Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model


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 study examined genetic testing and treatment strategies, based on clozapine and conventional antipsychotics, for schizophrenia. One strategy (pharmacogenetic testing) consisted of testing for the alleles associated with better clozapine response, with those who tested positive being given clozapine as a first-line treatment. If the patient failed to recover, relapsed, or developed agranulocytosis, their treatment was changed to conventional antipsychotics. If the patient tested negative for the alleles associated with better clozapine response, they were given conventional antipsychotics as first- and second-line treatments, followed by clozapine as a third-line treatment. Another strategy (clozapine first-line) consisted of using clozapine as a first-line treatment for all patients, followed by conventional antipsychotics if the patient failed to recover, relapsed, or developed agranulocytosis.

Type of intervention
Genetic testing and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population was a hypothetical 30-year-old schizophrenic patient hospitalised for a psychotic episode.

Setting
The setting was tertiary and institutional care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were taken from papers published between 1986 and 2000. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of published studies.

Modelling
A decision analysis model and a Markov model were used to identify the clinical effectiveness, health utility and resource use for the three treatment strategies considered in this study. The models were run for the life span of a hypothetical 30-year-old patient. Three-month cycles were used, at the end of which patients were moved between health states according to transition probabilities.
Outcomes assessed in the review
The following model parameters were identified from published papers.

The probability of the following transitions in a 3-month period:
psychosis to recovered on conventional antipsychotics and on clozapine,
recovered to relapse on conventional antipsychotics and on clozapine,
death by suicide on conventional antipsychotics and on clozapine,
no tardive dyskinesia to tardive dyskinesia on conventional antipsychotics,
no agranulocytosis to agranulocytosis on clozapine, and
agranulocytosis to death on clozapine; and
the sensitivity and specificity of pharmacogenetic tests.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
The model parameters were identified using data from 10 published papers.

Methods of combining primary studies
Not relevant.

Investigation of differences between primary studies
Not reported.

Results of the review
The following model parameters were identified.

The probability of the following transitions in a 3-month period:
psychosis to recovered on conventional antipsychotics, 40%;
psychosis to recovered on clozapine, 42.9%;
recovered to relapse on conventional antipsychotics, 13%;
recovered to relapse on clozapine, 8%;
death by suicide on conventional antipsychotics, 0.07%;
death by suicide on clozapine, 0.02%;
no tardive dyskinesia to tardive dyskinesia on conventional antipsychotics, 1.3%;
no agranulocytosis to agranulocytosis on clozapine, 0.019%; and
agranulocytosis to death on clozapine, 3.141%.

The sensitivity of the pharmacogenetic test was 95.89% and the specificity was 38.3%.

**Measure of benefits used in the economic analysis**
The measure of health benefit used was the quality-adjusted life expectancy (quality-adjusted life-years, QALYs) estimated by the model detailed above. Valuations of health states were taken from published studies. The health states were valued using standard gamble, rating scales and paired comparison questions.

**Direct costs**
The direct costs of the health care payer were identified in this study. The costs included were for medication, white blood cell monitoring for clozapine users, inpatient care, outpatient care, residential treatment, treatment for tardive dyskinesia and treatment for agranulocytosis. Medication use was estimated on the basis of median recommended dosages. The costs of medication (clozapine and haloperidol) were taken from the average wholesale price reported in the Red Book. The cost of white blood cell monitoring was taken from a published estimate. The length of inpatient stay and outpatient usage was estimated from published studies. The unit cost of inpatient care was taken from average costs identified by the Inventory of Mental Health Organizations and General Hospital Mental Health Services, while the unit cost of outpatient and residential care was taken from median Medicaid costs. The total costs of treating tardive dyskinesia and agranulocytosis were taken from published estimates. The resource use data were obtained from studies published between 1993 and 1999. The price year was 1999 and all costs were reflated to this year using the medical care component of the Consumer Price Index. Future costs were discounted at a rate of 3%.

**Statistical analysis of costs**
The cost data was treated deterministically.

**Indirect Costs**
No indirect costs were included in the study.

**Currency**
US dollars ($).

**Sensitivity analysis**
A one-way sensitivity analysis was undertaken to assess variability in the data. The ranges for costs were taken as the base-case plus or minus 25%. The ranges for all other variables were published 95% confidence intervals.

**Estimated benefits used in the economic analysis**
In the base-case analysis, testing for alleles associated with better clozapine response resulted in a life expectancy of
14.59 QALYs, compared with 14.58 QALYs for the strategy using clozapine as a third-line treatment. The use of clozapine as a first-line treatment without testing resulted in a life expectancy of 14.59 QALYs. The health benefits have been discounted at a rate of 3% per annum.

Cost results
The total costs of the three treatment strategies were not identified in the paper.

Synthesis of costs and benefits
Testing patients and only giving clozapine to those who showed the alleles suggestive of better response was dominated by the use of clozapine as a first-line treatment for all patients. Testing patients and giving clozapine to those with a positive test, compared with not testing and using clozapine as a third-line treatment, cost $47,705 per additional QALY.

The sensitivity analysis showed that the cost-effectiveness ratio of testing and providing clozapine as a first-line treatment in patients with a positive result, compared with using clozapine as a third-line treatment, was the utility attributed to the state of recovered from psychosis (Range: $36,071 to $79,295). The cost-effectiveness ratio was also sensitive to response rates for clozapine and conventional antipsychotics, the cost of psychiatric hospitalisation and the relapse rate on clozapine.

Authors' conclusions
The authors suggested that pharmacogenetic testing to predict clozapine efficacy may increase quality-adjusted life expectancy at a moderate costs.

CRD COMMENTARY - Selection of comparators
This study compared three possible treatment strategies. One of these, use of clozapine as a third-line treatment for schizophrenia, represented standard practice in the authors' setting. You should consider how each of the three strategies compares with usual practice in your own setting before applying the results of this study.

Validity of estimate of measure of effectiveness
The measure of effectiveness used in this study was taken from a decision analysis model. Model parameters were taken from published studies. No details of the methods used or sources searched to identify primary studies were provided. In addition, the authors did not report their selection criteria or methods of extracting the data. This means that it is not possible to identify whether the authors undertook a systematic search and robust assessment of the primary studies used to inform the model parameters. The authors acknowledged that their study was limited by the fact that model parameters were taken from primary studies that used different study designs, and that these study designs may have their own flaws.

Validity of estimate of measure of benefit
The measure of health benefit was estimated by the model that provided the clinical effectiveness data. Valuations of the different health states were taken from published papers. It would appear that the methods used to value the health states in these studies were not consistent. This means that the values identified for each of the health states may not be directly comparable. In addition, the authors acknowledged that they over simplified the number of health states likely to be experienced by their patient population.

Validity of estimate of costs
The authors stated that a societal perspective was adopted but no indirect costs (e.g. lost productivity or nonmedical costs incurred by the patients) were included in the study. In fact, this study only identified the costs to the health care payer. The inclusion of all societal costs is likely to increase the costs of all three treatment strategies. The unit costs
were reported in the paper, but resource use was not specified. This limits the scope to apply the results of this study to other settings. Sensitivity analyses varying the cost and resource use data were undertaken. A clear price year was reported, which will enable future reflation exercises. Future costs were appropriately discounted.

**Other issues**

The authors did not present their results in a comprehensive manner. In particular, they did not report the total costs of each of the treatment strategies. The authors did not compare their economic results with similar studies, nor did they comment on the scope to apply their findings to other countries.

**Implications of the study**

The authors did not make any recommendations for further research or changes to practice.

**Source of funding**

None stated.

**Bibliographic details**


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**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

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