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Original papers

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Disease progression in amyotrophic lateral sclerosis

Identifying the cost-utility of riluzole by disease stage

Abstract

This study reports the results of a long-term economic evaluation of riluzole in the treatment of amyotrophic lateral sclerosis (ALS) versus best supportive care in the United Kingdom. The analysis included in this contribution aims to provide an update of the determination of the phase of the disease that is prolonged by riluzole and also to assess the quality of the life extension offered by riluzole by taking into account the patients' utility score. Specifically, the analysis provides a more specific estimate of the cost-utility of riluzole dependent disease stage, thereby providing a useful insight of the cost-effectiveness of therapy. A Markov model was used to assess the cost-effectiveness of riluzole versus best supportive care. Transition possibilities and the distribution of patients by health states were taken from a cohort of 954 patients drawn from a large randomised, double blind, placebo-controlled, multicentre trial between 1992 and 1994. Costs associated with riluzole included the acquisition cost and bi-monthly monitoring for raised ALT levels. Patient assessed utilities were collected by use of the SG technique from two centres (King's, London and Preston) in the UK. Four distinct health states were used corresponding to mild, moderate, severe and terminal states. Applying the Markov model and extending the transitional probabilities using linear interpolation, the base case cost per life year gained was estimated at £15,192 while applying Standard Gamble utility scores, the base case cost per quality-adjusted life-year (QALY) was assessed at £22,086. Carrying out a probabilistic sensitivity analysis, the cost per QALY was estimated at £22,236 with standard deviation of £612. The results of the long-term analysis also show that riluzole on average increases survival in ALS patients by 6 months with approximately 5 months of the additional life gained in the early disease states, of which 4 months is spent in disease state 2, where quality of life is relatively high. However, the model is sensitive in the way in which the long-term transitional probabilities are estimated. Using averages of the first nine cycles, the cost per QALY would increase to £33,420 with standard deviation of £972. Thus, this analysis highlights some of the difficulties associated with extending the short clinical effectiveness data; one way forward would be to obtain long-term observations data for both groups.

Keywords

ALS · Cost-utility · Cost-effectiveness · Markov models · Riluzole

This study reviews the assessment of the quality of life and discounting utilities based on the recent guidance from National Institute for Clinical Excellent (NICE) on cost effectiveness of riluzole in the treatment of amyotrophic lateral sclerosis (ALS). ALS is the most common form of motor neurone disease (MND) and it is estimated to account for 65–90% of all cases [1]. The first cost-effectiveness analysis for the United Kingdom was published in 1999 [2] which looked at cost per life year gained. However, after publication it was noted that a software error had led to incorrect labelling of a particular arm of the decision-tree. To rectify this error and provide a more complete discussion an update to the original 1999 paper was produced and published in the *Journal of Neurological Sciences* [3]. This analysis uses Markov modelling, a method introduced to this area (MND) by Riviere et al. [4] The analysis included in this contribution aims to provide an update of the assessment of quality of the life extension offered by riluzole by taking into account the patients' utility score. Specifically, the analysis provides a more specific estimate of the cost-utility of riluzole-dependent disease stage, thereby providing a useful insight of the cost-effectiveness of therapy.

The precise causes of the neurodegenerative process of ALS or MND remain unknown, and at present there is no cure. The majority of patients eventually die from respiratory failure [4, 5]. The average survival from the onset of symptoms ranges between 2.5 and 5 years [5, 6, 7, 8].

The disease is found more predominantly amongst men [9], and international estimates of prevalence range between 4 and 10 cases per 100,000 popu-

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lation, with annual incidence estimated between 1 and 3 cases per 100,000 population [4, 10, 11]. In the United Kingdom it is estimated that there are currently between 2,400 and 5,400 persons suffering from ALS [10, 12], and a general practice with 10,000 patients is likely to encounter a case of motor neurone disease every two to 3 years [5].

There is no standard presentation for ALS. In about 70% of patients the first symptoms appear in the limbs and these symptoms are usually manifested in the form of difficulty walking and/or manipulating objects with a hand. Approximately 30% of patients have bulbar onset disease, where they face difficulties in articulating and swallowing due to damage to the bulbar motor neurones. Such heterogeneity in disease presentation, together with the relative rarity of the condition, often leads to difficulty in diagnosis, which therefore often occurs when the disease is well advanced; in some cases 16 months after the onset of initial symptoms [13]. Patients with ALS suffer no impairment to either memory or intellect throughout the disease process. Other functions that are not normally impaired by the disease include: bladder and bowel control, vision and eye movement, sensation and sexual function [1].

The range of pharmacological interventions available is rather limited [5] while surgical interventions might be necessary to improve breathing or feeding. ALS occurs in two forms: sporadic and familial, with the former accounting for 90% of all cases [5]. Although the exact pathogenic mechanisms governing the onset of ALS are still unknown, one of the theories put forward argues that the excessive accumulation of glutamate to toxic levels causes neurones to die via a calcium-dependent pathway [14, 15]. This has led to the development of drugs such as riluzole, which are designed to decrease the exitotoxic potential of glutamate [12]. Riluzole has been shown to alter glutamatergic transmission [16], retard disease progression [12], and improve survival in ALS patients, albeit to a limited extent [3, 15, 17].

The severity and relatively short survival of patients who suffer from ALS, coupled with the direct cost of treatment with riluzole (£3,742 per year) prompted NICE to review the clinical and cost-effectiveness of this therapy prior to issuing guidance to the NHS. NICE published its guidance on riluzole in January 2001 and recommended that riluzole be made available for the treatment of individuals with the ALS form of MND in accordance with its licensed indications. However, treatment should be aimed at not only retarding or arresting motor neurone injury, but close attention should also be paid to the quality of the additional life gained by using riluzole [5].

Table 1
Patients transitional probabilities: riluzole group

	1	2	3	4	5
Cycle 1					
State 1	60.58	4.01	–	–	–
State 2	37.96	78.48	1.27	–	–
State 3	–	15.40	73.42	–	–
State 4	–	–	18.99	100.00	–
State 5	1.46	2.11	6.33	–	100.00
Cycle 2					
State 1	63.73	0.96	–	–	–
State 2	36.27	82.17	3.31	–	–
State 3	–	13.25	75.21	6.25	–
State 4	–	0.96	7.44	87.50	–
State 5	–	2.65	14.05	6.25	100.00
Cycle 3					
State 1	75.00	2.45	–	–	–
State 2	25.00	83.65	5.71	–	–
State 3	–	11.44	71.43	–	–
State 4	–	0.27	14.29	66.67	–
State 5	–	2.18	8.57	33.33	100.00
Cycle 4					
State 1	66.67	3.14	–	–	–
State 2	33.33	81.45	3.68	–	–
State 3	–	11.64	69.85	5.88	–
State 4	–	–	13.97	82.35	–
State 5	–	3.77	12.50	11.76	100.00
Cycle 5					
State 1	70.21	0.73	–	–	–
State 2	29.79	79.93	3.14	–	–
State 3	–	15.69	79.07	4.65	–
State 4	–	0.36	11.63	86.05	–
State 5	–	3.28	6.16	9.30	100.00
Cycle 6					
State 1	71.43	3.02	–	–	–
State 2	28.57	78.88	5.00	–	–
State 3	–	16.38	72.86	2.08	–
State 4	–	–	9.29	64.58	–
State 5	–	1.72	12.86	33.33	100.00
Cycle 7					
State 1	83.87	1.05	–	–	–
State 2	16.13	77.49	5.34	–	–
State 3	–	17.28	78.63	7.89	–
State 4	–	–	5.34	76.32	–
State 5	–	4.19	10.69	15.79	100.00
Cycle 8					
State 1	88.46	0.69	–	–	–
State 2	11.54	82.07	3.60	–	–
State 3	–	16.55	75.68	6.25	–
State 4	–	–	8.11	78.13	–
State 5	–	0.69	12.61	15.63	100.00
Cycle 9					
State 1	73.68	4.21	–	–	–
State 2	26.32	82.11	2.50	–	–
State 3	–	12.63	77.50	3.85	–
State 4	–	–	8.75	69.23	–
State 5	–	1.05	11.25	26.92	100.00

Table 2
Patients transitional probabilities: usual care group

	1	2	3	4	5
Cycle 1					
State 1	67.44	1.91	–	–	–
State 2	32.56	77.07	5.71	–	–
State 3	–	17.83	85.71	–	–
State 4	–	–	5.71	100.00	–
State 5	–	3.18	2.86	–	100.00
Cycle 2					
State 1	62.50	3.70	–	–	–
State 2	37.50	72.59	–	–	–
State 3	–	18.52	81.03	–	–
State 4	–	0.74	5.17	8–	–
State 5	–	4.44	13.79	2–	100.00
Cycle 3					
State 1	6–	1.89	–	–	–
State 2	4–	81.13	1.45	–	–
State 3	–	12.26	71.01	–	–
State 4	–	–	13.04	71.43	–
State 5	–	4.72	14.49	28.57	100.00
Cycle 4					
State 1	62.50	5.43	–	–	–
State 2	31.25	75.00	1.69	–	–
State 3	–	14.13	77.97	–	–
State 4	–	–	10.17	69.23	–
State 5	6.25	5.43	10.17	30.77	100.00
Cycle 5					
State 1	66.67	–	–	–	–
State 2	33.33	81.33	1.82	–	–
State 3	–	14.67	76.36	–	–
State 4	–	–	9.09	69.23	–
State 5	–	4.00	12.73	30.77	100.00
Cycle 6					
State 1	7–	3.08	–	–	–
State 2	3–	76.92	1.89	–	–
State 3	–	2–	75.47	7.14	–
State 4	–	–	13.21	64.29	–
State 5	–	–	9.43	28.57	100.00
Cycle 7					
State 1	66.67	1.89	–	–	–
State 2	33.33	81.13	6.00	–	–
State 3	–	13.21	74.00	–	–
State 4	–	–	14.00	93.33	–
State 5	–	3.77	6.00	6.67	100.00
Cycle 8					
State 1	71.43	2.27	–	–	–
State 2	82.57	79.55	2.56	–	–
State 3	–	13.64	71.79	6.25	–
State 4	–	–	23.08	81.25	–
State 5	–	4.55	2.56	12.50	100.00
Cycle 9					
State 1	66.67	–	–	–	–
State 2	33.33	70.37	4.17	–	–
State 3	–	25.93	75.00	–	–
State 4	–	–	8.33	68.75	–
State 5	–	3.70	12.50	31.25	100.00

Aims

The principal aim of this study is to update the determination of the phase of the disease that is prolonged by riluzole. Information on the cost-effectiveness of riluzole has been reported in another study [3] and a secondary aim is also to update the cost implications of the effect of riluzole using the recent NICE guidance of discounting utilities. The viewpoint considered is, again, that of the National Health Service, and therefore savings in terms of indirect costs (i.e. production loss) and non-medical direct costs have not been considered, although this may lead to an underestimation of the benefit of riluzole in the treatment of ALS as seen from a societal point of view. This is consistent with the perspective of the study and removes any debate regarding the most appropriate measure of these outcomes.

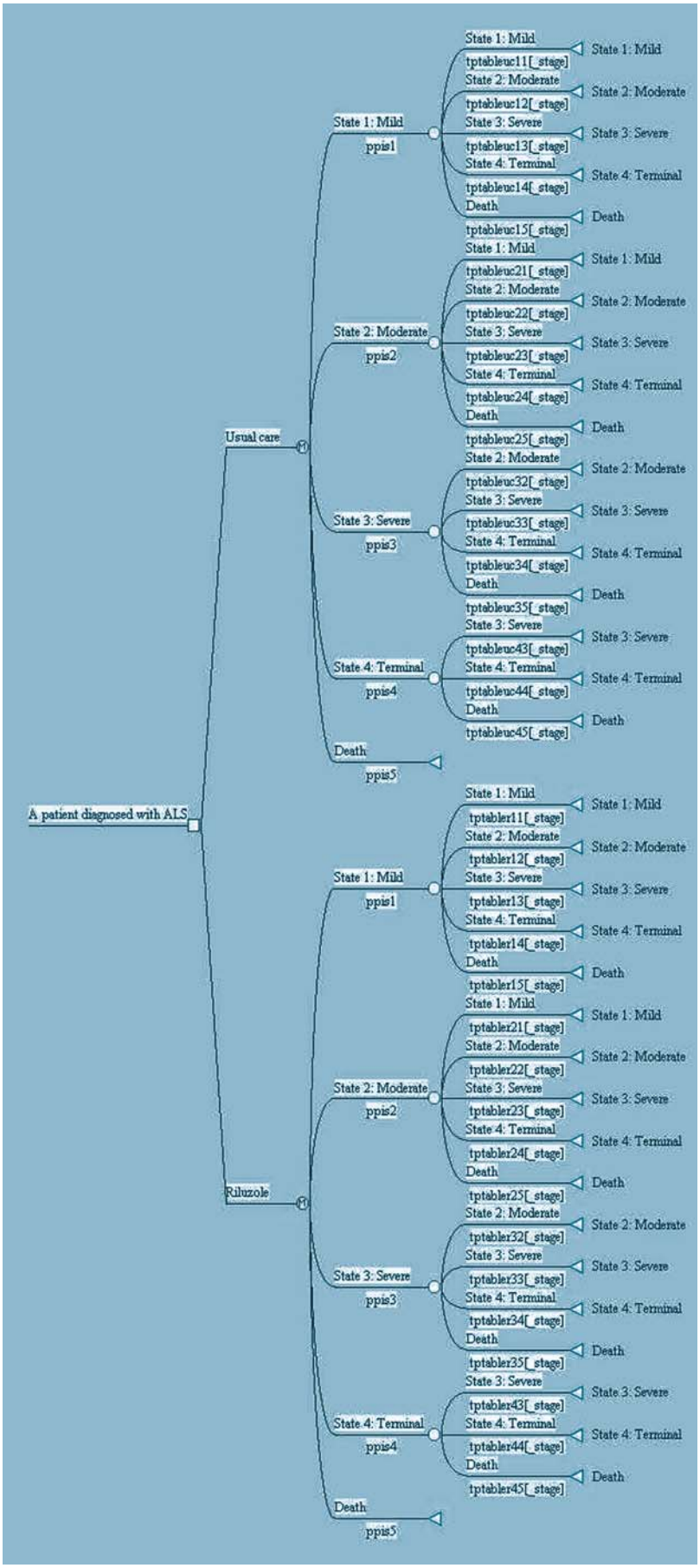
Methods

Model and data

In cost-effectiveness analysis the need for modelling arises largely (in chronic diseases) when the evidence of effectiveness is rather short, but decisions have to be made with a view to the long-term effectiveness of the intervention. Furthermore, explicit modelling can highlight the potential uncertainty surrounding the subject matter. ALS is a case in point. It is a chronic disease, and the data from the clinical studies [17] provide evidence of effectiveness for only a short period; it was terminated early, after 18 months, due to ethical reasons. Furthermore, the long-term efficacy of treatment depends to some extent not only on the type of the model used but also on the assumptions made to generate the long-term data. The

Table 3
Annual costs (£) of the best supportive care for each ALS health state (1998) (from [12, 44])

	State 1: mild	State 2: moderate	State 3: severe	State 4: terminal
Average (baseline)	1,224	805	1,754	3,231
Maximum	1,343	868	1,871	11,819
Minimum	889	640	1,376	1,895



model in this study draws on earlier work by Riviere et al. [4], who compared the best supportive care group with that of riluzole group and introduced the Markov model into ALS therapy assessment. The analysis used previously published data [12] on another earlier analysis of the likely impact of riluzole on costs and health benefits in the UK [3]. The patient data are based on a cohort of 954 patients drawn from a randomised double-blind, placebo-controlled multicentre (France, Belgium, North America, UK, Germany and Spain) trial, which took place between December 1992 and December 1994 [4, 17]. Tables 1 and 2 show the starting distribution of patients for both arms of the Markov model. However, although these data could be criticised for their weaknesses [4], they are the best data available, as it would be ethically difficult to run long-term trials with a placebo arm once the clinical trial shows positive effect of therapy. This analysis incorporated the health state progression analysis in which patients' progress is categorised in terms of the following stages (baseline distribution from [4]):

- State 1: Mild – 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 (baseline: 19.18%)
- State 2: Moderate – mild deficit in all three regions, or moderate to severe deficit in one region, while the other two regions are normal or mildly affected (baseline: 67.29%)
- State 3: Severe – needs assistance in two or three regions; speech dysarthric and/or need for assistance in walking and/or with upper extremity activities of daily living (baseline: 12.57%)
- State 4: Terminal – on-functional use of at least two regions and moderate or non-functional use of the third region (baseline: 0.96%)
- State 5: Death

Fig. 1 ◀ **Full structure of the Markov model for simulating the life time experiences of ALS patients and assessing the duration in individual health states based upon the progression rates observed over the first 18 months in a randomised placebo controlled trial of riluzole**

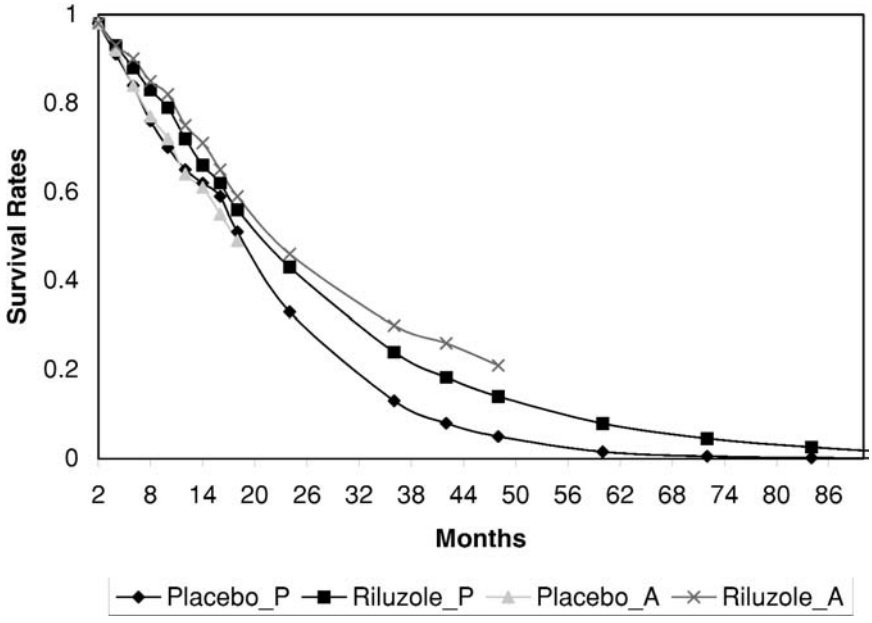


Fig. 2 ▲ **Actual and predicted survival rates. After 18 months patients in the placebo arm of the trial were offered riluzole. Therefore there are no follow-up data available for the placebo group. *Placebo A* Actual survival rates; *placebo P* survival prediction rates from the Markov model; *riluzole A* actual survival rates including follow-up data; *riluzole P* survival prediction rates from the Markov model**

Also assessed were the respective costs associated with these different disease states [4, 12] (Table 3).

A Markov model was used in this study to simulate the life time experiences of ALS patients and to assess duration in each specific health state based upon the progression rates observed over the first 18 months in a randomised placebo controlled trial of riluzole [4, 17]. For the base case, the model extends transition probabilities using linear interpolation between successive probabilities to calculate the number of patients in each different health state. In this study, this means that the last sets of transition probabilities observed in the trial are repeated for all the remaining cycles as they are the most recent observations and could be considered as a good predictor of survival, given the short duration of survival among ALS patients. However, following the recent Health Technology Assessment report [18] the last sets of transition probabilities were replaced with the mean of the nine probabilities in each case in the sensitivity analysis. The problem, however, with such alternatives is that it gives equal weighting to all the observed data and thus should be weighted to take into account different numbers in the various states through the nine cycles. This, however, could not be done due to lack of data. Markov models have been widely used in economic evaluations and are particularly suited to modelling the progression of chronic disease over time [19]. That is the patient outcomes generated by the model are based upon the probability of a patient moving from one health state to another identified in the clinical trial. In this Markov model the transition probabilities were time dependent. Throughout each cycle a patient could remain in one state or transfer to another, more serious, level of the disease. It was assumed that only one transition could be made in any cycle, and the cycles were assumed to last for 2 months (based upon the clinical trial observations) with the process ending when more than 99% of the patients had died.

The full structure of the model used is shown in Fig. 1.

Survival analysis

The long-term follow-up of patients from the clinical trial records survival times but not disease state progression. Thus, the observed state transition probabilities were used to extend the model beyond the 18 months of the trial. The results of the model can then be compared to the observational data beyond 18 months, i.e. the true survival observed for the patients in the riluzole group. No follow-up comparison was possible for the patients of the "best supportive care arm" beyond 18-months because all patients were given riluzole on completion of the original trial. This was to establish longer term safety data and also the ethical considerations that had to be taken into account in terminating the placebo arm at 18 months.

Figure 2 shows the long-term effects of riluzole on survival after the actual 18-month transitional probabilities for both riluzole and best supportive care groups. The results showed a close fit in terms of percentage survival rates for both arms of the model within the sample period from the observed trial (the first 18 months). The model tends to underestimate the actual survival rate in the riluzole arm after 18 months compared with the additional observational data in the treatment arm over the next 2.5 years. However, although this may imply that the model underestimates the quality-adjusted life-year (QALY) for the riluzole arm over the life time of the treated patients, no inference can be made regarding the benefits of treatment as there are no observational data available for the best supportive care after 18 months.

Table 4
Utility scores (from [25])

ALS severity level	Visual analogue scale	Standard gamble	
	Mean	Mean	Median
1	0.74	0.79	0.80
2	0.63	0.67	0.75
3	0.51	0.71	0.78
4	0.37	0.45	0.50

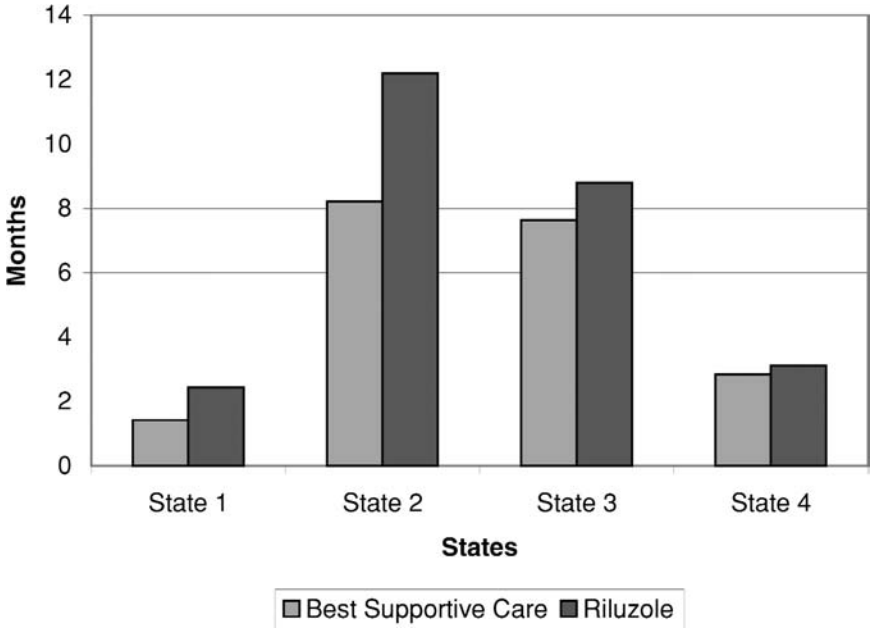


Fig. 3 ▲ **Average number of months spent in each state over the life time per cohort**

Utility assessment

All cost-utility studies should always use valuations derived from a choice-based method [20, 21]. Utilities provide an approach to the measurement of health-related quality of life [22]. Crucial to decision making is the calculation of QALYs, which incorporates utilities in an attempt to assess improved quality of life as well as additional years gained. Measuring health utilities involves first designing a set of health states specific to the particular disease under consideration, identifying individuals who participate in providing judgement of the desirability of each health state, deciding on a choice-based method such as Standard Gamble (SG) or Time Trade-Off (TTO), and finally aggregating across the individuals to yield utility scores for each health state [23].

There are a number of methods used to measure patients' utility directly (e.g. SG) or indirectly (e.g. EuroQol EQ-5D) for different health states [24]. The utilities/values used in this study are those derived by Kiebert et al. [25], who elicited SG and visual analogue scale (VAS) responses from a representative sample of UK MND patients. Kiebert et al. [25] interviewed 77 patients with different levels of disease severity from two centres (King's, London and Preston). Patients were asked to complete a number of measures including SG exercise and VAS rating of current health for their own health state (for more details see [25]).

SG asks patients to make a choice between two alternatives, where one of the alternatives has the certain outcome of current health state *i* for life (*t* years) [26]. On the other hand, the VAS allows patients to mark their current health state, under the condition of certainty, on a scale between "worst imaginable health state" and "best imaginable health state", and not "full health" and "death" as required for estimating QALYs [20]. In this sense the VAS values give only preference values and are not utilities. Although, theoretically, it could be possible to transform VAS scores into utilities, results suggest that the corrected scores and SG utilities are not stable [27]. For this reason VAS values in this study are used only for illustrative purposes (sensitivity analysis).

SG is based on expected utility theory with an underlying theoretical base, which captures the individual's risk attitude. Because future health outcomes are uncertain in the real world, it is argued that utility scores are preferable to values in the setting of decision analysis [20, 21]. The SG has been used extensively as a method of utility measurement [22, 26, 28, 29] and is generally considered to be reliable. However, the SG can be confusing to administer and hence can lead to some inconsistencies as shown in this study, whereas the VAS is not. For this reason the base case results for cost utility analysis report the mean SG utilities, but the effects of using median SG results (although they are still inconsistent but to a lesser degree) or VAS values are explored in the sensitivity analysis.

Table 4 shows preference values and utility scores obtained from the VAS and SG techniques. Although they look on a low magnitude for the mild states, the mean values for VAS are a priori in the right direction. However, the mean (and the median) values for the SG scores are rather unexpected as the utility score in state 2 is lower than the utility score in state 3. A possible reason for this may be that in the severe stage of disease patients are typically receiving more dedicated medical attention, and hence their level of satisfaction could be slightly elevated since they might feel that their disease is being managed.

It is customary in long-term studies to apply discounting rates to bring long-term costs and outcomes to their present values for comparative purposes. However, although there is no controversy on discounting variables such as costs and income expressed in monetary terms, discounting non-monetary variables or health

Table 5
Sensitivity of the results to discounting. Costs (£) are discounted at 6%

Cost per life-year gained	
Only costs discounted	14,370
Both costs and outcomes discounted	
Outcome discounted at 1.5%	15,192
Outcome discounted at 6%	17,760
Cost per QALY	
Visual analogue scale, mean	
Only costs discounted	23,400
Both costs and outcomes discounted	
Outcome discounted at 1.5%	24,678
Outcome discounted at 6%	28,674
Standard gamble, mean	
Only costs discounted	20,904
Both costs and outcomes discounted	
Outcome discounted at 1.5%	22,086
Outcome discounted at 6%	25,794
Standard gamble, median	
Only costs discounted	19,092
Both costs and outcomes discounted	
Outcome discounted at 1.5%	20,172
Outcome discounted at 6%	23,556

Table 6
Sensitivity of the results associated with all patients starting treatment in different disease states. Costs and utilities are discounted at 6% and 1.5%, respectively

	Visual analogue scale	Standard gamble	
	Mean	Mean	Median
Existing patient distribution			
QALY gained	0.30	0.34	0.37
Cost per QALY gained (£)	24,678	22,086	20,172
All in state 1			
QALY gained	0.39	0.43	0.47
Cost per QALY gained (£)	24,186	21,702	19,920
All in state 2			
QALY gained	0.33	0.37	0.40
Cost per QALY gained (£)	23,190	20,694	18,870
All in state 3			
QALY gained	0.063	0.065	0.071
Cost per QALY gained (£)	69,714	68,154	61,812

benefits such as QALY, and what discount rate should be used have remained controversial [30, 31, 32, 33], In this study, for the base case we have followed the NICE guidelines ('Guidance for Manufacturers and Sponsors', 2001: http:/www.nice.org.uk): costs are discounted at 6% while the benefits are discounted at 1.5%. Sensitivity analyses include the combinations: 6% both costs and benefits, and 6% costs and 0% benefits.

Costs

The cost data were obtained from Munsat et al. [12] and updated using the NHS price index. The model estimates only direct health service costs and not the full economic costs of care. The direct medical costs were derived from resource utilisation patterns associated with treatment of ALS in the United Kingdom. Table 3 shows the updated average, maximum and minimum annual costs for each ALS health state. There is a clear pattern of rising costs, starting with diagnosis and testing, and then increasing further with disease severity and progression, with the exception of the moderate state. This can be attributed to a reduction in hospitalisation after the extensive diagnosis phase is completed. The annual cost of treatment with riluzole has remained the same at £3,742, which includes the cost of the product [34] in addition to the cost of bimonthly serum ALT testing (taken from Ninewells Hospital, Dundee, Scotland). The cost of side effects was assumed to be zero as patients were taken off treatment until symptoms were relieved (personal communication with a consultant neurologist in Ninewells Hospital, Dundee, Scotland).

Results

Base case

Riluzole has been shown in this study to increase survival in ALS patients by over 6 months with approximately 5 months of the additional life gained in the early disease states (Fig. 3), of which 4 months is spent in disease state 2, which is likely to be a period when the quality of life is relatively high and the costs of care low [35, 36, 37].

Using the recently published NICE guidelines ('Guidance for Manufacturers and Sponsors', 2001: http:/www.nice.org.uk) for discounting costs and outcomes at 6% and 1.5%, respectively, for the base case gives a mean cost of £22,086 per QALY (median £20,172) and a cost of £14,370 per life-year gained, with an average equivalent of over 4 months of perfect health over the life time of ALS patients.

Sensitivity analysis

A sensitivity analysis using the existing patient distribution (see above, ‚Model and data') shows that additional cost of riluzole can vary from £14,370 to over £28,000 depending on whether utilities are incorporated in the analysis, the type of preference values and also on the discounting rates (Table 5).

Given the cost of treatment, an important question has always been on when to start treatment: early or at a later stage. Clearly such a decision is driven by the clinical profile of the patient. However, information on the cost-effectiveness of initiating therapy at a certain stage is also increasingly important information that is taken into account in decision making. Table 6 shows such an analysis. A further analysis was conducted to assess the cost per QALY by varying the distribution of patients according to the disease state at which patients begin treatment (Table 6). Using mean

Table 7
Variable parameters for stochastic sensitivity analysis: Annual cost of the best supportive care and utility score

Variable	Distribution	Minimum	Average	Maximum
Annual cost of the best supportive care (£)				
State 1	Triangular	889	1,224	1,343
State 2	Triangular	640	805	868
State 3	Triangular	1,376	1,754	1,871
State 4	Triangular	1,895	3,231	11,819
Utility scores				
State 1	Triangular	0.74	0.79	0.80
State 2	Triangular	0.63	0.67	0.75
State 3	Triangular	0.51	0.71	0.78
State 4	Triangular	0.37	0.45	0.50

Table 8
Variable parameters for stochastic sensitivity analysis: probabilities of cycles 10

Probabilities of cycles 10	Average over the first 9 cycles (18 months)
tptableuc11	0.659866
tptableuc12	0.333189
tptableuc13	0.000000
tptableuc14	0.000000
tptableuc15	0.006944
tptableuc21	0.022411
tptableuc22	0.772322
tptableuc23	0.166878
tptableuc24	0.000822
tptableuc25	0.03756
tptableuc32	0.0281
tptableuc33	0.764822
tptableuc34	0.113111
tptableuc35	0.09396
tptableuc43	0.014877
tptableuc44	0.775011
tptableuc45	0.210111
tptabler11	0.726
tptabler12	0.272
tptabler13	0.0000
tptabler14	0.0000
tptabler15	0.0016222
tptabler21	0.0225
tptabler22	0.8069
tptabler23	0.1447
tptabler24	0.001767
tptabler25	0.024067
tptabler32	0.037277
tptabler33	0.7485
tptabler34	0.108677
tptabler35	0.105544
tptabler43	0.040944
tptabler44	0.789811
tptabler45	0.169244/2

SG values, if all patients start in state 1, i.e. treatment starts as soon as a patient is diagnosed with MND, an average of over 5 months is gained, at a cost of £21,702 per QALY. If treatment starts at state 2 (moderate) the additional QALYs gained is just under 4.5 months with a reduced cost of per QALY of £20,694. If all patients start treatment in state 3, the cost per QALY rises to over £68,000. The results thus confirm that the marginal costs decrease when the treatment period is extended from the third to the second and first. However, although the likelihood of a patient starting therapy at this severe stage of illness is low, the cost of treating patients who start in disease state 3 is substantially higher than that of treating state 1 or state 2 patients, or those in the normal baseline distribution, mainly due to the small gains in QALY (just under 1 month of equivalent of perfect life). The findings suggest that although the extended life is rather modest, if a diagnosis of ALS is made early, and treatment started as soon as possible, the degree of benefit to patients, in terms of QALYs gained, will be higher and the overall cost per QALY will be lower.

Given that the model contains a number of uncertain variables, a probabilistic (stochastic) sensitivity analysis using distribution sampling was also performed, in which probability distributions were assigned to the point estimates of all the key variables (see Tables 7, 8). The uncertainties on costs and utility scores were represented with triangular distributions of minimum, most likely and maximum values, while the uncertainty in transition probabilities was assessed by replacing the last sets used in the model by the set of transition probabilities averaged over the first nine cycles. Monte Carlo simulation was performed using 10,000 distribution samples. Probabilistic sensitivity analysis yielded a mean baseline cost of £22,236±612 per QALY based on simple extrapolation and one of £33,420±972 based on the first nine cycles. These results suggest that the model is sensitive to the way in which transition probabilities are extended beyond the clinical trial period.

Discussion

It is generally accepted that the outlook for patients diagnosed with MMD is currently poor. Riluzole is the only drug available which has been shown to extend survival in these patients when compared to usual care. The result of the Markov model suggests an increased life expectancy of over 6 months, of which 1 month is spent in health state 1 and 4 months is spent in health state 2, where functional status is still relatively good. However, this gain in life expectancy, although modest, should be put in context considering that the median survival is just 2.5–5 years from diagnosis. Furthermore, the indirect cost to carers and their families as well as the direct cost to the community services can be significant. These costs could not be included in the present study due to the perspective of the analysis, but the incremental QALYs gained could be interpreted as potential savings in these areas.

The baseline cost per QALY gained, using the based patient distribution from the trial, varies from £19,092 to under £29,000 depending on which scenarios are used, and the sensitivity analysis suggests that patients would benefit more if the disease is diagnosed and treated at the early stage. Uncertainty in key variables was assessed using both multiple one-way and stochastic sensitivity analyses, in which probability dis-

tributions were assigned to the point estimates of the key variables. The results suggest that the model is sensitive in the way in which transition probabilities are extrapolated beyond the clinical trial period. Given that survival rates among ALS patients is rather short, it is not surprising that the cost per QALY can vary substantially depending on the model(s) and the assumption(s) used.

One major limitation of this study, as in other similar chronic diseases, is the short duration of clinical trial where it is difficult to justify long-term clinical trials due to ethical issues. However, observational data could be collected which would then be incorporated into the model to make better estimates of cost per QALY.

MND is not a common disease and with a prevalence of 4.0–4.7 per 100,000 in the UK and Republic of Ireland [38, 39, 40, 41], the overall burden of illness is relatively low, and the additional cost of treating all patients with ALS to the NHS in England and Wales is about 5 million per year ('NICE issues guidance on riluzole for motor neurone disease', 19 January2001: http:/www.nice.org.uk.).

Whilst the cost-effectiveness of riluzole by disease stage has not been previously estimated, the overall cost-effectiveness has been addressed in other countries. Messori et al. [42] reported £27,028 per life-year gained for the UK (U.S. $45,048, exchange rate of $1.0=£0.60), £32,500 for Italy ($54,166) and £37,565 ($62,609) for the United States, while a study in Israel by Ginsberg and Lev [43] suggests that riluzole is cost effective. However, the variation in the cost per life-year gained can be explained by a number of factors: different cost structure, patient transitional probability and patient reported utility data. In the UK a recent appraisal by NICE (2001: http:/www.nice.org.uk) suggests that "Riluzole be used to treat patients suffering from the Amyotrophic Lateral Sclerosis (ALS) form of Motor Neurone Disease (MND)" , and a recent HTA report (part 2) also suggested that revised analysis provides "a more attractive cost-effectiveness profile for riluzole" (2001: 'The clinical effectiveness and cost effectiveness or riluzole for motor neuron disease – an update. Riluzole for motor neurone disease – HTA report part 2. http://www.nice.org.uk.

However, we have seen that in many chronic disease areas such as MND and multiple sclerosis judging cost-effectiveness is not going to be easy or uncontroversial. Results of this study are therefore only a guide rather than an exact measurement of the cost-effectiveness of riluzole. Defining acceptable upper limits for cost-effectiveness figures remains both elusive and controversial. An article in *The Financial Times* (10 August 2001) asked whether NICE is moving towards a cut-off point for the treatments of about £30,000 per QALY. It claims, "In effect, a league table of cost-effectiveness is starting to emerge. Below the line the NHS will fund it; above the line it will not." Sir Michael Rawlins, chairman of NICE, emphasises that although the QALY is crucial in making decisions regarding the cost-effectiveness of interventions, other factors such as patients' views, a judgment and balancing a whole range of issues including price must be taken into consideration.

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