THE USE OF OLANZAPINE AS A FIRST AND SECOND CHOICE TREATMENT IN SCHIZOPHRENIA

A West Midlands Development and Evaluation Committee Report

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About InterDEC

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West Midlands Development and Evaluation Committee Recommendation:

The recommendation for the use of Olanzapine in the management of people with schizophrenia as a first and second choice treatment:

Strongly supported

This does not mean that there is evidence of superiority to other atypical psychotic preparations.

Contents

1 Summary of the report

- The proposed service is that olanzapine should be made available as a first and second choice agent for the treatment of all people with schizophrenia.
- Olanzapine is an atypical neuroleptic which has a better reported efficacy and side effects profile than conventional neuroleptics such as haloperidol, and has potential for use as first and second choice therapy in the acute treatment of schizophrenia.
- Incidence of first episodes of schizophrenia has been estimated as 7.4 per 100,000 per annum. The one day prevalence of schizophrenia has been estimated as 2.6 per 1,000 population. Thus 390 new cases of schizophrenia per year might be expected in the West Midlands, with around 15,900 prevalent cases per year. Olanzapine is potentially a treatment option for all of these patients.
- The evidence on the efficacy of olanzapine comes from four published double blind randomised clinical trials of only six weeks duration and from three extension phases. Higher response rates and fewer side effects have been achieved with olanzapine compared with haloperidol, along with better control of negative symptoms over the six weeks of the trials.
- Possible quality of life benefits from olanzapine use compared to no treatment or haloperidol were modelled using two quality of life weightings applied to a hypothetical cohort of 1,000 people being treated for a year. The Index of Health Related Quality of Life suggests gains of 0.049 QALYs in the first year of treatment compared to no treatment and 0.027 compared to haloperidol. Using the disability weights for schizophrenia from the World Bank DALYs study suggests greater benefits could accrue: 0.068 and 0.038 QALYs compared to no treatment or haloperidol respectively.
- Drug costs were modelled as £836 per annum per patient where olanzapine is choice of treatment and as £78 where haloperidol is first choice of treatment, but these are overwhelmed by hospital costs.
- In a simple costs model, neuroleptic treatment of schizophrenia of any sort produced cost savings over no neuroleptic treatment. In all cases, savings associated with olanzapine were greater than those associated with haloperidol. Potential savings are from reduced inpatient and intensive community care and may be absorbed in the general psychiatric budget and not be realised.
- When it is assumed that patients who do not respond to their first two neuroleptics will all need continuing hospital or intensive out-patient treatment, then olanzapine as first choice therapy had a cost advantage of £7,800 per QALY over haloperidol. When the requirements for hospital or intensive community care were reduced, the cost advantage of olanzapine fell to £2,500. These findings apply to a prevalent cohort of patients for one year only, pending further evidence.
- These findings are based on some very significant assumptions: (i) That the short duration of the trials truly represents a longer time period; (ii) That the trial patients, particularly those enrolled in extension phases, are representative; (iii) Potential savings from reduced hospitalisation can be realised.
- Schizophrenia remains a significant health problem despite neuroleptic drugs. Many patients are refractory and others experience significant side effects. Social and health service costs are much greater than drug costs, therefore analyses such as the one presented are likely to favour widening the armoury of neuroleptics. Definitive proof of the primacy of a particular neuroleptic requires longer-term trials and follow-up.

2 Introduction

Although the development of neuroleptic drugs revolutionised the treatment of schizophrenia, there remain problems with their efficacy[1,2,3].

Side effects from conventional neuroleptics, in particular extrapyramidal side effects (involuntary movements, agitation and parkinsonianism), limit their use for some patients, lead to non-compliance from others and adversely affect the quality of life of many more. Patients taking conventional neuroleptics risk the slowly emergent and sometimes permanent side effect, tardive dyskinesia, which develops in 25% of drug treated patients[4]. Increased prolactin levels can also occur.

Although conventional neuroleptic drugs often control psychotic symptoms, they are less effective or ineffective in control of the deficit (negative) symptoms of schizophrenia[5].

Individual patient response to neuroleptic drugs varies, and a proportion of "treatment refractory" patients do not respond to conventional neuroleptics[1,2,3,6].
New "atypical" neuroleptic drugs in development or relatively recently licensed have been produced in attempts to address these problems, and it is likely that there would be substantial markets for any drug proven to perform on these fronts. Clozapine, an older drug, was discovered to be effective in some cases of refractory disease[7,8], but requires blood monitoring because of an increased risk of agranulocytosis[9,10]. More recently, risperidone and sertindole have been licensed[1,3,4,11].

Olanzapine (Zyprexa) is a new atypical neuroleptic and, given the side effect profile and limited efficacy of traditional neuroleptics, could potentially have many applications in the treatment of schizophrenia. It is described by the manufacturers as giving "excellent control of positive symptoms such as delusions, hallucinations and disordered thinking" and "excellent control of negative symptoms such as emotional withdrawal, flat affect, and inability to experience pleasure" (Eli Lilly promotional literature). The extrapyramidal side effects profile of olanzapine is said to be superior to those of conventional neuroleptics. The pharmacological basis for these claims lies in olanzapine's neuroreceptor profile as it has an affinity for $5\text{-}HT_2$, D_1, D_2 and muscarinic receptor sites[12,13]. The manufacturers are marketing olanzapine as a first choice treatment for schizophrenia.

The potential use of olanzapine if proven cost-effective as a first choice or second choice of acute therapy in the West Midlands region would include its use for in-patients and day cases (2550 hospital episodes in 1995[14]) and further use in the community.

3 Incidence/prevalence

In 1994 to 1995 there were 137 per 100,000 population admissions of patients with a diagnosis of schizophrenia to mental illness hospitals or units in England (130 in the West Midlands[14]. Incidence of first episodes of schizophrenia has been estimated as 7.4 per 100,000 per annum[15]. Increased incidence has been associated with residence in areas with high proportions of Census variables indicating social isolation or poverty [16]. The Salford Register gave a one day prevalence of schizophrenia as 2.6 per 1000 population and a one year prevalence of 3.0 per 1000[17]. The one day rate represents the contact rate, which is nearly as high as the one year prevalence, indicating the high

persistent morbidity attached to the diagnosis. It follows that around 390 new cases of schizophrenia per year and 15,900 prevalent cases per year might be expected in the West Midlands[14].

A WHO study has suggested that the incidence of schizophrenia is similar in a range of different countries[18]. Associations with schizophrenia include migration between countries, movement to urban socially isolated areas, never having married, downward social mobility, perinatal abnormalities and an increased incidence in family members. Such associations are not necessarily causal, but may reflect the downward social drift of many schizophrenic patients.

Some 10 to 15 percent of diagnosed cases commit suicide[19]. All cause mortality rates are also high for schizophrenic patients[20]. Prognosis in schizophrenia varies, with good, intermediate and poor outcomes. Estimates for the proportional distribution of outcomes varies: one estimate[21] suggests 50%, are "cured" or only slightly disabled, with 40 to 50% severely disabled, while a paper summarising 10 studies with 10 year follow-up in the US[3, 22] reported 40% of patients had committed suicide or had prolonged hospital stays. After 5 years, 60-70% have relatively severe disturbances of social adaptation. In a five year follow up study of a representative sample of schizophrenic patients, 22% of first admission patients had one episode only with no residual impairment, 35% had several episodes with no or residual impairments between episodes, 8% had impairment after the first episode with subsequent exacerbations and no return to normality between episodes and 35% were left with impairments that increased after succeeding episodes[15]. Although conventional neuroleptic drugs are effective in many cases, a minority of patients, perhaps 25%, do not respond to them[2,3].

4 Outline of typical current alternative service

First line treatment of acute schizophrenia is with a traditional neuroleptic[1,25]. Haloperidol up to 15mg/day is considered to be adequate as a trial dosage. Different classes of conventional neuroleptic drugs have varying chemical structures and neuroreceptor profiles, though all block D_2 (dopamine) receptors, and have different side effect profiles. Extra-pyramidal side-effects are distressing and disabling. High potency drugs, for example haloperidol (a butyrophenone) and fluphenazine (a piperazine phenothiazine), are more likely to cause extrapyramidal side effects. Low potency drugs, for example chlorpromazine (an aliphatic phenothiazine), have less selective effects, with reduced chance of extrapyramidal effects, but an increased chance of antimuscarinic effects, sedation and hypotension. Extrapyramidal side effects can be moderated by antimuscarinic (anticholinergic) drugs.

Dosage is an important consideration in both first choice of acute treatment and in subsequent drugs tried[1,2]. Dose should be titrated against clinical response and further increases in dose after initial titration are unlikely to be helpful[1 23]. A trial comparing "neuroleptic threshold" doses of haloperidol with higher doses[24] found that higher doses did not lead to a greater improvement in psychosis, but gave rise to significant increases in distressing side effects.

Nearly all acute episodes of schizophrenia will be treated with neuroleptics, and it is likely that early treatment influences prognosis[25]. Individual response to neuroleptics varies, and patient history and preference should be taken into account in making an

initial choice of drug. Figure 1 is a flow diagram of pharmacological treatment in the acute phase of schizophrenia adapted from recent US guidelines[1]. Although clinician drug preferences in the UK might be somewhat different, trials of more than one drug will often be needed before a satisfactory response is achieved. If no response is achieved with conventional neuroleptics, an "atypical" neuroleptic, risperidone, sertindole (although prolongation of the QT interval is found in 1.7% of patients which will limit the use of this drug) or clozapine (for treatment resistant patients with blood monitoring), may be tried[1,26].

Maintenance therapy with neuroleptics is usually needed after treatment of an acute episode[1,3], as most patients relapse without it. Family factors and treatment compliance are also involved in relapse[1]. Maintenance drugs can be delivered orally or through depot injection.

Figure 1: Pharmacological treatment of schizophrenia in the acute phase

If a patient has a specific contraindication to any medication, remove that medication from the possibilities for that patient.
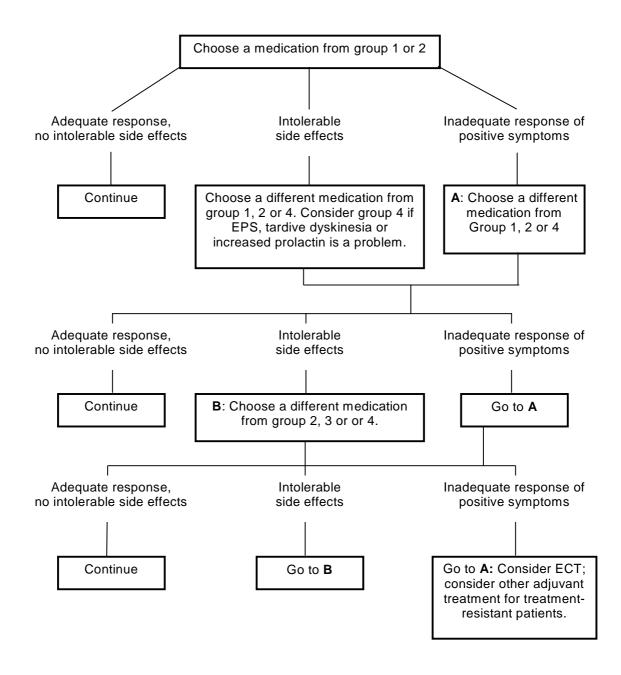
At each point in the algorithm, medications are chosen on the basis of past response, side effects, patient preference and planned route of administration.

GROUP 1: Conventional antipsychotic medications

GROUP 2: Risperidone

GROUP 3: Clozapine

GROUP 4: New antipsychotics: sertindole, olanzapine

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                    ┌─────────────────────────────────────┐
                    │   Choose a medication from group 1 or 2 │
                    └─────────────────────────────────────┘
           ┌──────────────────┬──────────────────────┐
  Adequate response,        Intolerable         Inadequate response of
  no intolerable side effects  side effects        positive symptoms
           │                   │                      │
     ┌──────────┐   ┌────────────────────────┐  ┌──────────────────┐
     │ Continue │   │ Choose a different      │  │ A: Choose a      │
     └──────────┘   │ medication from group   │  │ different        │
                    │ 1, 2 or 4. Consider     │  │ medication from  │
                    │ group 4 if EPS, tardive │  │ Group 1, 2 or 4  │
                    │ dyskinesia or increased │  └──────────────────┘
                    │ prolactin is a problem. │
                    └────────────────────────┘
           ┌──────────────────┬──────────────────────┐
  Adequate response,        Intolerable         Inadequate response of
  no intolerable side effects  side effects        positive symptoms
           │                   │                      │
     ┌──────────┐   ┌────────────────────────┐  ┌──────────────┐
     │ Continue │   │ B: Choose a different   │  │  Go to A     │
     └──────────┘   │ medication from group   │  └──────────────┘
                    │ 2, 3 or or 4.           │
                    └────────────────────────┘
           ┌──────────────────┬──────────────────────┐
  Adequate response,        Intolerable         Inadequate response of
  no intolerable side effects  side effects        positive symptoms
           │                   │                      │
     ┌──────────┐       ┌──────────┐      ┌──────────────────────┐
     │ Continue │       │ Go to B  │      │ Go to A: Consider ECT;│
     └──────────┘       └──────────┘      │ consider other adjuvant│
                                          │ treatment for treatment-│
                                          │ resistant patients.   │
                                          └──────────────────────┘
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Adapted from "Practice guidelines for the treatment of patients with schizophrenia"[1].

Other elements of the current service for the schizophrenic sufferer include many components of mental health services - community teams, day care, acute hospitalisation and long-term care in some instances. The average annual resource use for a patient with schizophrenia in the UK included 35.3 days of institutional or residential care, 1.4 hospital outpatient visits, 11.1 days of day-care, 11.3 community visits and 31.1 depot injection clinic visits[27]. Patients with the most severe disease would have continuous residential care.

Different levels of drug efficacy will have an important bearing on this resource consumption.

5 Questions addressed by this review

Questions concerning the use of olanzapine addressed here are:

- Should olanzapine be used as a first choice neuroleptic, instead of a standard ("typical") neuroleptic at optimal dose, in the treatment of acute episodes of schizophrenia?

- Should olanzapine be used in the treatment of acute episodes of schizophrenia as a second choice neuroleptic in cases with poor compliance, non-response or adverse reaction to initial treatment in place of a typical neuroleptic?

The use of olanzapine in treatment of acute episodes of schizophrenia would inevitably lead to the long-term maintenance of a proportion of patients on the drug. The evidence concerning the longer-term use of olanzapine therefore also must be considered.

6 Methods

Search strategy
"olanzapine" and "Zyprexa" as text, excluding animal studies

Searches
Medline, Science Citation Index, Embase, DARE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, ISI Conference Proceedings and Transcripts, Need.

Other sources
Hand search: Drugs and Therapeutic Bulletin (1996 and 1997), Br J Psych, Am J Psych, Schizophrenia Bulletin (1997), BNP (olanzapine not included in Sept. 1996 edition), MIMMs (March 1997, olanzapine included), Eli Lilly and Co., West Midlands Regional Drugs Information Service.

Inclusion criteria for the evidence
Although a search would be made for both intervention studies and observational studies, good quality randomised control trials of olanzapine versus placebo or standard neuroleptics would be given greatest weight.

Criteria for the evaluation of the evidence

Trials were to be evaluated in accordance with suggested guidelines[28] and were scored using the Jadad scale[29]. Too much weight should not be given to small effect sizes or to conclusions based on small numbers of cases or sub group analyses: these results generally need to be confirmed in further trials.

In addition, criteria were specified to take into account the particular problems associated with trials of psychiatric interventions. Trial comparisons as far as possible should be with "best practice" use of neuroleptics including use of low neuroleptic threshold doses, rather than with higher equivalent doses or doses with limited titration (common in control trials). Comparisons should give explicit information about dosages, if possible incorporating like-for-like comparisons. Short term side effects, including extra pyramidal movements disorders, can be evaluated, but long term side effects cannot be evaluated until a drug has been in use for a considerable time: late development of tardive dyskinesia with a latent period of up to twenty years indicates caution. Aspects of trial design that cause particular problems in trials of psychoactive drugs include the carryover of effects from other drugs, the adequacy of washout periods, the influence of other drugs allowed as required in the trial, differences in patient disposition and follow-up, lack of inter-observer reliability, particularly in multicentre trials.

7 Justification: direction, strength and quality of the evidence

There have been four randomised double-blind clinical trials of olanzapine for treatment of schizophrenia prior to license (summary in Table 1. Appendix 1, Table 1.1 gives fuller details)[30,31,32,33,34,35]. All the trials scored 4 on the Jadad score: they were good quality trials, but the methods of random allocation were not described[29].

All trials were of 6 weeks duration and covered the acute phase of treatment. Two were placebo controlled (HGAD,HGAP)[30,31] and one had an arm with a low 1 mg/day dose of olanzapine (E003)[34]. Three of these trials included haloperidol treatment arms, two of which had arms with a range of fixed doses with of olanzapine (HGAD and E003, titration $\pm$ 2.5mg/day)[31, 32] and a single fixed dose (10mg/day) of haloperidol (HGAD and E003, titration of $\pm$ 5mg/day). A further trial, the largest, HGAJ allowed a range of dosages of olanzapine and haloperidol, titrated according to patient response[33]. A further small case series of olanzapine in the treatment of drug-induced psychosis in Parkinson's disease has been reported[36].

The trials were analysed on an intention-to-treat basis. The primary statistical analysis of the trial data was a last-observation-carried-forward mean change in clinical rating scales (the rating scales used in the trials are described in Appendix 1, Table 1.2). There were large standard deviations attached to the mean indicating that there tended to be good responses and poor responses, rather than middle range responses. The secondary analysis of response rates gives a clearer picture of individual patient outcomes. The evidence on the effectiveness of olanzapine is summarised here (Table 2). Further details are given in Appendix 2.

Table 1: Multicentre, double-blind, randomised control trials of olanzapine (6 week acute phase)

Trial	Comparison	N	Completed acute phase	Response rates*:	Comments
HGAP[30]	Olanzapine fixed dose/ olanzapine low fixed dose/ placebo	152	Placebo 20% Ola 1mg/day 23% Ola 10mg/day 38%	Placebo 10% Ola 1mg/day 12% Ola 10mg/day 28%	Olanzapine significantly better than placebo.
HGAD[31]	Olanzapine fixed dose ranges /haloperidol fixed dose range/ placebo	335	Placebo 32% Ola 5mg/day 42% Ola 10mg/day 41% Ola 15mg/day 49% Hal 15mg/day 44%	Placebo 59% Ola 5mg/day 58% Ola 10mg/day 64% Ola 15mg/day 67% Hal 15mg/day 62%	Olanzapine 10mg/day, 15mg/day and haloperidol 15mg.day significantly better than placebo. No significant difference between haloperidol and placebo. Also extension phase
HGAJ[33]	Olanzapine/ haloperidol – titrated doses	1996	Ola 66% Hal 47%	Ola 52% Hal 34%	Olanzapine significantly better than haloperidol. Titrated doses over wide range Also extension phase
E003[34]	Olanzapine fixed dose ranges /olanzapine low fixed dose/ haloperidol fixed dose range	431	Ola 10mg/day & Ola 15mg/day > Ola 1mg/day &Hal 15mg/day but not statistically significant	Ola 1mg/day 42% Ola 5 mg/day 47% Ola 10mg/day 52% Ola 15mg/day 58% Hal 15mg/day 48%	No significant differences from placebo equivalent on overall clinical rating (BPRS). Poorer quality, no peer reviewed publication: *Probably inadequate washout, greater benzodiazepine prescribing* Also extension phase

* HGAP: completed> 3 weeks, HGAD: completed approx. 4 weeks, E003: completed acute phase, HGAJ: completed >= 3 weeks
For further details see Appendix 1, Table 1

It is likely that the protocol or implementation of the E003 trial[32] was seriously flawed. No significant difference in efficacy was found between haloperidol 15mg/day (a known effective treatment) and olanzapine 1mg/day (a regime considered to have no anti-psychotic effect). This may have been a result of E003 patients having had more depot antipsychotics shortly before commencement of the trial (inadequate washout) and a higher use of benzodiazapines (concomitant administration of other medications influencing the trial outcomes) than HGAD patients. This trial therefore provides little useful evidence.

7.1 Efficacy as an antipsychotic

Three trials indicate that olanzapine is an effective antipsychotic in patients with schizophrenia and schizophreniform disorders[30,31,31]. The primary analysis of the trials was mean changes in clinical rating scales on intention-to-treat basis, but the analysis of response rates, a clinically relevant outcome, was not presented on an intention to treat basis.

In the largest trial, HGAJ[33], olanzapine (titrated doses) produced greater change in overall psychiatric symptoms (BPRS scale) than haloperidol (titrated doses). This trial probably comes closest to a comparison of olanzapine with "best practice" dose of a conventional neuroleptic and recruited patients with a wider spectrum of disease. Olanzapine patients were also more likely to complete the course of treatment. In the HGAD trial, olanzapine did not yield significantly different changes in overall symptoms to haloperidol[31]. This trial, however, was relatively small, and HGAJ[33] had more power to detect a difference in efficacy between olanzapine and haloperidol. Haloperidol has a narrow therapeutic window and 15mg/day will not be the optimum dose of this neuroleptic for all patients.

Metanalyses of response recalculated on an intention to treat basis (Figure 2, 3 and 4) indicate that:

- olanzapine (10mg/day,± 2.5mg) is more effective than placebo;

- olanzapine at fixed doses of at least 5mg/day±2.5mg or in a dose titrated to response starting at 5mg/day is more effective than haloperidol at 15mg/day or in a titrated dose starting at 5mg day;

- olanzapine at fixed doses of at least 10mg/day+2.5mg or in a dose titrated to response starting at 5mg/day is more effective than haloperidol at 15mg/day or in a titrated dose starting at 5mg day.

Notes: Use separate sheet

7.2 Adverse events

Extrapyramidal symptoms (EPS)
Olanzapine has a better EPS side effects profile than haloperidol, with improved discontinuation rates because of such events (5% of all olanzapine treated patients compared with 8% of haloperidol treated patients)[32,37]. In the HGAP trial[31], change in EPS in olanzapine treated patients was not significantly different from placebo. In the HGAJ[33] trial, 19.2% of olanzapine treated patients experienced any extrapyramidal adverse event, compared with 45.2% in the haloperidol group.

Treatment emergent tardive dyskinesia
A study of the comparative incidence of long term treatment emergent tardive dyskinesia pooled data from three trials[31,33,34] on 904 patients who had no tardive dyskinesia at baseline[38]. Of the olanzapine treated patients, 2.3% compared with 7.6% of the haloperidol treated patients, manifested treatment-emergent tardive dyskinesia at their last visit, a statistically significant difference,. Although these results favour olanzapine, adverse event reporting will be confounded by past history of neuroleptic use and further long-term randomised controlled trials are required, if the risks of tardive dyskinesia associated with olanzapine are to be clarified.

The manufacturers comment that "in the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia"[32].

Other adverse events
Weight gain and sedation were relatively common side effects of olanzapine. Prolactin concentrations were lower in olanzapine than in haloperidol treated patients [30,31,30,31,32,37].

7.3 Negative symptoms

For further details see Appendix 1.
Schizophrenia is characterised by psychosis defined by hallucinations and delusions, by formal thought disorder and by a deficit defined by negative symptoms including restricted emotional experience and expression, low social drive, limited spontaneous speech and anhedonia[5]. Prominent negative symptoms have been associated with a poor prognosis[39]. In the two higher quality trials out of the three where olanzapine was compared to haloperidol, olanzapine has been shown to be superior to haloperidol in respect to mean change in rating scales for negative symptoms in short term treatment[31,33].

Improvements in negative symptoms may result from reduction in psychosis, reduction in side effects and reduction in depression, as well from an improvement in primary negative trait symptoms[5]. A path analysis of the HGAD trial data[40] (further details are given in Appendix 1) showed the direct therapeutic effect of high-dose olanzapine on negative symptoms relative to placebo accounted for 55% of the olanzapine advantage, suggesting that olanzapine does have some effect on the deficit component of schizophrenia.

7.4 Depressive symptoms

Depression is in common in schizophrenic patients. The HGAJ[33] trial found that greater reduction in depression scores with olanzapine than with haloperidol. This finding, however, needs to be confirmed in further trials.

7.5 First episodes of schizophrenic illness

An analysis of 59 first episode patients from the HGAJ trial has been presented at a conference but not yet published[41]. Significantly more olanzapine patients completed the acute phase of the study (olanzapine, 72.9%, haloperidol, 37.5%). A response rate of 67% was obtained with olanzapine compared with 29% for haloperidol (p<.003). While these results suggest that olanzapine is superior to haloperidol in first line use in first episode psychosis, the results are preliminary and the sample size is small.

7.6 Longer term efficacy

Data from the three trials including double-blind extension phases giving one year's clinical experience with olanzapine, HGAD, E003 and HGAJ were pooled[32,35]. Maintenance of response (no requirement for hospitalisation) was significantly better with olanzapine than placebo (71% compared with 30%), and olanzapine was better than haloperidol (80% compared with 72%). Full analyses of these data have not yet been published[32,35,42,43], and the evidence must be regarded as relatively weak until more information is available. No information is available on the use of olanzapine for periods greater than one year. Patient compliance, the absence of life events and expressed emotion within families are also important in the prevention of relapse.

7.7 Olanzapine and risperidone

A double blind randomised trial compared olanzapine to risperidone and found them equally safe and effective[44]. Three hundred and thirty-nine patients diagnosed with schizophrenia, schizophreniform disorder and schizoaffective disorder (DSM-IV) with a minimum BPRS score of 24 were randomised. Drugs were administered within the range 2-20mg/day (olanzapine) and 4-12mg/day (risperidone) with titration. Olanzapine had greater efficacy in negative symptoms (SANS) and in overall response (>=40% decrease in PANSS). Significantly more olanzapine patients than risperidone patients maintained response at 28 weeks. Extrapyramidal side effects were reported less frequently with olanzapine. Results suggest that olanzapine may have advantages over risperidone, primarily in its side effects profile. There are no published comparisons with sertindole.

Table 2: Summary of the evidence on the effectiveness of olanzapine

Antipsychotic efficacy	More effective than placebo[30,31] Olanzapine 5mg/day, 10gm/day, 15mg/day not significantly different from haloperidol 15mg/day (total N=335)[31] Olanzapine 5-20mg/day titrated to response more effective than haloperidol 15mg/day titrated to response (total N=1996)[33]
Extrapyramidal side effects	In all three good quality trials, olanzapine had a more favourable EPS side effect profile. In the HGAJ[33] trial 19.2% of olanzapine patients and 45% of haloperidol patients experienced any EPS (titrated doses).
Negative symptoms	In two good quality trials[31,31], olanzapine was superior to haloperidol in the control of negative symptoms.
Depressive symptoms	In the one trial that measured control of depressive symptoms, olanzapine was unexpectedly superior to haloperiodol[33] .
First episode of schizophrenia	In a subgroup analysis of the largest trial[33], olanzapine achieved higher response rates than haloperidol.
Longer term efficacy	With a maximum experience of one year, more olanzapine patients maintained their response than did placebo or haloperidol treated patients (preliminary analysis)[32,35] .
Compared with risperidone	Olanzapine was found to be as safe and effective as risperidone with less extrapyramidal side effects[44] .

8 Summary: quality and direction of the evidence

Olanzapine is an effective antipsychotic in the treatment of acute episodes of schizophrenia. The largest trial which used titrated doses suggests that better compliance and response is achieved with olanzapine than with haloperidol. Olanzapine has a reduced rate of extra pyramidal side effects compared with haloperidol, although adverse effects in the long term cannot yet be evaluated. Haloperidol, however, is more likely to cause unpleasant side effects than drugs such as trifluoperazine and thioridazine which are favoured for this reason in many settings. It is possible than olanzapine has a greater impact on the negative symptoms of schizophrenia than haloperidol, but further studies are needed. Longer term efficacy has only been evaluated in the extension phases of the four phase three trials, and suggests that olanzapine maintenance has lower relapse rates than haloperidol, but further trials are needed to confirm this.

9 Benefits and disbenefits

The benefits and disbenefits associated with olanzapine treatment were modelled. The aim was to produce a cost-utility model that allowed potential improvements in quality of life from interventions in schizophrenia to be compared with other interventions impacting on other diseases. The model is thus of low resolution and quality of life is estimated in relation to the full spectrum of health, and is not taken from measurements of quality of life designed and tested in schizophrenia patients. The quality of life estimates were intended only to discriminate between interventions that have low, moderate and high costs per life year[a], and the model should not be extrapolated beyond these limits. The IHQL is used, not because it is particularly appropriate for schizophrenia, but because it was designed as a generic index of quality of life.

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[a]   Low circa less than £3,000 per year, moderate £3,000-£20,000 per life year and high more than £20,000 per life year. Additionally an intervention might have negative life years.

Further details of the model including decision trees, transition probabilities and their sources and quality of life weightings are given in Appendix 3. A summary is given below. Probabilities for olanzapine and haloperidol are taken from the HGAJ trial[33] which was the only one to allow titrated doses over a wide dose range, and which was closest to probable clinical practice.

9.1 Interventions

The benefits and disbenefits of olanzapine in an acute episode of schizophrenia as a first choice neuroleptic and second choice neuroleptic treatment over the course of one year are considered. Some responders to olanzapine might be maintained on the drug, while others will switch to depot neuroleptics. The hypothetical case of no treatment and two treatment packages with olanzapine and haloperidol respectively as first choice therapies have been modelled and are listed in Table 3.

Table 3: Treatment packages[b]

No neuroleptic treatment
Olanzapine as first choice drug in acute treatment with oral maintenance for respond as second choice neuroleptic with oral maintenance for responders. Non-responders continue on neuroleptics that are cost neutral with haloperidol.
Haloperidol as first choice drug in acute treatment with oral maintenance for respon fluphenazine as second choice neuroleptic with oral maintenance for responders. No assumed to continue on neuroleptics that are cost neutral with haloperidol.

9.2 Outcomes

For each treatment package, some patients will respond to the first choice of drug, some will respond and then relapse, some will respond to a second drug, some respond to a second drug and then relapse, while some do not respond to treatment. Because the treatment packages vary in their efficacy, different proportions of patients will experience these outcomes. These proportions are used to obtain the Index of Health-related Quality of Life[45] (see Appendix 2 for a detailed description) associated with each treatment package. As the IHQL is weighted towards physical disability, disability weightings used in the "Global Burden of Disease" study[46] are used in a sensitivity analysis[c].

Table 4 shows these quality of life weightings applied to the proportions falling into the different outcome groups in a model of a cohort of 1,000 patients receiving the treatment packages of Table 3.

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[b] Also considered: 1. Olanzapine as first choice treatment with haloperidol depot maintenance for responders, 2. Haloperidol as first choice treatment with depot maintenance for responders, 3. Haloperidol as first choice treatment with depot maintenance for responders as first choice treatment, olanzapine as second choice neuroleptic with oral maintenance for responders, 4. Haloperidol as first choice treatment with depot maintenance for responders as first choice treatment, olanzapine as second choice neuroleptic with depot maintenance for responders. The IHQL over one year for options with depot maintenance were very close to those for oral maintenance (option 1: .049, option 2: .022). The IHQL for olanzapine as a second choice therapy was .045 (oral maintenance) and .044 for depot maintenance.

[c] Age specific weights for age 15-44 for treated and untreated schizophrenia.

Table 4: Model of outcomes and quality of life for no active treatment and olanzapine and haloperidol treatment packages

	Outcome in 1000 patients	IHQL over 1 year per patient
No active treatment		
Responds	96	0.937
Responds then relapses	52	0.865
No response	852	0.762
IHQL (DW) per patient with no active treatment		*0.784 (0.382)*
Olanzapine as first choice and maintenance		
Responds	279	0.937
Responds then relapses	70	0.865
No response	547	0.762
Responds on second choice neuroleptic	77	0.922
Responds on 2nd choice neuroleptic then relapses	27	0.850
IHQL (DW) per patient for treatment package		*0.833 (0.450)*
Haloperiodol as first choice drug and maintenance		
Responds	115	0.937
Responds then relapses	45	0.865
No response	706	0.762
Responds on second choice neuroleptic	97	0.922
Responds on 2nd choice neuroleptic then relapses	38	0.850
IHQL (DW) per patient for treatment package		*0.806 (0.412)*

Finally, Table 5 summarises the quality of life gains of neuroleptic drug treatment over no drug treatment. These gains were relatively small, but were greatest for treatment packages that included olanzapine where the Disability Weighting from the "Global Burden of Disease" was used. The gain in quality of life is the average obtained when outcomes for 1,000 patients are modelled, and reflects the range of possible outcomes of drug treatment.

Table 5: IHQL gained over no active treatment

	IHQL	IHQL over no active treatment	DW	DW over no active treatment
No active treatment	0.784	-	0.382	-
Olanzapine as first choice and maintenance	0.833	0.049	0.450	0.068
Haloperiodol as first choice and maintenance	0.806	0.022	0.412	0.03

9.3 Quality of life and schizophrenia

While a cost-utility model allows the benefits of olanzapine to be compared with other interventions for other conditions, the domains covered in the quality of life indices used in published studies of QALYs in schizophrenia may not clearly reflect improvements in mental health outcomes[47]. "Bottom up" approaches to quality of life in mental health suggest that psychological well-being, personal autonomy and social participation are important[47,48] and that distress and social disability rather than physical disability are the most important dimensions in mental illness. A further study[49] showed that the distress dimension of the Charing Cross Health Indicator (CH-X) was associated with the distress and burden of the illness on patient and family members while the disability dimension was associated with social functioning, but "distress and burden" accounted for over half of the variance. Thus QOL indices which

weight physical disability strongly are thus likely to be insensitive to mental health programme specific changes[48]. The three dimensional IHQL[45] has this problem to some degree.

The estimation of QALYs is thus sensitive to the index that is used, and while the IHQL with three dimensions probably better reflects the disutility that society places on mental illness, no information is available on how such an index correlates with the available outcome measures for olanzapine. Although the HGAJ olanzapine trial included Quality of Life Scale measurements, and greater mean improvements in Quality of Life scores have been reported[49,50,51], full results are not available. The above discussion stands as a caveat to the simple analysis presented above.

10 Costs and savings to the NHS

The costs of psychiatric services and of medications were estimated for a subset of patients enrolled in the HGAJ trial acute and extension phases, but these data are not yet available[52].

As prospectively collected cost data were not available, a simple costs model was produced, modelling the costs of the use of olanzapine in an acute episode of schizophrenia as a first and second choice drug in the treatment packages given in Table 3. Decision trees, transition probability and outcomes are described in Appendix 3 and resource use and costs in Appendix 4.

10.1 Drug costs

The cost of olanzapine was compared with the cost of haloperidol and of fluphenazine as representative of other typical neuroleptics. The median modal dose of olanzapine in the HGAJ[33] trial was 15mg/day compared to a median modal dose of haloperidol of 10mg/day. These doses and the dose equivalent for fluphenazine were used in the costs model. This trial was used as it was thought to be closest to best practice use of haloperidol and olanzapine outside trial settings. Drug costs were taken from the BNF for March 1997 (Appendix 4, Table 4.1).

Patients not completing or responding to their initial therapy were assumed to switch to a conventional neuroleptic (haloperidol or fluphenazine) with the same probability of response as haloperidol in the HGAJ trial. Non-responders were switched to second choice therapy with a further conventional neuroleptic cost neutral with haloperidol. Further options for treatment resistant patients were not considered, nor was the use of risperidone or clozapine.

Drug use in the acute phase was determined from the mean modal doses (olanzapine 15mg/day and haloperidol 10mg/day) and the outcomes of the HGAJ trial. The therapeutic equivalent dose to haloperidol 10mg/day for fluphenazine was 10mg/day. Response (defined as a >=40 improvement in BPRS score over baseline) rates, except for the no treatment arm of the model, have been calculated from the HGAJ trial by incorporating the probability of completing the acute phase of the trial (that is, on an intention to treat basis). It was assumed that lesser improvements would not change resource use, although they would have some effect on disease severity. Fluphenazine was assumed to perform similarly to haloperidol. No responses were allowed for after 6

weeks of treatment or with third choice therapies, although some lesser improvement might be expected.

Use of antimuscarinic medication was taken from the HGAJ trial and the use associated with fluphenazine was assumed to be the same as for haloperidol (mean dose olanzapine 0.33mg/day, haloperidol 1.29mg/day). It is assumed that there were no differences in the use of other drugs such as benzodiazapines and no costs for these drugs were included.

10.2 Other health service costs

The costs of schizophrenia vary dramatically according to disease severity[53]. The model attempts to allow for this by deriving the use of resources other than drugs from Davies and Drummond[27] who provide lifetime costs according to case mix. Costs other than drug costs were long run opportunity costs taken from Netton and Dennett[54] (Appendix 4, Table 4.1). Resource use excluding drugs over a one year period has been estimated for each of Davies and Drummond's groups of patients (Appendix 4, Table 4.2). Estimates for groups 3, 4a and 4b were made by assuming they share resource use of group 2 for the prevalent episode and that resource is used over 6 months. Mean annual resource use was then calculated from remaining duration of illness, two years for group 3 and 36.5 years for group 4a and 4b. It was assumed that non-responders will need Group 4b resource package + drugs. As Group 4b require continual hospital care, patients who do not respond to any drugs would have longer periods of hospitalisation. Patients who respond and who do not relapse were assumed to fall into Group 1 for resource use. Following Davies and Drummond, it was calculated that, of responders who subsequently relapse, 42% would fall in group 2, 14% into group 3 and 44% into group 4a. The use of Netton and Dennett's costs with Davies and Drummond's resource use yielded considerably higher costs than Davies and Drummond's estimates which were based on 1990/91 costs. The results of the cost model are summarised in Table 6, and fuller details are given in Appendix 4, Table 4.3.

10.3 Sensitivity analyses

The costs assumed that all patients with no response require hospital or intensive community care. As this may be an over-estimate of the proportions of patients requiring the most expensive forms of care, and of potential savings from greater drug efficacy, a sensitivity analysis was carried out. In the sensitivity analysis, it was assumed that only one third of patients with no response would require hospital or intensive community care.

Clinical trials often are over-estimates of the results that can be achieved outside trial settings. In further sensitivity analyses, the model was modified firstly to include a reduced maintenance of response rate of 77% for olanzapine and secondly to include an olanzapine maintenance of response rate of 77% and a reduced olanzapine response rate of 43%.

Table 6: Annual direct cost per patient of a range of treatment options with sensitivity analyses[d]

		1 — All patients with no response require hospital or intensive community care		2 — One third of patients with no response require hospital or intensive community care		3 — As 1 except olan. relapse rate = 77%		4 — As 3 except olan. response rate = 43%		5[***] — Potential savings are not realised
		Annual cost	*Saving over (a)*	*Annual cost*	*Saving over (a)*	*Annual cost*	*Saving over (a)*	*Annual cost*	*Saving over (a)*	*Costs over (a)*
No neuroleptic treatment	*Total cost*	£37,194	-	£16,747	-	£37,194	-	£37,194	-	
Olanzapine as first choice treatment, haloperidol/depot second choice	*Total cost* *Drug costs* *Other direct costs*	£26,200 *£836* *£25,364*	£10,993	£13,023 *£836* *£12,187*	£3,723	£26,191 *£827* *£25,364*	£11,003	£28,085 *£729* *£27,356*	£9,109	£836
Haloperidol/oral as first choice treatment, fluphenazine/oral 2nd choice	*Total cost* *Drug costs* *Other direct costs*	£31,627 *£78* *£31,550*	£5,566	£14,654 *£78* *£14,576*	£2.093	£31,627 *£78* *£31,550*	£5,567	£31,627 *£78* *£31,550*	£5,566	£78

***   *Note*: Savings dependent upon changes in intensive resource use may not be realised. If no savings are realised, the most extreme scenario, then drug costs alone represent the difference in direct costs and haloperidol is cheaper.

10.4 Results of cost model

Neuroleptic treatment of schizophrenia produced theoretical cost savings over no neuroleptic treatment. In all sensitivity analyses, savings associated with olanzapine were greater than those associated with haloperidol. Savings may not be realised, and, in the hypothetical extreme case where no potential savings at all are realised, haloperidol would have lower costs than olanzapine.

10.5 Literature on schizophrenia costs

There are several good quality reports on schizophrenia costs. Calculation of cost effectiveness of interventions in schizophrenia is complex, as costs are sensitive to outcomes which enable patients to move out of intensive residential settings, and achievement of these outcomes is dependent on case mix and the impact of new interventions on patients with the highest dependency. The total costs of treating schizophrenia are high, but drug therapy costs are relatively low[27]. Davies and Drummond provide estimates of both direct and indirect costs (for patients only) by outcome group at 1990/91 prices. 97% of the total direct lifetime treatment costs were incurred by those who had episodes with a duration of more than two and one half years who had the largest number of days of expensive institutional/ residential care days. The authors conclude "treatments which improve the symptoms of schizophrenia

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d   Also considered: 1. Olanzapine as first choice treatment with haloperidol depot maintenance for responders, 2. Haloperidol as first choice treatment with depot maintenance for responders, 3. Haloperidol as first choice treatment with depot maintenance for responders as first choice treatment, olanzapine as second choice neuroleptic with oral maintenance for responders, 4. Haloperidol as first choice treatment with depot maintenance for responders as first choice treatment, olanzapine as second choice neuroleptic with depot maintenance for responders. The cost per patient over one year for haloperidol with depot maintenance was £26,200, and for olanzapine with haloperidol depot maintenance was £31,618. The cost for olanzapine as a second choice therapy was £26,007 (oral maintenance) and £25,683 for depot maintenance.

will reduce direct and indirect costs of the disease if they reduce disability and thus the need for support from health care and personal social services". Lifetime direct costs were most sensitive to changes in the proportions of patients falling into the most severe outcome groups. Thus effective treatment of the most severely ill with the longest duration of illness will provide the most cost-effective interventions where direct treatment costs are considered.

An analysis of the use of clozapine in treatment-resistant schizophrenia by the same authors[55] concluded that clozapine was cost effective in the treatment of moderate or severe schizophrenia for patients in long-stay institutions or staffed group homes. The total direct service costs of using clozapine were £91 per annum less than the costs of using standard neuroleptics and clozapine would be cost saving or cost neutral under many different assumptions. More expensive but more effective drug therapy for the treatment of moderate or severe schizophrenia may be cost neutral or better. If, however, as preliminary evidence suggests[41], olanzapine is particularly effective in first episode psychosis, then clinical use of olanzapine may be directed in part to less severe cases where the potential savings are smaller.

A cost-effectiveness study of olanzapine commissioned by the manufacturers compared olanzapine with haloperidol over a five year period modelled in three month cycles[56]. The analysis used a decision tree developed for the US setting. Depot was not included in the care model. The treatment of schizophrenic patients who experienced multiple episodes was modelled. First episode patients and patients with treatment resistant disease were excluded. Five types of patients were included, those who continued on their original drug, those who relapsed, those who switched drugs, those who dropped out of treatment and those who committed suicide. Suicide rates were taken from a US study, drop-out rates from HGAJ[33], relapse rates from the first 12 months clinical trial data[32] with hospitalisation as an operational definition of relapse. Three groups of maintenance patients were used, those with negative symptoms, positive symptoms and no symptoms. Resource use was taken from the authors' reading of the literature. Resource utilisation on maintenance treatment was assumed to be greatest for patients with negative symptoms, halved for patients with positive symptoms and halved again for patients with no symptoms, although no information was available on service use by these groups. No costs were incorporated for the monitoring of treatment or for treatment of EPS.

The study yielded base model direct costs over five years for olanzapine of £33,459 and for haloperidol of £34,074. This contrasts with the lifetime direct costs calculated by Davies and Drummond[27] which ranged from £1715 for patients with a single episode to £231,776 for patients requiring long term care in hospital or community programs. For patients requiring community based care who had had episodes for more than 2.5 years, lifetime costs were estimated to be £22, 579. This difference was attributed to the allocation of all patients to intensive treatment at the start of the model, effectively modelling an initially intensively treated cohort. The HGAJ trial[33] however, mostly included patients who were moderately rather than severely ill (mean BPRS total score 33), CGI severity score 4.7), so the cost estimates do appear to be high.

Olanzapine raised treatment costs relative to haloperidol because of its higher price and reduced drop-out rate, but lowered them through reduced relapse rates, alleviation of symptoms (leading to reduced use of health care resources) and a reduced risk of switching to more expensive treatments.

Problems with this cost-effectiveness analysis include:

The *timescale*: there is no evidence on the effectiveness of olanzapine over a five year period, and little evidence on the use of olanzapine for maintenance therapy.

Maintenance regimes do not include depot medication, an unrealistic model of the UK situation where 50 to 67% of patients might be on depot medication[57].

Considerable *weighting* is given to the relatively poor prognosis of the persistence *of negative symptoms* after an acute episode. This is likely to favour olanzapine. McGlashan and Fenton[39] conclude "Negative symptoms … do not become consistently prognostic until well after the acute and/or initial phases. Negative symptoms are then consistent predictors of poor medium-term and longer-term outcome, more so than positive symptoms". Olanzapine's apparently favourable effect on negative symptoms, may not translate into improved longer term prognosis and reduced resource use.

10.6 Note on costs

The costs of olanzapine in the uses considered in this report would be born by secondary care sector. The economic analyses presented take into account direct costs, no matter who are the providers, as the movement of costs born by primary and secondary providers of care are between sectors which do not have an impact on the costs of schizophrenia to the public sector as a whole. The interests of particular budget holders are not taken into account.

10.7 Summary

Neuroleptic treatment of schizophrenia produced theoretical cost savings over no neuroleptic treatment. In all cases, savings associated with olanzapine were greater than those associated with haloperidol. As much of the cost burden of schizophrenia is for expensive inpatient and intensive community care, any treatment which reduces the need for this care will result in cost savings, dependent upon the initial severity of disease in responders to treatment. It may not be possible, however, to realise potential savings from the reduction of inpatient and intensive day care stays[55].

Although the model suggests that the use of olanzapine is cost saving or cost neutral compared with other neuroleptics, too much weight should not be given to this relatively simple model. The evidence on which this model is based is strongest on short term effects, weaker on effects over one year, and absent for effects over longer periods. The model may have been over-optimistic in assuming that a good clinical response results in a reduction in the care required. The olanzapine trials offer no data on this question, except that the definition of relapse used in the analysis of the extension phases was the operational one of requirement for hospitalisation. Potential savings may not be realised in practice, and in those circumstances, olanzapine might not have the cost advantage. There may be, however, be direct savings in health authorities where inpatient care is purchased from the private sector.

If potential savings are not realised, the opportunity costs of drug interventions in acquire greater importance. Other interventions that reduce hospital stays and the need for intensive care may be squeezed by expansions in drug budgets. For example,

modelling of relapse rates in the maintenance phase of treatment has shown that there are gains to be made from improving drug efficacy and from improving compliance, but that compliance and efficacy are synergistic, so that the most benefit will be gained when both compliance and efficacy are improved together[58].

One cautionary note to any cost-effectiveness models based on current patterns of care in schizophrenia is that staff and revenue costs of hospitals scheduled to close are high, and there are transitional costs. Good quality community provision for former hospital patients can have the same or lower costs than hospital treatment, so some changes of the cost profile produced by Davies and Drummond, particularly for patients with the most severe disease, might be expected over the next few years[20].

11 Implications for other parties

Indirect costs to families and informal carers can be substantial [55]. Wyatt[59] estimated costs of lost family productivity in a US setting, giving an estimate of $7,000 million dollars, 11.2% of the total. All indirect costs of schizophrenia were estimated to be $46,520 million in 1991, 71% of the total. Indirect family costs are also likely to be relatively high in the UK. No information is available on how these costs might be affected by changes in treatment effectiveness.

The impact upon formal carers of clinical improvement will be influenced by changes in the setting of care. This review has not attempted to estimate the potential impact of olanzapine and the trials provide no direct evidence. If, however, olanzapine is proven to be more effective than conventional neuroleptics with regard to social functioning, as opposed to clinical rating scores, benefits might be expected.

Where schizophrenic patients drop out of care, direct costs to the NHS decrease, but indirect costs to other public sector budgets (for example, prison, benefit costs) are likely to rise. It could and probably should be argued that increased costs to the NHS from reduced drop out rates should be disregarded, as this may result in an increase in costs to the public sector as a whole.

12 Conclusion

The evidence from three double blind trials supported by evidence from a fourth which was of poorer quality indicates that olanzapine is an effective and safe antipsychotic drug. In a short term trial with titrated doses of both drugs, olanzapine performed better than haloperidol with respect to mean changes in clinical rating scores and numbers of responders, and this was confirmed in a metanalysis that included two smaller trials with doses with limited titration. Olanzapine also has a better EPS side effects profile than haloperidol, and a superior effect on negative symptoms (although the clinical importance of the latter might be debated).

There is some evidence from one trial to indicate that olanzapine performs better than haloperidol in treatment of first episode schizophrenia and from extension phases of the trials that olanzapine is associated with a better maintenance of response. One trial indicated that olanzapine is superior to haloperidol in treating depressive symptoms. The evidence on these topics is based on sub-group analyses of the main trials and is somewhat weaker than evidence on overall efficacy. Although these results come from good quality studies, firm conclusions, in particular on the superiority of olanzapine to

haloperidol in the maintenance of relapse, must await full publication of the results and possibly confirmation in further studies.

Table 7 gives the savings (reduced costs) per QALY using the decision tree, outcome probabilities and assumptions about quality of life described earlier in this report. The model assumes that no other atypical neuroleptics are in use: where these drugs are used as first or second choice drugs (rather than in refractory disease alone), costs of acute episodes of care would be higher. No account of side effects has been taken in the quality of life analysis.

When it is assumed that patients who do not respond to their first two neuroleptics will all need continuing hospital or intensive out-patient treatment, then olanzapine as first choice therapy had a cost advantage of £7,759 per QALY over haloperidol. When the requirements for hospital or intensive community care were reduced, the cost advantage of olanzapine fell to £2,533. The models presented here are relatively simple, but suggest that the use of olanzapine is likely to be at least cost neutral. The longer term evidence on olanzapine, however, though positive, is relatively weak, and potential savings are unlikely to be realised.

Table 7: Cost utility analysis: acute episode of schizophrenia modelled over one year[e]

| | IHQL | a — All patients with no response require hospital or intensive community care | | | b — One third of patients with no response require hospital or intensive community care | | | Savings (reduced costs) per QALY over no treatment | |
		Annual cost	Cost per QALY	Savings per QALY over no neuroleptic treatment	Annual cost	Cost per QALY	Saving over no neuroleptic treatment	a	b
No active treatment	0.799	£37,194	£47,432	-	£16,747	£21,356	-	-	-
Olanzapine as first choice and maintenance	0.833	£26,200	£31,463	£15,969	£13,023	£15,639	£5,717	£15,969	£5,717
Haloperiodol as first choice and maintenance	0.806	£31,627	£39,222	£8,210	£2,093	£18,172	£3,184	£8,210	£3,184

12.1 Areas of uncertainty

One area of uncertainty in the economic appraisal of olanzapine is its potential to cause tardive dyskinesia. No good quality evidence on this is available at present, and certain evidence will not be available until olanzapine has been in use for a number of years. As tardive dyskinesia is a serious and often irreversible side effect of existing neuroleptics that results in considerable distress and some physical disability in some 20% of conventionally treated patients, prevention of TD in treated schizophrenia patients would considerably increase the QALYs attached to the use of olanzapine in all settings, should olanzapine prove to have very low or zero risk of TD.

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[e] Treatment with haloperidol as first choice therapy with olanzapine as second choice therapy was also considered and gave a cost saving over the hypothetical case of no treatment of £16,080 for model a and £5,741 on model b.

13 Time limit for this report

Olanzapine was only licensed in the UK and US in 1996. Full results from the original trials, in particular from the extension phases are not available yet, but should be forthcoming. Further evidence on the effectiveness of olanzapine will become available over the next few years. There is as yet no evidence on tardive dyskinesia and olanzapine. Previous experience with new atypical neuroleptics (clozapine, fluperlapine and remoxipride) has been that some unexpected and serious side effects have emerged after licensing[2].

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