioration of the psychotic illness must be considered before discontinuing clozapine.
- Consideration should be given to the possibility that, if the patient's mental state deteriorates, they may retract their consent for chemotherapy.
- When clozapine treatment is continued during chemotherapy, a collaborative approach is strongly recommended, involving an oncologist, a psychiatrist, a haematologist, a pharmacist, the patient and their relatives/carers and the relevant clozapine monitoring service.

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Genetic testing for clozapine treatment

A great number of studies have sought to detect genetic predictors of clozapine outcomes, both therapeutic and adverse. Generally, only small effects have been uncovered and clinical utility is limited unless genetic variant effects are mathematically combined. Sensitivity (the likelihood of accurately predicting a specific outcome) is usually low but specificity (the likelihood of correctly excluding that outcome) is often very high. Numerical values for these categories can be combined with population incidence data to generate positive predictive value (PPV – the % of people who will experience the outcome when predicted) and negative predictive value (NPV – the % of people who will not experience that outcome when it is not predicted). This concept is applicable to genetic variants linked to agranulocytosis. The presence of a candidate variant (see PPV below) should provoke caution and perhaps more frequent testing. The absence of a candidate variant (see NPV) may give some reassurance about the likelihood of agranulocytosis, especially if the NPV is >99.6% (that is, 100 minus 0.4%, the risk of agranulocytosis in the wider population).

Response

Three variants have been reliably shown to predict therapeutic outcome with clozapine:[1]

HTR2A rs6313C	CC carriers less likely to respond than T carriers CC 146/272 response, CT/TT 366/596 response (54% vs 62%)
HTR2A rs6314	C allele more likely to respond than T allele C allele response 685/1,215, T allele 55/127 (56% vs 43%)
HTR3A rs1062613	C allele less likely to respond than T allele C allele response 528/841, T allele 134/185 (63% vs 72%)

Mathematical modelling of these three variants can generate an overall percentage chance of response with confidence intervals. Other variants may be linked to response.

Agranulocytosis

Several genetic variants are reliably associated with altered risk of agranulocytosis. Some variants are found only in certain ethnic groups.

HLA-DQB1	Sequence variant 6672G>C (REC 21G) confers 1,175% higher risk of agranulocytosis than general population. Sensitivity 21.5%, specificity 98.4%.[2] PPV 5.1%, NPV 99.7%. In people of European ancestry, sensitivity is 53.7% and this variant confers a 10-fold greater risk of agranulocytosis.[3]
HLA-DQB1	DQB1*0502 allele is associated with agranulocytosis in 5 of 7 studies (e.g. Dettling and colleagues,[4] Yunis and colleagues[5]). Effect size variable.

HLA-B*59:01	Presence of allele highly predictive of agranulocytosis but is rare in East Asian populations and almost absent in people of European descent. Sensitivity 31.8%, specificity 95.3%.[6] PPV 6.4%, NPV 99.3%.
HLA DQB1/HLA-B	Single amino acid changes HLA DQB1 126Q and HLA-B 158T associated with increased risk of agranulocytosis. Overall, 39 of 95 cases had one or both alleles; 175 of 206 controls had neither allele. Sensitivity 41.0%, specificity 85.0%[7,8] (36% and 89% figures given elsewhere).[9] PPV/NPV not given but can be calculated.
HLA-DRB1	DRB1*04:02 confers a six-fold higher risk of agranulocytosis. NPV is 99.3%.[10]

The HLA-DQB1 variants and the HLA-B variants are in linkage disequilibrium[9] and are likely to convey the same association signal. Variants in linkage disequilibrium are inherited together.

Benign ethnic neutropenia

ACKR1 rs2814778	CC genotype at rs2814778 (Duffy Null Status) is considered to be the cause of BEN.[11]

All patients starting clozapine should undergo genetic testing for BEN.[12]

Metabolism

Clozapine is largely metabolised by CYP1A2 and, to a lesser extent in most people, CYP3A4/5. Despite early reports, CYP2D6 plays almost no role in the metabolism of clozapine.[13] Metabolic rate is usually classified as poor (PM), intermediate (IM) or extensive (EM) and each is associated with a particular genetic variant. Genetic analysis can therefore allow an estimate of the target dose of clozapine for an individual. This is the most accurate method of predicting clozapine dose.[14]

Cytochrome p4501A2	PM/IM/EM status as normally defined by analysis of e.g. CYP1A2*1F/1C/1A/1K.[15]
Cytochrome p4503A4	PM/IM/EM status. CYP3A4 is usually a minor route of clozapine metabolism but metaboliser status affects blood concentration.[16]
Cytochrome p4503A5	PM/IM/EM status. CYP3A5 PM status associated with elevated clozapine blood levels.[17]

Other non-CYP genetic associations have also been demonstrated.

NFIB rs28379954 *T*>*C* CT carriers have much lower blood concentrations than TT carriers in both smokers and non-smokers.[18]

Also, the **rs2472297** genotype independently predicts clozapine plasma levels.[19] Levels are highest in C/C carriers and lowest in T/T carriers (C/T somewhere in between).

Genetic analysis of CYP function can identify the cause of low clozapine blood concentrations and allow selection of appropriate enzyme inhibitors.[20]

Other adverse effects

Genetic predictors of myocarditis[21] and weight gain[22] have also been found, but associations are probably too weak to allow clinical application.[15]

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