Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis
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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 clozapine for the management of hospitalised treatment-resistant schizophrenic patients with moderate symptomatology. Treatment resistance was defined as an inadequate response to therapeutic doses (greater than 1,000 mg/day chlorpromazine equivalents) of at least two antipsychotic agents from at least two drug classes, for an adequate treatment duration (longer than 6 weeks’ duration per trial).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised hospitalised treatment-resistant schizophrenic patients with moderate symptomatology. Treatment-resistant patients may include partial responders or patients who cannot tolerate sufficient antipsychotic doses of conventional agents.

Setting
The setting was a hospital and the community. The economic study was carried out in Ontario (Canada).

Dates to which data relate
The effectiveness data were derived from studies published between 1988 and 1994. The cost data relate to studies and reports published between 1992 and 1998. The price year was 1995.

Source of effectiveness data
The effectiveness data were derived from a comprehensive review of published studies plus estimates made by an expert (physician) panel.

Modelling
An incidence-based, deterministic decision-analytical model was constructed in order to evaluate treatment sequences, and to calculate the expected costs and utilities of the alternative therapies.

Outcomes assessed in the review
The following outcomes were assessed in the review for both clozapine and the comparators (chlorpromazine or haloperidol, combined), for treatment-resistant schizophrenia:
the efficacy, i.e. the proportion of patients with a clinically significant response to therapy;

the drop-out rates due to both adverse effects and inefficacy;

the success rates; and

the discontinue rates due to adverse effects.

"Success" was defined according to the criteria used in the clinical trials. These were a 20% decrease in the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Symptoms Scale (PANSS), and a Clinical Global Impression (CGI) rating of "very much" or "much" improved.

**Study designs and other criteria for inclusion in the review**

A comprehensive literature search was conducted to retrieve all randomised controlled trials involving clozapine, haloperidol or chlorpromazine, compared with placebo or active therapy, in the treatment of treatment-resistant schizophrenia.

The inclusion criteria in the original clinical trial included:

random allocation to treatment groups;

control by a placebo or comparator medication;

double-blind techniques;

women or men aged at least 18 years;

treatment-resistant schizophrenia, as defined by standardised criteria;

the use of acceptable criteria to define treatment-resistant schizophrenia;

a length of treatment of at least 4 weeks;

a treatment arm with clozapine, haloperidol or chlorpromazine; and

the use of appropriate standardised instruments for the outcome measures.

Papers were excluded if all the required information could not be extracted. The information considered essential included the following:

medications compared, in terms of dose and duration;

the characteristics of the patient sample, in terms of age, gender, severity and duration of illness, diagnosis, inpatients and/or outpatients;

the definition of treatment-resistant psychosis;

the instruments used;

the proportion improved;,

the duration of hospitalisation; and

drop-outs due to both adverse events and lack of efficacy.
Sources searched to identify primary studies
MEDLINE, EMBASE and International Pharmaceutical Abstracts databases were searched. All papers and recently published review articles were also cross-referenced manually.

Criteria used to ensure the validity of primary studies
The inclusion and exclusion criteria used in the review (see 'Study Designs And Other Criteria For Inclusion In The Review' section) seem to have helped ensure the validity of the primary studies.

Methods used to judge relevance and validity, and for extracting data
Two raters examined the 'Methods' and 'Results' sections of each paper, comparing study parameters with the established criteria. Any differences were resolved through consensus.

Number of primary studies included
Forty-two studies of clozapine were identified, of which 3 were included in the review.

Methods of combining primary studies
The primary studies were combined using a meta-analysis.

Investigation of differences between primary studies
A random-effects model was used to combine the outcomes of the individual primary studies. The authors reported that this technique minimised the influence of heterogeneity among the primary studies.

Results of the review
The numbers in parenthesis (n) indicate the combined sample from the included studies.

For therapy with clozapine:
the efficacy (all) rate was 0.59 (95% confidence interval, CI: 0.13 - 1.0; n=141);
the efficacy (inpatients) rate was 0.65 (95% CI: 0.04 - 1.2; n=123);
the efficacy (outpatients) rate was 0.44 (95% CI: 0.28 - 0.61; n=18);
the drop-out rate due to adverse effects was 0.05 (95% CI: 0.02 - 0.09; n=157);
the drop-out rate due to inefficacy was 0.2 (95% CI: 0.0 - 0.47; n=143);
the success rate was 0.65 (95% CI: 0.04 - 1.0); and
the discontinue rate due to adverse effects was 0.05 (95% CI: 0.02 - 0.09).

For therapy with chlorpromazine or haloperidol:
the efficacy rate was 0.04 (95% CI: 0.01 - 0.08; n=154);
the drop-out rate due to adverse effects was 0.05 (95% CI: 0.02 - 0.09; n=172);
the drop-out rate due to inefficacy was 0.2 (95% CI: 0 - 0.04; n=156);
the success rate was 0.04 (95% CI: 0.01 - 0.08); and
the discontinue rate due to adverse effects was 0.05 (95% CI: 0.02 - 0.09).

Methods used to derive estimates of effectiveness
The estimates for the discharge rate if symptoms improved, and the relapse rate within one year, were derived using an expert panel of four academic psychiatrists combined with the review of the literature.

Estimates of effectiveness and key assumptions
The discharge rate if symptoms improved was 0.81 (95% CI: 0 - 1).

The relapse rate within one year was 0.16 (95% CI: 0 - 1).

Measure of benefits used in the economic analysis
Quality-adjusted life-years (QALYs) were used as the measure of benefits. The expected number of QALYs was determined by identifying the health states, their individual values and their duration. Health state utilities were obtained through one-on-one interviews with seven patients with schizophrenia using the Standard Gamble technique and a rating scale.

Direct costs
The direct costs included in the analysis were for drugs, psychiatric care and hospitalisation. The costs of psychiatric care included psychiatric visits, nursing visits, social work visits, community care manager and residential care. The hospitalisation costs included the costs of a hospital day for acute admission and for prolonged admissions beyond 8 weeks, and the costs of relapse. The quantities and the costs were reported separately. The quantities were estimated using actual data obtained from various sources. The dates to which the resource quantities related varied between 1992 and 1998. The price year was 1995. Discounting was not carried out as the time period considered was less than 2 years.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were not considered due to the perspective adopted. If researchers wish to adopt a societal perspective, indirect costs (primarily productivity losses) should be considered.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A sensitivity analysis was carried out to evaluate the impact of several variables on the overall cost and QALY values. Key parameters of costs, probabilities and utilities were varied. A threshold analysis was also performed for those in which the rank order for QALYs for clozapine was displaced. The area of uncertainty investigated was variability in the data. The ranges used were, appropriately, derived from the statistically significant CIs obtained in the meta-analysis. The expert panel also determined a clinically relevant range for the parameters.

Estimated benefits used in the economic analysis
The expected QALYs over one year were 0.86 for clozapine and 0.82 for chlorpromazine or haloperidol.

The incremental QALYs gained with clozapine were 0.04. A discount rate was not applied because the period of time
was less than 2 years.

Cost results
The total expected cost over one year was Can$90,186 for clozapine, and Can$129,607 for chlorpromazine or haloperidol. No discount rate was applied, which was appropriate given the period of time considered.

Synthesis of costs and benefits
The costs and the benefit results were not combined into cost-utility ratios. Clozapine provided better outcomes at a lower cost when compared with chlorpromazine or haloperidol, and was therefore considered to be the dominant strategy. The sensitivity analysis showed that these results were sensitive to changes in the costs of hospitalisation and the cost of residential care. The results of the threshold analysis on probabilities and utilities showed that the only statistically significant variable in the sensitivity analysis was the success rate for clozapine. However, the thresholds that altered the decision in favour of the other therapy were at the lower end of the 95% CI, suggesting that these thresholds may not be relevant. For example, the baseline value for the probability of success of clozapine was 0.65 (95% CI: 0.04 - 1.0). Thus, a success rate less than 0.13 would make chlorpromazine cheaper, while a success rate less than 0.02 would lead to chlorpromazine having more QALYs.

Authors' conclusions
Clozapine appeared to be a cost-effective therapy in patients with treatment-resistant schizophrenia, compared with chlorpromazine and haloperidol. This was mainly because of the reduction in hospitalisation and, consequently, in the costs.

CRD COMMENTARY - Selection of comparators
The justification given for the choice of the comparator (chlorpromazine and haloperidol, combined) was that they are accepted standard antipsychotic agents, and that clinical trials in treatment-resistant patients were available. However, no justification was given for combining chlorpromazine and haloperidol in the one comparator. In addition, the authors did not explain how they were combined.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken, although their methods indicate that this was the case. As the authors reported, one of the limitations of the study was that they were able to identify only three publications (among 42 studies selected) from which useful clinical data could be extracted according to their meta-analysis protocol. Moreover, these studies were of short duration and did not report some of the parameters relevant to the economic analysis (for example, the discharge rates from hospital). Therefore, modelling was required.

The inclusion and exclusion criteria for the studies were clearly reported. The effectiveness results were rigorously combined using a meta-analysis, which enhances the validity of the results. The authors reported the methods used to derive the estimates of effectiveness. They also adopted a weighting scheme to reflect differences in the sample sizes. However, some of the estimates of effectiveness were derived from a combination of the expert panel and the literature review. The process by which the expert panel's psychiatrists were selected was not reported. In addition, the methods used to combine the results derived from the expert panel with those obtained from the literature review were not described. CIs derived from the meta-analyses and estimates were used in the sensitivity analysis, which again enhances the validity of the effectiveness findings.

Validity of estimate of measure of benefit
The benefit measure (QALYs) was derived, appropriately, by modelling.

Utility scores for the different health states were derived from interviews with seven patients with schizophrenia. Although they were deemed by their respective psychiatrists to be sufficiently stable to complete the interview process,
the number of interviewed was very small and, moreover, only men were interviewed. Therefore, the resulting utility scores may have some limitations in terms of being representative utility proxies for the study population.

**Validity of estimate of costs**
The costing was comprehensively conducted and reported.

All the categories of cost relevant to the perspective adopted appear to have been included in the analysis. The costs and the quantities were reported separately. The sensitivity analysis showed that the results were generally robust to wide variations in the values of costs, probabilities and utilities. However, sensitivity analyses of the quantities were not conducted, which may limit the interpretation of the study's findings. The price year was reported.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies. With regard to the issue of generalisability to other settings, the authors stated that it was unclear whether clozapine offers advantages over the standard therapies offered to patients early in the course of their illness. They reported that the economic attractiveness of clozapine rests not only on its higher efficacy, but also on the availability of structured community programmes that facilitate discharge from institutional settings. In terms of clinical practice, clozapine offers both economic and clinical benefits within the caveats of this study. The authors suggest further study of the clinical outcomes and cost-effectiveness of clozapine in the more general schizophrenia population. In particular, for those patients in the early stages of their condition.

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**Other publications of related interest**


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