Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (Review)

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TABLE OF CONTENTS

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ABSTRACT

Background
Riluzole has been approved for treatment of patients with amyotrophic lateral sclerosis in many countries but not all. Questions persist about its clinical utility because of high cost, modest efficacy and concern over adverse effects.

Objectives
To examine the efficacy of riluzole in prolonging survival, and in delaying the use of surrogates (tracheostomy and mechanical ventilation) to sustain survival.

Search strategy
Search of the Cochrane Neuromuscular Disease Group Register for randomized trials and enquiry from authors of trials, Aventis (manufacturer of riluzole) and other experts in the field. The most recent search was November 2002.

Selection criteria
Types of studies: randomized trials
Types of participants: adults with a diagnosis of amyotrophic lateral sclerosis
Types of interventions: treatment with riluzole or placebo
Types of outcome measures:
Primary: pooled hazard ratio of tracheostomy-free survival over all time points with riluzole 100 mg.
Secondary: per cent mortality as a function of time with riluzole 100 mg and other doses of riluzole; neurologic function, quality of life, muscle strength and adverse events.

Data collection and analysis
We identified four eligible randomized trials. Each reviewer graded them for methodological quality. Data extraction was performed by a single reviewer and checked by two others. We obtained some missing data from investigators and regulatory agencies. We performed meta-analyses with Review Manager 4.1 software using a fixed effects model. A test of drug efficacy was based on the Parmar pooled hazard ratio.

Main results
The three trials examining tracheostomy-free survival included a total of 876 riluzole treated patients and 406 placebo treated patients. The data for tracheostomy-free survival was not available from the fourth trial. The methodological quality was acceptable and the three trials were easily comparable, although one trial included older patients in more advanced stages of amyotrophic lateral sclerosis.

Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials ($p = 0.039$, hazard ratio 0.80, 95% confidence interval 0.64 to 0.99) and there was no evidence of heterogeneity ($p = 0.33$). When the third trial (which included older and more seriously affected patients) is added, there is evidence of heterogeneity ($p<0.0001$) and the random effects model, which takes this into account results in the overall treatment effect estimate falling just short of significance ($p = 0.056$, hazard ratio 0.84, 95% confidence interval 0.70 to 1.01). This represents a 9% gain in the probability of surviving one year (57% in the placebo and

66% in the riluzole group). In secondary analyses of survival at separate time points, there was a significant survival advantage with riluzole 100 mg at six, nine, 12 and 15 months, but not at three or 18 months. There was a small beneficial effect on both bulbar and limb function, but not on muscle strength. There were no data on quality of life, but patients treated with riluzole remained in a more moderately affected health state significantly longer than placebo-treated patients (weighted mean difference 35.5 days, 95% confidence interval 5.9 to 65.0). A threefold increase in serum alanine transferase was more frequent in riluzole treated patients than controls (weighted mean difference 2.62, 95% confidence interval 1.59 to 4.31).

Authors' conclusions

Riluzole 100 mg daily is reasonably safe and probably prolongs survival by about two months in patients with amyotrophic lateral sclerosis. More studies are needed, especially to clarify its effect in older patients (over 75 years), and those with more advanced disease.

PLAIN LANGUAGE SUMMARY

Riluzole 100 mg probably prolongs survival in patients with amyotrophic lateral sclerosis by about two months and the safety of the drug is not a major concern.

The evidence from randomized controlled trials indicates that patients taking riluzole probably survive longer than patients taking placebo. The beneficial effects are very modest and the drug is expensive. Adverse effects from riluzole are relatively minor and for the most part reversible after stopping the drug.

BACKGROUND

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative motor neuron disease characterized by weakness in limb and bulbar muscles with atrophy, spasticity, weight loss and ultimately respiratory failure. The incidence is approximately two per 100,000 per annum, and it is estimated that there are about 25,000 prevalent patients in North America (McGuire 1996). The disease is virtually always fatal and approximately half of patients die within three to four years after the onset of symptomatic weakness. There is a combination of upper motor neuron and lower motor neuron abnormalities, and relentless and nearly linear progression of impaired function in almost all patients.

The burden of disease upon patients, family members and caregivers is substantial with increasing cost associated with increasing disability and the need for assisted medical care. At present in ALS, disease-specific therapy can at best only slow disease progression and does not stabilize or improve the underlying disorder.

There have been many controlled clinical trials of disease-specific therapy for ALS. Until quite recently, all were negative. Emerging evidence that chronic glutamate excitotoxicity may accumulate to toxic levels and contribute to neuronal death in ALS provided a rational basis for undertaking a clinical trial with riluzole, a drug that appears to block the presynaptic release of glutamate (Rothstein 1996). The first randomized trial demonstrated a modest increase in survival in treated patients compared to placebo controls (Bensimon 1994). However, many questions were raised by this study, especially in view of the disproportionate benefit observed in patients with onset of disease in bulbar (oropharyngeal) as opposed to limb muscles (Rowland 1994).

To address these concerns, a much larger dose-ranging study was carried out and again there was a small but statistically significant prolongation of survival in patients receiving the intermediate and high dose of riluzole (Lacomblez 1996). A trial was also carried out in France and Belgium involving patients with more advanced ALS who did not qualify for the large trial (Bensimon 2002). In this study, there was no significant survival advantage from riluzole. A fourth trial was carried out in Japan with multiple outcome measures that differed from the other three trials (Yanagisawa 1997). This study, which involved small numbers of patients and different end points was negative. The results from this trial are not included in this review because of the difference in outcomes and the lack of survival-specific data.

Subsequently, the drug was approved in the USA and just recently in Canada (conditional, upon completion of a phase IV study to include a natural history arm) and in a number of European countries, but not in Australia.

A number of concerns about the therapeutic effect persist: the lack of benefit observed for some secondary measures of efficacy, the modest prolongation of survival (on average a few months), and the relatively high cost of the drug (approximately $10,000US/year). A Practice Advisory was issued in 1997 by the Quality Standards Subcommittee of the American Academy of Neurology recommending that the drug should be offered to patients, but with some restrictions (Neurology 1997). Some published reviews have favoured the use of riluzole, but their conclusions were not based on a systematic review of the evidence (Hugon 1996; Hugon

1996(a); Miller 1996; Wokke 1996; Meininger 1997). The Trent Institute report on purchasing did not recommend riluzole expressing concern about cost effectiveness (Chilcott 1997). A report from Wessex reached a similar conclusion (Booth-Clibborn 1997). The Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the evaluation of additional products reported that riluzole had demonstrated a modest prolongation of survival (CPMP 1999). Their report indicated that there was adequate evidence of efficacy of riluzole and a satisfactory benefit profile to recommend marketing authorization. The National Institute for Clinical Effectiveness recommended riluzole use in the UK (NICE 2001), based upon the systematic review from the Midlands Group (HTA 2000) as well as input from experts and user groups. The present review was initially published in the Cochrane Library including only the first two clinical trials (Bensimon 1994 and Lacomblez 1996). This revision of that systematic review now contains a full analysis of three trials with partial data from a fourth and a revised primary outcome measure to take into account all data at all timepoints.

In our revised review, we report that Riluzole 100 mg appears to prolong survival in patients with ALS by about two months which is shorter than that suggested in previous versions of this review. This reduction in estimated survival prolongation occurred as a result of the inclusion of a study (Bensimon 2002), not included in earlier versions, which enrolled older patients with more advanced disease. Inclusion of such a study might a priori be expected to weaken the evidence of efficacy in terms of survival prolongation. Conversely, recent studies using large databases spanning five to 10 years have suggested that treatment with riluzole might be associated with a median survival prolongation of six months (Meininger 2000), 12 months (Traynor 2001), or even 21 months (Turner 2001). It is not clear to what extent the greater reported efficacy of riluzole in these uncontrolled studies was influenced by other factors, such as riluzole users having less advanced disease than non-users, or differential use of interventions such as gastrostomy and non-invasive respiratory support. These studies had the advantage of longer term follow up than the RCTs (Bensimon 1994; Lacomblez 1996; Bensimon 2002) and included patients treated earlier in the course of ALS which may approximate routine clinical practice more closely, but the effects of uncontrolled potential confounders on survival could have biased the survival results.

The goal of the present review is to examine systematically all evidence from randomized clinical trials relating to the effects of riluzole in ALS, in order to supply the best evidence currently available on which to base clinical decision making and future research.

OBJECTIVES

The main objective of this systematic review is to examine the efficacy of riluzole in prolonging survival, and in delaying the use of surrogates (tracheostomy and mechanical ventilation) to sustain survival. The effect of riluzole upon functional health will also be assessed.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized trials involving riluzole treatment of ALS.

Types of participants

Adults with a clinical diagnosis of ALS.

Types of intervention

Treatment with oral riluzole or placebo.

Types of outcome measures

Primary
(1) Pooled hazard ratio based on per cent mortality (or tracheostomy) for 100 mg riluzole versus placebo over all time points.

Secondary
(1) Risk ratios based on per cent mortality as a function of time (3, 6, 9, 12, 15, 18 months) for 100 mg riluzole versus placebo.
(2) Risk ratios based on per cent mortality as a function of time (3, 6, 9, 12, 15, 18 months) - all doses of riluzole versus placebo.
(3) Muscle strength assessed by manual muscle testing.
(4) Functional scales.
(5) Quality of life of patients and caregivers.
(6) Adverse effects from riluzole.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: Cochrane Neuromuscular Disease Group Search Strategy

A search was carried out using the Cochrane Neuromuscular Disease Group register with amyotrophic lateral sclerosis OR motor neuron disease OR motor neurone OR motoneurone disease as the search terms. The date of the last search was November 2002 which revealed no new studies. We contacted the company (Aventis) and the authors of trials identified to find additional published or unpublished data and to clarify issues concerning trial design and loss of patients to follow up. We also obtained the reviews of the Food and Drug Administration, the Trent Institute (UK) (Chilcott 1997), the European Agency for the Evaluation of Medicinal Products (UK) (CPMP 1999), Booth-Clibborn 1997, Chilcott 1997, HTA 2000 and NICE 2001 and checked their references.

METHODS OF THE REVIEW

Titles and abstracts identified from the register were checked by two reviewers. The full texts of all potentially relevant studies were obtained for independent assessment by all reviewers. The reviewers decided which trials fit the inclusion criteria and graded their methodological quality. The reviewers contacted the authors for clarification of data where necessary. Disagreements about inclusion criteria and methodological quality were resolved by discussion between the reviewers.

The methodological quality of the trials was assessed by each reviewer with particular emphasis on the allocation concealment, which was ranked using the Cochrane approach: Grade A: Adequate, Grade B: Uncertain, Grade C: Inadequate, Grade D: Not specified. The methodological quality assessment also took into account: baseline comparison of the experimental groups, explicit diagnostic criteria, explicit outcome criteria, completeness of follow up, blind outcome assessment, and blind administration of riluzole. Data extraction was performed by one reviewer and checked by two of the others. Data were checked and entered into the computer by one reviewer and verified by the other reviewers. Missing data were obtained from the authors whenever possible.

For the primary outcome variable, we calculated an overall measure of treatment efficacy which combined survival results at different time points. This measure is based on estimating a pooled hazard ratio (i.e. risk of death for treated divided by risk of death for controls). The methods are described in (Parmar 1998). We used this measure in place of the summary relative risk calculated by the RevMan program, which is based on the assumption that results of independent studies are being combined. Since the set of patients are the same at each time point in each study, the assumption of independence is not valid. The summary method we used recognizes that results at different time points are correlated due to the use of a single set of patients in each study. The only dose of riluzole that was included in all trials was 100 mg, therefore this dose was chosen for the primary outcome measure.

We also evaluated, as a secondary outcome measure chosen for this review, survival at 12 months, because it was the longest time point common to all studies. In addition, separate tables have been created for each time point.

Tracheostomy was a surrogate endpoint for survival but there were no criteria which stipulated when tracheostomy should be performed. Timing of tracheostomy is a variable of patient care that may influence study outcome. Since a very small number of patients received tracheostomy, it appears unlikely that this influenced the results, but future studies should explicitly state criteria for both invasive and non-invasive ventilation. The number of patients who had tracheostomy or intubation was low and balanced (17 riluzole, 16 placebo), across the earlier trial by Bensimon et al. (Bensimon 1994) and that by Lacomblez et al. (Lacomblez 1996) compared to 124 deaths in the riluzole group and 156 deaths in the placebo group. Pulmonary function tests were measured infrequently (six month intervals) and were not well standardized. Future studies should include accurate and more frequent measures of respiratory function.

Manual muscle testing was carried out using the Medical Research Council system (Lacomblez 1989). Limb function and bulbar function were evaluated every two months with modified Norris Scales (Lacomblez 1989). Quality of life was not measured but health status was assessed using a classification of five discrete health states which reflect increasing impairment in activities of daily living (Riviere 1998).

For secondary outcomes, including survival at individual time points, we calculated a weighted treatment effect (using a fixed effects analysis) across trials using the Cochrane statistical package, RevMan version 4.0.3. Results were expressed as relative risks (RR) and 95% confidence intervals (CI) for dichotomous outcomes as a function of time, and weighted mean difference (WMD and 95% CI) for continuous outcomes. Analysis was performed on both short term outcomes (adverse effects of riluzole, quality of life, strength and functional scale ratings) and long term outcomes (survival).

We tested for heterogeneity of the results across studies based on predicting the number of deaths at different time points from a pooled hazard compared with predictions based on estimating separate hazards for each study.

We examined the effects of known prognostic factors on survival (Stambler 1998) including age, gender, anatomical site of onset, disease severity (forced vital capacity) and disease duration (defined as being from the onset of weakness to randomization).

DESCRIPTION OF STUDIES

A search of the Cochrane Neuromuscular Disease Group register revealed four possible randomized controlled trials. One trial (Bensimon 2002), a study of severely affected patients who did not meet inclusion criteria for the larger trial (Lacomblez 1996), had not been published when the review was first written but the data are now available. Another trial was carried out in Japan (Yanagisawa 1997), but the full data specific to survival are still not available. The primary outcome measure in this study was different from the other three trials encompassing multiple measures of disease progression rather than tracheostomy-free survival. Despite repeated attempts, we have been unable to obtain comparable data on survival, and the reported outcome measures were different from the other three trials. This review will be revised again, if and when comparable survival data (tracheostomy-free survival, intention-to-treat analysis) become available from the Japanese trial.

Sojka 1997 compared symptom progression during a lead-in phase and a treatment phase in five patients with ALS taking riluzole.

The results were highly variable. The study was excluded because it was non-randomized and uncontrolled.

Riviere 1998 is a post hoc analysis of the health states of patients in the larger trial (Lacomblez 1996). This study was the only one with data that bear on quality of life and was discussed in our review. There was significant prolongation of the mild health state in patients taking riluzole.

Kalra 1998 analyzed magnetic resonance spectroscopy (MRS) data in 11 patients and found that riluzole improved results. Results were quite variable. The study was excluded because it was not randomized.

Another open-label non-randomized uncontrolled study of 50 Mexican patients was carried out by Arriada-Mendicoa '99. The study suggested that progression was slowed in patients taking riluzole but was excluded because it was not randomized and uncontrolled.

Pongratz 1999 studied primarily the safety of riluzole in an open-label German study involving 7916 patients with ALS. The major result was that serious adverse events associated with riluzole use occurred in only 1.7% of patients. This study was excluded because it was uncontrolled and not randomized.

A small study of 31 patients carried out by Desiato 1999 employed transcranial magnetic stimulation in 31 patients with ALS receiving riluzole and 30 controls. Differences in motor evoked potential duration and silent period duration were noted between treated patients and controls. The study was excluded because it was not randomized.

Couratier 2000 published an observational series of 340 patients with ALS at a single center, half of whom were treated with riluzole. This study was excluded because it was not randomized.

There remained four studies that fulfilled the selection criteria. Only three trials contained full data on tracheostomy-free survival, these included results on a total of 876 riluzole treated patients and 406 placebo treated patients. The first was a smaller trial (Bensimon 1994) which compared riluzole 100 mg to placebo in 155 patients. The second, a larger trial (Lacomblez 1996), was a dose ranging study comparing 50, 100 and 200 mg riluzole with placebo in 959 patients. The third trial (Bensimon 2002), a study involving more advanced patients (age >75, duration of illness > 5 years, FVC < 60%) compared riluzole 100 mg with placebo in 168 patients. The fourth trial involved 195 patients in Japan with inclusion criteria that were comparable to the first two trials. This trial by Yanagisawa 1997 was negative. Unfortunately, full data on tracheostomy-free survival are not available from this trial. Thus it was not included in the analyses. The primary outcome measure in the Japanese trial was disease progression utilizing multiple outcomes including walking, arm function, tracheostomy, ventilation and tube feeding.

METHODOLOGICAL QUALITY

In all three trials, patients were randomly assigned to receive riluzole or an identical appearing placebo and the allocation concealment was considered adequate. Patient as well as evaluator blinding was intended in both trials, but no information was provided to assess the effectiveness of patient or evaluator blinding.

Each trial used internationally accepted diagnostic criteria. All trials examined baseline demographic and clinical features, and there were no marked differences between placebo treated and riluzole treated patients at entry. In all trials, a full intention-to-treat analysis was carried out, and all randomized patients were accounted for as dead or alive. In the earlier study by Bensimon et al. (Bensimon 1994), 24 patients were included although they did not entirely meet inclusion criteria. The patients were distributed evenly between groups (11 riluzole, 13 placebo) and probably had little impact on the results. No protocol violations were reported in the other two trials. In the study by Lacomblez et al. (Lacomblez 1996), although the balance of clinical features was not different at baseline between the study groups, patients from France and Belgium were more severely affected at the start of the study, than those from other regions. When these differences were adjusted for in the survival analysis, a beneficial treatment effect was still present. In the Bensimon 2002 trial disease severity was more marked in participants in this trial (% FVC, duration of illness, age and weight) compared to the other two trials.

The methodologic quality assessment took into account patient blinding, observer blinding, explicit diagnostic criteria, explicit outcome criteria, how studies dealt with baseline differences of the groups, and completeness of follow-up. We each graded these items: A: adequate, B: moderate risk of bias, C: inadequate, D: not specified. All studies explicitly stated their diagnostic criteria as being those of the World Federation of Neurology (Brooks 1994), thus all three trials were graded A for this measure. The gradings were the unanimous and independent view of all four reviewers. The scores of each trial for the other quality measures, allocation concealment, patient blinding, observer blinding, explicit outcome criteria, baseline differences, completeness of follow up were all A.

RESULTS

Primary outcome measure: pooled hazard ratio based on percent mortality (or tracheostomy) for patients on riluzole 100 mg versus placebo from all three trials over all time points.

Using recently described methods (Parmar 1998) for combining survival results from different studies, we found riluzole 100 mg per day provided a slight benefit for the homogeneous group of patients in the first two trials (p = 0.039, HR 0.80, CI 0.64 to 0.99) and there was no evidence of heterogeneity (p = 0.33). When the

third trial (which included older and more seriously affected patients) is added, there is evidence of heterogeneity (p<0.0001) and the random effects model, which takes this into account results in the overall treatment effect estimate falling just short of significance (p = 0.056, HR 0.84, CI 0.70 to 1.01). Thus, further trials are warranted to clarify these issues. The calculations are shown in a table available from the Neuromuscular Disease Group (email: kate.jewitt@kcl.ac.uk). The graph at Figure 1 shows the pooled analyses for survival. The pooled hazard ratio for the three trials decreased during zero to six months and then increased from six to 18 months. An overall assessment, based on the hazard ratios for the three trials at all time points, indicated a 16% reduction in the hazard ratio for those taking 100 mg riluzole, which was not quite statistically significant (p = 0.056). This represents a 9% absolute increase in the probability of surviving for one year (57% in the placebo and 66% in the riluzole group).

Secondary outcome measures

(1) Relative risk based on per cent mortality at 12 months for riluzole 100 mg versus placebo.

In the earlier trial by Bensimon et al.(Bensimon 1994), there was significantly lower per cent mortality in riluzole treated patients than in placebo treated patients at 12 months. The relative risk was 0.61 (95% CI 0.39 to 0.97). In the trial by Lacomblez et al.(Lacomblez 1996) there was lower per cent mortality in riluzole treated patients at 12 months with a hazard ratio of 0.71 (95% CI 0.54 to 0.92). In the later trial by Bensimon et al. (Bensimon 2002), there was no significant difference between riluzole treated patients and placebo treated patients, with a relative risk of 0.99 (95% CI 0.79 to 1.25). From a combined analysis of all three trials, there was a survival advantage (p = 0.004) with riluzole at 12 months with relative risk of 0.78 (95%CI 0.65 to 0.92).

There was evidence of heterogeneity in the results (worse survival in the third trial) attributable to the inclusion of patients with more advanced ALS in the later trial by Bensimon et al. (Bensimon 2002). However, the combined results in terms of relative risk from all three trials are nearly the same as those based on the two published trials. The hazard ratio for the combined data from all three studies was 0.78 (95%CI 0.65 to 0.92) at 12 months, compared to the relative risk for the combined data from the studies by Bensimon 1994 and Lacomblez 1996 (excluding the later trial Bensimon 2002) which was 0.68 (95%CI 0.54 to 0.86) at 12 months. Although the survival data show heterogeneity, there was virtually no impact of combining the studies on the overall relative risk results because of the relatively small size of the trial by Bensimon 2002. The Bensimon 2002 trial did not show a beneficial effect, but because of the small size of the trial, this result should not be interpreted as proving that there is no effect in patients with advanced ALS.

(2) Per cent mortality as a function of time - riluzole 100 mg

In the earlier trial by Bensimon et al. (Bensimon 1994) there was significantly lower per cent mortality in riluzole treated patients than placebo treated patients at six, nine and twelve months but the differences were not significant at three, 15 or 18 months. In the trial by Lacomblez et al. (Lacomblez 1996) there was a lower per cent mortality in riluzole treated patients at 9, 12 and 15 months but it was not significantly lower at three, six or 18 months. In the Bensimon 2002 trial, there were no significant differences in mortality at any time point. From the combined analysis of all three trials there was a survival advantage with riluzole at nine, 12 and 15 months but not at three, six or 18 months (RevMan plots and Figure 1 or contact the Cochrane Neuromuscular Disease Group for a copy of the table showing calculations (email: kate.jewitt@kcl.ac.uk).

(3) Per cent survival as a function of time - all doses of riluzole

Pooled data from the 50, 100 and 200 mg dose groups across all three trials showed no significant difference in mortality with riluzole compared to placebo at any timepoint (see RevMan analysis).

(4) Muscle strength assessed by manual muscle testing

In the earlier trial by Bensimon et al.(Bensimon 1994) there was a beneficial effect upon strength (Medical Research Council Scale) in patients treated with riluzole compared to placebo (weighted mean difference -11.50, 95% CI -21.69 to -1.36). However in the trial by Lacomblez et al. (Lacomblez 1996). and in the later trial by Bensimon 2002, no beneficial effect was seen (weighted mean difference 0.40, 95% CI -4.18 to 4.98 trial Lacomblez 1996; and -3.90, 95% CI -15.00 to 7.20 trial Bensimon 2002). When the data were combined, there was no positive effect from riluzole (weighted mean difference -1.88, 95% CI -5.79 to 2.03).

(5) Functional scales

(a) bulbar function:

Although there was no beneficial effect of riluzole on bulbar function in any of the three trials, there was a beneficial effect in the combined data (weighted mean difference -2.06, 95% CI -3.86 to -0.27).

(b) limb function:

There was a small positive benefit on limb function in the trial by Lacomblez et al. (Lacomblez 1996) (weighted mean difference -4.00, 95% CI -7.89 to -0.11), and a positive effect of the combined limb data (weighted mean difference -3.94, 95% CI -7.25 to -0.64).

(6) Quality of life of patients and caregivers

There are no data which directly measured quality of life from the published trials, but patients treated with riluzole in the trial by Lacomblez et al.(Lacomblez 1996) remained in a more moderately affected health state significantly longer than placebo-treated patients (weighted mean difference 35.5 days, 95% CI 5.9 to 65.0). There was no significant prolongation of the mild, severe or terminal health states. When the mild and moderate health states were combined, patients receiving riluzole remained in these states longer than patients receiving placebo. There was no significant prolongation of the combined severe and terminal states.

(7) Adverse effects from riluzole

(a) nausea
In the study by Lacomblez et al.(Lacomblez 1996), nausea was more frequent in riluzole-treated patients than with placebo. Similar results were found when the data from the three studies (Bensimon 1994; Lacomblez 1996; Bensimon 2002) were combined (relative risk 1.55, 95% CI 1.06 to 2.28).

(b) asthenia
There was a trend toward more asthenia among the treated patients in each trial, and this became statistically significant when the data from the three trials (Bensimon 1994; Lacomblez 1996; Bensimon 2002) were combined (relative risk 1.50, 95% CI 1.07 to 2.12).

(c) other clinical adverse effects
Vomiting, diarrhoea, anorexia and dizziness were somewhat more frequent in treated patients compared to controls, but differences did not reach statistical significance. Five riluzole-treated patients reported circumoral paresthesias in the trial by Lacomblez et al. (Lacomblez 1996) but this symptom was not reported by any controls (weighted mean difference 7.71, 95% CI 1.33 to 44.84).

(d) increased alanine transferase (more than three times the upper limit of normal).
More treated patients developed a threefold or greater elevation of serum alanine transferase compared to controls in the study by Lacomblez et al. (Lacomblez 1996), the later trial by Bensimon (Bensimon 2002) and in the combined data (relative risk 2.62, 95% CI 1.59 to 4.31).

(e) low hemoglobin
There was a trend to low hemoglobin in treated patients in the trial by Lacomblez et al. (Lacomblez 1996), but this was not significant (weighted mean difference 4.36 with 95% CI 0.98, 19.37).

Subgroup Analysis:
In the studies Bensimon 1994 and Lacomblez 1996 there was a significant association of survival and three prognostic variables: age, disease severity (forced vital capacity) and disease duration. However, when each of these variables was incorporated into the Cox model, there was no impact of any variable upon the drug treatment effect.

Bulbar score was significantly correlated with survival in the earlier study by Bensimon et al. (Bensimon 1994), but not in the study by Lacomblez et al. (Lacomblez 1996) nor in the (Bensimon 2002) trial. Gender as a prognostic variable was not reported.

DISCUSSION

Three reports of randomized trials of riluzole in a total of 1282 patients with ALS were available for this review. A fourth report from Japan was not sufficiently detailed to include in the meta-analysis. The methodological quality of these trials was judged as adequate by the reviewers. The therapeutic effects of riluzole at 100 mg dose on survival were significant when the homogeneous group of patients in the first two trials are considered ($p = 0.039$). However, when all three trials are analyzed, there is heterogeneity ($p<0.0001$) due to the addition of more seriously affected and older patients, and the combined treatment effect fell just short of significance ($p = 0.056$). Thus, the difference in survival pooled over all patients at all time periods was not quite statistically significant, and the increase in median survival for the riluzole group was very modest (two months). Although the authors described a dose response in the trial by Lacomblez et al, we agree with the HTA assessment that there is no statistically significant evidence for a dose response and that the claim in Lacomblez et al. (Lacomblez 1996) is based on faulty statistics. Also, there was modest impact on functional measures. The studies were stratified to balance the number of patients with bulbar onset and limb onset in each treatment arm because of the important prognostic significance of this variable, with shorter survival on average in patients with bulbar onset. In the earlier study by Bensimon et al. (Bensimon 1994), the therapeutic effect was most prominent in patients with bulbar onset. In the trial by Lacomblez et al., there was no significant difference in therapeutic response between the bulbar and limb onset groups. In the second trial by Bensimon et al. (Bensimon 2002), patients with bulbar onset had a worsening of mortality from riluzole. Overall, there was no correlation between site of onset and benefit from riluzole. In the earlier study by Bensimon et al. (Bensimon 1994), 24 patients were enrolled who did not meet inclusion criteria constituting protocol violations. When these patients were dropped in a separate post hoc analysis, the therapeutic effect of riluzole was not statistically significant, possibly due to reduced power. In the study by Lacomblez et al., protocol violations were found in 35 patients (details not provided) and these patients were included in the intent-to-treat analysis. Data on protocol violations were not available for the study Bensimon 2002 or the Japanese trial.

There was a significant beneficial effect of riluzole in two of three studies, although not at all time points. The survival data for the 100 mg dose of riluzole, the only dosage common to all studies, did not show significance in the early and late time periods, perhaps related to the diminished numbers of events and power in those timeframes. When data from all doses of riluzole from three trials are combined, no comparison was significant, perhaps related to the very modest and non-significant beneficial effect of the 50 mg dose. The absolute risk reduction with the 100 mg dose at 12 months was 9%. Therefore the number-needed-to-treat to delay one death until after 12 months is 11.

Although the therapeutic effects of riluzole on survival were consistent in two of the three studies with comparable outcomes, the impact on functional measures varied among the studies. There was no positive effect on muscle strength when the data were combined. Small beneficial effects on patient function were found in the limb and bulbar scale at the 100 mg dose. The beneficial ef-

fect of drug on health status was derived from post-hoc analysis of blinded data from the study by Lacomblez et al (Riviere 1998). Patients treated with riluzole remained longer in a more moderately affected health state compared with placebo treated patients. These results should be interpreted with caution, however, since no validation study of remaining in a specific health state has been carried out in ALS.

Although we were unable to obtain tracheostomy-free survival for the trial by Yanagisawa et al., an addendum to the HTA indicated that some data were made available by Aventis. Their analysis, including the Yanagisawa data, shifts the pooled hazard ratio result from 0.83 (0.69-0.99) to 0.89 (0.75-1.05). They conclude that 'the differences between these results are of no practical importance'. They also state that the impression of heterogeneity is strengthened.

Future trials should include health-related quality of life measures as an outcome measure. Cost effectiveness calculations should also be included in the trial design since this is an expensive drug (nearly $10,000 U.S. per year). Moreover, in future trials where survival is a primary outcome measure, the standards of care must be carefully delineated in the protocol because percutaneous endoscopic gastrostomy and non-invasive mechanical ventilation appear to extend or prolong survival to a significant degree (Miller 1999). Future trials should focus more carefully on gathering pulmonary function data because of the critical role of respiratory function in prognosis. Older and more advanced patients should also be studied to determine whether or not they receive the same benefit as younger, less advanced patients.

There were no serious adverse effects from riluzole in any study. Nausea and asthenia were the most frequently documented adverse events from riluzole treatment. Elevated liver function tests were also seen in patients treated with riluzole and support the clinical recommendations: (1) to undertake monthly liver function tests for the first three months and then at three month intervals thereafter, and (2) to avoid riluzole in patients with significant hepatic impairment.

AUTHORS' CONCLUSIONS

Implications for practice

Riluzole 100 mg daily probably prolonged life by about two months in patients with Probable and Definite amyotrophic lateral sclerosis with symptoms less than five years, forced vital capacity greater than 60% and age less than 75 years. More studies are needed, especially to determine whether older, more advanced patients with longstanding disease derive the same benefit. Benefits are not apparent to individual patients.

The most frequent side effects are nausea and asthenia. Liver function becomes altered and requires monitoring.

Implications for research

Future trials should examine the effect on quality of life and in different subgroups (for example, more severely affected compared with mildly affected patients). Data from all clinical trials should be made available to the scientific community.

POTENTIAL CONFLICT OF INTEREST

Two authors (Robert G. Miller, M.D. and John D. Mitchell, M.D.) have accepted speakers' honoraria from several pharmaceutical firms, including Aventis, the manufacturer of riluzole. Both Drs. Miller and Mitchell were investigators in the second large trial of riluzole in ALS, but neither participated in data analysis or manuscript preparation. Dr. Robert Miller and Dr. John Mitchell have participated in other scientific activities (Consensus conferences, ALS CARE National database and ALS Practice Parameters) where financial support has come from Aventis. Dan H. Moore, Ph.D. received an honorarium for his participation in the ALS CARE program, supported by Aventis. Mary Lyon has received no compensation from Aventis.

ACKNOWLEDGEMENTS

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Internal sources of support

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Bensimon 1994**
Methods	Double blind, parallel group, randomized, placebo- controlled trial
Participants	155 adult patients with ALS
Interventions	Oral placebo bid or riluzole 50 mg bid
Outcomes	Primary: Percent mortality, without tracheostomy or endotracheal intubation, and functional scales Secondary: Muscle strength, respiratory function
Notes	International (France, Belgium), multicenter
Allocation concealment	A – Adequate

Study	**Bensimon 2002**
Methods	Double blind, parallel group, placebo-controlled, randomized trial
Participants	168 adult patients with ALS, not qualifying for the Lacomblez trial (age >75, FVC < 60%, > five years duration
Interventions	Oral placebo bid or riluzole 50 mg bid
Outcomes	Primary: Percent survival without tracheostomy or endotracheal intubation

	Secondary: functional scales, muscle strength, respiratory function
Notes	International (France and Belgium), multi-center
Allocation concealment	A – Adequate

Study	**Lacomblez 1996**
Methods	Double blind, parallel group, placebo-controlled, randomized, dose-ranging trial
Participants	959 adult patients with ALS fulfilling WFN criteria (Brooks 1994)
Interventions	Placebo, riluzole 50 mg, riluzole 100 mg or riluzole 200 mg per day
Outcomes	Primary: Percent mortality without tracheostomy or endotracheal intubation, by intention-to-treat analysis. Secondary: Muscle strength, functional status, respiratory function, clinician's global impression scale and patient subjective assessments of fasciculations, cramps, tiredness, and stiffness. Respiratory function measured only at 6 month intervals
Notes	International (Europe and North America), multicenter.Protocol violations (35 patients) included in the intention-to-treat analysis. Patients were evenly distributed among groups. Interim analysis (October 1994) did not meet conditions for stopping trial.
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Arriada-Mendicoa '99	Non-randomized uncontrolled study
Couratier 2000	Non-randomized uncontrolled study
Desiato 1999	Non-randomized uncontrolled study
Kalra 1998	Non-randomized uncontrolled study
Pongratz 1999	Non-randomized uncontrolled study
Riviere 1998	Post hoc analysis of randomized controlled trial
Sojka 1997	Non-randomized uncontrolled study
Yanagisawa 1997	Tracheostomy-free survival-specific data unavailable for the intention to treat analysis.

ANALYSES

Comparison 01. riluzole 100mg vs placebo

Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 percent mortality at 12 months	3	799	Relative Risk (Fixed) 95% CI	0.78 [0.65, 0.92]

Comparison 02. riluzole 100 mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 3 months	3	800	Relative Risk (Fixed) 95% CI	0.81 [0.53, 1.24]

Comparison 03. riluzole 100 mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 6 months	3	799	Relative Risk (Fixed) 95% CI	0.85 [0.65, 1.10]

Comparison 04. riluzole 100 mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 9 months	3	799	Relative Risk (Fixed) 95% CI	0.74 [0.60, 0.92]

Comparison 05. riluzole 100 mg vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 15 months	3	771	Relative Risk (Fixed) 95% CI	0.83 [0.71, 0.96]

Comparison 06. riluzole 100 mg vs. placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 18 months	3	634	Relative Risk (Fixed) 95% CI	0.92 [0.83, 1.02]

Comparison 07. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 3 months	3	1282	Relative Risk (Fixed) 95% CI	0.82 [0.56, 1.22]

Comparison 08. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 6 months	3	1248	Relative Risk (Fixed) 95% CI	0.84 [0.66, 1.06]

Comparison 09. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 9 months	3	1196	Relative Risk (Fixed) 95% CI	0.84 [0.70, 1.01]

Comparison 10. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 12 months	3	1136	Relative Risk (Fixed) 95% CI	0.90 [0.78, 1.04]

Comparison 11. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 15 months	3	1066	Relative Risk (Fixed) 95% CI	1.02 [0.90, 1.16]

Comparison 12. riluzole all doses vs placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 percent mortality at 18 months	3	889	Relative Risk (Fixed) 95% CI	0.99 [0.91, 1.09]

Comparison 13. Muscle strength

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 manual muscle testing	3	732	Weighted Mean Difference (Fixed) 95% CI	-1.88 [-5.79, 2.03]

Comparison 14. Functional scales

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 rate of decline of Norris Scale	3	742	Weighted Mean Difference (Fixed) 95% CI	-2.06 [-3.86, -0.27]

Comparison 15. Functional Scales

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 rate of decline of Norris Scale	3	731	Weighted Mean Difference (Fixed) 95% CI	-3.94 [-7.25, -0.64]

Comparison 16. Adverse effects from riluzole 100 mg

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical	3	801	Relative Risk (Fixed) 95% CI	1.55 [1.06, 2.28]

Comparison 17. Adverse effects from riluzole 100 mg

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical	3	801	Relative Risk (Fixed) 95% CI	1.50 [1.07, 2.12]

Comparison 18. Adverse effects from riluzole 100 mg

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Laboratory	3	801	Relative Risk (Fixed) 95% CI	2.62 [1.59, 4.31]

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [*drug therapy]; Excitatory Amino Acid Antagonists [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; Randomized Controlled Trials; Riluzole [*therapeutic use]

MeSH check words

Humans

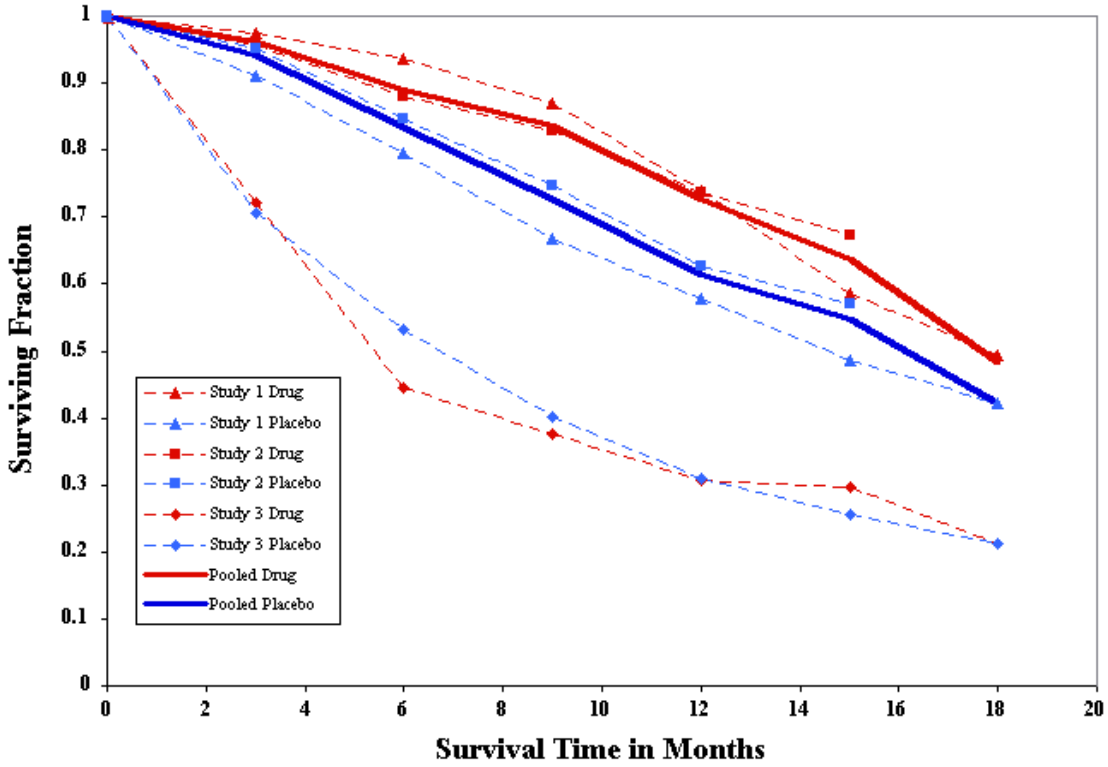
COVER SHEET

Title	Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)
Authors	Miller RG, Mitchell JD, Lyon M, Moore DH
Contribution of author(s)	This review was jointly written by all four reviewers. The lead author (RGM) coordinated the review, abstracted data from the papers, requested additional data from authors, entered the data into Revman and wrote the review. The co-reviewers (JDM, DHM) checked the data, appraised the quality of the studies (especially for allocation concealment) and offered revisions of the review. One co-reviewer is a statistician (DHM). He offered help and advice to the lead author at all stages, and performed the additional statistical analysis of survival at multiple timepoints not provided by Revman. One co-reviewer (ML) is a nurse and patient advocate and offered revisions of the review.
Issue protocol first published	1999/1
Review first published	2000/1
Date of most recent amendment	10 May 2005
Date of most recent SUBSTANTIVE amendment	20 February 2002
What's New	A search of the Cochrane Neuromuscular Disease Group register in November 2002 identified no new trials. Further searches of MEDLINE (January 1966 to December 23 2002) and EMBASE (January 1980 to December 23 2002) identified no new trials. July 2003 The reference to one of the included studies previously cited as Meininger 1995, an unpublished report, was updated throughout the review to Bensimon 2002 on publication of the study in the Journal of Neurology. The reviewers incorporated data from the published report on side effects nausea and asthenia into the pooled analysis.
Date new studies sought but none found	16 January 2003
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author

Date authors' conclusions section amended	20 February 2002
Contact address	Dr Robert Miller Chairman Department of Neurology California Pacific Medical Center 2324 Sacramento Street, Suite 150 San Francisco 94115 USA E-mail: rmiller@cooper.cpmc.org Tel: 1 415 923 3604 Fax: 1 415 923 6567
DOI	10.1002/14651858.CD001447
Cochrane Library number	CD001447
Editorial group	Cochrane Neuromuscular Disease Group
Editorial group code	HM-NEUROMUSC

GRAPHS AND OTHER TABLES

Figure 01. Pooled survival time in months

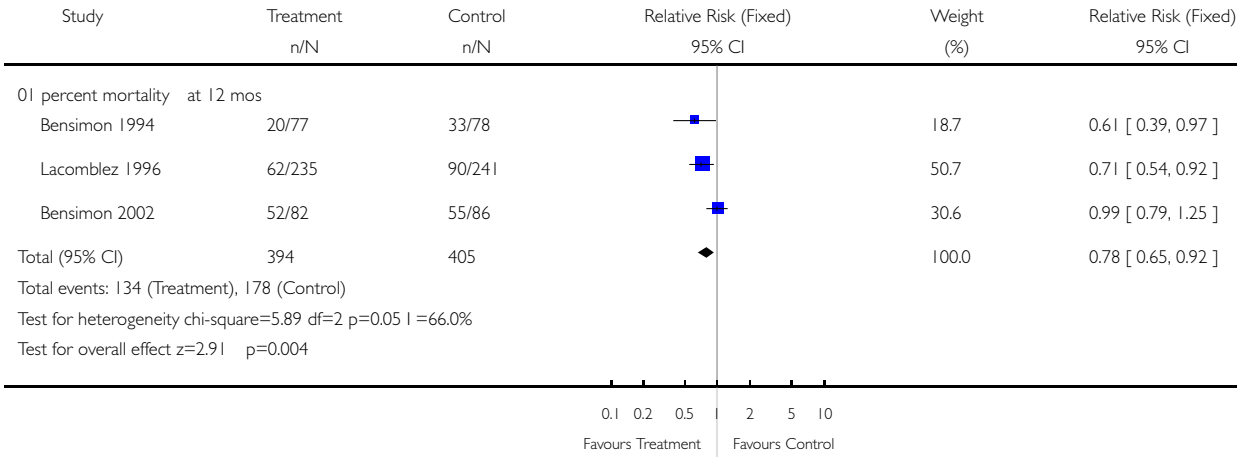


Analysis 01.01. Comparison 01 riluzole 100mg vs placebo, Outcome 01 percent mortality at 12 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 01 riluzole 100mg vs placebo

Outcome: 01 percent mortality at 12 months

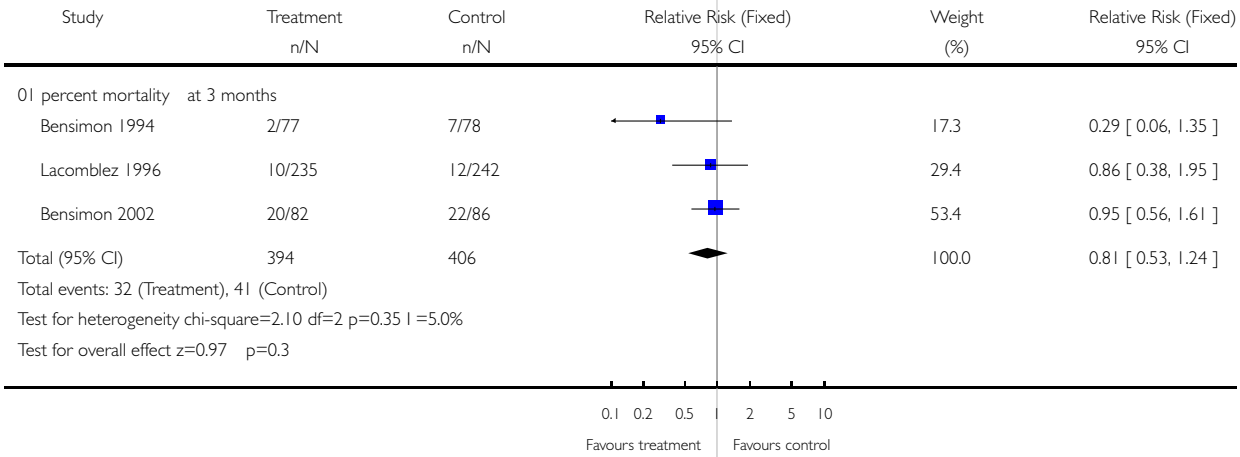


Analysis 02.01. Comparison 02 riluzole 100 mg vs placebo, Outcome 01 percent mortality at 3 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 02 riluzole 100 mg vs placebo

Outcome: 01 percent mortality at 3 months

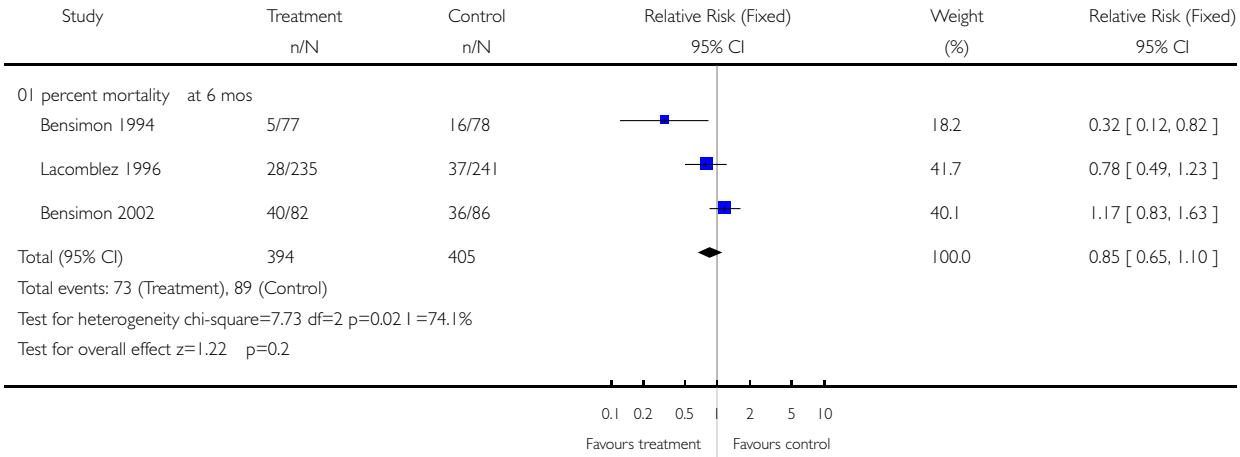


Analysis 03.01. Comparison 03 riluzole 100 mg vs placebo, Outcome 01 percent mortality at 6 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 03 riluzole 100 mg vs placebo

Outcome: 01 percent mortality at 6 months

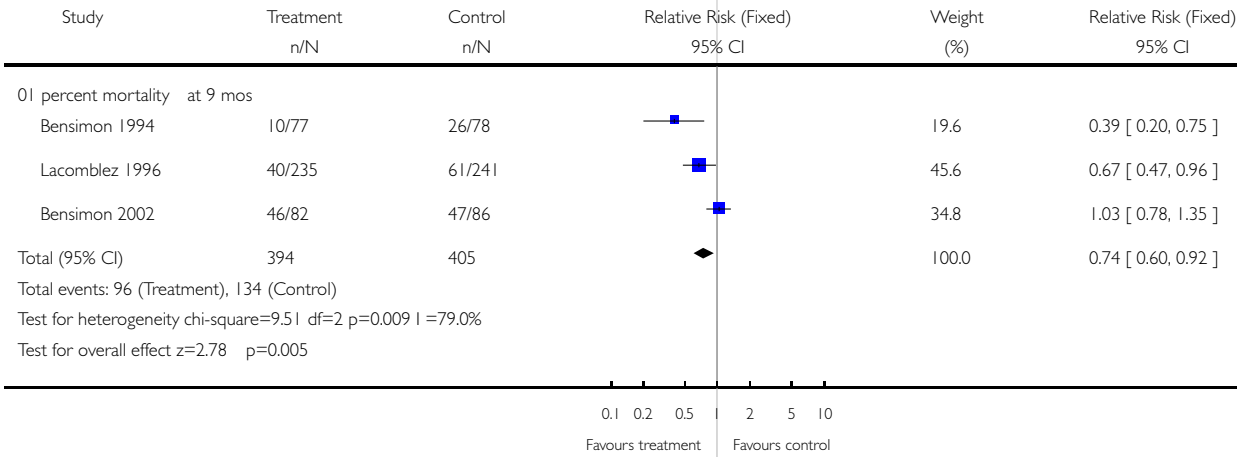


Analysis 04.01. Comparison 04 riluzole 100 mg vs placebo, Outcome 01 percent mortality at 9 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 04 riluzole 100 mg vs placebo

Outcome: 01 percent mortality at 9 months



Analysis 05.01. Comparison 05 riluzole 100 mg vs placebo, Outcome 01 percent mortality at 15 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 05 riluzole 100 mg vs placebo

Outcome: 01 percent mortality at 15 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 15 mos					
Bensimon 1994	32/77	40/78		20.0	0.81 [0.58, 1.14]
Lacomblez 1996	76/218	103/230		50.5	0.78 [0.62, 0.98]
Bensimon 2002	53/82	60/86		29.5	0.93 [0.75, 1.15]
Total (95% CI)	377	394		100.0	0.83 [0.71, 0.96]
Total events: 161 (Treatment), 203 (Control)					
Test for heterogeneity chi-square=1.36 df=2 p=0.51 I =0.0%					
Test for overall effect z=2.50 p=0.01					

Analysis 06.01. Comparison 06 riluzole 100 mg vs. placebo, Outcome 01 percent mortality at 18 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 06 riluzole 100 mg vs. placebo

Outcome: 01 percent mortality at 18 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 18 mos					
Bensimon 1994	39/77	45/78		20.0	0.88 [0.66, 1.17]
Lacomblez 1996	102/153	120/161		52.3	0.89 [0.77, 1.03]
Bensimon 2002	60/80	64/85		27.7	1.00 [0.84, 1.19]
Total (95% CI)	310	324		100.0	0.92 [0.83, 1.02]
Total events: 201 (Treatment), 229 (Control)					
Test for heterogeneity chi-square=1.04 df=2 p=0.60 I =0.0%					
Test for overall effect z=1.55 p=0.1					

Analysis 07.01. Comparison 07 riluzole all doses vs placebo, Outcome 01 percent mortality at 3 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 07 riluzole all doses vs placebo

Outcome: 01 percent mortality at 3 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 3 mos					
Bensimon 1994	2/77	7/78		15.0	0.29 [0.06, 1.35]
Lacomblez 1996	31/717	12/242		38.7	0.87 [0.46, 1.67]
Bensimon 2002	20/82	22/86		46.3	0.95 [0.56, 1.61]
Total (95% CI)	876	406		100.0	0.82 [0.56, 1.22]
Total events: 53 (Treatment), 41 (Control)					
Test for heterogeneity chi-square=2.10 df=2 p=0.35 I =4.9%					
Test for overall effect z=0.98 p=0.3					

Analysis 08.01. Comparison 08 riluzole all doses vs placebo, Outcome 01 percent mortality at 6 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 08 riluzole all doses vs placebo

Outcome: 01 percent mortality at 6 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 6 mos					
Bensimon 1994	5/77	16/78		15.0	0.32 [0.12, 0.82]
Lacomblez 1996	82/684	37/241		51.7	0.78 [0.55, 1.12]
Bensimon 2002	40/82	36/86		33.2	1.17 [0.83, 1.63]
Total (95% CI)	843	405		100.0	0.84 [0.66, 1.06]
Total events: 127 (Treatment), 89 (Control)					
Test for heterogeneity chi-square=7.90 df=2 p=0.02 I =74.7%					
Test for overall effect z=1.44 p=0.1					

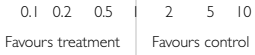
Analysis 09.01. Comparison 09 riluzole all doses vs placebo, Outcome 01 percent mortality at 9 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 09 riluzole all doses vs placebo

Outcome: 01 percent mortality at 9 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 9 mos					
Bensimon 1994	10/77	26/78		16.1	0.39 [0.20, 0.75]
Lacomblez 1996	140/632	61/241		55.2	0.88 [0.67, 1.14]
Bensimon 2002	46/82	47/86		28.7	1.03 [0.78, 1.35]
Total (95% CI)	791	405		100.0	0.84 [0.70, 1.01]
Total events: 196 (Treatment), 134 (Control)					
Test for heterogeneity chi-square=7.43 df=2 p=0.02 I =73.1%					
Test for overall effect z=1.84 p=0.07					



Analysis 10.01. Comparison 10 riluzole all doses vs placebo, Outcome 01 percent mortality at 12 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 10 riluzole all doses vs placebo

Outcome: 01 percent mortality at 12 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 12 mos					
Bensimon 1994	20/77	33/78		15.4	0.61 [0.39, 0.97]
Lacomblez 1996	199/572	90/241		59.4	0.93 [0.76, 1.14]
Bensimon 2002	52/82	55/86		25.2	0.99 [0.79, 1.25]
Total (95% CI)	731	405		100.0	0.90 [0.78, 1.04]
Total events: 271 (Treatment), 178 (Control)					
Test for heterogeneity chi-square=3.51 df=2 p=0.17 I =43.0%					
Test for overall effect z=1.44 p=0.1					

Analysis 11.01. Comparison 11 riluzole all doses vs placebo, Outcome 01 percent mortality at 15 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 11 riluzole all doses vs placebo

Outcome: 01 percent mortality at 15 months

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 15 mos					
Bensimon 1994	32/77	40/78		16.5	0.81 [0.58, 1.14]
Lacomblez 1996	257/513	103/230		59.1	1.12 [0.95, 1.32]
Bensimon 2002	53/82	60/86		24.3	0.93 [0.75, 1.15]
Total (95% CI)	672	394		100.0	1.02 [0.90, 1.16]
Total events: 342 (Treatment), 203 (Control)					
Test for heterogeneity chi-square=3.70 df=2 p=0.161 =46.0%					
Test for overall effect z=0.32 p=0.7					

Analysis 12.01. Comparison 12 riluzole all doses vs placebo, Outcome 01 percent mortality at 18 months

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 12 riluzole all doses vs placebo

Outcome: 01 percent mortality at 18 months

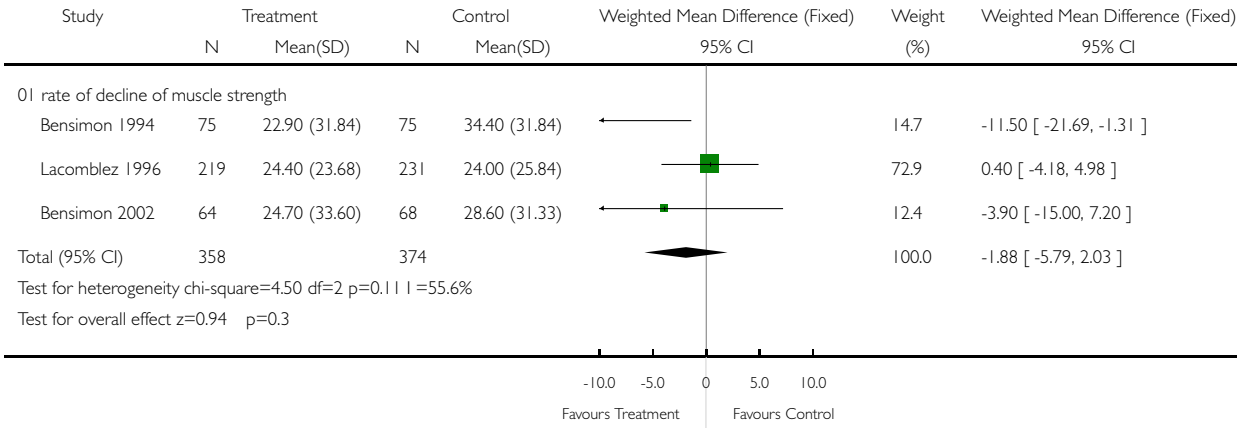
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 percent mortality at 18 mos					
Bensimon 1994	39/77	45/78		16.0	0.88 [0.66, 1.17]
Lacomblez 1996	311/408	120/161		61.7	1.02 [0.92, 1.14]
Bensimon 2002	60/80	64/85		22.3	1.00 [0.84, 1.19]
Total (95% CI)	565	324		100.0	0.99 [0.91, 1.09]
Total events: 410 (Treatment), 229 (Control)					
Test for heterogeneity chi-square=0.98 df=2 p=0.611 =0.0%					
Test for overall effect z=0.14 p=0.9					

Analysis 13.01. Comparison 13 Muscle strength, Outcome 01 manual muscle testing

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 13 Muscle strength

Outcome: 01 manual muscle testing

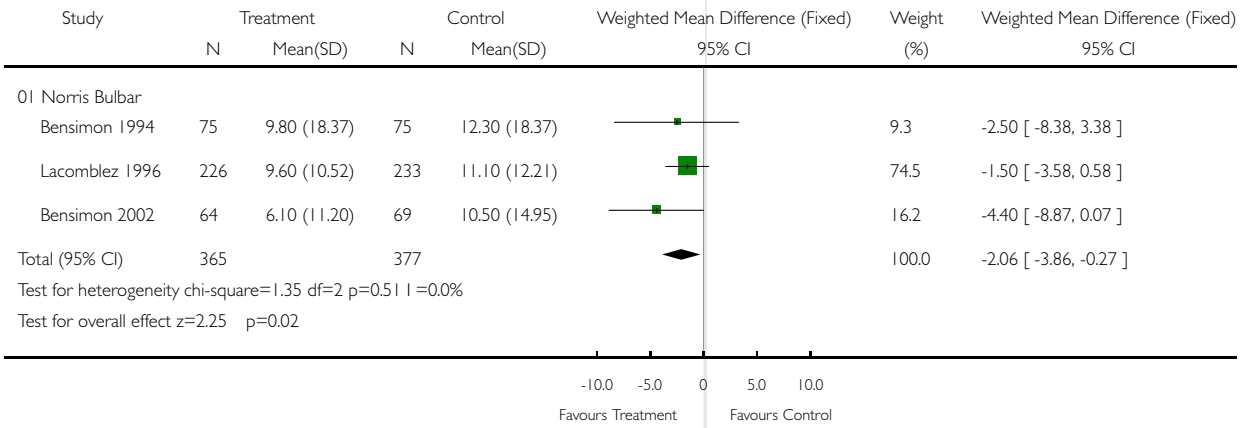


Analysis 14.01. Comparison 14 Functional scales, Outcome 01 rate of decline of Norris Scale

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 14 Functional scales

Outcome: 01 rate of decline of Norris Scale



Analysis 15.01. Comparison 15 Functional Scales, Outcome 01 rate of decline of Norris Scale

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

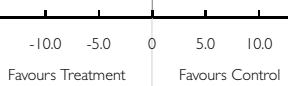
Comparison: 15 Functional Scales

Outcome: 01 rate of decline of Norris Scale

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Norris Limb							
Bensimon 1994	75	21.80 (31.84)	75	28.10 (31.84)		10.5	-6.30 [-16.49, 3.89]
Lacomblez 1996	218	20.10 (19.19)	230	24.10 (22.75)		72.0	-4.00 [-7.89, -0.11]
Bensimon 2002	64	14.60 (23.20)	69	16.90 (23.26)		17.5	-2.30 [-10.20, 5.60]
Total (95% CI)	357		374			100.0	-3.94 [-7.25, -0.64]

Test for heterogeneity chi-square=0.37 df=2 p=0.83 I =0.0%

Test for overall effect z=2.34 p=0.02



Analysis 16.01. Comparison 16 Adverse effects from riluzole 100 mg, Outcome 01 Clinical

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 16 Adverse effects from riluzole 100 mg

Outcome: 01 Clinical

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nausea					
Bensimon 1994	3/77	3/78		8.2	1.01 [0.21, 4.86]
Lacomblez 1996	49/236	31/242		83.8	1.62 [1.07, 2.45]
Bensimon 2002	4/82	3/86		8.0	1.40 [0.32, 6.06]
Total (95% CI)	395	406		100.0	1.55 [1.06, 2.28]

Total events: 56 (Treatment), 37 (Control)

Test for heterogeneity chi-square=0.35 df=2 p=0.84 I =0.0%

Test for overall effect z=2.24 p=0.02

Analysis 17.01. Comparison 17 Adverse effects from riluzole 100 mg, Outcome 01 Clinical

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 17 Adverse effects from riluzole 100 mg

Outcome: 01 Clinical

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 asthenia					
Bensimon 1994	20/77	11/78		23.5	1.84 [0.95, 3.58]
Lacomblez 1996	42/236	30/242		63.8	1.44 [0.93, 2.21]
Bensimon 2002	7/82	6/86		12.6	1.22 [0.43, 3.49]
Total (95% CI)	395	406		100.0	1.50 [1.07, 2.12]
Total events: 69 (Treatment), 47 (Control)					
Test for heterogeneity chi-square=0.55 df=2 p=0.76 I =0.0%					
Test for overall effect z=2.34 p=0.02					

Analysis 18.01. Comparison 18 Adverse effects from riluzole 100 mg, Outcome 01 Laboratory

Review: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)

Comparison: 18 Adverse effects from riluzole 100 mg

Outcome: 01 Laboratory

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 increased ALT (>3 times normal)					
Bensimon 1994	13/77	6/78		30.2	2.19 [0.88, 5.48]
Lacomblez 1996	25/236	9/242		45.0	2.85 [1.36, 5.97]
Bensimon 2002	13/82	5/86		24.7	2.73 [1.02, 7.31]
Total (95% CI)	395	406		100.0	2.62 [1.59, 4.31]
Total events: 51 (Treatment), 20 (Control)					
Test for heterogeneity chi-square=0.20 df=2 p=0.91 I =0.0%					
Test for overall effect z=3.80 p=0.0001