An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics

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**Record Status**
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

**Health technology**
The use of quetiapine versus haloperidol for the treatment of patients with schizophrenia who were only partially responsive to conventional antipsychotics.

**Type of intervention**
Treatment.

**Economic study type**
Cost-effectiveness analysis.

**Study population**
The study population comprised patients who met the following criteria:

- Schizophrenia according to the DSM-IV diagnostic criteria;
- Age less than or equal to 18 years;
- A history of persistent positive symptoms while taking therapeutic doses of an antipsychotic agent and a score of at least 15 on the Positive and Negative Syndrome Scale (PANSS), with a score of at least 4 (moderately ill) on one or more of the items of delusion, conceptual disorganisation, hallucinatory behaviour, or suspicion/persecution; and
- A score of at least 3 on the Clinical Global Impression Severity of Illness scale.

These patients received 4 weeks of treatment with fluphenazine (20 mg/dL). Those who showed a partial response or no response to fluphenazine (defined as an improvement in the PANSS total score of less than 30% from baseline to week 4 and a PANSS total score at week 4 of at least 15) participated in a randomised clinical trial (RCT) that constituted the basis for this modelling study.

**Setting**
The setting was secondary care. The economic study was carried out in the UK.

**Dates to which data relate**
The effectiveness data were mainly taken from a study published in 2000. The remaining effectiveness data required for the construction of the model were extracted from literature published between 1974 and 1995. The resource use data were derived from the main source-study (2000) and one additional paper published in 1998. Prices relating to 1998 to 2000 were used.

**Source of effectiveness data**
NHS Economic Evaluation Database (NHS EED)
The effectiveness data were derived from a review of completed studies. The authors made some key assumptions, some of which were supported by expert opinion.

Modelling
A Markov model was constructed to extrapolate the effectiveness and cost results of an 8-week RCT over a 5-year period. The model included 11 health states and had a cycle time of 3 months. The first five health states were adopted from end points in the RCT. They involved states of PANSS (full, partial, or no improvement) following treatment with quetiapine or haloperidol, combined with the presence or absence of extrapyramidal symptoms (EPS). The remaining six states included states of relapses (fully, partially, or not responsive to treatment) plus a state of suicide.

Outcomes assessed in the review
The outcomes assessed in the review included:

- the response and EPS rates in patients, partially responsive to fluphenazine, who were receiving quetiapine or haloperidol for 8 weeks;
- the transition probabilities of patients with or without EPS to noncompliance;
- the transition probabilities of compliant, noncompliant, or nonresponding patients to relapse; and
- the transition probabilities of patients with relapse to suicide.

Study designs and other criteria for inclusion in the review
The main study used for the construction of the Markov model was a multi-centre, randomised, double-blind prospective trial (the PRIZE study). This study was selected as the basis of the model because the study population comprised partial responders, a common treatment group in schizophrenia, but a group for whom specific studies were scarce. Further details of the study are provided elsewhere (see Other Publications of Related Interest). The inclusion criteria for the remaining studies in the review were not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
The effectiveness evidence was derived from 3 primary studies and one review.

Methods of combining primary studies
The results of the primary studies may have been used selectively. No method of combination was stated.

Investigation of differences between primary studies
Not stated.
Results of the review
The response and EPS rates for partially responsive patients receiving quetiapine for 8 weeks were:

for PANSS improvement of +/- 30% and no EPS, 22%;
for PANSS improvement of +/- 30% and EPS, 6%;
for PANSS improvement of +/- 20% but less than 30% and no EPS, 8%;
for PANSS improvement of +/- 20% but less than 30% and EPS, 7%; and
for PANSS improvement of less than 20% (independent of EPS status), 56%.

The response and EPS rates of partially responsive patients receiving haloperidol for 8 weeks were:

for PANSS improvement of +/- 30% and no EPS, 8%;
for PANSS improvement of +/- 30% and EPS, 9%;
for PANSS improvement of +/- 20% but less than 30% and no EPS, 9%;
for PANSS improvement of +/- 20% but less than 30% and EPS, 8%;
for PANSS improvement of less than 20% (independent of EPS status), 67%.

The transition probabilities were:

for patients with EPS to noncompliance, 0.180;
for patients without EPS to noncompliance, 0.013;
for recently stabilised and compliant patients to relapse, 0.051;
for noncompliant or nonresponding patients to relapse, 0.209; and
for suicide following relapse, 0.002.

Methods used to derive estimates of effectiveness
The authors’ assumptions about one estimate of effectiveness were supported by a panel of experts from the UK, experienced in treating patients with the same characteristics as those of the target population used in the model. The authors also made other key assumptions in the construction of the model.

Estimates of effectiveness and key assumptions
The relapse rate for nonresponding patients was assumed to be the same as that for noncompliant patients (0.209). In addition, the same relapse rates were assumed for both quetiapine- and haloperidol-treated patients. However, in clinical practice, although the probability of relapse for nonresponding patients is the same, the responsiveness to treatment differs depending on the drug administered. Another key assumption was that the response rates observed in the 8-week RCT were maintained for the 5-year duration of the Markov model, as long as the patients remained compliant with the treatment. This might not be the case in a clinical setting.

Measure of benefits used in the economic analysis
The benefit measures used in the economic analysis were the number of relapses avoided, and the time spent (per patient) in a response state due to treatment.
Direct costs
The direct costs included in the economic analysis were consistent with the perspective of the study (the UK NHS). The costs were for medication (quetiapine or haloperidol) and the medical services required at each health state of the model. The quantities were not reported separately from the unit costs. However, in most cases, the resources required were individually estimated for each state, and then a unit cost was attached. The final total costs were derived using modelling techniques. The resources needed were estimated using actual data from the main source-study (for medication costs), and treatment protocols described in another study. The drug prices were derived from the British National Formulary (1999). The unit costs for the medical services were taken from "Unit costs of health and social care, 2000" and the Chartered Institute of Public Finance and Accountancy (2000). The costs of three health states were directly derived from a study published in 1998. The costs were discounted at a rate of 6%, which was appropriate as they were incurred during a 5-year period. The price year was not explicitly stated.

Statistical analysis of costs
The costs were treated deterministically. No statistical tests were carried out when analysing the costs.

Indirect Costs
The indirect costs were not included in the analysis. This was consistent with the perspective adopted.

Currency
UK pounds sterling ().
Cost results
The costs were discounted at a rate of 6%.

The total costs per patient over 5 years were 38,106 for quetiapine and 38,350 for haloperidol.

The total incremental cost of quetiapine was -244 per patient treated (-316 undiscounted). This meant that treatment with quetiapine was less costly than with haloperidol.

The cost of the one side effect (EPS) considered in the study was included in every health state cost.

Synthesis of costs and benefits
The estimated costs and benefits were not combined into a single ratio, as treatment with quetiapine dominated treatment with haloperidol. Quetiapine was associated with a slight reduction in costs compared with haloperidol, and an improvement in outcomes (lower number of relapses and longer period spent in a response state). The results were, in general, robust to sensitivity analyses. Quetiapine was shown to be more effective than haloperidol under any scenario examined. It also remained cost-saving or cost-neutral under most scenarios. The only parameters that reversed this result (led to quetiapine being more costly) were reductions in the following:

- the difference in the proportion of patients in each response/EPS state between the two groups;
- the probability of relapse in nonresponding or noncompliant patients;
- the cost of relapse; and
- the cost of the nonresponse state.

Authors’ conclusions
Quetiapine was more effective and less costly than haloperidol for the treatment of patients with schizophrenia who were partially responsive to conventional antipsychotics.

CRD COMMENTARY - Selection of comparators
Quetiapine was studied as it had been proven, in an RCT, to be effective in patients with partially responding schizophrenia. The choice of the comparator (haloperidol) was not justified. However, it is a drug indicated for the treatment of schizophrenia. You should decide whether this comparator represents current practice in your setting.

Validity of estimate of measure of effectiveness
No systematic review was undertaken for the estimation of effectiveness. Most of the data were taken from an RCT, which is the optimal study design for the evaluation of effectiveness. The rest of the effectiveness estimates were derived from other studies, possibly selectively. The number of primary studies used, besides the main source-study, was very limited. Thus, the authors did not report any consideration of the validity or the impact of differences between the primary studies when estimating the effectiveness. In terms of the key assumptions made, the authors did not always justify their choices, although in one case there was expert agreement. Most of the assumptions were subjected to a sensitivity analysis. The internal validity of the RCT is likely to have been high. However, given the ad hoc use of other sources, it was not possible to judge the validity of all model inputs.

Validity of estimate of measure of benefit
The estimation of benefits was based on a Markov model. This was appropriate for this purpose since it included all possible health outcomes resulting from the treatment of partially responding schizophrenia. In addition, its duration allowed the long-term effectiveness of therapy to be evaluated.
Validity of estimate of costs
All the categories of costs relevant to the perspective adopted (NHS) were included in the analysis. The costs and the quantities were not reported separately, which may limit the replication of the study results in other settings. A sensitivity analysis of some cost components was conducted. However, this was not extensive and, as such, only partially addressed the uncertainty surrounding the estimates. Discounting was carried out as appropriate. The unit costs were derived from sources published within a 3-year period. It was not stated whether the prices were all uplifted to the same year. The use of a single price year would aid future reflation exercises.

Other issues
The authors made appropriate comparisons of their results with the findings of other studies, and found them to be consistent. However, the issue of generalisability to other settings was not explicitly addressed. The results were adequately reported and reflected the scope of the study, which involved only patients with schizophrenia who were partially responsive to conventional antipsychotics. The authors were aware that their findings might not be relevant to patients with other forms of schizophrenia.

One limitation of the study was the assumption that the response rates observed in the 8-week RCT were maintained over the 5-year duration of the Markov model, as long as patients remained compliant with the treatment. However, the authors justified this key assumption by stating that no long-term data were available for quetiapine in partially responsive patients, and that this assumption was consistent with data from patients with acute schizophrenia. Another limitation reported was that the model included only one side effect of treatment. The authors felt that the analysis might have missed some benefits of quetiapine treatment, such as a reduction in the frequency of other side effects.

Implications of the study
The authors suggested that quetiapine could significantly improve the treatment of patients with schizophrenia who are partially responsive to conventional antipsychotics, and who are often difficult to treat adequately, without increasing the economic burden on the health service.

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None stated.

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Antipsychotic Agents /adverse effects /economics /therapeutic use; Costs and Cost Analysis; Dibenzothiazepines /adverse effects /economics /therapeutic use; Haloperidol /adverse effects /economics /therapeutic use; Humans; Markov Chains; Models, Economic; Quetiapine Fumarate; Randomized Controlled Trials as Topic; Schizophrenia /drug therapy; Treatment Outcome