Assessing cost-effectiveness of drug interventions for 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
New neuroleptics for the treatment of patients with schizophrenia were examined. These were clozapine (CLO; 400 mg/day), risperidone (RIS; 5 mg/day) and olanzapine (OLA; 15 mg/day). Eight treatment strategies were considered:

- RIS versus typical neuroleptics,
- RIS versus typical neuroleptics with side effects,
- RIS versus low-dose typical neuroleptics,
- OLA versus typical neuroleptics,
- OLA versus typical neuroleptics with side effects,
- OLA versus RIS,
- CLO versus typical neuroleptics for patients with a chronic course of disorder with little deterioration, and
- CLO versus typical neuroleptics for patients with a chronic course of disorder with clear deterioration.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with schizophrenia. This included paranoid, hebephrenic, catatonic, undifferentiated, schizoaffective, delusional disorder and other non-organic non-affective psychotic disorders.

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

Dates to which data relate

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.
Modelling
A Markov model was constructed to model prevalent cases of schizophrenia and related conditions in Australia in the year 2000, through annual cycles with relevant hazards and marginal costs until the whole cohort had died or reached 100 years of age. No further details of the decision model were reported.

Outcomes assessed in the review
The outcomes assessed from the literature were:

the length of illness in patients with schizophrenia;

the number of Australians in the year 2000 affected by schizophrenia;

the annual remission rate;

the disease prevalence (male and female);

the baseline adherence level for people taking typical neuroleptics;

the percentage of typical and atypical neuroleptics with moderate or severe side effects;

the percentage of persons on typical neuroleptics taking a low dose;

the relative risk of all-cause mortality for individuals older than 15 years of age;

the disability weights (DW) associated with specific health states;

the impact of weight gain on ischaemic heart disease, ischaemic stroke, diabetes mellitus and colorectal cancer;

the reduction in suicide risk;

the effect size for each strategy compared; and

improvements in DW due to symptom reduction and side effect profile.

The health benefits associated with CLO, RIS and OLA were also obtained from the literature, but only data for RIS compared with typical neuroleptics were reported.

Study designs and other criteria for inclusion in the review
Published evidence was used to derive clinical estimates. It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The authors stated that systematic reviews and recent randomised trials were searched for clinical evidence. The mortality risk for schizophrenia was derived from Australian Bureau of Statistics, while the relative risk of all-cause mortality came from a meta-analysis. The DWs came from a study that used a questionnaire based on six selected items from the World Health Organization Disability Assessment Schedule, the Lancaster Lancashire Quality of Life Profile and the Social Contact Questionnaire, plus two questions capturing the respondents' self-rating of satisfaction with independence and with life in general. The statistical approaches used to calculate the effect size were reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Twenty-nine primary studies appear to have been used to provide clinical data. Other studies were probably used to derive the health benefits associated with the drugs under investigation, but were not reported.

Methods of combining primary studies
Statistical methods were used to combine some primary estimates. In particular, the average effect size within studies was calculated, and then pooled across studies using the random-effects method.

Investigation of differences between primary studies
Not stated.

Results of the review
The average length of illness in patients with schizophrenia was 15 years (range: 0 - 54). Disease prevalence was 0.23% (range: 0.16 - 0.31) among men and 0.15% (range: 0.1 - 0.19) among women. Thus, there were 37 000 Australians in the year 2000 affected by schizophrenia.

The annual remission rate was 1.5% (range: 1 - 2).

The baseline adherence level for people taking typical neuroleptics was 54%.

The relative risk of all-cause mortality for individuals older than 15 years of age was 1.56.

The DWs ranged from 0.21 for the mildest health state to 0.96 for the worst health state.

For the impact of weight gain on ischaemic heart disease, ischaemic stroke, diabetes mellitus and colorectal cancer, the mean relative risks was 1.03 (range: 1.01 - 1.05) for colon cancer, 1.04 (range: 1.02 - 1.06) for ischaemic heart disease and stroke, and 1.11 (range: 1.07 - 1.14) for diabetes.

Moderate side effects were observed for 15% of persons on typical neuroleptics and 9% of those on atypical neuroleptics. Severe side effects were found in 10% (typicals) and 6% (atypicals), respectively. Seventy per cent of persons on typical neuroleptics were taking a low dose.

The reduction in suicide risk was 50% for patients on CLO and 0 for patients on other drugs.

The effect size was:

0.219 for RIS versus typical neuroleptics;
0.219 for RIS versus typical neuroleptics with side effects;
0.126 for RIS versus low-dose typical neuroleptics;
0.251 for OLA versus typical neuroleptics with or without side effects;
0.096 for OLA versus RIS;
0.416 for CLO versus typical neuroleptics with little deterioration; and
0.63 for CLO versus typical neuroleptics with clear deterioration.

The improvements in DW due to symptom reduction and side effect profile (and the combined improvement) were, respectively:

0.033 and 0.010 (0.043, 95% confidence interval, CI: 0.018 - 0.079) for RIS versus typical neuroleptics;
0.031 and 0.073 (0.105, 95% CI: 0.077 - 0.142) for RIS versus typical neuroleptics with side effects;
0.019 and 0.008 (0.027, 95% CI: -0.001 - 0.060) for RIS versus low-dose typical neuroleptics;
0.038 and 0.010 (0.046, 95% CI: 0.027 - 0.078) for OLA versus typical neuroleptics;
0.038 and 0.073 (0.109, 95% CI: 0.086 - 0.143) for OLA versus typical neuroleptics with side effects;
0.015 and 0.0 (0.015, 95% CI: -0.014 - 0.046) for OLA versus RIS;
0.064 and 0.007 (0.071, 95% CI: 0.042 - 0.131) for CLO versus typical neuroleptics with little deterioration; and
0.104 and 0.010 (0.109, 95% CI: 0.065 - 0.188) for CLO versus typical neuroleptics clear deterioration.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of disability-adjusted life-years (DALYs) associated with each treatment strategy. DALYs were estimated using the modelling approach and combining years of life lost to premature mortality and years lived with disability. Given the long time horizon, a discount rate of 3% was applied.

Direct costs
The cost analysis was performed from the perspective of the health sector. However, the costs to the patient associated with medication were also reported. The health services included in the economic evaluation were the marginal cost of changing from one medication regimen to another. Thus, with the exception of blood testing associated with CLO, only drug costs were considered. Physician visits were assumed to be constant and were not included. The authors stated that cost-offsets due to a fall in resource use associated with more effective drugs were not taken into consideration because of a lack of data. The unit costs and some information on resource use were provided. Resource use was estimated on the basis of published data and recommended daily doses. The costs came from official Australian sources, such as the Department of Health and the Pharmaceutical Benefit Scheme. Given the long time horizon, a discount rate of 3% was applied. The price year was 2000.

Statistical analysis of costs
The costs were treated deterministically.

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

Currency
Australian dollars (Aus$).

Sensitivity analysis
A Monte Carlo simulation was used to represent uncertainty ranges of costs, benefits and cost-utility ratios. Probability
distributions of the parameters were derived from published data or experts' opinions and were reported.

**Estimated benefits used in the economic analysis**
The incremental DALYs were:

- 3,600 (95% CI: 1,500 - 7,300) with RIS versus typical neuroleptics (eligible population 9,300);
- 3,000 (95% CI: 2,000 - 4,300) with RIS versus typical neuroleptics with side effects (eligible population 1,800);
- 2,200 (95% CI: -150 - 5,300) with RIS versus low-dose typical neuroleptics (eligible population 9,300);
- 4,300 (95% CI: 2,100 - 8,100) with OLA versus typical neuroleptics (eligible population 9,300);
- 3,100 (95% CI: 2,100 - 4,400) with OLA versus typical neuroleptics with side effects (eligible population 1,800);
- 340 (95% CI: -470 - 1,200) with OLA versus RIS (eligible population 3,300);
- 11,000 (95% CI: 6,900 - 17,000) with CLO versus typical neuroleptics, chronic with little deterioration (eligible population 11,000); and
- 9,900 (95% CI: 4,600 - 15,000) with CLO versus typical neuroleptics, chronic with clear deterioration (eligible population 5,400).

**Cost results**
The incremental costs (in Aus$millions) were:

- Aus$180 (95% CI: 130 - 240) with RIS versus typical neuroleptics (eligible population 9,300);
- Aus$60 (95% CI: 46 - 75) with RIS versus typical neuroleptics with side effects (eligible population 1,800);
- Aus$180 (95% CI: 130 - 240) with RIS versus low-dose typical neuroleptics (eligible population 9,300);
- Aus$390 (95% CI: 280 - 530) with OLA versus typical neuroleptics (eligible population 9,300);
- Aus$120 (95% CI: 87 - 140) with OLA versus typical neuroleptics with side effects (eligible population 1,800);
- Aus$53 (95% CI: 39 - 72) with OLA versus RIS (eligible population 3,300);
- Aus$470 (95% CI: 330 - 630) with CLO versus typical neuroleptics, chronic with little deterioration (eligible population 11,000); and
- Aus$230 (95% CI: 160 - 310) with CLO versus typical neuroleptics, chronic with clear deterioration (eligible population 5,400).

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative treatment strategies examined in the study.

The incremental cost per DALY (in Aus$thousands) was:

- Aus$48 (95% CI: 27 - 110) with RIS versus typical neuroleptics (eligible population 9,300);
- Aus$20 (95% CI: 15 - 27) with RIS versus typical neuroleptics with side effects (eligible population 1,800);
Aus$80 (95% CI: 36 - dominated) with RIS versus low-dose typical neuroleptics (eligible population 9,300);
Aus$92 (95% CI: 53 - 170) with OLA versus typical neuroleptics (eligible population 9,300);
Aus$38 (95% CI: 87 - 50) with OLA versus typical neuroleptics with side effects (eligible population 1,800);
Aus$160 (95% CI: 44 - dominated) with OLA versus RIS (eligible population 3,300);
Aus$42 (95% CI: 31 - 62) with CLO versus typical neuroleptics, chronic with little deterioration (eligible population 11,000);
Aus$23 (95% CI: 17 - 47) with CLO versus typical neuroleptics, chronic with clear deterioration (eligible population 5,400).

The authors also evaluated specific elements of the interventions that related to aspects of equity, strength of evidence, feasibility and acceptability. The analysis revealed the following results. First, there was sufficient evidence to make valid comparisons between drug interventions for established schizophrenia. Second, increased prescribing of CLO was feasible while maintaining strict monitoring of haematological side effects. Third, clinicians and patients place different value on side effects of neuroleptics and the importance given them in the analysis. Finally, the arbitrary use of an A$50,000 threshold was considered too low or inappropriate for schizophrenia.

Authors' conclusions
In general, the high costs of risperidone (RIS) and olanzapine (OLA) did not balance the modest clinical effects (expect in the case of those experiencing moderate to severe side effects on typical neuroleptics), while greater clinical improvements associated with clozapine (CLO) appear to justify its high cost. Using a threshold of Aus$50,000 per disability-adjusted life-year (DALY), low-dose typical neuroleptics were a cost-effective strategy for patients with established schizophrenia, while RIS should be reserved for those experiencing moderate to severe side effects on typical neuroleptics. OLA should only be prescribed when RIS is not clinically indicated. Earlier introduction of CLO might be cost-effective.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear. In addition, the choice of the interventions was appropriate for the study question. Newer drugs were compared with medications commonly used to treat schizophrenia. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from the literature. However, the methods and conduct of the review were not reported. No information on the search and inclusion or exclusion criteria was provided. The number of studies included in the review was reported but, with the exception of a few clinical trials, the primary studies were not described. Thus, it was not possible to assess the validity of the primary studies. The methods used to calculate some clinical inputs were reported. The authors noted that some data estimated from clinical trials did not consider specific side effects that would have been relevant to the current analysis. The clinical outcomes were varied appropriately in a probabilistic sensitivity analysis.

Validity of estimate of measure of benefit
A justification for the use of DALYs was provided. In general, scarce information on quality of life was available in the literature. DALYs also have the advantage of being fairly comparable with the benefits of other health care interventions. However, it was stated that the current treatments had a substantial impact on quality of life rather than on life extension. Thus, caution is required when making comparisons with the benefits of other strategies. Further, the authors noted that the DWs were based on clinician-rated values rather than on patient-rated ones.
Validity of estimate of costs
The authors stated that the cost analysis was carried out from the perspective of the health care sector. Only the drug costs (and blood tests, whenever relevant) were included in the analysis. However, it was unclear which types of patient costs were considered since they were broken down into those relevant to the government and those relevant to the patients. The unit costs were reported. The resource use data reflected treatment patterns in the authors’ setting. The price year was reported, which aids reflation exercises in other settings. The costs were specific to the study setting but probabilistic distributions were assigned in the Monte Carlo simulation.

Other issues
The authors reported extensively findings of other economic evaluations, but noted some drawbacks of published studies. The issue of the generalisability of the study results to other settings was not addressed, but CIs for cost, benefits and cost-utility ratios were calculated to address the issue of uncertainty in the final estimates. The authors discussed the problems of feasibility, in particular acceptability of the interventions to stakeholders. The limitations of the clinical trials carried out among patients with schizophrenia were pointed out. These included, for example, the high drop-out rate, the short time horizon, the inclusion of patients with established schizophrenia and the exclusion of patients with a history of drug abuse.

Implications of the study
The study results suggested that low-dose neuroleptics should be used for the treatment of established schizophrenia, with RIS being restricted to patients experiencing moderate to severe side effects on typical neuroleptics. The authors noted that when the patent period expires, the cost of drugs should fall substantially, making OLA and RIS more cost-effective than the actual price levels. The authors recommended "outcome measurement in such studies include quality of life (both patient- and clinician-rated), social and economic functioning, drug tolerability, compliance, satisfaction and side effects".

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