Cost-effectiveness model of long-acting risperidone in schizophrenia in the US
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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 a long-acting injection (LAI) formulation of risperidone (RIS) for the treatment of patients with schizophrenia. Patients could receive LAI RIS 25 mg, 37.5 mg or 50 mg, given at 14-day intervals.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of community-dwelling patients with a diagnosis of schizophrenia, who had previously suffered a relapse requiring hospitalisation.

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 2004. Some resource use data and costs came from sources published from 1992 to 2003. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and experts’ opinions.

Modelling
A decision tree model was constructed to compare the costs and benefits of the four treatments for the outpatient treatment of individuals with schizophrenia. The model structure was based on a published decision model. The time horizon of the analysis was one year. The patients could receive RIS LAI, oral RIS, OLA or HAL. In the first stage, the model considered that patients could be compliant, partially compliant or non-compliant with the treatment regimen. In the second stage, and dependent on level of compliance, the patients could remain stable, suffer exacerbations or relapse not severe enough to warrant re-hospitalisation, or suffer relapses requiring re-hospitalisation.

Outcomes assessed in the review
The outcomes estimated from the literature were:
the compliance rates,
the relapse rates,
the frequency of relapse,
the duration of relapse, and
the frequency of adverse events.

**Study designs and other criteria for inclusion in the review**
A comprehensive literature search was undertaken to identify primary studies, which reported relapse, with which to populate the decision model. The following inclusion criteria were used:

the study was required to report relapse rates according to different levels of compliance;
the study had to use an appropriate definition of compliance;
the study was required to include a broad patient population;
the study was required to report relapses requiring and not requiring hospitalisation; and the study had to be US based.

Since only one study was identified, one inclusion criteria was relaxed in order to include another study. In addition, unpublished data from clinical trials were used. The primary studies used to derive other clinical estimates appear to have been identified selectively. No information on the design and characteristics of most of the studies was provided.

**Sources searched to identify primary studies**
PubMed was searched.

**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**
Seventeen primary studies provided evidence.

**Methods of combining primary studies**
A narrative method was used to combine the primary estimates. A weighted average was used for a few clinical end points.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The compliance rate with RIS LAI was 59.2% with a compliant patient, 36.2% with a partially compliant patient, and 4.6% with a non-compliant patient.
The compliance rate with oral RIS or oral OLA was 20% with a compliant patient, 70.9% with a partially compliant patient, and 9.1% with a non-compliant patient.

The compliance rate with HAL LAI was 13.4% with a compliant patient, 73% with a partially compliant patient, and 13.6% with a non-compliant patient.

The relapse rate requiring hospitalisation with atypical antipsychotics (RIS LAI, oral RIS and oral OLA) was 10.1% with a compliant patient, 45.2% with a partially compliant patient, and 78.7% with a non-compliant patient.

The relapse rate requiring hospitalisation with typical antipsychotics (HAL LAI) was 18.3% with a compliant patient, 68.9% with a partially compliant patient, and 95.6% with a non-compliant patient.

The relapse rate not requiring hospitalisation with atypical antipsychotics (RIS LAI, oral RIS, and oral OLA) was 10.1% with a compliant patient, 39.6% with a partially compliant patient, and 70.7% with a non-compliant patient.

The relapse rate not requiring hospitalisation with typical antipsychotics (HAL LAI) was 18.3% with a compliant patient, 62.4% with a partially compliant patient, and 91.4% with a non-compliant patient.

The frequency of relapse (number of episodes per relapsing patient per year) was 1.9 when requiring hospitalisation and 2.6 when not requiring hospitalisation.

The duration of relapse (number of days per episode) when requiring hospitalisation was 23.1.

The rate of extrapyramidal adverse events was 9% with oral RIS, 7.4% with oral OLA, and 29.7% with HAL LAI.

The rate of bodyweight gain was 22.8% with RIS LAI, 31.9% with oral RIS, 40.5% with oral OLA, and 14.2% with HAL LAI.

Methods used to derive estimates of effectiveness
A modified Delphi panel approach was used to elicit inputs from two experts when data from published sources were not available.

Estimates of effectiveness and key assumptions
The duration of relapse (number of days per episode) when not requiring hospitalisation was 5. The rate of extrapyramidal adverse events was 9% with RIS LAI.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of days of relapse averted. This was derived using the decision model. Other model outputs were also reported. These included the number of stable days per patient, the proportion of patients with relapse, and the frequency of relapses per patient. No discount rate was applied given the short time horizon.

Direct costs
Discounting was not relevant since the costs were incurred during a short timeframe (one year). The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were inpatient care, outpatient care and medications (including the cost of injection administration). Inpatient care covered hospitalisation, day hospital and emergency room. Outpatient care covered physician office visit, mental health clinic visit, home health care, social/group therapy meetings, and nutritionist. The cost/resource boundary of the health care system was adopted. Both the costs and resource use data were derived from published sources. Some economic estimates were based on authors' and experts' assumptions. Drug dosages were based on information provided by manufacturers. All costs were inflated to 2002 values using the Medical Care Services Consumer Price Index.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were carried out to determine the most influential model inputs. The ranges of values used were based on published CIs or were set by experts' opinions.

Estimated benefits used in the economic analysis
The mean number of days of relapse per patient was 14.3 (11.2 requiring hospitalisation and 3.1 not requiring hospitalisation) with RIS LAI, 22.6 (17.7 and 4.8, respectively) with oral RIS and with oral OLA, and 36.3 (28.3 and 8, respectively) with HAL LAI.

The mean number of stable days per patient was 350.7 with RIS LAI, 342.4 with oral RIS and with oral OLA, and 328.7 with HAL LAI.

The proportion of patients with relapse not requiring hospitalisation was 23.6% with RIS LAI, 36.5% with oral RIS and with oral OLA, and 60.4% with HAL LAI.

The proportion of patients with relapse requiring hospitalisation was 25.9% with RIS LAI, 41.2% with oral RIS and with oral OLA, and 65.8% with HAL LAI.

The mean number of relapses per patient was 1.1% with RIS LAI, 1.7% with oral RIS and with oral OLA, and 2.8% with HAL LAI.

Cost results
The total costs were $19,589 with RIS LAI, $19,986 with oral RIS, $21,331 with oral OLA, and $27,917 with HAL LAI.

The largest cost component was the cost for hospitalisation, with the overall cost per treatment largely attributable to the cost of relapses.

Synthesis of costs and benefits
The calculation of a cost-effectiveness ratio was not required in the base-case. In fact, RIS LAI was the dominant strategy, being the most effective in reducing days of relapse and least costly. In the comparison among the other three medications, oral RIS and oral OLA had the same effectiveness, thus the use of a cost-minimisation analysis showed that the least costly treatment strategy was oral RIS. Oral RIS was more effective and less costly than HAL LAI and was, therefore, a dominant therapy. Similarly, oral OLA dominated HAL LAI.

The sensitivity analysis showed that variations in the frequency of relapse requiring hospitalisation led to the largest range of costs and clinical outcomes. The rank order of the alternative medications was, in general, not affected by variations of clinical and economic inputs. However, RIS LAI was no longer dominant in several scenarios. First, when the relapse rate requiring hospitalisation for compliant patients was increased to the highest possible values. Second, when the rate of relapse rate requiring hospitalisation of partially compliant patients was set to the lowest values. Third,
when the proportion of compliant patients was increased to the highest value. Fourth, when the proportion of non-compliant patients was set to the lowest value. Finally, when the frequency of relapse was set at the lowest value. Further, when the cost of hospitalisation was decreased by 10% or 25%, costs associated with receiving RIS LAI became higher than those for oral RIS. However, in all these cases, the incremental cost per day of hospitalisation or relapse averted for RIS LAI compared with the other strategies remained relatively low.

Authors' conclusions
Risperidone (RIS) long-acting injection (LAI) was a dominant strategy for the treatment of patients with schizophrenia because it was more clinically effective and less costly than the next most effective comparators, oral RIS and oral OLA.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was consistent with the objective of the study. The comparators under investigation were widely used drugs for patients with schizophrenia. The dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published sources. An extensive review of the literature was carried out to derive the relapse rates. The inclusion and exclusion criteria for the primary studies were reported. Other clinical parameters were obtained from studies which appear to have been identified selectively. Overall, no information on the design of the studies was provided and it was only stated that some unpublished data came from clinical trials. Thus, it was difficult to assess the validity of the clinical inputs. Some assumptions were also made. These were based on expert opinion, although the authors stated that the use of assumptions was minimised. The issue of uncertainty was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The benefit measure was specific to the disease considered in the study and is not comparable with the benefits of other health care interventions. Several model outputs were also reported.

Validity of estimate of costs
The perspective adopted in the study was explicitly stated. It appears that the relevant categories of costs were included in the analysis. Extensive details on the unit costs and quantities of resources used were provided, which enhances the possibility of replicating the analysis in other settings. The source of the data was reported. The costs were treated deterministically but economic estimates were extensively varied in the sensitivity analysis. The price year was reported, which aids reflation exercises.

Other issues
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were performed. This enhances the external validity of the analysis. The authors stated that the shortcomings of the data used in the model represented the main limitations of the study. The model highlighted the most relevant clinical inputs, which should be further investigated in other studies. The authors noted that advantages from the patient's perspective might have been greater than those observed in the study.

Implications of the study
The study results supported the use of RIS LAI for the treatment of community-dwelling patients with schizophrenia. The advent of LAI agents such as RIS LAI would facilitate patient adherence to prescribed treatments and would result in improved long-term outcomes. The authors suggested that further research should quantify the patient's perception of
their condition.

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