Decision analysis model evaluating the cost-effectiveness of risperidone, olanzapine and haloperidol in the treatment of schizophrenia

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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 study examined three drug treatments for patients with schizophrenia. Specifically, a conventional antipsychotic, haloperidol (HAL), and two newer atypical antipsychotics, risperidone (RIS) and olanzapine (OLA). The dosages assumed were 15 mg/day for OLA, 6 g/day for RIS (6 mg/day quoted in discussion section) and 20 mg/day for HAL.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of adult patients with a diagnosis of schizophrenia or schizoaffective disorders.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2006. Some resource use data came from studies published between 1996 and 2003. The price year was 2005.

Source of effectiveness data
The clinical data used in the decision model were:

the rates of responders and non-responders with the three antipsychotic treatments,

the proportion of patients experiencing controlled or uncontrolled EPS,

the rates of patients in stable conditions,

the rates of re-hospitalisation, and

the rates of switch in non-responders.

Modelling
A decision analytic model was constructed to simulate the treatment of schizophrenia with the three therapies in a
hypothetical cohort of 1,000 patients in each arm. The structure of the decision tree was presented graphically. Patients not responding to any of the three medications under investigation were switched to clozapine therapy. Similarly, patients with uncontrolled EPS or who needed hospitalisation were assumed to discontinue the initial treatment and switch to clozapine. Patients who did not respond to the clozapine therapy were all assumed to respond to the electroconvulsive therapy. Responders were defined as those achieving a 20% or greater reduction in the PANSS from baseline. The time horizon of the model was 16 weeks, including 8 weeks of the acute phase of schizophrenia and 8 weeks of the maintenance phase.

Sources searched to identify primary studies
The vast majority of clinical data came from double-blind, randomised, prospective clinical trials evaluating at least two of the three drugs under examination. Only rates of hospitalisation were based on expert opinion.

Methods used to judge relevance and validity, and for extracting data
The clinical data were derived from studies identified from a review of the literature. Details such as the inclusion and exclusion criteria, use of specific keywords, and patient population were reported. Only double-blind, randomised, prospective clinical trials were included in the analysis. As no study was found that compared all three treatments investigated, studies involving patients with similar demographics were chosen. The primary estimates from different studies were combined using weighted averages based on sample size.

Measure of benefits used in the economic analysis
The summary benefit measure used was the rate of successfully treated patients (proportion of patients achieving at least a 20% reduction in the PANSS from baseline). This was derived directly from the literature.

Direct costs
The study was conducted from the perspective of the health care system. The direct costs included in the analysis were for study medications, days of inpatient stay, doctor visits, emergency department visits, pharmacy dispensing fees, adjunct treatment options, and side effects of treatment of EPS. The unit costs and the quantities of resources used were presented separately. The quantities of resources used were derived from published sources such as, for example, the Expert Consensus Guideline Series, Treatment of Schizophrenia 1999 and the Length of Stay by Diagnosis and Operations, United States. Authors’ opinion was also used where there was a lack of published evidence. With the exception of OLA and RIS, which were estimated using trade names because of a lack of generic equivalents, the drug costs were based on the average wholesale prices of generics, Other costs were based on national averages. Discounting was not relevant as the time horizon of the study was short. The price year was 2005.

Statistical analysis of costs
The costs and quantities were treated deterministically.

Indirect Costs
Productivity costs were not relevant given the perspective of the study.

Currency
US dollars ($).

Sensitivity analysis
A deterministic sensitivity analysis was carried out to assess the robustness of the cost-effectiveness ratios to variations in clinical efficacy, drug acquisition costs and re-hospitalisation rates. Both one- and two-way sensitivity analyses were performed. The ranges of values used were chosen on the basis of conservative assumptions based on published
evidence. Threshold values for equivalent total costs between OLA and RIS were also calculated.

**Estimated benefits used in the economic analysis**
The treatment effectiveness (percentage of responders) was 63% with RIS, 60% with OLA and 34% with HAL.

**Cost results**
In a hypothetical cohort of 1,000 patients, the expected total costs were $13,409,892.71 with RIS ($13,409 per patient), $13,591,573.24 with OLA ($13,591 per patient) and $15,513,379.42 with HAL ($15,513 per patient).

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The average cost per successfully treated patient was $21,285.54 with RIS, $22,652.62 with OLA and $45,627.59 with HAL.

The incremental analysis showed that RIS and OLA dominated HAL, which was both less effective and more expensive. In the comparison between the two atypical antipsychotics, the incremental analysis indicated that RIS dominated OLA.

The key results of the sensitivity analysis (conducted only for OLA versus RIS) were as follows:

the number of responders with RIS would have to decrease by approximately 3% in order for the costs to equal those of OLA;

the difference in drug costs between OLA and RIS would have to increase from $2.12 in the base-case to $4.12 in order for the total costs to be equal;

the difference in re-hospitalisation rates between RIS and OLA would have to increase from RIS having 3% greater hospitalisations in the base-case analysis to RIS having 33% more re-hospitalisations than the OLA group.

**Authors’ conclusions**
Despite higher initial acquisition costs, atypical antipsychotics such as risperidone (RIS) and olanzapine (OLA) were a dominant strategy over haloperidol (HAL) for the treatment of schizophrenia, primarily because of increased efficacy and lower re-hospitalisations. RIS was the most cost-effective therapy.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear. The authors provided a justification for the comparison between the conventional therapy and the new atypical antipsychotics. Dosages were reported. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data came from a review of the literature, the methods and conduct of which were extensively described. The database searched and the inclusion criteria were reported. The approach used to combine the primary estimates was stated. As only clinical trials were included in the review, the validity of the primary estimates was high. The authors selected appropriately similar patient populations in order to address the issue of a lack of direct comparisons among the strategies investigated, but did not conduct any statistical analysis to deal with the potential heterogeneity between the primary studies.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the intervention considered in the study. It is not comparable with the benefits of other health care interventions. However, the rate of responders is commonly used in studies evaluating the effectiveness of drug treatments for schizophrenia. The authors illustrated the advantages of using the PANSS as a predictor of clinical efficacy in schizophrenia with respect to other instruments such as the Brief Psychiatric Rating Scale.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective adopted in the study. Extensive information on the unit costs and resource quantities was given, which will help in replicating the analysis in other settings. The sources of the costs and resource use were reported for all items. Some assumptions were also made in order to derive some data on resource consumption. Statistical analyses of the costs were not performed. The use of alternative cost data was investigated in the sensitivity analysis, in which the cost of drugs and hospitalisation rates were varied. The price year was reported, which will aid reflation exercises in other time periods.

Other issues
The authors stated that the cost-effectiveness of newer antipsychotics over HAL was consistent with findings from other studies. When discrepancies with the results of a published study were found, the authors discussed the potential reasons for these differences. The issue of the generalisability of the study results to other settings was not explicitly addressed. The authors noted some limitations of the analysis, such as the short duration of the model and the use of data from selective trials. The sensitivity analysis only partially addressed the issue of potential uncertainties around model parameters since it focused on the comparison between OLA and RIS. However, it should be noted that the clinical effectiveness results found for HAL were substantially worse than those for the other two treatments.

Implications of the study
The study results support the use of newer atypical antipsychotics, especially RIS, for the treatment of schizophrenia. However, the authors stated that larger, prospective, randomised studies should be carried out to corroborate the current findings.

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