Effectiveness bulletin

Drug treatments for schizophrenia

Clive Adams, Paul Wilson, Simon Gilbody, Anne-Marie Bagnall, Ruth Lewis

This paper summarises the research evidence presented in a recent issue of *Effective Health Care* on drug treatments for schizophrenia.[1]

Background

Schizophrenia is an illness or a group of illnesses affecting language, planning, emotion, perceptions, and movement. In the UK, approximately 250 000 people suffer from schizophrenia or a schizophrenia-like illness.[2]

A quarter of those who have experienced an episode of schizophrenia recover and the illness does not recur. Another 25% experience an unremitting illness. The remaining 50% have a recurrent illness, but with long episodes of considerable recovery from positive symptoms such as delusions, hallucinations, disordered thinking, and catatonic movements.[3] Many with recurrent illness have enduring problems from schizophrenia such as persistent psychotic symptoms, but, for most people, the problems consist of negative symptoms such as loss of enthusiasm and emotional responsiveness, apathy, and social withdrawal.[3] These negative symptoms, though intrinsic to schizophrenia, are compounded by the adverse effects of drugs, living in impoverished circumstances, and by the social stigma associated with mental illness. Recovery from episodes of schizophrenia for some people is often complicated by episodes of depression, substance abuse, and anxiety. People with schizophrenia have a shortened life expectancy[4] due to physical illness, accidents, and other causes of violent death, especially suicide.[5]

Treatments for schizophrenia are divided into the so-called "physical interventions" of drugs, psychological and social managements and, rarely in the UK, electroconvulsant treatment. This article draws upon evidence from systematic reviews undertaken by the Cochrane Schizophrenia Group, and summarises the evidence on the effectiveness of the main drugs used in the treatment of schizophrenia. More detailed information is available on each treatment within the referenced reviews. These reviews are regularly updated in the *Cochrane Library*.[6]

The main class of drugs used to treat or manage schizophrenia is antipsychotics (also known as neuroleptics, anti-schizophrenia drugs, and, inaccurately, as major tranquillisers). The antipsychotic action of these drugs is more than just the promotion of sedation and probably depends upon specific receptors in the brain. The advent of antipsychotic drugs in the 1950s was revolutionary. Countless people for whom little hope then existed were, at least partially, freed from the constraints of an insidious and unpredictable illness that would have kept them out of touch with reality for large periods of their lives.[7]

Adverse effects associated with antipsychotics are common, however. These include troublesome and socially disabling movement disorders that resemble the symptoms of Parkinson's disease. Involuntary facial movements (tardive dyskinesia) also occur in over 20% of those using older drugs and do not necessarily recede once the antipsychotic is stopped or reduced.[8] Other distressing side effects include sedation, dry mouth, blurred vision, constipation, weight gain, and, occasionally, impotence.

Although conventional drugs are generally an effective treatment for many of the symptoms of schizophrenia, the above side effects can limit their use for a significant portion of people with schizophrenia. Continual medication is often necessary during periods of relative wellness, and poor compliance can precipitate relapse and necessitate (costly) readmission to hospital. It has been felt that the side effect profile of older drugs has contributed to poor patient compliance and relapsing illness after discharge into the community ("revolving door" patients).

Over a decade ago, with the re-introduction of the drug clozapine into common use, older drugs began to be labelled as "typical" in their propensity to cause movement disorders. Clozapine was "atypical" in that it did not seem to cause these side effects as readily. In truth, rather than such a dichotomy of typical and atypical, there is a continuum and some inexpensive, older, drugs may have an atypical profile.[9 10]

The claims being made for the newer atypical compounds are exciting,[11] but take place in the context of ever greater conflicts of interest, both academic[12] and monetary.[13 14] Yet the quality of trials, as measured by clear reporting and clinical applicability, is poor, and has not increased during the past 50 years[15]—in fact there is some evidence it has declined.[16] Trials are, on average, small, short in duration, include participants that are not typical of everyday practice, randomise care regimens that are difficult to generalise, have high attrition rates, and report outcomes that are of dubious clini-

Cochrane Schizophrenia Group, Oxford, UK
C Adams, *editor*

NHS Centre for Reviews and Dissemination, University of York, UK
P Wilson, *research fellow*
S Gilbody, *research fellow*
A-M Bagnall, *research fellow*
R Lewis, *research fellow*

Correspondence to:
Paul Wilson, NHS Centre for Reviews and Dissemination, University of York, York YO1 5DD, UK
Email: pmw7@york.ac.uk

Table 1 The most typical antipsychotics

Intervention		*Outcomes*			
Experimental	*Control*	*Immediate*	*Short term (0–6 weeks)*	*Medium term (7 weeks to 6 months)*	*Long term (>6 months)*
Chlorpromazine[17]	Placebo	Movement disorders ⇑ (RR=3; CI 1.3 to 8)	Improved ⇑ (RR=1.6; CI 1.3 to 1.8)	Improved ⇑ (RR=2; CI 1.8 to 2.4)	Relapse ⇓ (RR=0.6; CI 0.5 to 0.7)
1646 participants	1470 participants		Relapse ⇓ (RR=0.3; CI 0.1 to 0.8)	Relapse ⇓ (RR=0.5; CI 0.4 to 0.6)	Attrition ⇔ (RR=1.0; CI 0.7 to 1.6)
			Attrition ⇓ (RR=0.7; CI 0.6 to 0.9)	Attrition ⇓ (RR=0.6; CI 0.5 to 0.8)	Movement disorders ⇑ (RR=2.8; CI 1.4 to 6)
			Movement disorders ⇑ (RR=1.8; CI 1.1 to 4.7)	Movement disorders ⇑ (RR=2; CI 1.5 to 2.7)	Weight ⇑ (OR=5; CI 2 to 10)
				Sedation ⇑ (RR=2.3; CI 1.8 to 3)	
Zuclopenthixol acetate[26]	Chlorpromazine, haloperidol, clothiapine	Improved ⇔ (RR=1; CI 0.9 to 1.1)			
234 participants	179 participants	Requiring re-dosing ⇔ (RR=1.5; CI 0.8 to 2.9)			
		Attrition ⇔ (RR=0.7; CI 0.2 to 2.1)			
Haloperidol decanoate[23]	Oral haloperidol			Improved ⇔ (RR=0.9; CI 0.6 to 1.4)	
11 participants	11 participants				
Haloperidol decanoate[23]	Other depots			Relapse ⇔ (RR=1.2; CI 0.7 to 1.9)	
187 participants	184 participants			Attrition ⇔ (RR=0.9; CI 0.6 to 1.4)	
				Movement disorders ⇔ (RR=0.9; CI 0.8 to 1.1)	

RR = Relative risk—the experimental event rate/control event rate; CI = 95% confidence intervals—an estimate of the precision of RR; ⇓ = decreased; ⇑ = increased; ⇔ = no clear difference.

cal value.[15] It is in this context that the data from recent studies must be examined.

Typical antipsychotics

Traditional literature reviews and clinical experience suggest these drugs to be effective in relieving positive symptoms in the immediate, short, and medium term.

A systematic review of chlorpromazine versus placebo confirms and quantifies both the value and the adverse effects of this drug.[17] Quantitative reviews of haloperidol or trifluoperazine versus placebo were not identified, but a review comparing each with chlorpromazine did not identify significant differences in clinical outcomes.[18]

Long term compliance with any medication is difficult, and depot preparations, which slowly release medication over periods of weeks to months, have been formulated for those with schizophrenia. Systematic reviews of the depots of bromperidol,[19] flupenthixol,[20] fluphenazine,[21] fluspiriline,[22] haloperidol,[23] perphenazine,[24] and pipothiazine[25] have been undertaken. Table 1 presents some results from the haloperidol decanoate Cochrane review.[23] These reviews of trials all tend to report little difference between depot and oral preparations, or between differing depots. The findings are probably due to the selective recruitment to trials of people who, by definition, are reasonably compliant. Within these particular studies poor generalisability is likely to mask any potential benefit of the depot medication. For example, the outcome of relapse due to poor compliance with medication is not likely to be much different between the compliant groups allocated oral or depot antipsychotic within a trial. In the real world, however, with people who may be very unlikely to enter a randomised trial, depot delivery of an antipsychotic may have great benefit over prescription of an oral equivalent.

The management of the acutely disturbed person necessitates the use of many skills on the part of carers, but rapid tranquillisation or sedation of a person may be necessary. Various regimens exist such as combinations of an antipsychotic drug with a tranquillising benzodiazapine or use of a short acting depot (zuclopenthixol acetate). A systematic review of limited trial derived evidence did not find any suggestion that zuclopenthixol acetate is more effective in controlling aggressive/disorganised behaviour, acute psychotic symptoms, or preventing side effects than standard antipsychotic regimens.[26] Other cheaper preparations such as droperidol or haloperidol are commonly used and might represent an important treatment alternative.

Less typical antipsychotics

Loxapine is a less typical drug by "receptor blockade profile" but its differential effects are unremarkable when compared with the better known typical drugs.[27] It is perhaps more tranquillising in an emergency than better known typical drugs.

No trial evidence exists that pimozide is of particular value for particular variants of schizophrenia, as has been claimed.[28 29] Used in appropriate doses it is, however, an effective less typical antipsychotic in both the medium and long term.[30] However, the Committee on Safety of Medicines recommends mandatory electrocardiogram (ECG) monitoring before treatment in all patients, and that people taking pimozide should have an annual ECG (see the *British National Formulary* for full details).[31] Pimozide's pattern of effect, with at least similar clinical efficacy to typical drugs and for certain people, where sedation is not desirable, a

Table 2 The less typical antipsychotics

Intervention		*Outcomes*			
Experimental	*Control*	*Immediate*	*Short term (0–6 weeks)*	*Medium term (7 weeks to 6 months)*	*Long term (>6 months)*
Loxapine[27] 535 participants	Typical antipsychotics 538 participants	Improved ⇑ (RR=2; CI 1.3 to 3) Requiring re-dosing ⇔ (RR=1.2; CI 0.6 to 2.4) Movement disorders ⇔ (RR=0.9; CI 0.4 to 2.5)	Improved ⇔ (RR=1; CI 0.9 to 1.2) Attrition ⇔ (RR=1; CI 0.8 to 1.3) Movement disorders ⇔ (RR=1.2; CI 0.98 to 1.6) Sedation ⇔ (RR=1.23; CI 0.9 to 1.7)		
Pimozide[30] 265 participants	Typical antipsychotics 263 participants			Improved ⇔ (RR=1; CI 0.8 to 1.4) Relapse ⇔ (RR=0.9; CI 0.4 to 2.1) Attrition ⇔ (RR=1.2; CI 0.6 to 2.3) Movement disorders ⇔ (RR=1.2; CI 0.8 to 1.8) Sedation ⇓ (RR=0.5; CI 0.3 to 0.9)	Improved ⇔ (RR=1.2; CI 0.9 to 1.5) Relapse ⇔ (RR=0.9; CI 0.8 to 1.1) Attrition ⇔ (RR=1.0; CI 0.7 to 1.5) Movement disorders ⇔ (RR=0.9; CI 0.5 to 1.8) Sedation ⇓ (RR=0.4; CI 0.2 to 0.7) Weight ⇔ (RR=1.5; CI 0.8 to 2.8)
Sulpiride[32] 219 participants	Typical antipsychotics 207 participants			Improved ⇔ (RR=0.8; CI 0.6 to 1.0) Attrition ⇔ (RR=0.8; CI 0.6 to 1.0) Movement disorders ⇓ (RR=0.7; CI 0.6 to 0.9) Sedation ⇔ (RR=0.8; CI 0.6 to 1.0)	

RR = Relative risk—the experimental event rate/control event rate; CI = 95% confidence intervals—an estimate of the precision of RR; ⇓ = decreased; ⇑ = increased; ⇔ = no clear difference.

more favourable adverse effect profile makes it still worthy of consideration (table 2).

The atypical sulpiride is under-researched. No evidence exists that it is of particular benefit for those with negative symptoms,[32] and what data there are suggest that it is an effective antipsychotic with less propensity to cause movement disorders than its typical cousins. Thioridazine is an old drug with an unusual profile of receptor blockade resembling the atypicals; a systematic review of its effectiveness is underway.[33]

Novel atypical drugs

Within this class of drug risperidone and olanzapine are the most widely used.[34] These drugs have been heavily promoted and the results of limited studies have been widely,[35] and sometimes subtly, disseminated.[36] The summary results of the respective systematic reviews are remarkably similar (table 3). Both compounds are reported to afford a greater clinical improvement than typical antipsychotics, with less attrition, movement disorders, and sedation. Attrition, although less than in some other atypical studies, is still great (olanzapine 42%, 8 weeks; risperidone 30%, 10 weeks). If the condition of even a small proportion of those who left the studies early deteriorated as a result of taking the novel compound, this would greatly change perspectives on the new drug.

Measures of improvement as defined within these studies may not have real meaning outside of the research setting. For example, the "improved" in the risperidone trials was largely a 20% change in the Positive and Negative Symptom Scale,[37] which is difficult to interpret clinically.[38] One large study dominates the olanzapine efficacy data.[39] The questionnaire in this short study asked hundreds of questions, yet simple and clinically relevant questions were either not asked or their response not reported.

The dose of comparison drugs, most usually haloperidol (which is prone to produce movement disorders), is frequently high for the type of participants within these studies. This may have artificially raised the frequency of adverse effects in the haloperidol group so exaggerating the benefits associated with the experimental drug. One guideline suggests that when the new compounds are compared with doses of haloperidol in the range of 12 mg/day there are no clear differences to be seen in symptom improvement or acceptability to patients (measured by drop out).[40]

The trial evidence is also difficult to interpret because of publication bias (where less favourable papers are difficult or impossible to trace).[38] There is also evidence of reporting bias (where less favourable results are poorly reported or not mentioned) within these reviews.[35] With genuine collaboration between reviewers and industry, some of these biases can be addressed.

Amisulpride and sulpiride are chemically similar drugs. Amisulpride is new, more expensive, and better researched than sulpiride. Trial data suggest that it is an effective antipsychotic, with fewer side effects than the typicals and less attrition. Similar claims about particular efficacy for those with negative symptoms are being made for amisulpride as were made for sulpiride two decades ago. Limited data support this claim.[41] A comparison of amisulpride versus sulpiride does not exist, however, but would be most informative.

Trials report that quetiapine is as effective as typical antipsychotics in the short term with less adverse movement disorders.[42] However, the greater than 50% attrition from the trials across the first few weeks of treatment makes these data almost impossible to interpret. Quetiapine may or may not be an effective antipsychotic, but the trials that have attempted to evaluate its effects are not sufficiently reliable.[43 44]

Table 3 The novel atypical antipsychotics

Intervention		*Outcomes*			
Experimental	*Control*	*Immediate*	*Short term (0–6 weeks)*	*Medium term (7 weeks—6 months)*	Long term (>6 months)
Amisulpride[41] 415 participants	Typical antipsychotics 219 participants			Improved ⇑ (RR=1.2; CI 1.06 to 1.4) Attrition ⇓ (RR=0.7; CI 0.5 to 0.9) Movement disorders ⇓ (RR=0.5; CI 0.3 to 0.6)	
Olanzapine[35] 2049 participants	Typical antipsychotics 925 participants		Improved ⇑ (RR=1.5; CI 1.3 to 1.7) Attrition ⇓ (RR=0.7; CI 0.6 to 0.8) Movement disorders ⇓ (RR=0.3; CI 0.2 to 0.4) Sedation ⇓ (RR=0.8; CI 0.7 to 0.9)		Relapse ⇔ (RR=0.9; CI 0.8 to 1.0) Attrition ⇓ (RR=0.9; CI 0.8 to 0.93)
Olanzapine[35] 193 participants	Risperidone 188 participants		Improved ⇔ (RR=1.2; CI 1 to 1.5) Attrition ⇔ (RR=0.8; CI 0.6 to 1.2) Movement disorders ⇓ (RR=0.6; CI 0.4 to 0.9)	Attrition ⇓ (RR=0.8; CI: 0.6–0.9)	Attrition ⇔ (RR=0.6; CI 0.4 to 1.2)
Quetiapine[42] 580 participants	Typical antipsychotics 379 participants		Improved ⇔ (RR=0.9; CI 0.7 to 1.2) Attrition ⇔ (RR=1; CI 0.9 to 1.1) Movement disorders ⇓ (RR=0.3; CI 0.2 to 0.4) Sedation ⇑ (RR=1.5; CI 1.1 to 2.2)		
Risperidone[38] 2299 participants	Typical antipsychotics 1113 participants		Improved ⇑ (RR=1.3; CI 1.1 to 2) Attrition ⇓ (RR=0.8; CI 0.7 to 0.9) Movement disorders ⇓ (RR=0.6; CI 0.5 to 0.7) Sedation ⇓ (RR=0.9; CI 0.8 to 0.99) Weight ⇑ (RR=1.4; CI 1.1 to 1.7)		
Zotepine[47] 269 participants	Typical antipsychotics 268 participants		Improved ⇑ (RR=1.4; CI 1.1 to 1.8) Attrition ⇔ (RR=0.8; CI 0.6 to 1) Movement disorders ⇓ (RR=0.7; CI 0.5 to 0.8) Sedation ⇔ (RR=1.6; CI 0.7 to 3)		
Zotepine[47] 55 participants	Clozapine, risperidone 55 participants		Attrition ⇔ (RR=1.4; CI 0.7 to 3) Movement disorders ⇑ (RR=2.8; CI 1.2 to 7)		
Ziprasidone[46] 517 participants	Typical antipsychotics 312 participants	Attrition ⇔ (RR=0.9; CI: 0.7–1.4) Movement disorders ⇓ (RR=0.34; CI: 0.2–0.6)		Improved ⇔ (RR=0.7; CI 0.5 to 1.01) Attrition ⇔ (RR=1.1; CI 0.7 to 1.6) Movement disorders ⇓ (RR=0.4; CI 0.2 to 0.6) Sedation ⇔ (RR=1.6; CI: 0.7–3)	

RR = Relative risk—the experimental event rate/control event rate; CI = 95% confidence intervals—an estimate of the precision of RR; ⇓ = decreased; ⇑ = increased; ⇔ = no clear difference.

Sertindole is structurally similar to clozapine (see below), and was licensed for use in the UK in 1996. Its licence was suspended in 1998, however, after reports of arrhythmias and sudden cardiac death. Sertindole remains available on a named patient basis for patients already stabilised on the drug in whom other antipsychotics are inappropriate.[31] There is no indication that sertindole had particular qualities to give it the unique place in the market afforded to clozapine. As it is not widely prescribed, data are not presented but are available if required.[45]

At the time of writing, only early studies on ziprasidone are available.[46] About 25% of people randomised to the most informative study, comparing ziprasidone to typical drugs, left the trial before completion. This degree of attrition is better than other compounds within the new atypical class. What limited data there are do suggest that ziprasidone may be as effective as haloperidol and cause fewer problems with movement disorders over a six month period. Ziprasidone is currently undergoing licensing procedures in the European Union and the USA.

Zotepine has 35% attrition in the short term. This suggests that the likelihood of improvement in mental state is greater for zotepine than various doses of several typical antipsychotics and that movement disorders are seen less frequently.[47]

Clozapine holds a unique place in the antipsychotic market (table 4) as it is an old drug, well researched by those with and without a clear pecuniary interest. Although those with a pecuniary interest do tend to make more favourable claims for it, these are not statistically significantly greater than those of more disinterested researchers.[48] With the relatively low attrition rates from within these studies, probably afforded by the necessity of blood monitoring with this compound, a more reliable estimate of efficacy can be gleaned. Clozapine is an effective antipsychotic, with fewer propensities to cause movement disorders than typical drugs. It is sedating, causes weight gain, and between 0.5–2% of people suffer sudden decline in blood white cells (agranulocytosis),[49] hence all recipients must have their blood monitored to avoid this potentially fatal effect. Clozapine was reintroduced into clinical use for treatment of those with unresponsive illnesses,[50] which is supported by the trial evidence.[51] Good, but far from perfect, studies show that clozapine improves schizophrenic symptoms of those

Table 4 Clozapine

Intervention		*Outcomes*			
Experimental	*Control*	*Immediate*	*Short term (0–6 weeks)*	*Medium term (7 weeks to 6 months)*	*Long term (>6 months)*
Clozapine[51]	Typical antipsychotics		Improved ⇑ (RR=1.6; CI 1.4 to 1.8)		Improved ⇑ (RR=2.1; CI 1.6 to 2.9)
1165 participants	1266 participants		Relapse ⇓ (RR=0.6; CI 0.5 to 0.8)		Relapse ⇓ (RR=0.2; CI 0.1 to 0.3)
			Attrition ⇔ (RR=0.8; CI 0.7 to 1.0) Movement disorders ⇓ (RR=0.7; CI 0.6 to 0.8) Sedation ⇑ (RR=1.3; CI 1.1 to 1.4) Weight ⇑ (RR=1.3; CI 1.0 to 1.5)		Attrition ⇔ (RR=0.6; CI 0.5 to 0.7)
Clozapine[51]	Typical antipsychotics (treatment resistant illness subgroup)		Improved ⇑ (RR=0.7; CI 0.6 to 0.8)		Improved ⇑ (RR=0.8; CI 0.7 to 0.9)
618 participants	600 participants		Relapse ⇔ (RR=1.0; CI 0.6 to 1.8)		Relapse ⇓ (RR=0.2; CI 0.1 to 0.3)
			Attrition ⇔ (RR=1.2; CI 0.7 to 2) Movement disorders ⇓ (RR=0.8; CI 0.7 to 0.9) Sedation ⇑ (RR=1.2; CI 1.1 to 1.3) Weight ⇑ (RR=1.3; CI 1.0 to 1.6)		Attrition ⇔ (RR=0.6; CI 0.50.7)
Clozapine[53]	Risperidone (treatment resistant illness subgroup)		Improved ⇔ (RR=1.0; CI 0.7 to 1.3)		
90 participants	90 participants		Attrition ⇔ (RR=1.0; CI 0.44 to 2.3) Movement disorders ⇔ (RR=1.0; CI 0.2 to 5) Sedation ⇔ (RR=0.9; CI 0.4 to 2.1) Weight ⇔ (RR=0.6; CI 0.3 to 1.2)		
Clozapine[53]	Olanzapine (treatment resistant illness subgroup)			Improved ⇔ (RR=0.9; CI 0.7 to 1.1)	
43 participants	43 participants			Attrition ⇔ (RR=1.0; CI 0.7 to 1.4) Movement disorders ⇔ (RR=0.8; CI 0.3 to 2) Sedation ⇔ (RR=0.6; CI 0.3 to 1.0)	

RR = Relative risk—the experimental event rate/control event rate; CI = 95% confidence intervals—an estimate of the precision of RR; ⇓ = decreased; ⇑ = increased; ⇔ = no clear difference.

whose illnesses have been difficult to treat yet who volunteer for trials. A recent large prevalence study suggests, however, that clozapine treatment may be associated with potentially fatal myocarditis and cardiomyopathy in physically healthy young adults with schizophrenia, further undermining confidence in its value in everyday practice.[52]

Small studies have not found a difference in clinical efficacy between clozapine and the atypicals olanzapine and risperidone for people with treatment resistant illness.[53] This is an important area for further research, where studies will need to be large enough to show equivalence.

Cost effectiveness

It has been estimated that the use of atypical antipsychotics could add up to £210 million to the annual UK drug budget if prescribed for all patients with schizophrenia, and £54 million if restricted to those with treatment resistant schizophrenia (Davies L, personal communication, 1998). Despite being considerably more expensive than compounds that have been available for some time, atypical antipsychotics are nevertheless a small proportion of total outlay for this illness. This, however, may not be of much consolation for those responsible for managing greatly increased demands on budgets that have not been responsive to changes in drug costs. It is likely to have contributed to considerable regional variations in access to newer drugs.[54 55]

Various economic evaluations have been published, which suggest there may be net savings in the overall costs of treating patients associated with clozapine, risperidone, and, to a lesser extent, olanzapine.[56–66] All studies of costs and patient outcomes, however, have been limited in scale and methodology, so results need to be treated with caution when extrapolating to alternative time frames, settings, and patient populations. Overall, the quantity and quality of economic evidence is not sufficient to enable decision makers to make choices between the drugs with any certainty.

Two controlled trial based evaluations of resource use and costs suggest that clozapine and risperidone are cost neutral compared with conventional antipsychotics.[67 68] These were conducted in the US and it is not clear to what extent the results are applicable to the UK.

Implications

- Those involved in the care of people with schizophrenia need to maintain their knowledge of current research evidence on antipsychotics. Given the nature of the available research evidence, practice guidelines should be appraised for bias and day to day applicability. Clinical use of relevant up to date information must, where possible, be in collaboration with the particular client and their carers and tailored to the individual's needs or situation
- Novel antipsychotics may be a further refinement, but not a revolution, in the care of those with schizophrenia. They may cause fewer adverse effects and be more acceptable to those with schizophrenia than drugs such as chlorpromazine and haloperidol
- At present, all statements on the effects of novel antipsychotics must be qualified. The trials include people, drug regimens, and

outcomes that are difficult to interpret for everyday use and have such loss to follow up that the reader is left to speculate on the meaning of the data. Most relevant trials are undertaken by those with clear pecuniary interest in the results

- Novel antipsychotics are expensive. Speculation that direct drug costs are offset by decreases in admission to hospital, indirect costs, and intangible savings is not based on unbiased widely applicable data, nor is it helpful to those responsible for management of limited drug budgets
- If the NHS is to fund novel antipsychotics fully, their use should be justified by trial data clearly supportive of their use in everyday practice. Large, long term randomised drug trials with participants, interventions, and primary outcomes familiar to health professionals who treat people with schizophrenia are long overdue.

1 NHS CRD. Drug treatments for schizophrenia. *Effective Health Care* 1999;**5**:(6).
2 OPCS. *OPCS survey of psychiatric morbidity in Great Britain*. London: HMSO, 1995.
3 Breier A, Schreiber J, Dyer J, *et al*. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch Gen Psychiatry* 1991;**48**:239–46.
4 Tsuang MT, Woolson RF, Fleming JA. Premature deaths in schizophrenia and affective disorders. An analysis of survival curves and variables affecting the shortened survival. *Arch Gen Psychiatry* 1980;**37**:979–83.
5 Caldwell C, II G. Schizophrenia—a high risk factor for suicide: clues to risk reduction. *Suicide Life Threat Behav* 1992;**22**:479–93.
6 *Cochrane Library*. Oxford: Update Software, 1999.
7 Grozier L. The third revolution in psychiatry: fluphenazine decanoate. In: Ayd FJ, editor. *The future of pharmacotherapy: drug delivery systems.* Baltimore: International Drug Therapy Newsletter, 1973.
8 American Psychiatric Association. *Tardive dyskinesia: a task force report of the American Psychiatric Association*. Washington DC: American Psychiatric Association, 1992.
9 Waddington JL, O'Callaghan E. What makes an antipsychotic "atypical"? Conserving the definition. *CNS Drugs* 1997;**7**:341–6.
10 Kane J. What makes an antipsychotic "atypical"? Should the definition be preserved? *CNS Drugs* 1997;**7**:347–8.
11 Meltzer H. Suicide and schizophrenia: clozapine and the InterSePT study. International clozaril/leponex suicide prevention trial. *J Clin Psychiatry* 1999;**60**(suppl 12):47–50.
12 Horrobin D. Beyond conflict of interest. Non-financial conflicts of interest are more serious than financial conflicts. *BMJ* 1999;**318**:466.
13 Smith R. Unscientific practice flourishes in science. *BMJ* 1998;**316**:1036.
14 Smith R. Beyond conflict of interest. Transparency is the key. *BMJ* 1998;**317**:291–2.
15 Thornley B, Adams CE. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *BMJ* 1998;**317**:1181–4.
16 Ahmed I, Soares K, Seifas R, *et al*. Randomized controlled trials (1959–1995): a prevalence study. *Arch Gen Psychiatry* 1998;**55**:754–5.
17 Thornley B, Adams CE, Awad G. Chlorpromazine versus placebo for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
18 Klein D, Davis J. Diagnosis and drug treatment of psychiatric disorders. *Review of antipsychotic drug literature*. Baltimore: Williams & Wilkins, 1969.
19 Quraishi S, David A, Adams C. Depot bromperidol decanoate for schizophrenia or other similar psychotic disorders (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
20 Quraishi S, David A. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
21 Adams C, Eisenbruch M. Depot fluphenazine versus oral fluphenazine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
22 Quraishi. Depot fluspirilene for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
23 Quraishi S, David A. Depot haloperidol decanoate for schizophrenia. (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
24 Quraishi S, David A. Depot perphenazine decanoate and enanthate for schizophrenia. (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
25 Quraishi S, David A. Depot pipothiazine palmitate and undeclynate for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
26 Fenton M, Coutinho E, Campbell C. Zuclopenthizol acetate for acute schizophrenia and similar serious mental illnesses (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
27 Murphy B, Fenton M, Bagnall A-M, *et al*. Lozapine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
28 Kaplan H, Sadock B, Grebb J. Other psychotic disorders. In: Kaplan H, Sadock B, Grebb J, editors. *Synopsis of psychiatry*. London: Williams and Wilkins, 1994:487–512.
29 Opler L, Klahr D, Ramirez P. Pharmacologic treatment of delusions. *Psychiatric Clin North Am* 1995;**18**:379–91.
30 Sultana A, McMonagle T. Pimozide for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
31 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary (38)*. London: BMA, RPSGB, September 1999.
32 Soares BGO, Fenton M, Chue P. Sulpiride for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
33 Sultana A. Thioridazine for schizophrenia (Cochrane protocol). *Cochrane Library*. Oxford: Update Software, 2000.
34 Wood MacKenzie Global Consultants. Review of the global schizophrenia market. *Pharmaforum*, 1998;**39**:9.
35 Duggan L, Fenton M, Dardennes R, *et al*. Olanzapine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
36 Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet* 1996;**347**:1024–6.
37 Kay S, Opler L, Fiszbein A. *Positive and negative syndrome scale (PANSS) manual.* North Tonawanda (NY): Multi-Health Systems, 1986.
38 Kennedy E, Song F, Hunter R, *et al*. Risperidone versus typical antipsychotic medication for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
39 Tollefson GD, Beasley CM, Tran PV, *et al*. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;**154**:457–65.
40 National Schizophrenia Guideline Group. *The early management of schizophrenia part 1. Pharmacological treatments. Evidence based clinical practice guideline*. Royal College of Psychiatrists Research Unit; British Psychological Society; Medicines Evaluation Group, Centre for Health Economics, University of York, 1999.
41 Mota Neto J, Lima M, Soares B. Amisulpride for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
42 Srisurapanont M, Disayavanish C, Taimkaew K. Quetiapine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
43 Roland M, Torgerson DJ. What are pragmatic trials? *BMJ* 1998;**316**:285.
44 Hotopf M, Churchill R, Lewis G. Pragmatic randomised controlled trials in pyschiatry. *Br J Psychiatry* 1999;**175**:217–23.
45 Lewis R, Bagnall A-M. Sertindole for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
46 Bagnall A, Lewis R. Ziprasidone for schizophrenia and severe mental illness (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
47 Fenton M, Morris S, De-Silva P, *et al*. Zotepine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 2000.
48 Wahlbeck K, Adams CE. Beyond conflict of interest. Sponsored drug trials show more-favourable outcomes. *BMJ* 1999;**318**:465.
49 Alvir J, Jeffrey P, Lieberman A, *et al*. Clozapine-induced agranulocytosis: incidence and risk factor in the United States. *New Engl J Med* 1993;**329**:162–7.
50 Kane J, Honigfeld G, Singer J, *et al*. Clozaril Collaborative Study Group. Clozapine for the treatment of treatment-resistant schizophrenia: a double blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;**45**:789–96.
51 Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
52 Kilian J, Kerr K, Lawerence C, *et al*. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 1999;**354**:1841–5.
53 Tuunainen A, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia (Cochrane Review). *Cochrane Library*. Oxford: Update Software, 1999.
54 Taylor D, Mir S, Mace S, *et al.* A national survey of antipsychotic prescribing. *Primary Care in Psychiatry* 2000; in press.
55 Hogman G. *Is cost a factor?* London: National Schizophrenia Fellowship, 1996.
56 Addington D, Jones B, Bloom D, *et al*. Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. *Clin Therap* 1993;**15**:917–26.
57 Aitchison K, Kerwin R. Cost-effectiveness of clozapine. *Br J Psychiatry* 1997;**171**:125–130.

58 Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK. A comparison of olanzapine and haloperidol. *PharmacoEconomics* 1998;**13**(5 Pt 2):575–88.
59 Chouinard G, Albright P. Economic and Health State utility determinations for schizophrenic patients treated with risperidone or haloperidol. *J Clin Psychopharm* 1997;**17**: 2998–307.
60 Davies L, Drummond M. Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. *Br J Psychiatry* 1993;**162**:38–42.
61 Fitton A, Benfield P. Clozpine an appraisal of its pharmacoeconomic benefits in the treatment of schizophrenia. *PharmacoEconomics* 1993;**4**:131–56.
62 Glazer W, Johnstone B. Pharmacoeconomic evaluation of antipsychotic therapy for schizophrenia. *J Clin Psychiatry* 1997;**58**(suppl 10):50–4.
63 Glennie JL. *Pharmacoeconomic evaluations of clozapine in treatment resistant schizophrenia and risperidone in chronic schizophrenia*. Ontario: Canadian Coordinating Office for Health Technology Assessment (CCOHTA), 1997.
64 Guest J, Hart W, Cookson R, *et al*. Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia. *Br J Med Econ* 1996;**10**:59–67.
65 Honigfeld G, Patin J. A Two-year clinical and economic follow-up of patients on clozapine. *Hosp Community Psychiatry* 1990;**41**:882–5.
66 Meltzer H, Cola P, Way L, *et al*. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. *Am J Psychiatry* 1993;**150**:1630–8.
67 Rosenheck R, Cramer J, Weichun X, *et al*. A comparison of clozapine and haloperidol in hospitalised patients with refractory schizophrenia. *N Engl J Med* 1997;**337**:809–15.
68 Mahmound RELP. Risperidone vs conventional antipsychotics in usual care: a prospective effectiveness trial of outcomes for patients with schizophrenia and schizoaffective disorder. *XXIst Collegium Internationale Neuro Psychopharmacologicum Congress* 1998;373.