DECEMBER 1999 VOLUME 5 NUMBER 6 ISSN: 0965-0288

Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin reviews the evidence for the effectiveness of the main drug treatments for schizophrenia.

Drug treatments for schizophrenia

- Schizophrenia is one of the most common of the severe mental illnesses. Drug treatment with antipsychotics forms the mainstay of effective management, but should be used alongside a range of psychosocial interventions.
- The newer 'atypical' antipsychotics may be a further refinement, but not a revolution, in the care of those with schizophrenia. They may cause less adverse effects and be more acceptable to those with schizophrenia than other older drugs.
- At present, all statements on the effects of 'atypical' antipsychotics must be qualified. The quality of much of the research evidence as measured by clear reporting and clinical applicability, is poor. This often limits the conclusions that can be drawn.
- 'Atypical' antipsychotics are expensive. Speculation that direct drug costs are offset by decreases in hospitalisation, indirect costs and intangible savings is not based on reliable data, nor is it helpful to those responsible for management of limited drug budgets.
- If the NHS is to fully fund 'atypical' antipsychotics 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.
- Those involved in the care of people with schizophrenia need to maintain up-to-date knowledge of the research evidence on antipsychotics. Guides to practice should be appraised for bias and day-to-day applicability.

The Royal Society of Medicine Press Limited

The University of York

NHS Centre for Reviews and Dissemination

Schizophrenia is one of the most common of the severe mental illnesses. The Department of Health has recently outlined policy initiatives to improve and standardise the care of schizophrenia in the National Service Framework for Mental Health.[1] The Framework promises national and regional support for health and social services and establishes the progress which should be made within certain timescales.

Treatments for schizophrenia are divided into the so-called 'physical interventions' of drugs, the psychological and social managements and, rarely in the UK, electroconvulsive therapy (ECT).

Drug treatment forms the mainstay of effective management of people with schizophrenia, but should be used alongside a range of psychosocial interventions. A future *Effective Health Care* bulletin will address psychosocial interventions and various methods of delivery of care. The purpose of this bulletin is to summarise the evidence of the effectiveness of the main, older and more recently introduced drugs used in the treatment of schizophrenia.

A. Background

Schizophrenia is an illness or a group of illnesses affecting language, planning, emotion, perceptions and movement. Many clinicians divide the signs and symptoms into 'positive' and 'negative' (Box 1).[2] Positive symptoms often accompany acute psychotic episodes. Negative symptoms refer to the absence of function[3] and are characteristically, but not inevitably, associated with long-standing and unremitting illness.

In acute psychotic episodes behaviour can be markedly disorganised. Some people become agitated and a few are aggressive, others may appear preoccupied with inner thoughts, appearing perplexed and withdrawn. Poor insight into the unusual nature of their experiences is common.

Box 1. The symptoms and signs of schizophrenia

Positive symptoms

- Delusions – strange beliefs, foreign to the person's background, which cannot be shaken by logic or reason. For example the sure belief that secret agents are watching or listening.
- Hallucinations – the person hears, sees, tastes, smells or feels things that are not there. The most common hallucination is hearing voices.
- Disordered thinking – fragmenting of the process of logical thought. One thought may simply not flow from its predecessor or connect to those that follow.
- Catatonic movements – the person may freeze like a statue, adopt odd postures, or become very excited, restless and agitated.

Negative symptoms

- Feelings of emotional numbness.
- Difficulty in communicating with others.
- Lack of motivation.
- Inability to care about or cope with everyday tasks such as getting out of bed in the morning, washing and dressing.

The International Classification of Diseases (ICD-10)[4] and the Fourth Edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association[5] both emphasise symptoms such as hallucinatory voices commenting on the person's actions, delusions, experiences of interference with the person's thoughts, incoherent or irrelevant speech, changes in a person's ability to experience emotions and decline in their general level of functioning.[6]

There are no diagnostic physical tests for schizophrenia. It is defined by symptoms and signs. Diagnosis can be difficult initially since the early features of schizophrenia such as anxiety, depression, a vague sense of unease, suspiciousness, social withdrawal, loss of concentration and moodiness,[7] are non-specific and common in adolescence.

Epidemiology

About 0.5% to 1% of the population – irrespective of culture, social class and race – suffer from schizophrenia at some time in their life.[8] This incidence is relatively consistent across the world. Every year one to two people per 10,000 begin to fall ill with schizophrenia,[9] making this illness about twice as common as epilepsy. In the UK, currently, approximately 250,000 people suffer from schizophrenia or a schizophrenia-like illness.[10]

One 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 the positive symptoms.[11] Many with recurrent illness have enduring problems from schizophrenia such as persistent psychotic symptoms, but, for most, the problems consist of negative symptoms such as loss of enthusiasm and emotional responsiveness, apathy and social withdrawal.[11] 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[12] due to physical illness, accidents, and other causes of violent death, especially suicide.[13]

Impact

In national and personal terms, the impact of schizophrenia is very large (Box 2). This relapsing illness often necessitates hospitalization and some sort of long-term care – the bulk of the direct costs to society. Drug treatments currently represent a small proportion of the total outlay for this illness.

Box 2. The impact of schizophrenia[15]

Direct:	Hospitalisation
	Residential care
	Drugs
	Other public agencies e.g. criminal justice system
	Social security
	Capital e.g. hospitals, residential homes, land value
Indirect:	Employment effects
	Family costs
Intangible costs:	Carer quality of life
	Other societal costs

The personal cost of schizophrenia is often catastrophic. Sufferers, even before symptoms are overt, frequently find it impossible to achieve expected levels of functioning,[14] and quickly encounter problems with employment and social stability. A family member with schizophrenia can also have a profound effect on the mental and physical health of their carers as well as their ability to maintain their every day lives.

B. Nature of evidence

This bulletin is based on a set of high quality systematic reviews from the Cochrane Schizophrenia Group, some of which form the basis of a forthcoming report on the new neuroleptics in schizophrenia (commissioned by NHS Health Technology Assessment Programme). This bulletin summarises the results of these reviews. More detailed information is available on each treatment within the referenced reviews. These reviews are regularly updated in the *Cochrane Library*.[16]

Despite the difficulties of carrying out research with participants where insight may be poor and outcomes difficult to record, the evaluation of care for those with schizophrenia has a strong tradition of randomised trials. These 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 clinical value.[17] Whilst within systematic reviews some of the shortcomings of individual trials can be managed, the paucity of large well conducted and clinically relevant trials often limits the conclusions that can be drawn.

C. Drug treatments for schizophrenia

This synopsis covers some areas of the drug management of people with schizophrenia that may currently concern managers and clinicians in the UK.

The main class of drugs used to treat or manage schizophrenia is the antipsychotics (also known as neuroleptics, anti-schizophrenia drugs and, inaccurately, as major tranquillisers). The antipsychotic

Box 3. Classification of antipsychotics

Classification	Oral preparations	Rec maintenance dose range/ day▪	Cost/ patient year ▪▪
Typical	chlorpromazine hydrochloride	75–300mg	£9–29
	trifluoperazine	10mg–	£22–
	fluphenazine hydrochloride	2.5–20mg	£24–129
	haloperidol	5–100mg	£45–790
	flupentixol	3–18mg	£57–344
	zuclopenthixol dihydrochloride	20–50mg	£66–132
	perphenazine	12–24mg	£240–481
Less typical	thioridazine	150–600mg	£38–141
	pimozide	2–20mg	£58–429 ▪▪▪
	loxapine	20–100mg	£69–250
	sulpiride	400–800mg	£130–260
	oxypertine	80–300mg	£242–909
	amisulpride	50–300mg	£100–565
Atypical	zotepine	75–300mg	£426–1205
	olanzapine	5–20mg	£687–2750
	risperidone	4–6mg	£940–1424
	clozapine	150–300mg	£979–1957
	quetiapine	300–450mg	£1376–2064

▪ Recommended dose range for maintenance therapy.[31]
▪▪ lowest non-proprietary cost/mg.[31]
▪▪▪ Excludes costs of ECG monitoring.

action of these drugs is more than simply the promotion of sedation and probably depends upon specific central nervous system receptor blockade.

The advent of these 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 proportions of their lives.[18] Adverse effects, however, were common with drugs such as chlorpromazine and haloperidol. Sedation can be problematic, as can dry mouth, blurred vision, constipation, impotence and dizziness resulting from lowered blood pressure. Movement disorders that resemble the symptoms of Parkinson's disease, with expressionless face, shuffling gait, paucity of movement and tremor occur frequently.[19]

Akathisia is a distressing early-onset movement disorder characterised by a subjective report of inner restlessness, mental unease, or dysphoria, which can be intense[20] and occurs in between 20% and 75% of people on typical antipsychotics.[21] Associated with this experience are patterns of restlessness.[22] Every year 4–5% of those who continually use these drugs begin to have abnormal, repetitive and involuntary movements, frequently around the mouth and face, characteristic of tardive dyskinesia. Tardive dyskinesia, a particularly severe form of movement disorder, occurs in over 20% of those using typical antipsychotics continually for longer than three months[23] and does not necessarily recede once the antipsychotic is stopped or reduced.

Over a decade ago, with the reintroduction of 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 cause profound catalepsy in rats (the animal model of drug-induced parkinsonism). In truth, rather than such a dichotomy of typical and atypical, there is a continuum[24,25] and some inexpensive, older, drugs may have an atypical profile (Box 3).

The claims being made for the newer atypical compounds are exciting[26] but take place in the context of ever greater conflicts of interest, both academic[27] and monetary.[28,29] Yet the quality of trials, as measured by clear reporting and clinical applicability, is poor, and has not increased over the last 50 years[17] – in fact there is some evidence it has declined.[30] It is in this context that the data from recent studies must be examined.

The most typical antipsychotics (Table 1)

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.[32] Quantitative reviews of haloperidol or trifluoperazine versus placebo were not identified but a review comparing each to chlorpromazine did not identify significant differences in clinical outcomes.[33]

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,[34] flupenthixol,[35] fluphenazine,[36] fluspiriline,[37] haloperidol,[38] perphenazine,[39] and pipothiazine[40] have been undertaken. Some results from the haloperidol decanoate Cochrane review[38] are presented in Table 1. These reviews of trials all tend to report little difference between depot and oral preparations, or between differing depots. The findings are likely due to the selective recruitment to trials of people who, by definition, are reasonably compliant. Within these particular studies poor generalizability 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 anti-psychotic within a trial. In the real world, however, with people who may be very unlikely to enter a randomised trial, depot delivery of an anti-psychotic 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.[41] Other cheaper preparations such as droperidol or haloperidol are commonly used and might represent an important treatment alternative.

The less typical antipsychotics (Table 2)

Loxapine is a less typical drug by 'receptor blockade profile' but its differential effects are unremarkable when compared to the better known typical drugs.[42] It is perhaps more tranquillising in an emergency than better known typical drugs.

There is no trial evidence that pimozide is of particular value for particular variants of schizophrenia, as has been claimed.[43,44] Used in appropriate doses it is, however, an effective

less typical antipsychotic in both the medium and long term.[45] 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 BNF 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 more favourable adverse effect profile may still make it worthy of consideration (see Table 2).

The atypical sulpiride is under-researched. There is no evidence that it is of particular benefit for those with negative symptoms[46] 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.[47]

The novel atypical drugs (Table 3)

Within this class of drug, risperidone and olanzapine are the most widely used.[48] These drugs have been heavily promoted and results of limited studies have been widely,[49] and sometimes subtly, disseminated.[50] The summary results of the respective systematic reviews are remarkably similar (see 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,[51] which is difficult to interpret clinically.[52] One large study dominates the olanzapine efficacy data.[53] 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 to doses of haloperidol in the range of 12mg per day there are no clear differences to be seen in symptom improvement or acceptability to patients (measured by drop-out).[54]

The trial evidence is also difficult to interpret because of publication bias (where less favourable papers are difficult or impossible to trace).[52] There is also evidence of reporting bias (where less favourable results are poorly reported or not mentioned) within these reviews.[49] With genuine collaboration between reviewers and industry, some of these biases can be addressed.

Amisulpride and sulpiride are chemically very 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 regarding 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.[55] 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.[56] 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.[57,58]

Sertindole is structurally similar to clozapine (see below), and was licensed for use in the UK in 1996. However, its license was suspended in 1998 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.[59]

At the time of writing only early studies on ziprazidone are available.[60] About 25% of people randomised to the most informative study, comparing ziprazidone to typical drugs, left the trial before completion. This degree of attrition is better than other compounds within the new atypical class. What very limited data there are do suggest that ziprazidone may be as effective as haloperidol and has less problems with movement disorders over a six-month period. Ziprazidone is currently undergoing licensing procedures in the EU and the USA.

Zotepine has 35% attrition in the short term.[61] This review 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.

Tables 1-4: Antipsychotic drugs for schizophrenia: tables of systematic review results

Key: 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

Intervention		Outcomes			
Experimental	**Control**	**Immediate**	**Short term (0-6 weeks)**	**Medium term (7 weeks - 6 months)**	**Long term (>6 months)**
Table 1- The most typical antipsychotics					
Chlorpromazine[32] 1646 participants	Placebo 1470 participants	Movement disorders ⇧ (RR=3; CI: 1.3-8)	Improved ⇧ (RR=1.6; CI: 1.3-1.8). Relapse ⇩ (RR=0.3; CI: 0.1-0.8) Attrition ⇩ (RR=0.7; CI: 0.6-0.9) Movement disorders ⇧ (RR=1.8; CI: 1.1-4.7)	Improved ⇧ (RR=2; CI: 1.8-2.4) Relapse ⇩ (RR=0.5; CI: 0.4-0.6) Attrition ⇩ (RR=0.6; CI: 0.5-0.8) Movement disorders ⇧ (RR=2; CI: 1.5-2.7) Sedation ⇧ (RR=2.3; CI: 1.8-3)	Relapse ⇩ (RR=0.6; CI: 0.5-0.7) Attrition ⇔ (RR=1.0; CI: 0.7-1.6) Movement disorders ⇧ (RR=2.8; CI: 1.4-6) Weight ⇧ (OR=5; CI: 2-10)
Zuclopenthixol acetate[41] 234 participants	Chlorpromazine, haloperidol, clothiapine 179 participants	Improved ⇔ (RR=1; CI: 0.9-1.1) Requiring re-dosing ⇔ (RR=1.5; CI: 0.8-2.9) Attrition ⇔ (RR=0.7; CI: 0.2-2.1)			
Haloperidol decanoate[38] 11 participants	oral haloperidol 11 participants			Improved ⇔ (RR=0.9; CI: 0.6-1.4)	
Haloperidol decanoate[38] 187 participants	other depots 184 participants			Relapse ⇔ (RR=1.2; CI: 0.7-1.9) Attrition ⇔ (RR=0.9; CI: 0.6-1.4) Movement disorders ⇔ (RR=0.9; CI: 0.8-1.1)	
Table 2- The less typical antipsychotics					
Loxapine[42] 535 participants	typical antipsychotics 538 participants	Improved ⇧ (RR=2; CI: 1.3-3) Requiring re-dosing ⇔ (RR=1.2; CI: 0.6-2.4) Movement disorders ⇔ (RR=0.9; CI: 0.4-2.5)	Improved ⇔ (RR=1; CI: 0.9-1.2) Attrition ⇔ (RR=1; CI: 0.8-1.3) Movement disorders ⇔ (RR=1.2; CI: 0.98-1.6) Sedation ⇔ (RR=1.23; CI: 0.9-1.7)		
Pimozide[45] 265 participants	typical antipsychotics 263 participants			Improved ⇔ (RR=1; CI: 0.8-1.4) Relapse ⇔ (RR=0.9; CI: 0.4-2.1) Attrition ⇔ (RR=1.2; CI: 0.6-2.3) Movement disorders ⇔ (RR=1.2; CI: 0.8-1.8) Sedation ⇩ (RR=0.5; CI: 0.3-0.9)	Improved ⇔ (RR=1.2; CI: 0.9-1.5) Relapse ⇔ (RR=0.9; CI: 0.8-1.1) Attrition ⇔ (RR=1.0; CI: 0.7-1.5) Movement disorders ⇔ (RR=0.9; CI: 0.5-1.8) Sedation ⇩ (RR=0.4; CI: 0.2-0.7) Weight ⇔ (RR=1.5; CI: 0.8-2.8)
Sulpiride[46] 219 participants	typical antipsychotics 207 participants			Improved ⇔ (RR=0.8; CI: 0.6-1.0) Attrition ⇔ (RR=0.8; CI: 0.6-1.0) Movement disorders ⇩ (RR=0.7; CI: 0.6-0.9) Sedation ⇔ (RR=0.8; CI: 0.6-1.0)	
Table 3- The novel atypical antipsychotics					
Amisulpride[55] 415 participants	typical antipsychotics 219 participants			Improved ⇧ (RR=1.2; CI: 1.06-1.4) Attrition ⇩ (RR=0.7; CI: 0.5-0.9) Movement disorders ⇩ (RR=0.5; CI: 0.3-0.6)	
Olanzapine[49] 2049 participants	typical antipsychotics 925 participants		Improved ⇧ (RR=1.5; CI: 1.3-1.7) Attrition ⇩ (RR=0.7; CI: 0.6-0.8) Movement disorders ⇩ (RR=0.3; CI: 0.2-0.4) Sedation ⇩ (RR=0.8; CI: 0.7-0.9)		Relapse ⇔ (RR=0.9; CI: 0.8-1.0) Attrition ⇩ (RR=0.9; CI: 0.8-0.93)

Table 3- The novel atypical antipsychotics (Cont.)					
Olanzapine[49] 193 participants	Risperidone 188 participants		Improved ⇔ (RR=1.2; CI: 1-1.5) Attrition ⇔ (RR=0.8; CI: 0.6-1.2) Movement disorders ⇩ (RR=0.6; CI: 0.4-0.9)	Attrition ⇩ (RR=0.8; CI: 0.6-0.9)	Attrition ⇔ (RR=0.6; CI: 0.4-1.2)
Quetiapine[56] 580 participants	typical antipsychotics 379 participants		Improved ⇔ (RR=0.9; CI: 0.7-1.2) Attrition ⇔ (RR=1; CI: 0.9-1.1) Movement disorders ⇩ (RR=0.3; CI: 0.2-0.4) Sedation ⇧ (RR=1.5; CI: 1.1-2.2)		
Risperidone[52] 2299 participants	typical antipsychotics 1113 participants		Improved ⇧ (RR=1.3; CI: 1.1-2) Attrition ⇩ (RR=0.8; CI: 0.7-0.9) Movement disorders ⇩ (RR=0.6; CI: 0.5-0.7) Sedation ⇩ (RR=0.9; CI: 0.8-0.99) Weight ⇧ (RR=1.4; CI: 1.1-1.7)		
Zotepine[61] 269 participants	typical antipsychotics 268 participants		Improved ⇧ (RR=1.4; CI: 1.1-1.8) Attrition ⇔ (RR=0.8; CI: 0.6-1) Movement disorders ⇩ (RR=0.7; CI: 0.5-0.8) Sedation ⇔ (RR=1.6; CI: 0.7-3)		
Zotepine[61] 55 participants	Clozapine, risperidone 55 participants		Attrition ⇔ (RR=1.4; CI: 0.7-3) Movement disorders ⇧ (RR=2.8; CI: 1.2-7)		
Ziprazidone[60] 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: 0.5-1.01) Attrition ⇔ (RR=1.1; CI: 0.7-1.6) Movement disorders ⇩ (RR=0.4; CI: 0.2-0.6) Sedation ⇔ (RR=1.6; CI: 0.7-3)	
Table 4- Clozapine					
Clozapine[65] 1165 participants	typical antipsychotics 1266 participants		Improved ⇧ (RR=1.6; CI: 1.4-1.8) Relapse ⇩ (RR=0.6; CI: 0.5-0.8) Attrition ⇔ (RR=0.8; CI: 0.7-1.0) Movement disorders ⇩ (RR=0.7; CI: 0.6-0.8)		Improved ⇧ (RR=2.1; CI: 1.6-2.9) Relapse ⇩ (RR=0.2; CI: 0.1-0.3) Attrition ⇔ (RR=0.6; CI: 0.5-0.7)
Clozapine[65] 618 participants	Typical antipsychotics (treatment resistant illness sub-group) 600 participants		Sedation ⇧ (RR=1.3; CI: 1.1-1.4) Weight ⇧ (RR=1.3; CI: 1.0-1.5) Improved ⇧ (RR=0.7; CI: 0.6-0.8) Relapse ⇔ (RR=1.0; CI: 0.6-1.8) Attrition ⇔ (RR=1.2; CI: 0.7-2) Movement disorders		Improved ⇧ (RR=0.8; CI: 0.7-0.9) Relapse ⇩ (RR=0.2; CI: 0.1-0.3) Attrition ⇔ (RR=0.6; CI: 0.5-0.7)
Clozapine[66] 90 participants	Risperidone (treatment resistant illness sub-group) 90 participants		⇩ (RR=0.8; CI: 0.7-0.9) Sedation ⇧ (RR=1.2; CI: 1.1-1.3) Weight ⇧ (RR=1.3; CI: 1.0-1.6) Improved ⇔ (RR=1.0; CI: 0.7-1.3)		
Clozapine[66] 43 participants	Olanzapine (treatment resistant illness sub-group) 43 participants		Attrition ⇔ (RR=1.0; CI: 0.44-2.3) Movement disorders ⇔ (RR=1.0; CI: 0.2-5) Sedation ⇔ (RR=0.9; CI: 0.4-2.1) Weight ⇔ (RR=0.6; CI: 0.3-1.2)	Improved ⇔ (RR=0.9; CI: 0.7-1.1) Attrition ⇔ (RR=1.0; CI: 0.7-1.4) Movement disorders ⇔ (RR=0.8; CI: 0.3-2) Sedation ⇔ (RR=0.6; CI: 0.3-1.0)	

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 the former do tend to make more favourable claims for it, these are not statistically significantly greater than those of more disinterested researchers.[62] 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, does cause weight gain and between 0.5–2% of people suffer sudden decline in white blood cells (agranulocytosis),[63] 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,[64] which is supported by the trial evidence.[65] Good, but far from perfect, studies show that clozapine improves schizophrenic symptoms of those whose illnesses have been difficult to treat yet who volunteer for trials.

A recent large prevalence study suggests, however, that clozapine therapy 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.[90]

Small studies have not found a difference in clinical efficacy between clozapine and the atypicals olanzapine and risperidone for people with treatment resistant illness.[66] This is an important area for further research, where studies will need to be large enough to demonstrate equivalence.

D. Cost-effectiveness

It has been estimated that the use of atypical antipsychotics as a first line treatment 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.[67] 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 with responsibility for managing greatly increased demands on budgets that have not been responsive to changes in drug costs. It is likely that budgetary constraints have contributed to considerable regional variations in access to newer drugs.[68,69]

A number of 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.[70-80] 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 to conventional antipsychotics.[81,82] These were

Table 5. Adjunctive drug treatments for schizophrenia

Interventions		Outcomes	
Experimental + standard antipsychotics	Control + Standard antipsychotics	Short term	Medium term
Beta-blockers[84]	Placebo	Relapse ⇔ (RR=not estimable - 0/21 vs 0/21) Attrition ⇔ (RR=1.1; CI: 0.08-17) Collapse ⇔ (RR=not estimable - 0/21 vs 0/21)	Improvement ⇔ (RR=not estimable - 0/10 vs 0/10) Relapse ⇔ (RR=5; CI: 0.3-93) Attrition ⇔ (RR=2; CI: 0.5-8) Collapse ⇔ (RR=1.5; CI: 0.3-8)
Carbamazepine[85]	Placebo	Improvement ⇔ (RR=6; CI: 1-36) Attrition ⇔ (RR=0.5; CI: 0.2-1.4) Movement disorder ⇔ (RR=0.4; CI: 0.1-1.0)	
Polyunsaturated fatty acid (fish oil)[86]	Placebo		Attrition ⇔ (RR=1.0; CI: 0.02-47)

Key: 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

conducted in the USA and it is not clear to what extent the results are applicable to the UK setting.

E. The adjunctive drug therapies

Often the results of drug treatment are not entirely satisfactory for those with schizophrenia or their carers. Residual symptoms are troublesome and/or adverse effects prohibit good antipsychotic outcome.[83] This has resulted in additional drug-based techniques for enhancing the effect of standard care with antipsychotic drugs. Adjunctive drug treatments, when the additional drug is from a different class than the index antipsychotic, have been evaluated. Three systematic reviews have been completed recently on the value of beta-blockers, carbamazepine and polyunsaturated fatty acid supplementation of antipsychotic drugs (Table 5).[84-86] Systematic reviews of adjunctive benzodiazapines and lithium have also been completed recently.[87,88]

Several trials of adjunctive use of beta-blockers have been undertaken but these are all so small that only a very profound effect would have been detectable. The results neither support nor refute their use as a complementary drug treatment to standard antipsychotics. Large, well-conducted and reported trials are needed.[84]

Although more people have been randomised to carbamazepine supplements than other adjunctive therapies there is no clear evidence that this strategy is of value.[85] Some continuous rating scale data do favour carbamazepine, however, and an impending update of this review may clarify the situation.

Trials are underway to assess whether fish oil is of value in schizophrenia.[86]

F. ECT

ECT is very rarely used for treatment of schizophrenia in the UK. It is, however, one of the treatments that may be used by some practitioners for those whose illness is complicated by depressive or manic symptoms, where all other measures have failed and for women with puerperal psychosis – a severe and acute form of illness following childbirth.

Evidence from trials is very limited and does not address the value of ECT for the specific subgroups outlined above.[89] There is some evidence that ECT may afford a short-lived improvement in global state. The issue of adverse effects has not been clearly addressed.

G. Implications

- Those involved in the care of people with schizophrenia need to maintain up-to-date knowledge by regularly checking one or more sources of relevant evidence. Guides to practice should be appraised for bias and day-to-day applicability. Clinical use of high quality information must, where possible, be in collaboration with the particular client and their carers and tailored to the person's needs or situation.
- It is feasible that drug treatment of people with schizophrenia could be based on high quality information that is as unbiased, precise and applicable as possible.
- Chlorpromazine has clinically valuable antipsychotic properties that are still evident after a year of continuous use but causes movement disorders that can adversely affect a person's functioning and integration in everyday life.
- Drugs such as pimozide and sulpiride are not well researched by today's standards but, if used carefully, may avoid some of the common adverse effects of, for example, chlorpromazine and haloperidol.
- The use of clozapine for the treatment of people whose illness has not responded to standard antipsychotics is supported by existing data. However, recent reports that clozapine may be associated with potentially fatal myocarditis and cardiomyopathy is of concern.
- Novel antipsychotics, such as amisulpride, olanzapine, quetiapine, risperidone, ziprasidone and zotepine, may be a further refinement, but not a revolution, in the care of those with schizophrenia. They may cause less 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 every-day 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 hospitalisation, indirect costs and intangible savings is not based on unbiased widely applicable data, nor is it helpful to those directly responsible for management of limited drug budgets.
- If the NHS is to fully fund novel antipsychotics for everyday practice the burden of proof falls firmly to the pharmaceutical industry. The cost of the novel antipsychotics should be fully 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.

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Effective Health Care

This bulletin is based on systematic reviews from the Cochrane Schizophrenia Group:

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The bulletin was written and produced by Clive Adams of the Cochrane Schizophrenia Group, and staff at the NHS Centre for Reviews and Dissemination, University of York.

Acknowledgements:

Effective Health Care would like to acknowledge the helpful assistance of the following who commented on the text:

- Joe Asghar, Northumberland HA
- Mark Baker, North Yorkshire HA
- Linda Davies, University of York
- Alison Evans, University of Leeds
- John Geddes, University of Oxford
- Ian Hammond, Bedfordshire & Luton Community NHS Trust
- Anna Higgitt, Department of Health
- Paul Hodgkin, Centre for Innovation in Primary Care, Sheffield
- Robert Kerwin, Institute of Psychiatry, London
- Dee Kyle, Bradford HA
- Shon Lewis, University of Manchester
- David Owens, University of Leeds
- Colin Pollock, Wakefield HA
- Cliff Prior, National Schizophrenia Fellowship
- Anne Richardson, Department of Health
- Trevor Sheldon, University of York
- Stephen Singleton, Northumberland HA
- Allan Young, University of Newcastle upon Tyne

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The NHS Centre for Reviews and Dissemination is funded by the NHS Executive and the Health Departments of Scotland, Wales and Northern Ireland; a contribution to the Centre is also made by the University of York. The views expressed in this publication are those of the authors and not necessarily those of the NHS Executive or the Health Departments of Scotland, Wales or Northern Ireland.

Printed and bound in Great Britain by Latimer Trend & Company Ltd., Plymouth. Printed on acid-free paper. ISSN: 0965-0288

The contents of this bulletin are likely to be valid for around one year, by which time significant new research evidence may have become available.