Cost-effectiveness of atypical antipsychotics in chronic schizophrenia

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It is nearly a decade since the first atypical antipsychotic, clozapine, was launched in the UK. There are now several other similar drugs on the market. They are all more expensive than traditional antipsychotics and the question of whether they are a cost-effective use of scarce NHS resources is an important one. This article reviews the evidence in the area of treatment-resistant schizophrenia.

Mental disorders account for approximately 17% of the total NHS budget and schizophrenia is one of the costliest of these disorders, accounting for more than 5% of all NHS inpatient expenditure in England (NHS Executive, 1996). The pharmaceutical expenditure for schizophrenia was over £32 million in 1992/3, and this was mainly because of the price of antipsychotic drugs. This figure has risen steadily over recent years with the marketing and increased use of the so-called 'atypical' or 'novel' antipsychotic drugs.

These atypical antipsychotic drugs are more expensive than the traditional or conventional antipsychotics, and it is still unclear whether they are a cost-effective use of NHS resources. Such questions may be answered in time by the new National Institute of Clinical Excellence (NICE) — but such an appraisal has yet to be announced.

This article reviews the current evidence on the cost effectiveness of atypicals in those patients who do not respond to traditional drugs — so-called 'treatment-resistant' schizophrenia (TRS).

DEFINING TREATMENT-RESISTANT SCHIZOPHRENIA

The most widely used criteria in defining TRS, or 'refractory' schizophrenia, are those used by Kane et al (1988). These include that the patient has not responded to at least three periods of treatment with antipsychotic drugs from at least two different chemical classes in the preceding 5 years. They also specify symptomatic severity criteria. These have been slightly modified in more recent studies so that two drug failures are required instead of three. The evaluation of TRS has become increasingly important since the introduction of the atypicals and has been extensively reviewed by Conley and Buchanan (1997).

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DEFINING 'COST EFFECTIVENESS'

This term is often loosely used to describe any study that measures costs and outcomes. In its strictest sense it only applies to studies that compare the cost of two or more treatments in achieving the same outcome (sometimes known as cost-minimization analysis), or compares the cost per unit of outcome benefit obtained.

Since none of the reviewed studies met this strict definition, for the purposes of this review the term cost effectiveness will encompass all forms of economic evaluations, including cost-utility analysis (in which the outcome measure incorporates a measure of the 'quality of life'). A detailed explanation of the different types of economic evaluations can be found in Drummond et al (1997).

WHICH ARE THE ATYPICAL ANTIPSYCHOTICS?

The currently available atypicals are shown in *Table 1*. This review will focus on the 'older' atypicals, i.e. clozapine, risperidone and olanzapine. Sertindole was withdrawn by the manufacturers in December 1998 after reports of serious cardiac arrhythmias and sudden cardiac deaths. The other atypicals are too new to have had their cost effectiveness evaluated to any significant extent, and will not be considered further. *Table 2* gives the relative monthly costs for the atypicals in comparison to haloperidol, a 'traditional' antipsychotic.

WHY 'ATYPICAL'?

Until the reintroduction of clozapine, antipsychotic drug treatments were based on the selective blockade of D2 (dopaminergic) pathways in the brain. The atypicals are so called because they act on a more diverse range of receptors, including serotonin (5-HT) and other dopamine receptor sites. They have other properties that distinguish

them from traditional antipsychotics — they cause little or no extrapyramidal side-effects at normal doses and they do not cause prolactin elevation, which may lead to gynaecomastia.

REVIEW METHODOLOGY

Publications in all languages were searched electronically in several databases using the following keywords: cost*, econ*, psych*, schiz*, antipsychotic* and neuroleptic*. The databases searched were: The NHS Economic Evaluation Database and the Health Technology Assessment Database (both at the University of York, NHS Centre for Reviews and Dissemination), the Cochrane Database of Systematic Reviews (1998), MEDLINE (1990-), and BIDS EMBASE (1980-). Several databases under the CHEST collection were also searched: Mental Health Collection (1995-), which contains many of the major mental health journals and Best Evidence (1991-) which incorporates the 'ACP Journal Club' and 'evidence-based medicine' journals. Reference lists of included papers were also searched.

CLOZAPINE

Kane et al's original study (1988), which showed that clozapine was effective in TRS, has been replicated several times with similar findings. A Cochrane systematic review of the effectiveness of clozapine included 29 studies, and concluded that 31% of patients with TRS treated with clozapine showed a clinical improvement, adding:

> **'clozapine is convincingly more effective than "typical" antipsychotic drugs in reducing symptoms of schizophrenia' (Wahlbeck et al, 1998).**

However, the cost-effectiveness data are less clear. Most studies have not been full economic evaluations but 'mirror-image' or 'pre-post' studies, where costs and consequences for a sample of patients are collected for a period before and after commencing clozapine (e.g. Revicki et al, 1990). These studies have several methodological shortcomings, especially the lack of control groups, and have been reviewed by Zito (1998). They have generally found that clozapine usage led to an overall cost saving in the region of between $9000 and $50 000 per patient per year, by reducing the need for inpatient service. Although most studies were conducted in the USA, these findings have been replicated in a chronic schizophrenia sample in the UK (Aitchison and Kerwin, 1997), and in a TRS sample in France (Bret et al, 1998). Economic models of data have produced inconclusive findings, e.g. Davies and Drummond (1993) found clozapine to be cost saving or cost neutral, depending upon the assumptions made.

One of the reasons why clozapine is more expensive than traditional antipsychotics is the mandatory blood monitoring that is required. Approximately 0.9% of all patients develop agranulocytosis after 12 months of clozapine therapy, which may be fatal. Zhang et al (1996) examined the cost effectiveness of clozapine blood monitoring. This was a cost-utility analysis and results showed that the costs per quality-adjusted life year (QALY) were much higher during the 2nd and 3rd 6-month periods after clozapine had been started ($925 000 and $421 000 respectively), than during the first 6 months ($62 000). Zhang et al concluded that monitoring beyond this period may not be cost effective. However, this interesting study has yet to be replicated.

There have been few published randomized controlled trials (RCTs) of the cost effectiveness of clozapine. Essock et al (1996) have reported preliminary findings from a RCT of clozapine treatment *vs* standard care in a cohort of 227 patients followed up for 2 years. The clozapine group had decreased readmission rates within the first 6 months compared with the control group (3% *vs* 29%), suggesting that clozapine may be cost effective. However, this study did not measure costs directly, and on

TABLE 1.
The atypical antipsychotics

Antipsychotic (brand name)	Company	Year licensed in UK
Clozapine (Clozaril®)	Novartis	1990
Risperidone (Risperdal®)	Janssen	1994
Sertindole* (Serdolect®)	Lundbeck	1996
Olanzapine (Zyprexa®)	Lilly	1996
Quetiapine (Seroquel®)	Zeneca	1997
Amisulpiride (Solian®)	Lorex	1998
Zotepine (Zoleptil®)	Orion	1998

*Withdrawn December 1998 — see Committee for the Safety of Medicine/Medicine Contorl Agency (1999) for further details

TABLE 2.
Relative costs of the atypical antipsychotics compared with haloperidol*

Antipsychotic	Daily dose range (mg)	Usual daily dose (mg)	Hospital cost per 28 days (£) (usual dose)	Relative cost to haloperidol
Clozapine	300–900	350	175.19	38:1
Risperidone	4–16	6	109.20	24:1
Olanzapine	5–20	15	158.20	34:1
Quetiapine	300–750	500	158.34	34:1
Amisulpiride	400–1200	800	112.00	24:1
Zotepine	75–300	200	61.60	13:1
Haloperidol	*3–100*	*10*	*4.61*	–

*Costs based on prices quoted in Monthly Index of Medical Specialities (MIMS), March 1999

other outcome measures the groups were similar, e.g. the actual discharge rates at 1 year.

Probably the 'best' study of the cost effectiveness of clozapine published to date in terms of its methodology is that of Rosenheck et al (1997). This was an RCT of clozapine *vs* haloperidol in 423 patients with TRS. Results showed that after 12 months of treatment the clozapine group had significantly less symptoms. In terms of costs they had lower inpatient but higher outpatient costs. Total costs of the clozapine group ($58 000) were not significantly lower than the haloperidol group ($61 000). Overall clozapine was concluded to be cost neutral, although it showed improved clinical outcomes, suggesting that it may be cost effective.

RISPERIDONE

There have only been a few cost-effectiveness studies examining the role of risperidone in chronic schizophrenia, and none have focussed on TRS alone. An often cited study by Addington et al (1993) indicates the limitations of 'pre-post' studies. This was an open study of 27 patients (out of 74 commencing treatment) with chronic schizophrenia (not TRS) who had completed risperidone treatment for a year. Hospital bed days were calculated in the 2 years before, and during, risperidone treatment. Results showed a 20% reduction in the mean number of hospital bed days. However, this was only because of reductions in a subset of 14 patients; three patients had an increase, while others were either not admitted at all over the 2-year period or were continuously hospitalized. Also, no hospitalization data were reported on the majority of patients (47/74) who did not complete risperidone treatment for a year.

The importance of analysing dropouts is illustrated in a similar study by Guest et al (1996), who reported that costs per patient in the group that discontinued risperidone after 1 year (n=13) were slightly higher than the pre-risperidone year. This was in contrast to the reduction shown by patients continuing risperidone for 2 years. Although further modelling of this data suggested that risperidone was cost effective, examining the actual results showed that the costs were reduced from £22 362 (pre-risperidone year) to £21 174 (during risperidone year) — a negligible reduction.

Chouinard and Albright (1997) undertook a cost-utility analysis based on data from a previous RCT comparing risperidone and haloperidol in 135 patients with chronic schizophrenia. This interesting study used psychiatric nursing staff to make the utility ratings (i.e. ratings on the quality of life for groups of patients with varying severity of illness) upon which the QALYs were calculated. They reported a 0.075 higher utility rating for risperidone than haloperidol (0.124 *vs* 0.049). Combined with an incremental cost of treatment of $1600 they calculated the cost per QALY to be Can$23 000, suggesting that this would be cost effective. The whole concept of cost-utility analysis is not widely used in mental health and it is difficult to interpret these findings. Again there were several methodological problems with this study, which have been reviewed by Hargreaves and Shumway (1996), who concluded that: 'the current results do not demonstrate the cost effectiveness of risperidone treatment for schizophrenia'.

OLANZAPINE

Since olanzapine has only been available for a few years, there are not yet published studies of its cost-effectiveness. Almond and O'Donnell (1998) published a 'decision tree' model comparing olanzapine with haloperidol in schizophrenia (not TRS), and found that olanzapine was cost neutral. They added that if this was combined with data suggesting that olanzapine was more effective that haloperidol, then 'this drug may represent a cost-effective treatment'. However, the relapse rates for this model were taken from clinical trial data from Lilly, the manufacturers of olanzapine. A well-conducted RCT of olanzapine *vs* chlorpromazine in 84 patients with TRS by Conley et al (1998) concluded that although olanzapine-treated patients had fewer side-effects, overall the drugs showed similar efficacy.

CAUTIONS IN INTERPRETING THE LITERATURE

Cost-effectiveness studies have been shown to be of variable quality in schizophrenia (Amin et al, 1998). Most of the available cost-effectiveness evidence reviewed above is from retrospective pre-post studies or economic computer models, which have considerable methodological limitations. Most studies only measure costs and outcomes over relatively short periods of time (less than 2 years); thus evidence of longer-term cost effectiveness is especially lacking. Also most studies originate from the USA and thus are of limited generalizability to the NHS.

CONCLUSIONS

Clozapine has been demonstrated to have better efficacy than traditional antipsychotics and is the drug of choice in TRS. Its cost effectiveness, however, has not yet been fully demonstrated. Current evidence showing that it is at least cost neutral could be combined with good evidence on better outcomes in TRS, suggesting that it may be cost effective. Risperidone and olanzapine have not yet been shown to be of superior

efficacy in TRS, thus the question of their cost effectiveness is of less importance at present.

The NHS has commissioned the Centre for Reviews and Dissemination at the University of York to undertake a review of the cost effectiveness of atypicals in general. This report is due to be published in November 1999.

A large multicentre RCT of atypicals *vs* conventional antipsychotics in TRS is to commence shortly. This is called the CUtLASS trial (Cost Utility of the Latest Antipsychotics in Severe Schizophrenia), and was funded as a result of the call for research proposals in this area by the NHS Health Technology Assessment exercise in 1997. Further details are available on the website (www.soton.ac.uk/~hta/projdets/961906.htm). Although results from this study will not be available for approximately 3 years, these should provide some definitive data on the cost effectiveness of clozapine and other atypicals in TRS. **HM**

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KEY POINTS

- Atypical antipsychotics are approximately 10–40 times more expensive than traditional antipsychotics.
- Clozapine is the drug of choice in treatment-resistant schizophrenia.
- There is as yet no good evidence of superior efficacy of other atypical antipsychotics in treatment-resistant schizophrenia.
- The cost effectiveness of atypical antipsychotics has not yet been fully established.
- Most cost-effectiveness data is based on economic computer models or retrospective 'pre-post' ('mirror-image') studies, which have considerable methodological limitations.
- There is a lack of evidence from randomized control trials (RCTs) on cost-effectiveness, although a multicentre RCT of atypical *vs* traditional antipsychotics is to commence shortly.