Meet the relatives: a reintroduction to the clinical pharmacology of 'typical' antipsychotics (Part 1)†

ARTICLE

David Cunningham Owens

SUMMARY

A number of pragmatic trials have cast doubt on the concept of 'atypicality' in relation to antipsychotic drugs, and some commentators have argued that the dichotomy between 'typical' ('first-generation') and 'atypical' ('second-generation') compounds is artificial and should be abandoned, leaving the entire class of antipsychotics available for consideration in more individualised treatment planning. However, younger psychiatrists now gain little or no experience in the use of older antipsychotics. This is the first of two articles addressing practical issues for consideration in prescribing the older antipsychotics available in the UK. It covers background, including the fundamental clinical action of antipsychotics, the nature of drug licensing and identification of pharmacological parameters that may be of value in prescribing decisions, and discusses the phenothiazines: chlorpromazine, promazine, levomepromazine, pericyazine, perphenazine, trifluoperazine and prochlorperazine.

DECLARATION OF INTEREST

None.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman 2005) is arguably the highest-profile psychopharmacology trial ever, for this was a study with a sting in its message – that, in effect, for over a decade, psychiatry had got it wrong (Owens 2008). There are still those who reject such radical interpretation (Naber 2009) but much of CATIE's prodigious output has been aimed at addressing potential design flaws and, overall, it has stood up well to a level of scrutiny most studies avoid. Furthermore, it is now only one of a series of pragmatic studies of differing designs and outcomes, and not sponsored by industry (Jones 2006; Kahn 2008; Fischer-Barnicol 2008; Sikich 2008), pointing to the unavoidable conclusion that the distinction between 'typical' and 'atypical' antipsychotics is artificial. This has led some to argue that any term implying a dichotomous split in antipsychotic drugs, such as

'atypical' or 'second-generation', should be banned from teaching and practice (Fischer-Barnicol 2008; Owens 2008; Leucht 2009), allowing the entire field of antipsychotics, old and new, to become available for equal consideration in individualised treatment planning.

This overlooks an obvious fact – that a generation of trainees has now reached seniority in psychiatry without gaining much, if any, experience in the use of antipsychotics available before the mid-1990s. This is important, for one lesson from CATIE might be that we were not very good at using the older drugs in the first place. This article offers a brief clinical overview of the so-called 'first-generation' ('conventional' or 'typical') antipsychotics currently available in the UK (Box 1). While a 'clinical pharmacology' approach would be ideal, formal study of these compounds was generally sparse, so a large part of what follows encompasses my own experience as a clinician now sufficiently 'senior' to have accrued some years of their utilisation.

The article focuses on oral preparations, as these still comprise the 'essential' first step in the treatment of most psychotic illnesses and are the group to have suffered most neglect with the introduction of new products.

History

The surgeon Henri Laborit was given belated access to the newly developed 'chlorpromazine' (*sic*) in 1951, after psychiatrists had noticed only sedation (Owens 1999). He detected something different – 'detachment', 'indifference', an affective change that was unique and distinct from sedation. And he noted this (subsequently termed ataraxy) after single and, by our standards, small doses (50–75 mg usually administered by intramuscular injection). 'Ataraxics' lost out to 'neuroleptics' in christening the new class of drugs, which was unfortunate, for ataraxy refers to a particular mental state effect (possibly the target action) that is key to understanding the clinical pharmacology of the entire class, whereas neuroleptic points to

David Cunningham Owens is Professor of Clinical Psychiatry at the University of Edinburgh and an honorary consultant psychiatrist at the Royal Edinburgh Hospital. He trained originally in general medicine and neurology before turning to psychiatry, where his interests have revolved around the biological basis and treatment of psychotic disorders, especially schizophrenia. He is a member of the teaching faculty of the British Association for Psychopharmacology and of the UK drug regulatory authority, the Commission on Human Medicines. Professor Owens is one of the few remaining clinical academics in the UK to partake in routine general adult psychiatric practice.
Correspondence Professor David Cunningham Owens, Royal Edinburgh Hospital, Kennedy Tower, Morningside Terrace, Edinburgh EH10 5HF, UK. Email: david.owens@ed.ac.uk

†See pp. 337–350 and 351–352, this issue

Phenothiazines
• Chlorpromazine
• Promazine[b]
• Levomepromazine (methotrimeprazine)
• Pericyazine (periciazine)
• Perphenazine
• Prochlorperazine[b]
• Trifluoperazine

Thioxanthenes
• Flupentixol (flupenthixol)
• Zuclopenthixol (zuclopentixol)[c]

Butyrophenones and diphenylbutylpiperidines
• Haloperidol
• Benperidol[b]
• Pimozide

Substituted benzamides
• Sulpiride

a. The following are also available as depots: flupentixol, zuclopenthixol (esterified with decanoic acid), fluphenazine, pipotiazine, haloperidol.
b. Uncommonly used as antipsychotics or with limited/no data for efficacy.
c. Also esterified with acetic acid.

a group of side-effects. The loss of the concept is the more regrettable for there has been hardly any investigation of the neural basis of ataraxy, an astonishing oversight of basic pharmacological mechanisms in such a widely utilised class of drugs. By the late 1950s, the subjective features comprising ataraxy had become subsumed under mild/early Parkinsonism, an assumption as significant if it is wrong as if it is correct.

The importance of this lies in the realisation that antipsychotics (as the neuroleptics came to be called) may create, as class effects, subjective states that, first, are difficult if not impossible to distinguish from illness-related disorders and second, can have detrimental consequences for quality of life and adherence. Antipsychotics can be difficult drugs for patients to take but can also be difficult for doctors to prescribe sensitively.

A note on 'indications'

In recent years, the pharmaceutical industry has moved to extend indications for new antipsychotics, especially to certain mood states. This has highlighted doctors' confusion about the nature of drug licensing.

Licensing is not about what doctors can and cannot prescribe. These are clinical decisions reserved to individual practitioners. Licensing was introduced in the wake of the thalidomide disaster of the 1960s and is about the claims manufacturers are permitted to make in pursuit of sales. For pharmaceutical companies, licensing is a commercial imperative, the mechanism that allows them to, in effect, advertise their wares. Just because a product has achieved a licence for an indication does not mean it is the only compound endowed with the necessary benefits. It simply means that the manufacturer has invested in the studies to justify promoting that drug for that indication. It is inevitable, therefore, that doctors hear a lot about 'new' licensed indications, for telling us was the point of all that expenditure in creating the script. This clamour does not allow us to infer that the story is either specific to their product or previously untold.

The clinical diversity of antipsychotics was evident from the start, with a number being advocated for anxiety and depression rather than – or in addition to – schizophrenia, as well as non-psychiatric indications. Furthermore, by the 1980s it was difficult to undertake studies on bipolar disorder treated with lithium alone, for clinical practice relied heavily on combined regimes of lithium and antipsychotics.

Antipsychotics licensed for use in mood disorders may reflect new drug actions. More probably, this simply formalises evidentially what was clinical wisdom before – that (some) antipsychotics beneficially affect mood.

Principles

There are no specific 'rules' for prescribing older antipsychotics that should not apply to the newer drugs also, though the formulations and marketing materials for newer drugs make it easier to suspend the decision-making 'algorithms' that should be exercised in making conscious choices. Prescribing has become all too mechanical.

For exam purposes, trainees tend to organise antipsychotics in terms of chemical groupings, although this was not the traditional emphasis. Initially, clinical considerations predominated (Ellenbroek 1993). Europeans dissented from US psychiatrists in believing that antipsychotics were fundamentally different and could be classified along various efficacy/tolerability axes, though none of the often intricate systems proposed (e.g. the star scheme of Bobon *et al* (1972) and the multifocal scheme of Fisher-Cornelsson *et al* (1974)), achieved general acceptance. Most clinicians would now accept the American view that in

terms of efficacy (and, post-CATIE, effectiveness too) all antipsychotics are comparable – though this is not to say that they achieve 'end-point' comparability by similar means. The Europeans were not necessarily wrong either. Chemical classifications can be helpful – but only in so far as they allow one to infer other, more clinically relevant characteristics about how a particular compound achieves its effects and at what cost. Two useful parameters are potency and breadth of receptor binding profile.

Potency, dosing and dose equivalence

Potency is another way of considering dose – higher-dosed compounds are in general of lower potency (see below for how pharmacokinetic variables can affect this principle). There are no clear-cut boundaries dividing compounds on the basis of potency, but a rough guide is that drugs with antipsychotic efficacy in units of milligram dosage per day are high potency; those with doses in tens of milligrams per day are intermediate; those where efficacy requires hundreds of milligrams per day are low potency.

Proper dose-finding studies were rarely done on early compounds and, with its consistently favourable therapeutic index, chlorpromazine became subject to relentless dose escalation soon after it arrived in North America (Healy 1996), a process repeated with all the older antipsychotics. One of the positive influences to flow from the development of newer antipsychotics has been the imprinting on prescribers of trial-based boundaries to dosing that hardly exist for older drugs. The importance of this difference between new and older antipsychotics to prescribing 'consciousness' cannot be overestimated. Trial-derived schedules endorsed by being licensed breed conservatism, a sense of moderation beneath a clearly defined dose ceiling. Perception could not be more different for older drugs, where dose recommendations arise for the most part from (bad) practice and repute, are seen to be infinitely flexible and beneath a ceiling that is barely evident.

Even where dose-finding data are available, attempts to produce relative dose equivalences have come up with little more than a general consensus (e.g. Davis 1976; Wyatt 1976; Rey 1989; Atkins 1997; Kane 2003; Woods 2003; Gardner 2010). There are many reasons for this, including the inherent variability of patient responses, the prescribing culture (e.g. varying conceptions of what is therapeutic in different parts of the world, at different times[a]) and the complex and varied pharmacokinetics these efforts cannot take into account. Furthermore, equivalences estimated by

experts must have greater credibility if expertise has been gained in the clinic rather than (or in addition to) the library, as the latter type of expertise risks perpetuating past misconceptions. Even sophisticated approaches to equivalence involving calculation of dose–response curves from fixed-dose randomised controlled trials have to acknowledge the influence of an 'uncertainty principle' (Davis 2004).

Dose equivalence has repeatedly been shown to be least accurate with the high-potency older drugs, which are accordingly administered in substantially greater equivalent doses than low-potency compounds (Baldessarini 1984; Dewan 1995). An obvious reason for this is that low-potency drugs set their own dosage ceiling by virtue of anti-autonomic and other 'non-target' actions.

Concepts of dose equivalence should never be seen as absolute. Importantly, tables of comparison (e.g. Table 1) are best thought of as presenting the median points of ranges of dosing within which the therapeutic effect is most likely to be manifest, with the clinician's aim always being to seek the minimum effective dose (see Owens 2012, this issue).

Breadth of receptor binding profile

Receptor binding profile allows inferences about, first, the extent to which a drug is likely to be endowed with non-extrapyramidal (general) adverse effects that bear on safety and tolerability, and second, what the likelihood might be of it possessing a built-in mechanism against the antidopaminergic actions it inevitably promotes (if one accepts the major inference of Laborit's observations, noted above), the most important of which is Parkinsonism, including its subjective component. The default position for clinicians should be that all antipsychotics have the potential to produce Parkinsonian features in a dose-dependent fashion – a potential modifiable by individual susceptibility (i.e. dopamine 'endowment') and whatever anti-Parkinsonian actions the drug exerts.

Again, however, clinicians should not view receptor binding profiles as absolute, as data vary from study to study, depending on methodology, sample studied, species, and so on. A further point is that binding profiles derived in the laboratory can project poorly onto clinical scenarios – for example, they do not take account of the actions of metabolites, many of which are active and have their own kinetic and dynamic properties. Also, the binding profiles advocated so prominently concentrate on pathways long

a. Gardner *et al*'s expert-based appraisal gave different equivalences for 'levomepromazine' (UK and Europe) and 'methotrimeprazine' (USA), even though they are the same drug, illustrating the importance of international differences in perception. In this instance, however, rather than advocating high-dose regimes, US psychiatrists rated 'methotrimeprazine' as more potent and with lower dose requirements than those outside the USA rated 'levomepromazine', albeit with a low level of confidence, undoubtedly reflecting a lack of hands-on experience.

TABLE 1 Older ('first-generation') antipsychotics: some suggested dose equivalences to chlorpromazine (CPZ)

	Dose (mg) equivalent to 100 mg CPZ							Kane 2003 (USA) 'Adequate dose' of CPZ, mg/day		Harrison-Read 2009 (UK) 'Optimal dose' of CPZ,[b] mg/day 300	Gardner 2010 (international)	
	Klerman 1974	Wyatt 1976	Davis 1976	Rey 1989	Atkins 1997	Kane 2003[a]	Andreasen 2010	1st episode 200–650	2nd+ episode 400–800		Relative to 100 mg CPZ	Target dose, mg/day
Promazine	100			200	100					200		
Levomepromazine				125						100	67	150–400
(USA: metho-trimeprazine)											50	100–300
Pericyazine				10–20	24						8.3	20–50
Perphenazine	10	8.8	9 ±0.6	6.7–20	8	6.4	6.9	8.0–38	16–48	24	5	12–24
Prochlorperazine	15	14	14 ±2	14.3–25	15						14.58	15–48
Trifluoperazine	5–10	3.7	2.8 ±0.4	3.3–6.6	5	5	5.09	5.0–30	10–35	30	3.3	10–20
Flupentixol		1.2		1.25–2	2					9	1.67	5–12
Clopentixol[c]	20	22	33–50							40	10	22–90
Zuclopenthixol			16.5–25								8.3	20–60
Haloperidol	2–5	2.4	1.6 ±0.5	1.7–2.5	<20 mg/day: 3 >20 mg/day: 5	2	1.84	3.0–13.5	7.0–18.5	8	1.67	5.0–10
Pimozide		1.2		1.25–2	2					8	1.33	4–6
Sulpiride				200–330	200					400	133	300–600

a. Extrapolated from 500 mg CPZ.
b. For mood/affective symptoms.
c. No longer available. Data are included here as they appear in the older literature to which more recent studies refer.

open to study – quite simply, those that can be readily investigated (relating predominantly to catecholamines, indoleamines, histamine and acetylcholine). The fact that these seem relevant to mode of action and tolerability is, one might say, a happy coincidence. As a diverse group of reactive compounds, however, antipsychotics interact with a wide range of proteins, including receptor types beyond the commonly studied (e.g. glutamatergic, sigmoid and ion channels), transporters (Tatsumi 1999) and variants of known structures whose roles remain to be delineated (e.g. 5-HT$_6$ and 5-HT$_7$).

With these many cautions and caveats, pie charts (Fig. 1) can nonetheless provide at-a-glance impressions of relative profiles to guide, more than determine, treatment choices. Likewise, recommendations for each drug can be presented in outline (as in the Tables 2, 3 and 4 below), though they represent no more than proposals based on the overriding principle of minimum effective dose ('start low, rise slow'). Confidence in choices as well as patterns of usage will only come with experience.

Phenothiazines

The substituted phenothiazines comprise a formidable group of over 40 compounds available around the world as anti-nausea/sickness treatments (especially vestibular-mediated forms associated with vertigo and with travel), antihistamines and drugs for post-operative and other forms of pain control, as well as antidepressants and anti-anxiety agents. Many more are in research use. Only a small proportion of the many synthesised survive as antipsychotics.

As psychiatry has become indifferent to the charms of phenothiazines, other disciplines have found excitement in their multiplicity of actions (Motohashi 2006; Sudeshna 2010). They have, for example, antimicrobial effects against bacteria (including *mycobacterium tuberculosis*), certain protozoa and fungi, and even prions, and they antagonise the calcium-controlling protein calmodulin, one of a number of possible ways in which they can facilitate cell death (Motohashi 1991). The potential of these multiple actions in anti-cancer therapy is under active investigation. This gives legs to a long-running debate – do patients with schizophrenia have lower rates of certain cancers? The question is difficult to address and results (over decades) have been contradictory. However, if general confusion does hide a specific negative association, the 'hidden' pharmacology of phenothiazines might be one explanatory contender.

Chlorpromazine (Table 2)

The original antipsychotic, chlorpromazine is a drug that trainees will still be familiar with, for its utility in clinical practice is such that even the onslaught of 'atypicality' has failed to extinguish its entrenched position, in Europe at least.

In vitro, chlorpromazine has moderate affinity for dopamine D_2 receptors across the board (Fig. 1), though affinity is greatest for the specific D_2 sub-type. Although this might suggest intermediate, not low, clinical potency, the paradox is probably explained by the drug's low bioavailability (~30%), the result of extensive distribution (compare with sulpiride in Owens 2012, this issue). With other D_2 family subtypes and with D_1 receptors, chlorpromazine binds with comparable affinity, though this is less than it is for the specific D_2 subtype (for representative values, see Owens 2010).

With acute usage, the most striking effect relates to central H_1 (antihistaminic) actions, as chlorpromazine is sedating on first exposure. This is a dose-related phenomenon that was not striking with the single low doses employed early in its development, as noted above, but is virtually universal with those now utilised in psychiatric practice (>100 mg). This action is unsurprising, for central antihistaminic activity was what was being sought when the compound was synthesised and was what selected it for development (Swazey 1974). In addition to feeling sedated, chlorpromazine-naive patients may sleep for protracted periods, but these potentially useful early effects tend to habituate rapidly (over a 48–72 h period). Re-emergence of sedation in the post-acute phase of management suggests resolution of the underlying illness process and is an indication for cautious dose reductions. Persistence of low-grade sedation (as opposed to apathy) is the major reason why chlorpromazine on its own is nowadays of limited use as a long-term maintenance agent.

Chlorpromazine is also a powerful antagonist of α_1 noradrenergic receptors (significantly more so than at D_2 sites), which points to the major constraint on its unbridled use in acute situations – a potent hypotensive action. This is mainly postural but early in exposure can affect supine blood pressure also, necessitating supportive measures: bed-rest and/or raising the foot of the bed are usually sufficient. This also tends to fairly rapid habituation but can result in dramatic declines in blood pressure, especially following parenteral administration. For this reason, chlorpromazine should never be administered intravenously and even the intramuscular route, previously popular, has fallen from favour with the identification of safer alternative drugs.
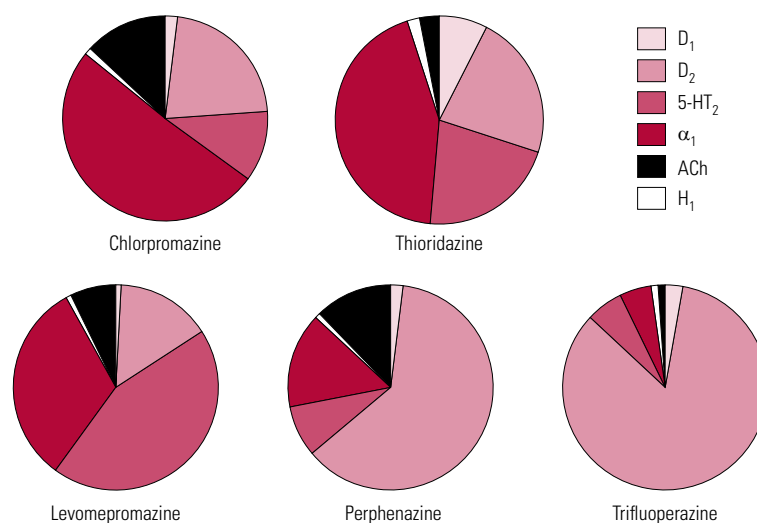

Receptor binding profiles of some of the phenothiazine antipsychotics, showing percentage of total binding contributed to by each transmitter type (after Hyttel 1985).

Relatively weaker activity at muscarinic cholinergic receptors (Owens 2010) predicts a modest anticholinergic adverse effect profile, in keeping with the greater tendency of chlorpromazine than some other low-potency phenothiazines to promote 'acute-end' extrapyramidal side-effects (EPS; i.e. acute dystonias, akathisia and Parkinsonism). It is also a potent antagonist at serotonergic $5\text{-}HT_{2A}$ sites, as well as having lesser effects on $5\text{-}HT_{2C}$ and especially $5\text{-}HT_{1A}$. In other words, this 'typical' antipsychotic is typically 'atypical'!

Promazine (Table 2)

It was known early that addition of electronegative moities at position 2 (the R_1 substitution) enhanced the antipsychotic potency of phenothiazines. Thus, promazine, the dechlorinated precursor of chlorpromazine, despite possessing the same general receptor binding profile, would be expected to be less potent. Early clinical comparisons confirmed this, with the same doses as with chlorpromazine providing no significant response (Fleming 1959). However, some authors suggested that potency might be only slightly diminished, with Azima & Durost (1957) reporting that an average daily increase of just 25% resulted in improvements similar to those with chlorpromazine. Rees (1960) estimated a chlorpromazine:promazine ratio of 1:3, while Rey *et al* (1989) calculated an overall potency of 1:2, which tends to reflect a long-standing consensus.

Early studies also tended to the conclusion that even in higher doses, promazine was better tolerated than chlorpromazine, with a low risk of jaundice (Azima 1957) and an especially low risk of EPS and postural hypotension (Azima 1957; Frain 1957; Simpson 1958).

TABLE 2 Older antipsychotics for oral use: aliphatic phenothiazines

Group	Type	Drug	Clinical pharmacology							
			Receptor binding		Liability to non-target actions		Suggested[a] (clinical) equivalence to 100mg CPZ, mg	Pros	Cons	Suggested[a] dosing
			Potency (D₂)	Breadth	General	Extrapyramidal				
Phenothiazines	Aliphatic	Chlorpromazine	Low	Broad	High (including toxic and allergic reactions)	Intermediate	(100)	Long-established use / High margin of safety over wide dosing schedules / Sedative (especially early in exposure) / Well-known to patients, and has a generally positive reputation	Tolerability less favourable than safety / Phenothiazine molecule has inherent toxicity: relatively higher risk of toxic/allergic reactions leads to need for monitoring / Generally too sedative for solo long-term use	Initial, drug-naive: 50mg 3 times a day, or 50mg twice a day + 100mg at night[b] / Assess blood pressure over 24–48h, then gradual upward titration to therapeutic range, using sleep as a pointer to rate of increments / Initial, drug-experienced: 200–300mg/day (divided doses)[b] / Therapeutic: ~400–500mg/day (divided doses);[b] maximum dose: 600mg/day
		Levomepromazine (methotrimeprazine)	Low	Broad	High (especially sedation and hypotension)	Low	60–110 (average from composite data: 80)	Widespread non-psychiatric use / Highly sedative / Lingering suggestion (unproven) of efficacy in patients poorly responsive to other drugs (i.e. possibly 'treatment resistant')	Can be sedating long-term / Potentially fatal depression of central nervous system in overdose / Risk of initial profound hypotension in older people (>50 years) / Split doses necessary	Generally not ideal for routine solo use unless profound or intractable agitation/behavioural disturbance predominates. May have value in emergency situations in young people and in second-line adjunctive or third-line solo treatment. Consider also in clozapine failure / Initial, drug-naive: 25mg daily (in young people: 50mg): assess blood pressure (over 5–7 days) / Initial, drug-experienced: 25–50mg (divided doses); gradual upward titration after 5 days to therapeutic range using subjective anxiety and agitation as pointers to rate of increment and final dose / Therapeutic: 200–300mg/day,[c] divided doses (treatment resistance: up to 600mg/day over 4–6 weeks)
		Promazine	Very low	Broad	Low/moderate	Low	~150–200	Long-established use / High margin of safety / Sedative	Antipsychotic efficacy poorly established	Generally not advisable as solo antipsychotic / Not recommended as major agent in management of non-specific symptomatology in elderly people / For adjunctive use in management of non-specific symptomatology (anxiety/agitation/insomnia), or limited use in elderly / Dose: 100–200mg/day (maximum: 400mg/day) / Vulnerable patients: 50mg/day and assess response / If >400mg/day is required (BNF maximum dose), consider appropriateness as primary agent

BNF, British National Formulary; CPZ, chlorpromazine.

a. Suggested values are based on 'minimum effective dose' in the literature and on the author's experience.

b. Chlorpromazine has an extremely long 'terminal phase' half-life representing elimination (~60 days) but a short 'peak–trough' half-life representing distribution (~6–8h). Thus, although efficacy may be satisfactorily attained with once-daily dosing or less, short-term control of non-specific symptoms is best achieved by split dosing regimes.

c. Therapeutic recommendations are often lower than the evaluated potency would suggest (Gardner 2010), perhaps reflecting levomepromazine's greater sedative effects.

In most early studies, which assumed equipotency or only slightly diminished potency, promazine fared badly (Mangun 1956). It has therefore come to be seen as a 'bland' drug, best suited to those with particularly poor tolerability – especially the elderly – or, in low dose, as a general anti-anxiety agent for one-off or short-term use. Whatever its true comparative 'anti-psychosis' potency, this view is unlikely to shift. Any favourable appraisal of tolerability must, however, take account of the fact that promazine is a phenothiazine, so may, in the elderly, increase the liability to cerebrovascular events (see Owens 2012, this issue).

Levomepromazine (methotrimeprazine) (Table 2)

This is the only psychotropic with two official names, though outside the USA the former is now preferred. Developed by the same team behind chlorpromazine, it was introduced in 1956, but French physicians could not settle on a precise indication. It was advocated for depressive states and for 'senile' patients, as well as for schizophrenia, particularly for those who were 'restless', indications which reflect its sedative profile. It also caught the eye of anaesthetists as a useful pre-operative sedative, with efficacy in managing nausea and post-operative and other forms of pain. And it alleviated bronchoconstriction!

In the UK, non-psychiatric uses (e.g. surgery, palliative care) have predominated and levomepromazine has struggled to find a substantial psychiatric market. It is not, however, a drug without interest. Its sedative profile makes it potentially useful in psychiatric intensive care, and from the start it acquired a reputation in 'treatment-resistant'[b] schizophrenia (Payne 1960) that has never entirely faded (Lal 2006). Whether this represents an effect independent of its sedative actions remains unclear.

Levomepromazine has a broad receptor binding profile (Fig. 1), covering antagonist actions at D_1–D_4, 5-HT_1 and 5-HT_2, noradrenergic (including, unlike chlorpromazine, α_2 as well as α_1), histamine H_1, and muscarinic M_1 and M_2 sites (Lal 1993). Clinical impression is of a drug that is more sedative than chlorpromazine. Indeed, levomepromazine may be the most powerfully sedative of all antipsychotics, perhaps related in this case to the potency of its anti-noradrenergic as opposed to its antihistaminic actions. Noradrenergic antagonism is also likely to be responsible for the tendency to hypotension, which can be profound. Its EPS liability seems somewhat, though not strikingly, less than chlorpromazine (Lal 2006).

Although generally considered a low-potency drug, the ideal levomepromazine dose regime for treating psychotic illness was never well established and experience remains scant. While 300 mg/day was not found to have efficacy (Milne 1960), 600 mg/day or more was (Payne 1960; Lal 1992, 2006). This may suggest equipotency with chlorpromazine, but most of these studies were in institutionalised patients with severe or treatment-resistant schizophrenia. In general, greater potency is usually accepted (Ban 1971), with figures varying between twice that of chlorpromazine and equipotency (Rees 1960; Rey 1989; Gardner 2010). Composite estimates (e.g. from Rey 1989 and Gardner 2010) do, however, suggest that the increase may only be slight, with a chlorpromazine:levomepromazine ratio of around 100:80. This is in line with the lower optimal maintenance doses (50–100 mg/day) suggested earlier (Payne 1960). The *British National Formulary* (BNF) upper recommended dose of 1 g/day remains more in line with the perception of equipotency and is undoubtedly on the high side (British Medical Association 2012).

Levomepromazine must be used with care in the elderly and others in whom hypotension could have serious consequences and, in line with its sedative effects, in those at risk of suicide, as it has been associated with higher toxicity and death rates following overdose than most antipsychotics (Schreinzer 2001). Although a powerful inhibitor of the cytochrome P450 2D6 (CYP2D6) enzyme system, this does not appear to cause significant problems in the antipsychotic combinations studied (such as risperidone; Yoshimura 2005), but it may produce a significant impairment of the O-demethylation of codeine to morphine, rendering codeine-based analgesics less effective (Vevelstad 2009). It is also possible that induction of CYP1A2 or CYP3A3/4 systems underlie a lowering of clozapine levels (Bugamelli 2007).

Psychiatry in the UK has probably unduly neglected levomepromazine as a tool in the management of marked and persistent behavioural disturbance or in adjunctive treatment of non-specific symptomatology (such as anxiety and insomnia). Its potential in treatment resistance, operationally defined or otherwise, requires further study, but this may be a drug worth considering in those for whom, by virtue of clozapine failure, few other options remain.

Pericyazine (periciazine) (Table 3)

Pericyazine also followed chlorpromazine from Rhône-Poulenc's laboratories, a decade later but accrued, largely *post hoc*, the sort of 'panacea' indications that foster scepticism – 'character disorders', 'psychopathy', anxiety states and organic

b. The concept of treatment resistance was operationalised for Kane *et al*'s US multicentre clozapine study in 1988. This modern, standardised and more tightly honed concept should not be considered equivalent to the concept as used in the older literature.

TABLE 3 Older antipsychotics for oral use: piperidine phenothiazines

Group	Type	Drug	Receptor binding		Liability to non-target actions		Suggested[a] (clinical) equivalence to 100 mg CPZ, mg	Pros	Cons	Suggested[a] dosing
			Potency (D$_2$)	Breadth	General	Extrapyramidal				
Phenothiazines	Piperidine	Pericyazine (periciazine)	Intermediate	? Broad	Moderate	Moderate	10–15	High margin of safety Good general tolerability Sedative (useful anti-anxiety properties) Relatively unknown to patients Commented on favourably on patient websites	Split dose schedules Too rapid escalation or overuse on PRN basis can reveal EPS liability	Best suited to adjunctive treatment (anxiety/agitation) 5 mg[b] twice a day + 10 mg at night and assess (bulk of dose at night on starting tends to mask early non-target actions that will habituate) Incremental increases (5–7 days) to 10 mg twice a day + 20 mg at night (can be equally spread depending on patient need) For solo treatment: Initial: 10 mg twice a day + 20 mg at night: increasing 7–10 days Therapeutic: 60–80 mg then assess. (BNF recommended upper limits of 300 mg/day should be viewed as high and likely to be associated with non-target actions, especially akathisia)

BNF, British National Formulary; CPZ, chlorpromazine; EPS, extrapyramidal side-effects; PRN, as required.
a. Suggested values are based on 'minimum effective dose' in the literature and on the author's experience.
b. Inconveniently, 5 mg strength tablets withdrawn some years ago.

disorders, as well as schizophrenia (Anonymous 1967). The likely common factor related to its benefits in situations, as opposed to disorders, characterised by overactive, confrontational or aggressive behaviour. With such an ill-sketched profile and life in the shadow of its elder sibling, it is hardly surprising that pericyazine has held on to a tenuous place in clinical practice and is little known, far less used, in the UK, where awareness stems largely from proceedings of a single sponsored symposium (Jenner 1965). However, pericyazine did enjoy popularity in Scandinavia, Russia and Japan.

No detailed *in vitro* receptor binding profile is available for pericyazine (Fleming 2010), though it is known to be more potent at α-adrenergic than dopamine sites and can therefore be associated with hypotension, especially on first exposure. It also has powerful antiserotonergic actions, the clinical significance of which is unclear. Its tolerability profile indicates anticholinergic-type actions, and with EPS liability probably comparable to chlorpromazine, this suggests a more potent action at muscarinic sites also. Reports of cardiac dysrhythmias, though rare, might suggest an ion channel action.

Such has been pericyazine's disregard that it is not possible to be confident about the optimal antipsychotic dosage, far less its relative potency. It is certainly several times (4–20) more potent as an anti-emetic than chlorpromazine (Anonymous 1967). Other data, not published in peer-reviewed literature, suggest comparable antipsychotic efficacy from 15 mg/day pericyazine as from 600 mg/day thioridazine (Heller 1965). However, Barker & Miller (1969), studying chronic schizophrenia, got comparable efficacy with a 1:10 ratio against thioridazine (approximately 1:9 against chlorpromazine). Taking these data together, Rey *et al* (1989) calculated a five- to tenfold greater potency. The BNF, on the other hand, seems to regard it as a sort of chlorpromazine-Mk 2, suggesting rough dose equivalence or only slightly enhanced potency (British Medical Association 2012).

Equivalence is not the clinical experience of most, which suggests that pericyazine is indeed in the order of four to ten times more potent as an antipsychotic than chlorpromazine (Atkins 1987; Rey 1989; Gardner 2010). Accounting for EPS liability, it would be prudent to go with the higher potency assumption to begin with (chlorpromazine:pericyazine ratio of 10:1) in order to minimise exposure.

Its most striking – and useful – characteristic is its powerful anti-autonomic and sedative effects,

no doubt arising from central antihistaminic actions. The impression is that pericyazine, at 'anti-psychosis' equivalence, is another drug disproportionately more sedative than chlorpromazine. Again, this can be a disadvantage for solo, long-term use but for short-term, acute and, especially, adjunctive use (in the management of non-specific symptomatology) pericyazine has, in my view, practical value beyond what its current utilisation would suggest. This enhanced sedative role is likely to be why it has been found to be more effective in treating aggression and hostility than chlorpromazine (Becker 1981) and why original indications became so blurred. It may also be why pericyazine is referred to surprisingly positively in patient-targeted online resources (Matar 2008).

Since the withdrawal from the European market in 2002 of thioridazine, a drug well regarded by both patients and doctors, pericyazine is the sole remaining oral piperidine phenothiazine in the UK. It is, however, debatable whether the QTc prolongation issue would have sunk thioridazine quite so conclusively had the safety profiles of the second-generation antipsychotics with which it was in competition been as comprehensively understood then as they are now (see Owens 2012, this issue). Thioridazine and its metabolites do continue to stimulate interest as potentially cheap and safe antituberculous and antimalarial agents for poorer countries (Amaral 2001; Thanacoody 2007).

Perphenazine (Table 4)

Perphenazine was introduced in 1957 and, in addition to an international market for the oral formulation, is also available as depots (decanoate and enanthate) in several European countries. It has recently grown to prominence as the 'standard' comparator in CATIE (Lieberman 2005).

Perphenazine is active at $5-HT_2$ sites (Fig. 1) and has significant anti-α-adrenergic actions, promoting hypotension on first exposure, especially if administered parenterally, though this is delayed compared with most other antipsychotics (Bhargava 1964), suggesting the action of a metabolite. It is also sufficiently antihistaminic to have sedative properties – low doses (e.g. 2 mg) can produce drowsiness without hypotension, even when administered intramuscularly, giving it a safety margin over chlorpromazine (Musey 1986). It has no significant anticholinergic action (Sweet 2000; Chew 2008) and although well known to promote EPS in higher doses, its relatively good EPS tolerability at low to medium doses probably reflects the fact that its major metabolite, N-dealkyl perphenazine, which with chronic use attains blood levels 1.5–2 times those of the parent

drug, shows modest antimuscarinic (M_1) binding (Sweet 2000). This might therefore be a drug to start and hold low in order to allow build-up of the metabolite in the expectation of an anti-EPS effect as doses rise.

Although often stated as being of comparable potency to haloperidol (Hartung 2005), perphenazine is best considered as of intermediate potency. Based on animal data, the originally suggested chlorpromazine:perphenazine potency of 5:1 or 6:1 (Rees 1960) would now seem an underestimate, with clinical potency best considered at about 10–15 times that of chlorpromazine (chlorpromazine:perphenazine = 100:8 mg), as some estimated from the start (DiMascio 1963a). The BNF reflects this more generous view, recommending an upper daily dose of 24 mg (British Medical Association 2012), though this may be overcautious. In the USA, traditional practice tended to a relative potency of between 8:1 and 9:1 (Wyatt 1976), in line with which CATIE allowed up to 32 mg/day (Lieberman 2005). However, modern specialist opinion also seems to be veering towards the lower range (24 mg) (Gardner 2010).

Perphenazine has rather poor kinetic properties, in particular low bioavailability (Hansen 1976), probably reflecting first-pass effects. This, combined with an average half-life of 8–12 h, means that the drug is best suited to administration three times a day, though for practical reasons twice daily is usual. However, in cases of poor response, increasing the frequency should be considered before a change of drug. In a small percentage of 'poor metabolisers', half-life is extended to up to 20 h, and in those who experience undue side-effects, especially sedation, reducing the frequency may be more appropriate than reducing the dose.

Like many psychotropics, perphenazine is metabolised predominantly by the CYP2D6 system. Although resistant to induction, this system is prone to inhibition. Paroxetine is a potent inhibitor of CYP2D6 isoenzymes and dramatic increases in perphenazine blood levels (2–13 fold) have been reported with the addition of the antipsychotic to stable paroxetine treatment, resulting in clinically relevant deteriorations in tolerability (sedation, EPS, impaired psychomotor performance and memory) (Ozdemir 1997). This type of kinetic interaction is likely to be relevant to all antipsychotics with significant metabolism via CYP2D6 when combined with a potent inhibitor. On the other hand, perphenazine is itself a weak inhibitor of this system, on which tricyclic antidepressants also depend for metabolism. Combinations of perphenazine and tricyclics are associated with up to 70% increases in tricyclic

TABLE 4 Older antipsychotics for oral use: piperazine phenothiazines

Group	Type	Drug	Clinical pharmacology				Suggested[a] (clinical) equivalence to 100 mg CPZ, mg	Pros	Cons	Suggested[a] dosing
			Receptor binding		Liability to non-target actions					
			Potency (D₂)	Breadth	General	Extrapyramidal				
Phenothiazines	Pipera-zine	Perphenazine	Inter-mediate	Moder-ate	Low	Moderate	6–8	Long-established use; High margin of safety; Better known through its use as comparator in CATIE	Short half-life (8–12 hours); ideally is best administered three times daily; Potency and tolerability make it easy for EPS to emerge undetected	Initial: 4 mg twice a day for 5–7 days then, if tolerated, 4 mg/day + 8 mg at night; Increase thereafter by 4 mg every 5–7 days; Therapeutic: 24 mg (as 8 + 16) in most instances; In cases of poor response, can be increased to 32 mg (as 12 + 20 or 8 + 8 + 16) but think of increasing frequency first
		Trifluoperazine	High	Narrow	Low	High	5 (precise figure unclear but probably lower than has been traditionally thought: ?2–3)	Long-established use; Cheap; High margin of safety; Relatively non-sedative yet with apparent anti-anxiety actions; With repeat dosing probably suitable for once-daily use	May be more potent than conventional use suggests, fostering higher than necessary dosing; Relatively high EPS liability	Best suited to 'ambulant' patients (i.e. not in need of acute/emergency in-patient care because of low levels/low risk of disturbed behaviour); Initial: 2 mg daily (if clinical situation permits) or twice a day; Hold for 5–7 days; Switch to once-daily dosing with gradual increments (over 5–7 days); Therapeutic: conventional view of 20–30 mg/day may be unduly high. Consider holding at 10–15 mg and assessing; With doses above 5–6 mg/day, consider prophylactic anticholinergic; No upper recommended limit specified in BNF for schizophrenia, but doses above 30 mg should trigger review
		Prochlorperazine	Inter-mediate	Moder-ate (broader with metabo-lite)	Moderate	Moderate	15–20 assumption is of greater in vitro affinity than clinical actions suggest, with efficacy compromised by poor pharmaco-kinetics	High margin of safety; Extensive non-psychiatric use also points to excellent general tolerability	Unstable pharmaco-kinetics with extensive first-pass effects, resulting in very low bioavailability; Half-life of tablets after single dosing is short (~4–6 hours) but cumulation with repeat dosing (half-life after 14 days ~18 hours) allows for twice-daily, but not once-daily, administration	No extensive experience of use as an anti-psychotic but historical evidence of efficacy persuasive. Might be considered as third line or for adjunctive use (mainly anxiety-mediated nausea/vertigo, etc.); Initial: 12.5 mg twice a day for 5–7 days; Then, if tolerated, increase by 12.5 mg every 5–7 days; Therapeutic: Unclear. Evidence suggests efficacy may be obtained with doses ~60 mg daily (i.e. lower than 75–100 mg suggested by BNF); In cases of poor response, consider increasing frequency of administration

BNF, British National Formulary; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CPZ, chlorpromazine; EPS, extrapyramidal side-effects.
a. Suggested values are based on 'minimum effective dose' in the literature and on the author's experience.

levels (Linnoila 1982). This fact is made use of in combination preparations (e.g. with amitriptyline in Triptafen®), though concern about whether, even then, adequate antidepressant levels can be achieved has resulted in a decline in their use.

Trifluoperazine (Table 4)

Trifluoperazine was previously widely used in the UK, not least in low dose as an 'anti-anxiety' agent and in combinations (e.g with the monoamine oxidase inhibitor tranylcypromine, comprising Parstelin®) as an 'antidepressant'.[c] It still enjoys international usage and is also a major research tool, as its inhibitory actions on calmodulin have long been known and the conformational changes it produces in the protein are to some extent characterised (Feldkamp 2010).

Trifluoperazine possesses high affinity for D_2 receptors but has low affinities at D_1 and serotonergic sites and relatively weak anti-α_1 (but no α_2) adrenergic actions (Huerta-Bahena 1983). It has little other receptor activity (Fig 1). Its predicted lack of effect on blood pressure and excellent general tolerability were confirmed early in healthy volunteers (DiMascio 1963b). Its potency, however, combined with little inherent antimuscarinic activity, means that EPS liability is high. Despite little anticholinergic action *in vitro,* its use may still be associated with dry mouth, blurred vision and so on (Marques 2004), symptoms usually attributed to muscarinic blockade. This may, however, reflect an unduly narrow interpretation of how such symptomatology arises or the activity of metabolites rather than the parent drug.

Although trifluoperazine can be sedative (Marques 2004), especially at high dose, clinical experience suggests that, compatible with its binding profile, it is one of the least sedative antipsychotics. Originally, much was made of its 'alerting' properties, particularly in long-term institutionalised patients (Gwynne 1962), something also inferred from improvements in psychomotor abilities and speed of performance (to some extent dose-related) reported in healthy volunteers (DiMascio 1963a). Apart from possible presynaptic dopaminergic (autoreceptor) effects, its known pharmacology does not offer a ready basis for such actions, which tend not to be commented on nowadays. Psychomotor test findings may have reflected mild Parkinsonism as, paradoxically, people with Parkinsonism may show enhanced performance in forced-choice paradigms, but as the first non-sedating antipsychotic, it was probably this characteristic that, in contrast with other phenothiazines, stood out to be interpreted as 'alerting'.

Early clinical research suggested trifluoperazine to be a moderate- to high-potency compound with treatment efficacy most frequently found in the 5–30 mg/day range (Madgwick 1958; Macdonald 1959; Payne 1959; Sarwer-Foner 1959), though maintenance regimes of less than 10 mg/day have also been found to be effective (Payne 1959). In the USA, it tended to be considered in the intermediate potency range (Wyatt 1976) but in the UK, relative chlorpromazine:trifluoperazine potency is usually taken to be around 20:1 (Owens 2010). However, as a drug relatively free from anti-autonomic side-effects and hence prone to early and potentially needless dose escalations, its true relative potency may be as high as 30:1 (Rey 1989; Gardner 2010), which is more in line with a calculated effective dose in the range 10–15 mg/day (Davis 2004). Unusually, the BNF offers no guidance on upper dose limits for trifluoperazine in schizophrenia (British Medical Association 2012), but the evidence suggests that, despite excellent tolerability, doses above 15–20 mg/day should be considered 'high'.

For a drug so widely used for over half a century, it is truly astonishing how little is known about trifluoperazine's pharmacokinetics. The only sure fact is that they are highly variable across individuals on both single and repeat administration (Midha 1983, 1988). Its terminal phase half-life, at around 12 h with single dosing (Midha 1983), suggests that it is barely suitable for once-daily dosing, though this may extend (to up to 30 h) with regular use. Perhaps because of this, the previously popular modified-release (or 'spansule') formulation has unfortunately now been withdrawn in the UK. With the standard formulation, cautious practice might still dictate twice-daily administration.

Prochlorperazine

Prochlorperazine has never found favour as an antipsychotic in the UK, despite being structurally very similar to trifluoperazine (chlorine substitution at the R_1 position instead of trifluoromethyl). Even the team behind its development was more interested in its much greater potency as an anti-emetic compared with chlorpromazine and its effects on migraine and vertigo (Rees 1960), actions that have sustained its market position since.

Prochlorperazine was, however, initially greeted with enthusiasm by some psychiatrists. A recurrent theme in the early literature was that chlorpromazine offered mainly non-specific behavioural advantages, whereas prochlorperazine had a more favourable impact on fundamental

c. It must be borne in mind that at the time of these earlier studies, operationalisation and standardisation had not been applied to psychiatric diagnosis, and it cannot be assumed that earlier writers using the terms 'anti-anxiety' and 'antidepressant' had in mind concepts similar to the ones now generally accepted.

domains of illness such as thought disturbances (Denham 1958; Wilson 1961) and affect (Milne 1958). Such observations probably reflected simply the conservative chlorpromazine doses at the time, especially in the UK, rather than any differential efficacy. It was also noted early that prochlorperazine had a greater liability to promote EPS than chlorpromazine (Dransfield 1958) – which actually fitted the prevailing view that EPS were an inherent part of 'anti-psychosis' and hence a sign of enhanced efficacy!

Prochlorperazine has actions at dopaminergic, muscarinic and α-adrenergic sites, evident on single dosing so probably reflecting the profile of the parent drug. However, antihistaminic effects are mainly evident with repeat dosing, suggesting the actions of a metabolite (Isah 1991). The resultant lack of sedative action with single dosing no doubt facilitated its approval in over-the-counter preparations for nausea/vomiting. *In vitro*, prochlorperazine is also active across a range of 5-HT subtypes, including 5-HT_2 (Roth 1994), though strangely this is one antipsychotic that never seems to have garnered an 'atypical' plaudit.

Prochlorperazine's R_1 substitution would indicate lower potency than its close piperazine relative, trifluoperazine, and this is clinical experience, but a second factor (in addition to limited usage) that makes equivalence difficult to determine is the drug's unfavourable kinetics. Prochlorperazine is subject to substantial first-pass effects and is very extensively cleared, resulting in bioavailability of only some 12.5% (Isah 1991), low even by the standards of the highly lipophilic phenothiazines. This may be why, conventionally, it has been treated as of intermediate, veering to low, potency (unusual for a piperazine compound).

The early literature suggested chlorpromazine: prochlorperazine ratios between 2:1 (Dransfield 1958) and 5:1 (Wilson 1961), whereas Wyatt (1976) calculated a relative potency of around 7:1, at the upper range of the 4:1 to 7:1 suggested by others (Rey 1989). On the other hand, Wilson *et al* (1961) found that patients on 30 mg/day did better than those on 90 mg/day, which is in line with the higher potency (~14:1) assessed more recently, albeit with the low confidence of a drug seldom used by the experts (Gardner 2010).

Thus, while there is a suggestion that efficacy may be achieved with doses lower than the 75–100 mg/day recommended in the BNF (British Medical Association 2012), such unclear dosage parameters and half a century of neglect make it unlikely that prochlorperazine will now find the favour psychiatry has hitherto denied it. It

would, however, be interesting to know how this generally well-tolerated drug performed as a low-dose antipsychotic in preparations formulated for buccal absorption (e.g. Buccastem®), which avoid first-pass effects and achieve blood levels twice those of oral formulations (Finn 2005).

The rest of the family

My second article examines non-phenothiazines and discusses issues in the prescribing of 'first-generation' antipsychotics (Owens 2012, this issue).

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MCQs

Select the single best option for each question stem

1 In the context of drug regulation, licensing implies:

a that a drug is safer than other members of its class which are unlicensed

b that a drug is more efficacious than other members of its class which are unlicensed

c that a manufacturer has provided sufficient data to allow for a favourable risk:benefit appraisal

d that a manufacturer has been granted copyright over the branded name of the product

e that only the licensed product can be prescribed for a particular indication.

2 Antihistaminic properties associated with the use of which one of the following are likely to reflect the actions of a metabolite?

a chlorpromazine

b pericyazine

c perphenazine

d prochlorperazine

e trifluoperazine.

3 Overdose of which one of the following is most likely to be associated with fatal respiratory depression?

a levomepromazine

b pericyazine

c promazine

d prochlorperazine

e thioridazine.

4 Of the following, the greatest first-pass effects are associated with:

a chlorpromazine

b levomepromazine

c pericyazine

d perphenazine

e trifluoperazine.

5 Dose equivalence estimates for antipsychotics are not contaminated by:

a actions of metabolites

b drug potency

c industry sponsorship

d when efficacy studies were undertaken

e where efficacy studies were undertaken.