

Management of schizophrenia: drug treatment

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6.1 Is medication always necessary in the treatment of schizophrenia?



Long-term studies of schizophrenia have shown that only about 10% of those diagnosed as having a schizophrenic illness can remain stable, at least in social and personal terms, without medication. The problem is that this cannot be predicted for any particular type of presentation or pattern of symptoms. The accepted view is therefore that medication remains the cornerstone of successful treatment in schizophrenia, without which other treatments, be they psychological and social, cannot really work. The history of the illness from the pre-pharmacological age is one of crowded asylums, chronic and distressing symptoms, and a form of 'secondary dementia', leading to loss of personal skills, incontinence, mutism and a high level of dependence. Ensuring adherence to medication, and methods of establishing 'compliance', are the essence of best practice.

6.2 Is there any particular medication that stands out from all the others?

No. The recent guidance from the National Institute for Clinical Excellence (NICE) has suggested that 'atypical' antipsychotics are probably the first-line treatment of choice, but no particular drug has been singled out. In addition, there is no evidence that the efficacy of 'atypical' medications is any greater than the traditional dopamine-blocking drugs (such as chlorpromazine) in dealing with symptoms. Whichever one is used, up to 70% of patients will, depending on the length and severity of their illness, respond with a partial or complete remission. Because of their apparently cleaner side-effect profile, the atypical agents are preferred, and it is thought – but not yet proven – that improved compliance should be a particular advantage of the newer drugs.

6.3 Are there any medications without side-effects?



Probably not. As with most drugs in the therapeutic armamentarium, there exists what is known as a therapeutic index. In practical terms, this is the difference in dosage between what will produce a beneficial, therapeutic response and what will generate a 'toxic' effect. This 'toxic' effect may be one or more unpleasant side-effects or may even lead to significant mortality. The dosage range outlined in the *British National Formulary (BNF)* is a core guide to safe prescribing, and most antipsychotic drugs are very safe in terms of toxicity if used within these limits. The use of dopamine-blockers can, however, lead

to side-effects even at fairly small doses in those sensitive to their impact on muscular or movement control. Virtually all antipsychotic drugs, of whatever class, seem to confer a degree of sedation, of a subtle or obvious type, and weight gain is not uncommon. It is generally accepted that having an honest but not alarmist discussion about these possible problems is an essential part of the preparation for treatment.

6.4 What's the best drug to start treating someone with schizophrenia?



There is no 'best' medication, given that all medications have equal efficacy. However, availability, the patients' attitude to medication and aspects of the presentation – are they withdrawn or are they agitated? – will influence the clinician's choice. The commonly prescribed medications in two main classes of antipsychotic drug – atypical and traditional – are outlined in *Table 6.1*. This assumes that a patient is willing to take medication orally and prefers so to do. Many of the drugs are available not only as tablets, but also as syrups or easily soluble preparations, and developing clinical experience with one or two of either class is the best practice. Supplementing with benzodiazepines, or providing additional medication – on a 'as required' (p.r.n.) basis to deal with side-effects – is also part and parcel of good management. Trying to stick to a single medication is of course always worthwhile but may not be possible in agitated states. Assuming a definite diagnosis, such treatment can readily be started in primary care. Obtaining an additional specialist opinion is probably a must in order to reassure the family and obtain specialist support in ongoing management.

6.5 What is the best treatment for acute schizophrenia if the patient is very agitated?

This will depend on whether the patient is compliant with medication – i.e. willing to take an oral preparation – or refuses to do. All antipsychotics are calming, hence their formal description as 'major tranquillizers', but chlorpromazine is particularly so because of its wide range of activity (i.e. it is also antihistaminic and anti-adrenergic). The dose (50–100 mg 3–4 times a day) can be fine-tuned every 2 or 3 hours, and because of its in-built anticholinergic effect it is less likely to generate side-effects in the short term. Supplementing with benzodiazepines (diazepam 5–10 mg or

TABLE 6.1 Commonly prescribed oral medications for the treatment of schizophrenia (proprietary names)

	Traditional (dopamine blockade)		Atypical (5-hydroxytryptamine effect +/- limited dopamine blockade)		
	Usual daily dose	Maximum dose	Usual daily dose	Maximum dose	
Chlorpromazine	100–800 mg	1 g	Olanzapine	5–20 mg	20–25 mg
Haloperidol	5–30 mg	60–80 mg	Quetiapine°	100–500 mg	750 mg
Trifluoperazine	5–30 mg	30 mg	Amisulpride	40–800 mg	1.2 g
Pimozide*	2–20 mg	20 mg	Risperidone†	2–6 mg	16 mg
Sulpiride	200–1600 mg	2.4 g	Clozapine°	200–400 mg	900 mg
Zuclophenthixol	20–50 mg	150 mg	Zotepine	100–200 mg	300 mg

*ECG required before treatment; †has dopamine blockade side-effects above this dosage;

°requires regular haematological monitoring

lorazepam 2 mg) reduces arousal, helps with sleep and is again very flexible in its dosage. The use of immediate, relatively high doses of atypical agents, along with benzodiazepines, is now also being recommended (especially to avoid side-effects), but more evidence on the efficacy of this approach is required, and the flexibility of 3–4 times a day dosage may not be available.

If injectable preparations are required for a resistant patient, transfer to hospital (under the Mental Health Act if necessary) is vital. Lorazepam 2–4 mg given intramuscularly is safe, effective in sedation and short-acting, while haloperidol 5–10 mg intramuscularly can also be used, either to supplement the lorazepam or on its own. A close monitoring of such patients' physical and mental state is a priority, as is the early use of intramuscular (or oral) anticholinergics such as procyclidine 5–10 mg to counteract any side-effects (e.g. acute dystonia).

6.6 If starting treatment with a typical medication, how readily can one switch to an atypical agent if there are side-effects?



As many doctors are rather more familiar, particularly at the primary care level, with traditional medications such as chlorpromazine and haloperidol, many patients, particularly if they are agitated, will have been started on these. This is perfectly good practice provided the side-effects are monitored closely. Initiating treatment with atypical agents in quieter, more compliant patients is – based on our current knowledge – worth encouraging, but these drugs are not entirely free of side-effects, and some patients simply do not respond to one class or the other.

BOX 6.1 Switching medications in schizophrenia

Reasons for:	Reasons against:
Intolerable side-effects	Poor insight or no clear reason
Partial or full resistance to treatment	Successful treatment
Relapse or worsening of symptoms	When dosage adjustment may suffice
Patient/family request	Major life changes are ongoing
Physical/psychiatric complications	Drug/alcohol abuse or risk of violence
	Known to be non-compliant

When switching from a traditional drug – *Box 6.1* outlining reasons for and against switching medication – such as chlorpromazine to an atypical agent, there is no need for a ‘washout’ period. It is usually best to build up the atypical agent to full dosage over the course of several weeks while continuing with, for example, the chlorpromazine and then gradually withdrawing the latter. Likewise, with a switch from an atypical to a traditional drug, building up the latter to a regular dosage over the course of a week or two and then gradually withdrawing the atypical agent is the safest practice. The main problem will be sedation, and both patient and family will need to have this temporary problem fully explained to them. (See refs 13 and 14.)

6.7 What are the common side-effects of ‘traditional’ antipsychotic drugs?



These are outlined in *Box 6.2*, most being the consequences of dopamine blockade. The three major areas of side-effects are therefore associated with lack of drive/sedation, sexual difficulties (as a result of a raised prolactin level with the release from inhibitory dopamine control) and movement disorders. Depending on the dosages used, such effects will occur in 30–70% of patients, some being more obvious than others. Abnormal movements can be monitored clinically and scored on standard rating scales (e.g. Abnormal Involuntary Movements Scale), whereas others, for example, erectile problems may need sensitive questioning to elicit them. There are also drug-specific problems (e.g. a sun-induced rash with chlorpromazine) and a host of minor idiosyncratic reactions (see the most recent *BNF*).

BOX 6.2 Side-effects of dopamine-blocking drugs (class specific)**Sedation**

Loss of drive and 'get up and go'
Drowsiness and hypersomnia
Loss of concentration and initiative
Feeling 'drugged' and 'flat'

Sexual

Loss of libido
Erectile failure (partial or full)
Delayed or absent ejaculation
Anorgasmia (in women)
Inappropriate lactation

Movement

Acute dystonia (especially face or jaw)
Akathisia (inability to sit still)
Parkinsonism (tremor, bradykinesia, cogwheel rigidity)
Tardive dyskinesia (late onset, variable range of movements)

6.8 What's the best way of treating these side-effects?

Assuming one cannot lower the dosage or change medication, which are the best practical approaches if possible, the treatment of side-effects will generally require anticholinergic medications (for movement disorders) or sometimes beta-blockers (e.g. propranolol) or benzodiazepines. Acute dystonia (use intravenous or intramuscular procyclidine if severe) and parkinsonism usually respond well to anticholinergic drugs (e.g. Procyclidine 5–10 mg up to three times daily, or orphenadrine 50–100 mg up to three times a day); akathisia is often less responsive. Propranolol (40–80 mg up to three times daily) and/or benzodiazepines (e.g. diazepam 5–10 mg up to three times a day) may be more effective in this regard. The later-onset condition known as tardive dyskinesia is usually resistant to such approaches, although an increased dosage of the dopamine blocker may abolish it (probably, however, to the detriment of the patient's mental state because of sedation).

Alternatively, giving lower doses of medication while supplementing with benzodiazepines can maintain stability in terms of the mental state yet make patients feel physically more comfortable.

Switching completely to atypical antipsychotic medications, if that is an option and they have not previously been shown to be ineffective, is nowadays an obvious alternative measure. These of course have their own side-effects (*see Q. 3.10*), which need to be acknowledged.

6.9 Can benzodiazepines or other tranquillizers be helpful in the treatment of schizophrenia?

Yes, they are very helpful. Not only are benzodiazepines such as lorazepam and diazepam useful in early, agitated states, particularly if patients require sedation on inpatient units, but they can also be of continuing use for those with an added anxiety component, this being a problem for up to a third of patients. Benzodiazepines can help lower arousal, thus reducing the requirement for higher doses of antipsychotics, they can promote sleep, and they can help with some movement disorders, such as akathisia or tremor. Concerns about dependence need to be viewed within the context of patients who are going to be taking major tranquillizers for a long time. Continuing or intermittent benzodiazepine usage is highly unlikely to generate dependence behaviours. Standard preparations such as diazepam, with its wide dosage range, and nitrazepam, with its long half-life (especially helpful for sleeping), are the most practical in this respect.

6.10 What are the usual side-effects of atypical medications?

Although they are clean in terms of movement disorder – although these have occasionally been reported – atypical agents tend to be sedating in some individuals, sometimes producing a rather marked degree of somnolence. Most of them are also associated with a tendency, in a third or more of patients, to put on weight, which can sometimes be quite distressing, although it does level. Concerns have also been raised about the development of hyperglycaemia or frank type 2 (non-insulin-dependent) diabetes, ECG abnormalities and (specifically with clozapine) forms of anaemia. The details of side-effects are listed in *Box 6.3*.

BOX 6.3 Side-effects of atypical medication

Sedation	Daytime drowsiness, hypersomnia, loss of drive, impaired concentration, postural hypotension
Metabolic	Weight gain, enhanced appetite +/- craving for carbohydrates, hyperglycaemia (especially clozapine)

6.11 Are any particular drugs effective for any particular symptoms?

There is no evidence that any specific antipsychotic drug is especially effective for hallucinations, for example, or thought broadcast or other forms of thought interference. If a drug is effective, it will generally be effective across the spectrum of 'positive' symptoms, and there is no evidence that using additional drugs will enhance the response. It should also be emphasized that both 'traditional' and 'atypical' types of antipsychotic are really effective only for positive symptoms, and the evidence for their reducing 'negative' symptoms is very limited. There may be an apparent improvement using atypical agents because over-sedation or parkinsonian effects (e.g. a somewhat unchanging facial expression) are no longer present. Better compliance may likewise reduce certain symptoms, for example thought broadcast (feeling that people can read your mind), as are likely to enhance the social withdrawal and limited speech so typical of the negative symptom group.

In a more general sense, patients who are aroused and anxious often benefit from drugs such as chlorpromazine that have additional anxiolytic properties, whereas those who are withdrawn or rather sluggish will do better on a drug such as trifluoperazine (from the traditional group). Such differential secondary effects are not especially apparent for the atypical drugs, although clozapine and olanzapine seem to be often slightly more sedating (and therefore anxiety-relieving?) than the others. The rule is, however, to take account of individual variation in response and thus tailor the medication to an individual's own pattern of symptoms and side-effects.

6.12 Can the newer medications ('atypicals') help with negative symptoms?

There continues to be a debate over this, part of which will depend on how the negative symptoms are characterized. Some studies show a limited improvement in negative symptom score on standard scales such as the Positive and Negative Symptoms Scale, but these differences are often not very large. They may reflect better compliance, and thus an improvement in underlying 'positive' symptoms such as intrusive voices, or they may reflect reduced sedation. There is a little evidence to support a modern version of sulpiride (called amisulpride), but corroborating research is still required. The strongest evidence base relates to the use of clozapine in patients with chronic resistant schizophrenia, which usually includes a degree of negative symptomatology, but this again usually works by reducing the intensity of positive symptoms. The use of antidepressants on a trial basis, given the big overlap in clinical assessment between 'depressive' and 'negative' symptoms, is well worth considering.

6.13 Are patients more compliant with any particular medications or forms of treatment?



Compliance with medication, now often termed 'adherence', is a major problem throughout medicine but particularly in the treatment of psychotic illnesses. Depending on a patient's upbringing, intelligence and insight into their illness, certain treatments may make more sense than others. Some patients prefer syrups to tablets; others prefer tablets to injections or vice versa. If a medication helps with a particular symptom, for example difficulty sleeping, patients will happily take it. If it also, for example, relieves headaches or reduces anxiety (secondary to paranoid beliefs), that is likewise a positive reinforcer.

Unpleasant effects, for example muscle spasms or not being able to attain an erection, will quite quickly put patients off. Remember too that whereas a third of 'refusers' cite side-effects as the reason for their refusal, doctors tend to recognize fewer than 10% of such concerns! The use of formal 'compliance training' tries to clarify these matters, and warning patients of temporary side-effects, explaining the rationale of medication and trying to fit medication to an individual's needs are all part of good practice.

Simply listing the good and bad aspects of taking a particular drug can start this dialogue off. The benefit of the greater range of antipsychotics now available, particularly with the atypical agents, is that a drug suited to an individual's reactions is more readily found. We still await formal studies showing that there is better compliance with atypical medications, although this is the general clinical impression.

6.14 Why do so many patients stop taking their medications?



Medication can be stopped because of side-effects, lack of insight, sheer forgetfulness, outside influences or simply patients feeling so well that they think they are 'cured'. The most distressing side-effects include excessive sedation, muscle spasms and tremors, weight gain and sexual difficulties. Insight is a particular problem for those who do not believe they are or have been ill (which affects at least 50% of patients), whereas all of us tend to forget to take our medications, particularly if the regime is a bit complicated or the drugs are to be taken more than once a day. There are also, unfortunately, many individuals or groups who do not 'believe' in medication, considering it to be addictive, unnecessary, less valuable than 'counselling' or less efficacious than the right diet, religious invocations or other alternative treatments. Finally, some individuals just feel so well that

they do not believe they need to continue with medication, a belief reinforced by standard health advice (e.g. taking antibiotics for only a week or 10 days) and the difficulty of distinguishing a 'cure' from maintenance therapy.

6.15 Are there any particular ways of improving compliance?

Getting patients to take medication is half the trick of psychiatric practice. The following rules generally apply (*see also Box 7.4*).

- Explain the nature of the illness to the patient and family without using euphemisms. Do, however, use the information packs or leaflets provided by voluntary organizations and the Royal College of Psychiatrists.
- Try to explain the role of medication. Emphasize that the illness is a physical problem of 'the nerves' or even 'brain chemicals' rather than a moral defect or something to be ashamed of.
- Warn about and monitor side-effects closely, adapting dosages and/or medications to make the patient as comfortable as possible.
- Use simple, once- or twice-daily regimes if possible rather than complicated prescribing approaches.
- Involve the family and/or carers in this approach and provide support for them as well if necessary.
- A formal, cognitive-behavioural approach to insight can show significant improvements, using trained nurses able to deliver a psycho-educational programme to both patient and family. The best programmes seem to cut the relapse rate by 20–30%.
- If necessary, engage an Assertive Outreach Team (as promoted by the NHS Plan and National Service Framework), and be prepared to use the Mental Health Act to insist on continued treatment since patients do have a 'right' to care.

6.16 What are the indications for starting people on depot injections?

Persistent relapse on oral medication, because of forgetfulness or non-compliance, or a need to maintain medication (e.g. because of at-risk behaviours when patients become unwell) are the usual indicators for using depot injections. A number of patients prefer them since there is much less hassle involved in having an injection every 3–4 weeks than in taking tablets two or three times a day. Furthermore, lower dosage can in general be used since injections avoid the 'first-pass metabolism' of the liver (which removes over 90% of the active agent!), the drug going essentially straight into the blood stream. Patients under longer-term Mental Health Act orders

(such as a restriction order under Section 41) are particularly well managed by depot injections because of the certainty of dose and prescribing, and (coincidentally?) because of the regular contact with the patient by a trained nurse (see Table 6.2). Again, there is no reason why GPs should not initiate depot treatment while engaging the specialist team to help to monitor effects and side-effects.

6.17 Are expensive newer drugs really worth prescribing?

There has been considerable debate around this issue over the past few years, but the cost-effectiveness data are increasingly showing that it is cheaper to keep people out of hospital than to give them the wrong medication. The mental health budget is dominated by inpatient care, which absorbs some 70–80% of all costs. A medication that a patient will accept, that does not have side-effects and that is easy to administer is well worth it in terms of avoiding such expenses. Furthermore, while these drugs may be expensive now, they will soon be out of patent, and the relative cost of all psychiatric medications, compared with some modern antibiotics, angiotensin-converting enzyme inhibitors or HIV treatments, is actually very small. In the broader context of prescribing costs, antipsychotic medications, apart from clozapine (approximately £2000–4000 per annum, largely because of the safety requirements and blood testing) are really not a major factor.

TABLE 6.2 Depot preparations for schizophrenia (intramuscular)

Equivalents (BNF)	Trade name	Proprietary name	Recommended dosage	Test dose
200	Clopixol	Zuclopenthixol decanoate	200–600 mg every 1–4 weeks	100 mg
40	Depixol	Flupenthixol decanoate	50–400 mg every 1–4 weeks	20 mg
100	Haldol	Haloperidol decanoate	50–300 mg every 2–4 weeks	25–50 mg
25	Modecate	Fluphenazine decanoate	25–150 mg every 2–4 weeks	12.5 mg
50	Piportil	Pipothiazine palmitate	50–200 mg every 2–4 weeks	25 mg

N.B. All of these preparations are given via deep intramuscular injection, ideally into the gluteal musculature by a trained nurse

Short-acting depot preparation

Clopixol Acuphase (zuclopenthixol zcetate) 50–150 mg every 3 days (maximum dosage 400 mg via a maximum of four injections)

6.18 How long does medication take to become effective?

In terms of a genuine antipsychotic effect, whether with a traditional or an atypical agent, antipsychotics usually take up to a month to eliminate (or start to eliminate) active, positive symptoms. Some patients will of course start to feel better within a few days, particularly if they feel calmer and less anxious because of the sedating effect. Other individuals may take up to 3 months or even more to improve, and the current NICE recommendation to change medications (if ineffective) after a couple of months is probably unrealistic for those people who have been ill for a long time. In essence, the longer the illness, the longer it will take to get people better, so someone who has been unwell for 2 or 3 years, slowly deteriorating in the community, is unlikely to get better within 1 or 2 months.

6.19 If a medication isn't effective, what should one do next?

There are a number of standard algorithms outlined by various research groups detailing what to do if medications are not effective. Assuming that one has started with an atypical agent and used it at a full dosage for at least 1 or 2 months, without even a partial alleviation of symptoms, it is worth considering an alternative. Patients clearly need close monitoring, either via standard rating scales (e.g. the Brief Psychiatric Rating Scale) or via careful clinical assessment. Compliance should always be carefully reviewed.

The next step is to switch to a traditional antipsychotic, again at the fullest dosage possible, monitoring its effects. If side-effects are the limiting factor, alternatives of either can be used to circumvent the problem. If one has used at least two drugs, either alone or in combination, or more usually three or four of the standard medications, without any significant improvement (i.e. there is resistant schizophrenia), clozapine is the drug of choice. Every unit should have a standard algorithm looking at alternatives before reaching clozapine, but such treatment should not be delayed for too long because the longer the active illness, the more uncertain the prognosis. Three standard algorithms are outlined in *Figures 6.1–6.3* for maintenance, poor response and treatment-intolerant patients.

6.20 Is it reasonable to combine typical and atypical medications?

All the official handouts say that one should not do this, but in fact, in the 'dirty' clinical situation, this can sometimes be helpful. For example, a patient who has side-effects when taking depot medication can be put on a lower dosage, with a supplementary atypical agent, thus maximizing their response and minimizing side-effects. Furthermore, if non-compliance or semi-compliance is a problem, the regular depot administration provides a safety measure, particularly if relapse means at-risk behaviours such as self-neglect or violence. Alternatively, the use of drugs such as chlorpromazine

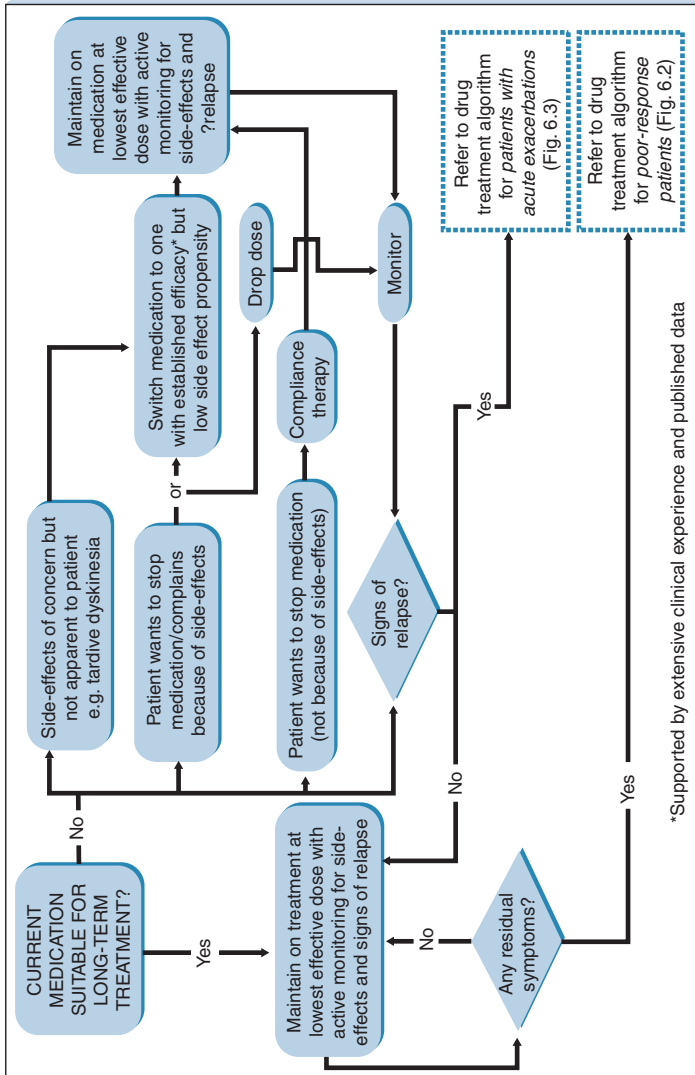


Fig. 6.1 Drug treatment algorithm for patients on maintenance therapy. From ??? with permission, author to confirm details.

simply to help with sleep, alongside, perhaps, a standard atypical drug, can help with a specific symptom or problem, again enhancing quality of life and compliance. It is clearly best practice to try to avoid combinations and multiple prescribing, but in the end the particular patient's needs should remain paramount.

6.21 What if the patient does not get better despite trying two or three different medications?

As outlined in *Q. 6.19*, every psychiatric unit should have guidelines on how to progress in terms of providing treatment. It is most important to review compliance (blood levels being available for some drugs), if necessary using an inpatient admission to check this (as well as to check the diagnosis as organic problems and personality disorders can fool even the best clinicians). The use of depot preparations rather than oral medication can (sometimes surprisingly) be extremely helpful in some patients, and a urinary drug screen (is the patient taking amphetamines or cocaine, on a regular basis, for example?) can also clarify some clinical situations. True resistant schizophrenia means that one has to consider clozapine, and a specialist clozapine clinic (*Box 6.4*) is usually a desirable resource given its

BOX 6.4 A specialist clozapine clinic

- Clozapine can be prescribed only by specialist clinicians registered with the Clozaril Patient Monitoring Service
- Regular blood tests (full blood count) must be coordinated with pharmacy prescribing
- Unless a 'green' blood count is received, the pharmacy cannot prescribe
- Blood tests are required weekly (for 18 weeks), then fortnightly (for 1 year) and then monthly (ad infinitum)
- Patients need to attend for blood tests (+/- clozapine level), provision of medication and regular review (mental state and side-effects)
- A specialist nurse attached to the clinic can supervise, monitor and help with advice on all aspects of care
- There are many common but transient side-effects, e.g. tremor, dizziness, headache, hypert/hypotension (on drug initiation), sedation, nausea and seizures (with higher doses)
- Common persistent side-effects, e.g. weight gain, hypersalivation, constipation and tachycardia, occur, requiring specialist management

complexities (weekly blood testing at first, closely monitored prescribing, and screening for other side-effects; *Case vignette 6.1*). Clozapine cannot currently be prescribed in general practice.



CASE VIGNETTE 6.1

A 38-year-old Chinese woman who had come to England 5 years previously was brought to the psychiatric emergency clinic by her family. She had in fact been 'ill' before emigrating and had received a combination of traditional medications (chlorpromazine) and herbal remedies while in the Far East. A key symptom was of regular voices, constantly talking about her and to her, and plaguing her with their presence. She attributed these to long-dead ancestors, sent to haunt her for her sins, and made several serious suicide attempts, including jumping out of a second-floor window. She had to be admitted under Section 3 of the Mental Health Act on three different occasions, partially responded to depot medication but was largely unable to care for her children even when she returned home in a relatively stable state. Her husband was initially supportive but became increasingly frustrated by her limited abilities in terms of childcare, her obvious tremor and parkinsonian appearance, and her limited self-care.

After the woman's third admission, it was agreed that, given the length of her illness and the chronicity of her symptoms – she continued to hear voices even when on medication – she should be offered clozapine. Her limited English required a Chinese support worker to help in explaining the protocols (e.g. regular blood tests) to her and to ensure that she took medication on a regular basis. Initiation of the drug began in hospital, and over the course of a 3-month admission, she gradually improved to a significant degree. She described her head becoming clearer and the voices fading, and even her appearance changed. She was much smarter in her grooming and self-care, was able to communicate better with her family and children, and lost her secondary depressive symptoms. Some 2 years after starting clozapine, she was back living with her family, no longer troubled by intrusive symptoms and helping to look after her children.

6.22 Are there any other drugs apart from the typical and atypical antipsychotics that can be useful in schizophrenia?

Some patients benefit from antidepressants, and distinguishing between depressive symptoms and negative symptoms is often difficult; a trial of antidepressants may even be worthwhile. Likewise, difficulties in sleeping can be addressed by standard hypnotics, and fears of the regular usage of, for example, benzodiazepines (i.e. minor tranquillisers) should be tempered by the fact that patients are already taking major tranquillisers. Such drugs can help to lower arousal and reduce the need for using higher doses of antipsychotics. The use of mood stabilizers (e.g. lithium, carbamazepine and sodium valproate) is controversial, but if there is clear evidence of mood swings, a trial of a mood stabilizer is again worth considering. Such decisions are best taken by specialist psychiatrists, in terms of examining the mental state and clarifying the diagnosis and symptomatology.

6.23 Is there a role for lithium in the treatment of schizophrenia?

No. A number of clinicians have tried using lithium, alongside antipsychotics, because of a pattern of what looks like mood swings, or even intermittent 'manic' type behaviours, and the differential diagnosis between a lithium-responsive condition such as manic depressive disorder and certain forms of schizophrenia can be quite difficult. There was a vogue for changing diagnoses in the 1960s and 70s simply because lithium was available, but this made clinicians more careful in their diagnostic practice. Given the need for regular blood tests, potential side-effects and established lack of efficacy, the use of lithium in patients who simply have schizophrenia is unjustified.

6.24 Is there a role for anticonvulsants, such as carbamazepine or sodium valproate, in the treatment of schizophrenia?

As with lithium, these drugs are not indicated unless there is a clear indication of mood swings (or even fits such, as from temporal lobe epilepsy). They do have a considerable role in the management of mood swing disorders and have also been used as a generalized form of 'anti-aggression' medication, but reports are again anecdotal, and there is no current justification for their use in straightforward schizophrenia.

6.25 Is there any justification for going beyond the *BNF* dosage limits?

Going beyond the *BNF* is sometimes justifiable provided one is quite clear about the diagnosis, has monitored the effects of all dosages, has confirmed compliance and is sure there is a reasonable likelihood of an improved effect. Individuals metabolize drugs with remarkable variety, some patients, for example, showing no evidence of an active level of flupenthixol (Depixol; usually given as a depot injection) even on weekly doses. High-dose medication has its risks, particularly in the aroused patient, and one should have a very low threshold for reviewing cardiac status, carrying out an ECG and closely monitoring both the physical and the mental state. Patients not responding to regular doses who do not seem to show any significant side-effects can be cautiously put on higher doses, at least on a trial basis. If improvement occurs, a gradual reduction to a more normal level can often be achieved, maintenance seeming to require less 'heroic' dosing than getting a patient into remission.

6.26 Are there any routine assessments that should be carried out before using antipsychotics?

Given that one is clear about the diagnosis and has eliminated possible alternatives caused by, for example, metabolic conditions (e.g.

hypothyroidism, drug abuse and temporal lobe epilepsy), the only assessment that is nowadays probably a 'must' is an ECG. It is, however, good practice to carry out baseline investigations, especially for blood sugar, given the higher rate of diabetes in all patients with schizophrenia and the potential of from some of the 'atypical' medications (e.g. clozapine) to enhance that. Using a test dose (e.g. half-strength depot administration) or an initially very low dose for 2 or 3 days of standard neuroleptics is also good practice. Checking the background history in case there is any pre-existing unusual, allergic or other reaction to antipsychotic agents is useful in choosing which particular drug to use. See *Table 6.3* for routine monitoring for clozapine and atypical agents.

6.27 What important interactions are there with the standard (typical and atypical) antipsychotics?

These drugs are, by and large, very clean and can be used alongside most other medications, whether those used in psychiatric practice or in general medicine. A list of possible interactions is outlined in *Table 6.4*, but it should be emphasized that these are unusual and rather idiosyncratic, and there are no absolute contraindications.

6.28 Can you measure drug levels in the blood routinely?

No. Certain specialist units can do blood level measurements, but variations in individual plasma levels are enormous given the range of different metabolites produced by most antipsychotics. There is no evidence that a particular level in a particular patient is effective or not effective, the most useful assessment being by clinical examination and a review of side-effects. If using typical, dopamine-blocking drugs, a prolactin level, at baseline (pre-medication) and after regular treatment, can indicate the level of dopamine blockade. This is to some extent also a measure of compliance, although not used routinely as such.

The one exception to this rule is the measurement of clozapine level, which is now quite routine. This both enables compliance to be checked (important in such a difficult drug to use clinically) and ensures the correct dosage as a level of less than 35 ng/ml is usually ineffective. The ability to measure drug levels more closely would certainly enhance the quality of care that could be offered to patients with schizophrenia and should be a priority for the future.

6.29 Is there a role for antidepressants in treating schizophrenia?

Depending on different studies, between 20% and 50% of patients with schizophrenia seem to have something approaching a depressive condition. This may be a combination of genuine depressive symptoms with negative symptoms, or the latter simply mimicking depression. It is also well known

TABLE 6.3 Management of treatment-resistant schizophrenia

Drug	Obligatory monitoring		Suggested additional monitoring		Actions
	Baseline	Continuation	Baseline	Continuation	
Clozapine	Full blood count (prescriber and pharmacist must register)	Full blood count weekly for 18 weeks, than at least fortnightly the for first year and monthly thereafter	ECG EEG Liver function tests Urea and electrolytes Blood pressure Creatine phosphokinase Temperature Weight	ECG – when maintenance dose is reached EEG – as above and if myoclonus or seizures occur Liver function tests/urea and electrolytes – every 3–6 months Blood pressure – 4-hourly during initiation Creatine phosphokinase – if neuroleptic malignant syndrom suspected Temperature – daily for the first 3 weeks and then weekly Weight – as needed	Stop clozapine if the neutrophil count is below $1.5 \times 10^9/l$ Refer to specialist care if the neutrophil count is below $0.5 \times 10^9/l$ Stop clozapine if the ECG changes or there are signs of heart failure Use sodium valproate if the EEG shows clear epileptiform changes or if seizures occur Stop clozapine if liver function tests indicate hepatitis Monitor closely if the temperature rises Stop if neutrophil count is below $1.5 \times 10^9/l$ Use with caution in hepatic or renal failure Stop if prolactin-related effects are intolerable
Risperidone	None	None	Full blood count Liver function tests Urea and electrolytes Blood pressure Prolactin Creatine phosphokinase	Full blood count – 3–6 monthly Liver function tests – 3–6 monthly Urea and electrolytes – 3–6 monthly	
Olanzapine	None	None			
Quetiapine	None	None			

TABLE 6.3 Management of treatment-resistant schizophrenia—cont'd

Drug	Obligatory monitoring			Suggested additional monitoring		Actions
	Baseline	Continuation	Baseline	Continuation		
Amisulpride	None	None	Blood sugar level Weight	Blood pressure – frequently during initiation Prolaction – if adverse effects occur Creatine phosphokinase – if neuroleptic malignant syndrom suspected Blood sugar level Weight – as needed	Stop if NMS is suspected	

TABLE 6.4 Routine monitoring for patients on atypical antipsychotics: antipsychotic interactions (see BNF for details)

	Effect
Alcohol	Enhanced sedative effect
Antacids	Reduced absorption, especially phenothiazines
Analgesics	Enhanced sedation/hypotension (e.g. indomethacin and haloperidol)
Anti-arrhythmics	Risk of arrhythmia, especially pimozide
Antibacterials	Risk of arrhythmia, especially pimozide
Antidepressants	As above and increased antipsychotic plasma concentrations
Anti-epileptics	Accelerated metabolism of the antipsychotic and reduced plasma concentrations
Antihypertensives	Enhanced hypotensive effect
Antivirals	May enhance the plasma concentration of specific antipsychotics
Lithium	Increased risk of extrapyramidal effects

that many patients with schizophrenia have been treated for ‘depression’ before the basis for their depression (i.e. their psychotic symptoms) has been clarified. Nevertheless, regular monitoring of potential depressive symptoms is part of good practice, and a trial of treatment with a standard antidepressant can be worthwhile in patients about whom one is uncertain. No particular group of antidepressants (e.g. tricyclics or selective serotonin reuptake inhibitors) is specifically indicated, but non-sedating medications are probably most useful in patients presenting with lack of drive, lack of motivation and a general slowing down.

6.30 How long should you go on with antipsychotic treatment?

The modern view is that, given the current role and effectiveness of the medications available, treatment is for life. That is not to say that a closely monitored trial of withdrawal should not be undertaken every now and then, with the patient’s and family’s agreement. In essence, however, antipsychotic treatment is like insulin therapy for diabetes, or thyroxine for hypothyroidism: one needs it as if it were a special ‘vitamin’ to supplement abnormal neurochemistry. Many clinicians will not use the ‘for life’ phrase, preferring to suggest that taking medication for up to 5 years at least should be the first aim. Given the possibilities of new treatments being marketed, this seems reasonably honest in terms of clarifying the nature of the condition and helping to enhance compliance.

6.31 Can patients get withdrawal effects from medication?

There are no specific withdrawal effects from antipsychotic agents, apart from a relapse of the symptoms of the illness. If anything, patients feel a little bit 'better' when off medication, particularly if they have been taking traditional antipsychotics, which tend to make them feel a degree of 'psychological parkinsonism' (e.g. lacking drive and sexual interest). This paradoxical 'feeling well window' is often the basis for patients and/or families blaming the illness on the medication. Furthermore, when relapse does occur, as it almost always does, there may have been a gap of 3 or 4 months, or even longer, so the patient does not link discontinuation of medication with getting ill. Other intervening factors, for example a row with a girlfriend or a change of housing, will (not unnaturally) be seen as much more significant.

6.32 What are the best arrangements for managing treatment between GPs and specialist teams (shared care)?

There is always a dilemma over who should prescribe, how patients should be followed up and how GPs communicate with community mental health teams (CMHTs) and consultant psychiatrists. Individual and local preferences will vary, but liaison attachments seem to be the most widely used. These involve a group of GPs meeting the relevant consultants, usually with another specified CMHT member (who acts as a regular liaison between that practice and the CMHT), and discussing clinical management. Problems usually arise when there is a gap in service, that is to say each side thinks the other is, for example, prescribing or monitoring. The Care Programme Approach review will usually identify a care coordinator, whose task is to check up on just these concerns. The motto should nevertheless be 'If in doubt, communicate.' Key aspects of such arrangements are summarised in *Box 6.5*.

BOX 6.5 Arrangements for shared care between GPs and the community mental health team (CMHT)

- Establishment of local agreements on the criteria for referral to, and discharge from, the local CMHT
- Establish in each practice a case register of those in shared care
- Clarify who does what – in terms of medication prescribing, medication monitoring, mental state assessment, physical assessment and (if required) blood level monitoring or urinary drug screening
- Planned and regular communication, via regular liaison meetings, for example reviewing those on the case register

- Agreeing on a liaison worker from the CMHT for each GP practice (or group of practices if single-handed, for example), with a defined role and tasks
- Agree on a crisis plan, with relapse indicators if useful and, if practicable, involving advanced directives
- Agree on the Care Programme Approach arrangements, on a regular updating of changes in prescribing, and consider regular audits of care arrangements

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PATIENT QUESTIONS

6.33 Can some patients stop medication without any relapse?

This is a perennial question, asked by many patients and families. Long-term studies show that perhaps 10% of patients seem to stay well – or at least socially stable – without medication, but no one can tell who this will be or what particular symptoms predict such stability. Sadly, most patients relapse on stopping medication, which is actually the commonest cause of relapse and the commonest cause of readmission to hospital. If planning to try to discontinue medication, for whatever reason, it is always best to do it slowly, to let your GP or community psychiatric nurse know and to try to do it while being closely supported. In that way, symptoms can be picked up quickly, medication can be restarted before things get out of hand, and harm can be minimised. It is also worth remembering that every time you become ill, the chances of a full recovery are slightly reduced, each relapse leaving patients with a bit of a ‘defect’ or even some stronger residual symptom, for example persistent hallucinations. Community care has essentially been made possible by the availability of medication, before which the great majority of patients with schizophrenia spent their lives in hospital.

6.34 What if I fall pregnant when taking medication?

Doctors agree that it is best not to take any medication during pregnancy, especially during the first 3 months (the first ‘trimester’), when a growing baby is most at risk. There is, however, absolutely no evidence that traditional antipsychotic drugs cause any harm and, as they have been in use for about 50 years, this evidence is very reliable. Staying on medication, and thereby keeping well during pregnancy, is the best advice, although stopping medication (which should be oral at this stage) for 2–3 days before delivery will reduce the chances of having a rather sedated baby at birth. The same applies for to newer ‘atypical’ drugs, but we have less long-term experience of their effects on babies so switching to a traditional drug might be theoretically safer.

After the birth, it is wisest to go back on your regular treatment – whatever medication you were on – because there is a very high risk of relapse at this time (a form of so-called ‘puerperal psychosis’). Since all antipsychotics are found in breast milk, albeit in small amounts, it is probably best not to breastfeed. A full discussion of all these factors with your psychiatrist during pregnancy, to get everything clear in your mind, is the best approach.

6.35 What if I’m being given a very high dose of medication?

This may be because you are not getting better on regular doses or even because you are ‘resistant’ to medication. The advice of the Royal College of Psychiatrists on doses above the *BNF* upper limit is as follows:

1. Alternative medications and even clozapine may need to be considered.
2. Overweight and elderly patients are especially at risk of side-effects.
3. Regular ECGs should be carried out, and the dose reduced if certain abnormalities are detected.
4. Regular pulse, blood pressure and temperature checks should be performed; those taking the medications should maintain an adequate fluid intake.
5. Doses should be increased only slowly (about weekly) and regularly reviewed. High doses for more than 3 months without any improvement should be discontinued.

6.36 How can I stop myself putting on weight if my medication makes me feel hungry?

A problem with both the traditional and atypical antipsychotics – in particular several of the latter – is some patients’ experience of feeling more hungry. Some patients even find that they develop a craving for certain foods, especially sweets or carbohydrates. Weight increase is compounded by reduced physical activity, particularly if they are being looked after on a hospital ward. The ready availability of sweet drinks and foods with a lot of sugar in, for example breakfast cereals and frozen pizzas, makes it very easy to put on weight quickly. Controlling your appetite can involve a number of careful steps:

1. Think about what you eat and drink, and try to avoid things with sugar in. Thus, diet brands of cola drinks and or unsweetened orange juice are good substitutes.
2. Try to eat regular meals, avoiding extra snacks, particularly late at night. Keeping a food diary can help you to see how much you really are eating. You have to be honest of course, putting down everything – even the odd packet of crisps – that you eat in the course of a day.
3. Reducing how much you eat can be helped by having a drink, for example a glass of water, before eating. This gives a sense of fullness without actually putting on calories.
4. Eat as many fruits and vegetables as you want rather than too much heavy pasta and sweet puddings.

5. Eating sometimes comes out of being bored so try to keep busy and, of course, physically active. Exercise won't necessarily make you lose weight, but it will make your body's metabolism increase, making it possible to eat more food without putting on weight.
6. Once you have got into the habit of avoiding sugar, eating regular meals and so forth, you can of course give yourself occasional treats. Break the rules once a week or once a fortnight, and don't try to lose weight too quickly. It is better to adapt slowly, over months, rather than suddenly lose weight (and put it back on again) in the space of several weeks.