Disease progression in amyotrophic lateral sclerosis: identifying the cost-utility of riluzole by disease stage

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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 riluzole for the treatment of amyotrophic lateral sclerosis (ALS).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis; cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with ALS.

Setting
The setting was likely to have been secondary care. The economic study was conducted in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2001. The costs and resource use data were derived from a study published in 1998. The price year was not explicitly reported.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.

Modelling
On the basis of prior work, a decision model was constructed to simulate the lifetime experiences of ALS patients and to assess their duration in each specific health state. The model was based on a Markov process. The health states considered were mild, moderate, severe, terminal and death.

Mild corresponded to recently diagnosed; mild deficit in only one of three regions (i.e. speech, arm, and leg); functionally independent in speech, upper extremity activities of daily living, and ambulation.

Moderate corresponded to mild deficit in all three regions, or moderate to severe in one region while the other two regions were normal or mildly affected.

Severe corresponded to need for assistance in two or three regions; speech dysarthric and/or need for assistance in walking and/or with upper extremity activities of daily living.
Terminal corresponded to non-functional use of at least two regions and moderate or non-functional use of the third region.

The time horizon of the model was lifetime. It was assumed that only one transition could be made in any cycle, and the cycles were assumed to last for 2 months. In the base-case, it was assumed that the last set of transition probabilities observed in the original trial (at 18 months) were repeated for all remaining cycles using simple linear regression. However, a secondary analysis, using the mean of transition probabilities occurred in the first 9 cycles or the following Markov cycles, was also performed.

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

- the transition probabilities for both arms of the decision model,
- the baseline distribution of patients in each health state, and
- the utility values associated with ALS severity levels.

The utility values were obtained using the visual analogue scale (VAS) and the standard gamble (SG) approach.

**Study designs and other criteria for inclusion in the review**
A formal review of the literature was not undertaken. Most of the effectiveness evidence came from a multi-centre, randomised, double-blind placebo-controlled trial. Other information on the primary studies was not given.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
The author did not discuss the validity of the primary studies. However, the use of a clinical trial as a main source of evidence ensured a high internal validity.

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

**Number of primary studies included**
Three primary studies provided the model inputs.

**Methods of combining primary studies**
Not stated.

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

**Results of the review**
The transition probabilities will not be reported here because of the large number of values used in the model.

The baseline distribution of the patients was 19.18% in state 1, 67.29% in state 2, 12.57% in state 3, and 0.96% in state
The mean utility values were:

for the mild state, 0.74 with the VAS and 0.79 (median 0.80) with the SG approach;
for the moderate state, 0.63 with the VAS and 0.67 (median 0.75) with the SG approach;
for the severe state, 0.51 with the VAS and 0.71 (median 0.78) with the SG approach; and
for the terminal state, 0.37 with the VAS and 0.45 (median 0.50) with the SG approach.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years and quality-adjusted life-years (QALYs). These were derived from the decision model. An annual discount rate of 1.5% was used in the base-case. The SG values were selected for base-case QALYs.

**Direct costs**
An annual discount rate of 6% was used for costs incurred in future years, owing to the long time horizon of the analysis. The unit costs were not presented separately from the quantities of resources used. A breakdown of the cost items was not reported. The costs referred mainly to diagnostic procedures and treatment. The cost of side effects was assumed to have been zero as patients were taken off treatment until symptoms were relieved. The cost/resource boundary of the NHS was adopted. The costs were estimated from a published study, while resource use reflected utilisation patterns in the UK. The price year was not explicitly reported, but it might have been 1998.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
UK pounds sterling ( ).

**Sensitivity analysis**
Univariate sensitivity analyses were conducted to assess the robustness of the estimated cost-utility and cost-effectiveness ratios. Variations in the discount rate, incorporation of utilities, and types of preferences were investigated. The analysis also investigated the most appropriate start of treatment (early versus late stage). A probabilistic sensitivity analysis was conducted to address the uncertainty surrounding the model inputs when the probabilities were extended over the timeframe of the trial. A Monte Carlo simulation with 10,000 distribution samples was used.

**Estimated benefits used in the economic analysis**
The estimated mean QALYs gained with riluzole over BSC were 0.34 (median 0.37).

Riluzole led to a survival gain of more than 6 months, with approximately 5 months of the additional life gained in the early disease states.

When the base-case distribution of patients among health states was varied in the sensitivity analyses, the QALYs
gained with riluzole ranged from 0.43 (all patients started in mild health state) to 0.065 (all patients started in severe health state).

**Cost results**
The estimated average costs per patient were not reported.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits of riluzole over BSC.

In the base-case, with health outcomes discounted at 1.5%, the mean cost per QALY was 22,086 (median 20,172) and the mean cost per life-year saved was 15,192, with an average equivalent of over 4 months of perfect health over the lifetime of ALS patients.

The sensitivity analysis showed that the additional cost per QALY or per life-year gained with riluzole ranged from 14,370 to 28,674, depending on the discount rate or the utility values used in the model.

The probabilistic sensitivity analysis yielded a mean baseline cost of 22,236 (+/- 612) per QALY when transition probabilities in the long period were based on a simple linear regression, and 33,420 (+/- 972) when transition probabilities in the long period were based on an average of the first 9 cycles. This suggested that the model was sensitive to the way in which transition probabilities were extended beyond the clinical trial period.

**Authors’ conclusions**
Riluzole increased survival in patients with amyotrophic lateral sclerosis (ALS), mainly in disease stages where quality of life was relatively high, at a cost that could be affordable to the National Health Service (NHS). However, the analysis revealed that the estimated cost-effectiveness was sensitive to model assumptions.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was appropriate as it reflected the standard treatment approach for patients with ALS in UK. However, details of BSC were not reported. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used data from published studies. However, a review of the literature was not undertaken and most of the evidence came from a primary clinical trial, which was randomised and double-blinded. The sample size and the period during which the trial was conducted were reported. This ensured the validity of the main source of evidence. The author stated the data used in the analysis represented the best data available. Other information was obtained from another published study, some details of which were given. Sensitivity analyses were conducted to address the issue of variability in the model inputs.

**Validity of estimate of measure of benefit**
Both summary benefit measures were appropriate for assessing the impact of the intervention on the patients’ health. They are both comparable with the benefits of other health care interventions. The use of alternative discount rates and different utility values was investigated in the sensitivity analysis.

**Validity of estimate of costs**
The author stated explicitly which perspective was adopted in the study. It appears that all the relevant categories of costs have been included in the analysis. The costs were derived from a published study and a detailed breakdown of the
cost items was not provided. Further, information on the unit costs and quantities of resources used was not given. This reduces the possibility of replicating the study. Discounting was appropriately conducted and the impact of varying the discount rate was investigated in the sensitivity analysis. The price year was not explicitly reported, which makes reflation exercises in other settings difficult. The author noted that the inclusion of the indirect costs could potentially improve the cost-effectiveness of the study intervention.

Other issues
The author stated that riluzole had been found relatively cost-effective in other countries, although differences in the final figures could be due to variations in country-specific data. The issue of the generalisability of the study results to other settings was not addressed, although extensive sensitivity analyses were conducted. This partly enhanced the external validity of the analysis. The study referred to patients with ALS and this was reflected in the author's conclusions.

Implications of the study
The author noted that future studies should use decision models incorporating long-term data for both groups, although such data can be obtained only from observational studies. It was also noted that the results of the current analysis should be considered only as a guide, rather than an exact estimation of the cost-effectiveness of riluzole.

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Other publications of related interest


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