Riluzole for the Treatment of Amyotrophic Lateral Sclerosis: an Assessment of Clinical Efficacy and Safety
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Kirsten Garces BSc BScPhm
Donald Husereau BScPharm MSc
Becky Skidmore BA MLS
John Turnbull MD

August 2003

1 Canadian Coordinating Office for Health Technology Assessment, Ottawa, Ontario, Canada
2 McMaster University Medical Centre, Hamilton, Ontario, Canada
Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Andrew Eisen, MD FRCPC
Professor Emeritus
University of British Columbia
Vancouver, British Columbia

Gerry Mugford, BSc PhD
Manager, Graduate Clinical Epidemiology Program
Faculty of Medicine
Memorial University of Newfoundland and Labrador
St. John’s, Newfoundland and Labrador

Angela Genge, BSc PT MD FRCPC
Neurologist
Director ALS Clinic Program
Montreal Neurological Hospital
McGill University
Montreal, Quebec

Luc Sauriol, MSc
Project Leader, Health Economics
Aventis Pharma Canada Inc.
Laval, Quebec

CCOHTA Scientific Advisory Panel Reviewers

Robert Coté MD
Neurologist
McGill University – Division of Neurology
The Montreal General Hospital
Montreal, Quebec

Doug Coyle, MA MSc
Senior Scientist, Clinical Epidemiology,
Ottawa Health Research Institute
Assistant Professor, Departments of Medicine and Epidemiology and Community Medicine,
University of Ottawa
Ottawa, Ontario

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CCOHTA takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CCOHTA and not of its Panel members or reviewers.
Authorship

All authors participated in the planning of the project, made comments on the draft reports and responded to reviewers’ comments.

Kirsten Garces, the lead author, was involved in all aspects of the project. She contributed to the literature search strategy, selected articles for inclusion, assessed article quality, abstracted data, analyzed results and wrote the draft and final versions of the report.

Donald Husereau contributed to the literature search strategy, selected articles for inclusion, assessed article quality, abstracted data and analyzed results. He wrote the report’s executive summary and conclusion sections.

Becky Skidmore was responsible for the design and execution of the literature search strategy, wrote the methods section and associated appendix on literature searching and verified and formatted bibliographic references.

John Turnbull, the clinical content expert, assisted in developing the protocol, provided clinical expertise in the interpretation of data, and assisted in writing the draft and final versions of the report.

Acknowledgements

The authors are grateful to David Moher, MSc, Director of the Chalmers Research Group, Children’s Hospital of Eastern Ontario Research Institute; Departments of Pediatrics and Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, for critiquing a previous review on this topic and identifying areas for further research. The authors are also grateful to Marie Sirdevan, BScPhm and Yuki Otsubo for their help in determining the eligibility of Japanese studies and for performing data abstraction from the included Japanese studies.

Conflicts of Interest

Kirsten Garces – none
Donald Husereau – none
Becky Skidmore – none
John Turnbull participated in the early release program for riluzole in Canada and in the ongoing Canadian study of riluzole in patients with amyotrophic lateral sclerosis (ALS). He received no remuneration for this participation.
Riluzole for the Treatment of Amyotrophic Lateral Sclerosis: an Assessment of Clinical Efficacy and Safety

**Technology Name**
Riluzole (Rilutek™)

**Disease/Condition**
Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a progressive neuromuscular disorder that results in death in the majority of individuals within three to five years of the onset of symptoms. There is no cure for ALS. Respiratory complications are inevitable with ALS. Endotracheal ventilation (e.g. tracheostomy) may be used to provide relief over the long term.

**Technology Description**
Riluzole is the only drug approved in Canada for treatment of ALS. Riluzole is prescribed for some patients to extend their survival or the time to tracheostomy. Riluzole is thought to work by inhibiting presynaptic glutamate release, which may be involved in the degeneration of motor neurons in patients with ALS.

**The Issue**
Several clinical reviews of riluzole for the treatment of patients with ALS have been conducted, but they do not provide adequate information on the drug’s safety.

**Assessment Objectives**
The overall objective of this report is to assess the potential benefits and harms of riluzole for the treatment of patients with ALS. Specific objectives are to assess the effect of riluzole on mortality, on morbidity and on quality of life for patients with ALS.

**Methods**
CCOHTA performed a systematic review of the literature reporting on the efficacy of treating ALS patients with riluzole. The outcomes examined were all-cause mortality and tracheostomy-free survival, all-cause morbidity, patient withdrawals due to adverse events, number of patients experiencing adverse events, quality of life and time to tracheostomy.

Published and unpublished literature was systematically searched. Two independent reviewers selected randomized controlled trials for inclusion, abstracted the data and assessed the quality of each trial. Four randomized controlled trials comparing riluzole to placebo were included in this report.

**Conclusions**
- Riluzole has the potential to reduce serious morbidity in some patients at the cost of causing some drug intolerance (withdrawals due to adverse events).
- There is no information to describe the impact of riluzole on quality of life or time to tracheostomy alone.
- More adequate reporting of adverse events is needed to complete the clinical picture.

EXECUTIVE SUMMARY

The Issue

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a progressive neuromuscular disorder for which there is no cure. It leads to death within three to five years in the majority of individuals with ALS. Riluzole, which is the only drug approved for treatment of the disease, is prescribed for some patients to extend their survival or the time to tracheostomy.

Objectives

The overall objective of this report is to assess the potential benefits and harms of riluzole when used for patients with ALS by performing a systematic review of the available evidence. Given the methodology and the comprehensiveness of two previously published systematic reviews, it was determined that another analysis would unlikely produce conclusions about efficacy that are more robust and valid than those already drawn. Neither review, however, provides sufficient information on all-cause mortality, morbidity (including drug-related morbidity) or the quality of life observed in patients with ALS during treatment. This review focuses on these outcomes.

Methods

Published literature was identified by searching a number of databases and was regularly updated. Unpublished (grey) literature was sought by manually searching bibliographies and contacting experts in the field and the drug manufacturer. Only randomized controlled trials (RCTs) were selected for inclusion. Articles reporting relevant RCTs were selected by two independent reviewers who applied a priori selection criteria. The quality of each included RCT report was assessed and the data were abstracted independently by two reviewers.

Results

From the literature search, we identified 164 unique citations. Four RCTs met the inclusion criteria and were included in this report. All four were double-blind, placebo-controlled, randomized trials comparing riluzole to placebo. One was a dose-ranging trial comparing riluzole 50 mg, 100 mg and 200 mg to placebo, while three compared riluzole 100 mg to placebo. Three trials included patients between 18 to 75 years who had been diagnosed with ALS for no more than five years. The fourth trial included patients who may have been excluded from the three other trials: patients who were older than 75 years or patients with a diagnosis of ALS for more than five years. The primary outcome reported in the included trials was tracheostomy-free survival (those who survived without a tracheostomy).

The four RCTs identified in our review had been identified in two previous systematic reviews. In each previous review, a meta-analysis of three RCTs concluded that riluzole provided an additional two to three months of tracheostomy-free survival compared with placebo, with borderline statistical significance. The addition of a fourth trial did not alter these findings. This pooled estimate exhibits substantial statistical heterogeneity.
All-cause mortality data were examined in two of the four included RCTs. Based on these data, the effect of riluzole on mortality from any cause is similar in magnitude and direction to that of the combined endpoint of death or tracheostomy. The number of overall tracheostomies was small, and there was no detectable statistical difference between estimates of all-cause mortality and tracheostomy-free survival. Thus, it was unlikely that performance or detection bias could have influenced the combined result. Based on these data, investigations using tracheostomy-free survival would be appropriate.

Information on serious adverse events, the number of patient withdrawals due to adverse events and adverse events are only partially reported in some of the included trials. There is sufficient evidence to suggest that the number of individuals experiencing and reporting an adverse event does not decrease with riluzole treatment. There is some evidence to suggest that 5% of patients (95% CI: 1% to 9%) could be required to withdraw from treatment due to an adverse event. Patients over 75 years or with long-term illness, however, reported fewer serious adverse events. This suggests that the drug could reduce serious morbidity. More adequate reporting of adverse events is desirable to complete the clinical picture.

The impact of riluzole treatment on quality of life is unknown. No information on this outcome or the impact of riluzole therapy on time to tracheostomy alone could be identified.

The magnitude of the effect of riluzole on survival was discordant in different populations studied. This makes the generalizability of results more difficult.

**Conclusions**

Riluzole has the potential to reduce serious morbidity in certain patients at the cost of causing some drug intolerance (withdrawals due to adverse events). There is no information available to describe its impact on quality of life or time to tracheostomy alone.
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ABBREVIATIONS

ALS amyotrophic lateral sclerosis
ALT alanine aminotransferase
AST aspartate aminotransferase
bid twice daily
CI confidence interval
CCOHTA Canadian Coordinating Office for Health Technology Assessment
CPMP Committee for Proprietary Medicinal Products
DB double-blind
EAP Early Access Program
FDA Food and Drug Administration
FVC forced vital capacity
HR hazard ratio
ITT intention to treat
LMN lower motor neuron
MND motor neuron disease
NA not available
NR not reported
NICE National Institute for Clinical Excellence
PC placebo-controlled
pc after meals
RCT randomized controlled trial
RD risk difference
RR relative risk
SD standard deviation
SE standard error
UK United Kingdom
UMN upper motor neuron
WFN World Federation of Neurology
1 INTRODUCTION

1.1 Amyotrophic Lateral Sclerosis

Motor neuron disease (MND) refers to a spectrum of syndromes that occur due to a degeneration of upper motor neurons (UMN), lower motor neurons (LMN) or both.1 Amyotrophic lateral sclerosis (ALS) is the most common form of MND.1 The incidence of ALS, also known as Lou Gehrig’s disease, is approximately 1 to 3 per 100,000 persons every year, with a prevalence of 4 to 6 persons per 100,000 in the US.2 There are no available Canadian data. The disorder occurs more often in males.1,3,4 The mean age of onset has been shown to be between the ages of 55 and 60 years, but it may also affect young people.3,4

Up to 95% of ALS cases are sporadic, while the remaining cases are inherited.4 Of the inherited cases, 10% to 20% are due to a mutation in the copper-zinc superoxide dismutase gene. Many theories have been proposed to explain the cause of sporadic ALS, including viral infection, glutamate excitotoxicity, autoimmune-mediated attack, cytoskeletal abnormalities, oxidative injury, deprivation of neurotrophic factors, exogenous toxins and apoptosis. The cause is still uncertain, and there may be multiple causes.5

As there are no biological markers used to diagnose ALS, the diagnosis must be based on the clinical presentation and the exclusion of other pathology that can explain the observed deficits. The diagnosis is based on the presence of LMN degeneration confirmed by clinical, electrophysiological or neuropathological examination; evidence of UMN degeneration by clinical examination; and evidence of progression in a region or to other regions of the nervous system, as determined by history or examination.5 UMN symptoms include weakness, hyperreflexia, pathologic reflexes, spasticity, loss of dexterity and slowed movements. LMN symptoms include weakness, hyporeflexia, muscle atrophy, fasciculations, muscle cramps and hypotonicity or flaccidity. Unusual symptoms include dementia, pain and sensory symptoms.5

The El Escorial diagnostic criteria for ALS were developed in 1994. Since then, they have been updated to increase their sensitivity. These criteria, revised at Airlie House, Virginia, are used to categorize the diagnosis of ALS into various levels of certainty depending on the presence and extent of UMN or LMN symptoms. Clinically definite ALS is based on clinical evidence of UMN signs, as well as LMN signs in at least three of four anatomic regions (bulbar, cervical, thoracic and lumbosacral). Clinically probable ALS is based on clinical evidence of UMN and LMN signs in at least two regions, with some UMN signs necessarily rostral to (above) the LMN signs.5

Depending on the site of neuronal degeneration, a patient may exhibit bulbar or limb symptoms. Bulbar symptoms include speech, swallowing and chewing difficulties. They are the initial symptoms in 17% to 25% of patients. Bulbar involvement, however, increases with time.5 Limb symptoms such as fatigue and weakness may also occur as initial symptoms in ALS.

The prognosis for ALS patients is variable and may depend on the type of symptoms that the patient experiences. The median survival time after the onset of ALS symptoms is 3.5 years.3 Age and family history of ALS are the only established risk factors.
1.2 Current Practice

Respiratory complications are inevitable in ALS patients. Patients may be unable to ventilate the lungs or create adequate flows for coughing to clear secretions. Transient relief from hypercarbia and hypoxia may be provided by positive-pressure ventilation through the mouth or nose. Endotracheal ventilation may be used in the long term.

Patients with bulbar involvement often experience speech difficulties that hinder their ability to communicate with others. Speech pathologists can train patients to speak slowly and to exaggerate their articulations. Sometimes, tongue-strengthening exercises are recommended. Speech synthesizers may also help communication.

Chewing and swallowing difficulties may hinder proper nutrition and hydration. A change from a solid to a liquid diet may be necessary for certain patients. If proper nutrition cannot be attained orally, tube feeding may be an option to maintain adequate caloric intake.

The only drug available for the treatment of ALS is riluzole, but several drugs have been recently evaluated. These include other antiglutamate agents, various antioxidants, neurotrophic factors, immunomodulatory agents, antiviral agents and others. Pharmacotherapy may also be used to relieve ALS symptoms. Pain medication and antidepressants are commonly used.

1.3 Riluzole

The mechanism of action of riluzole, which is unknown, may be attributed to an inhibitory effect on glutamate release, inactivation of voltage-dependent sodium channels and an ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

Health Canada issued marketing authorization for riluzole (Rilutek™) with the condition that the manufacturer undertake studies to verify the drug’s clinical benefit. Rilutek™ is indicated to extend the survival and/or time to tracheostomy in some patients with ALS. The manufacturer of Rilutek™ is conducting confirmatory studies for Health Canada (Ellen Dempsey, Aventis, Laval, PQ: personal communication, 2002 Oct 16). The manufacturer’s recommended dose is 50 mg every 12 hours, to be taken at least an hour before or two hours after a meal.

1.4 Economic Impact of Treating ALS with Riluzole

The treatment of ALS may involve other costs in addition to that of riluzole, including those for physician consultations, monitoring and treatment of adverse events. A specialist generally treats patients with ALS regularly, thus additional visits are unlikely for those on medication. Additional laboratory tests for monitoring may be needed at the start of riluzole treatment. Treatment may be required for adverse events due to the use of the drug. Other costs, such as those for medical devices (e.g. wheelchairs), appointments with other health care professionals
(e.g. speech therapists, physiotherapists) and palliative care, could be similar regardless of whether the patient is receiving or not receiving riluzole therapy. An economic analysis was not performed in this report, but previous economic reviews are available.8-13

1.5 Current Reviews of Riluzole

Systematic and narrative reviews that examine the use of riluzole for patients with ALS have been published. Systematic reviews include those by the Cochrane Collaboration Neuromuscular Disease Group14 and the National Institute for Clinical Excellence (NICE) in the United Kingdom (UK).12 The Cochrane systematic review concluded that riluzole 100 mg daily was reasonably safe and probably prolongs survival by about two months in patients with ALS. The review also concluded that more studies are needed to clarify the effect of riluzole in older patients (over 75 years old), and in those with more advanced disease.

The systematic review by NICE also suggests limited evidence of a benefit in tracheostomy-free survival – a combined endpoint of time to tracheostomy and death – for patients taking riluzole. At best, riluzole postpones death for a few months without precluding the need for supportive care and practical help.

Both systematic reviews identify four eligible RCTs. The Cochrane review, however, ultimately excluded one trial, as it was considered insufficiently detailed to include in the meta-analysis. The NICE authors retrieved the tracheostomy-free survival results of this fourth trial from the manufacturer and included these data in their analysis. The overall conclusion with respect to tracheostomy-free survival, however, is similar in the two reviews.

The NICE review recommended to the National Health Service in the UK that riluzole should be available for the treatment of individuals with MND in accordance with its licensed indication.

Other reviews have been conducted in order to provide guidance to authorities about whether to approve riluzole for the treatment of ALS. Riluzole was granted marketing authority in the European Union based on a review conducted by the Committee for Proprietary Medicinal Products (CPMP). This review determined that riluzole demonstrated adequate efficacy for the approved indication and a satisfactory risk versus benefit profile.15 Similarly, the US Food and Drug Administration (FDA) approved the use of riluzole in part based on its efficacy and a favourable safety profile.16

Other reports did not view riluzole as favourably. A 1997 review conducted by Booth-Clibborn et al. for the Wessex Institute in the UK concluded that riluzole did not produce a significant functional improvement compared with placebo, and that there was insufficient evidence on which to judge the benefits of treatment.17

Another 1997 review, conducted by Chilcott et al. for the Trent Institute for Health Services Research in the UK, decided that, due to the uncertainty in the interpretation and analysis of trial evidence on survival, the lack of quality of life information, the limited benefit that is claimed
and the high cost-effectiveness ratio, the Trent Development and Evaluation Committee could not support the use of riluzole.\textsuperscript{18}

When the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) examined whether it would be feasible and useful for CCOHTA to conduct a review of riluzole for the treatment of ALS, the NICE review was closely scrutinized. Given its methodology and comprehensiveness, it was determined that another analysis would be unlikely to produce conclusions about efficacy outcomes that were more robust and valid than those already drawn. It was decided, however, that information about drug- and disease-related morbidity, which was lacking in the NICE report, would complete the clinical picture (Professor David Moher, Chalmers Research Group, Children’s Hospital of Eastern Ontario, Ottawa: personal communication, 2001 Oct 5).

Thus, this CCOHTA review was conducted to examine the role of riluzole in ALS through an analysis of its ability to reduce the incidence of death and morbidity and to improve the quality of life for patients with ALS.
2 OBJECTIVES

The overall objective of this report is to assess the efficacy and safety of riluzole for the treatment of patients with ALS. The specific objectives regarding patients with ALS are to assess the effect of riluzole on:

- mortality
- morbidity, e.g. adverse events, serious adverse events, withdrawals due to adverse events
- quality of life.
3 METHODS

3.1 Literature Search

Published literature was identified by searching several databases (Appendix 1). Where possible, retrieval was limited to the human population. There were no language restrictions. BIOSIS Previews®, EMBASE®, MEDLINE®, PASCAL and ToxFile were searched on DIALOG®, with regular alerts/updates scheduled throughout the project. A separate search was also undertaken on DIALOG® to identify review articles. Parallel searches were also run and updated on PubMed and on the CD-ROM version of The Cochrane Library.

Unpublished (grey) literature was obtained through a search of web sites of health technology assessment and other related agencies and their databases. Google™ and other Internet search engines were used to search for web-based materials. Further information was sought by manually searching the bibliographies of selected papers, and through consultation with the clinical expert on the project team.

The drug manufacturer was invited to submit published and unpublished information about riluzole’s clinical effectiveness and economic information relating to the drug.

3.2 Eligibility Criteria

The following criteria were used when considering material for this review:

- **Type of studies**: randomized controlled trials (RCTs) comparing riluzole with placebo or another treatment
- **Type of participants**: patients with ALS as defined by World Federation of Neurology (WFN) criteria (Appendix 2)
- **Type of intervention**: riluzole of any dose for any duration
- **Types of outcome measures**: primary outcome measures of interest including all-cause mortality, all-cause morbidity, patient withdrawals due to adverse events, number of patients with adverse events and quality of life; and secondary outcomes including time to tracheostomy.

3.3 Selection Process

3.3.1 Article selection

Two reviewers (KG and DH) independently reviewed citations identified through the literature search. Citations were excluded after a review of titles and abstracts. In cases of doubt on the part of a reviewer, full articles were retrieved to gather further information. From this, potentially relevant citations were retained and the remaining articles were used for manual searches and the preparation of background information.
3.3.2 Selection of relevant articles

Full-text versions of all potentially relevant articles were acquired. Two reviewers (KG and DH) independently made the final selection of the relevant articles to be included in the systematic review, based on the eligibility criteria mentioned in section 3.2. The trial eligibility criteria appears in Appendix 3. Disagreement about the inclusion of any article was resolved through discussion and consensus. The use of a third party to resolve persisting differences was unnecessary.

3.3.3 Assessment of quality

The quality of the included RCT reports was assessed independently by two reviewers (KG and DH) using the Jadad scale (Appendix 4). A calibration exercise, using 10 randomized trials chosen by an information specialist, was conducted before the relevant trials included in this review were assessed. The rationale for doing the calibration exercise was to ensure that the two reviewers agreed on the components of the Jadad scale. Allocation concealment was also assessed using a three-item system: adequate, inadequate and unclear.

3.3.4 Data abstraction

Two reviewers (KG and DH) used a standard form to perform data abstraction (Appendix 5). Information on aspects such as trial design and patient characteristics was collected for each RCT. Outcome information was also collected for each trial using a separate form for each outcome. Disagreements were resolved by discussion and consensus.

3.3.5 Statistical analysis

Statistical analysis was performed using intention to treat (ITT) data whenever possible. Where outcome information from the trials was sufficiently descriptive and the trials were sufficiently clinically homogeneous for combined outcomes to be informative, a meta-analysis of data was done.

Cochrane Review Manager 4.1 software, with MetaView 4.1, was used to compute risk differences and to generate forest plots to compare outcomes in the treatment and placebo arms of the trials. DerSimonian-Laird random effects and Mantel-Haenszel fixed effects models were used to combine dichotomous outcomes. DerSimonian-Laird random and inverse variance fixed effects models were used to combine continuous outcomes. Both random and fixed effects models were applied to all outcomes for comparison.

The statistical heterogeneity across trials was assessed by performing a chi-square test procedure using MetaView. A threshold value of p=0.1 was used to detect heterogeneity.\textsuperscript{19,20} Publication bias was assessed via visual inspection of a funnel plot. Meta analysis was done using a 95% CI.
4 RESULTS

4.1 Quantity and Quality of Research Available

A total of 151 citations were identified in the original electronic literature search. Four of these were duplicates. Thus, 147 unique citations were identified in the electronic literature search. Other articles were identified through alerts (n=11), regulatory bodies (n=5) and manual searching (n=1), for a total of 164. After reviewing the titles and abstracts of these unique citations, two reviewers (KG and DH) rejected 95 based on titles and abstracts, and retained 69 that were potentially relevant for further examination.

The \textit{kappa} statistic (\(\kappa\)), which quantifies agreement between reviewers for the broad selection of articles that may be potentially relevant, was 0.238 (95\% CI: 0.054 to 0.422). The low score reflects the authors’ attempts to capture all the available literature. Both reviewers independently reviewed each article to determine whether it met the \textit{a priori} eligibility criteria.

Both reviewers agreed to accept 6 and exclude 63 reports of the 69 potentially relevant reports. Of the 63 rejected reports (Appendix 6), 32 were review articles, 6 did not have a control group, 5 did not measure the outcomes of interest, 3 were not RCTs, 1 was a retrospective study, 1 did not involve ALS patients and 15 were rejected for other reasons (5 were letters, 3 were news items, 5 were pharmacoeconomic studies, 1 was a comment and 1 was a miscellaneous article).

After consultation with the translators of several articles, 2 of the 6 retained reports\textsuperscript{21,22} were excluded as they were reviews and not original RCT reports. Thus, only 4 RCTs met the eligibility criteria (Figure 1).\textsuperscript{23-26} The reviewers’ agreement on the inclusion of trials for analysis was 100\% (\(\kappa = 1.0\)).

The authors contacted the drug manufacturer regarding the unpublished results of one RCT and 50-month follow-up data, but the data were not provided. During the preparation of this report, however, the unpublished RCT was published as Bensimon \textit{et al.} 2002.\textsuperscript{26}

Drug approval information, which was unavailable from the US FDA’s web site, was requested and received through the Freedom of Information Act.\textsuperscript{16}

All four trials were randomized, double-blinded and placebo-controlled and all evaluated riluzole 100 mg daily compared with a placebo (Tables 1 and 2). The patient populations in the Bensimon \textit{et al.} 1994 and the Lacomblez \textit{et al.} 1996 trials were identical: adults up to 75 years of age with diagnoses of probable or definite ALS for less than five years and lung forced vital capacities (FVCs) greater than 60\% of the expected value. The trial by Yanagisawa \textit{et al.} was similar but also included patients with greater respiratory compromise. The trial conducted by Bensimon \textit{et al.} in 2002\textsuperscript{26} enrolled types of patients who may have been excluded from the other three trials: patients over 75 years of age, or those with ALS for more than five years or those with FVCs below 60\% of the theoretical maximum value (or not assessable).
Figure 1: Summary of literature search

- Citations identified by electronic search (n=147)
- Citations identified by alerts (n=11)
- Reviews performed by regulatory bodies (n=5)
- Citations identified by manual searching (n=1)

Citations rejected based on title or abstract (n=95)

Potentially relevant reports for detailed examination (n=69)

Excluded reports and reason for exclusion (n=65)
- Review articles (n=34)
- No control group (n=6)
- Not outcome of interest (n=5)
- Not RCT (n=3)
- Retrospective study (n=1)
- Not ALS (n=1)
- Other:
  - Letter (n=5)
  - News item (n=3)
  - Pharmacoeconomic study (n=5)
  - Comment (n=1)
  - Miscellaneous (n=1)

Total relevant RCTs included for review (n=4)
All four trials defined the primary endpoint as tracheostomy-free survival (patients who had survived without a tracheostomy). One trial defined additional primary endpoints: progression-free survival, which included death, tube nutrition, dependence on a respirator, loss of upper extremity function, loss of independent ambulation and tracheostomy and overall survival.

Trials were considered to be of moderate quality according to the Jadad scale. The allocation concealment in the trials conducted by Bensimon et al. 1994 and 2002 was considered to be adequate, but it was unclear whether the randomization sequence was kept adequately concealed in the Lacomblez et al. 1996 and Yanagisawa et al. 1997 trials. The agreement between reviewers in assessing trial reports for allocation concealment and using the Jadad scale was 100%.
# Table 1: Summary of trial characteristics

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Design</th>
<th>Number of Patients (placebo/riluzole)</th>
<th>Intervention</th>
<th>Eligibility of Trial Participants</th>
<th>Outcome Measures</th>
<th>Quality of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensimon et al., 1994&lt;sup&gt;23&lt;/sup&gt;</td>
<td>RCT, DB, PC</td>
<td>78/77</td>
<td>Riluzole 50 mg bid or placebo</td>
<td>• Probable or definite ALS&lt;br&gt;• ALS less than five years duration&lt;br&gt;• Age 20 to 75 years&lt;br&gt;• FVC greater than 60% of the expected value</td>
<td>Survival and changes in functional status after 12 months of treatment&lt;br&gt;Principal events included in the determination of survival rate were death (from any cause) and tracheostomy</td>
<td>3</td>
</tr>
<tr>
<td>Lacomblez et al., 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>RCT, DB, PC, dose-ranging</td>
<td>242/717</td>
<td>Riluzole 50 mg, 100 mg or 200 mg daily or placebo</td>
<td>• Probable or definite ALS&lt;br&gt;• ALS less than five years duration&lt;br&gt;• Age 18 to 75 years&lt;br&gt;• FVC at least 60% of predicted</td>
<td>Tracheostomy-free survival (included death (from any cause), tracheostomy, and intubation with artificial ventilation leading to tracheostomy)</td>
<td>4</td>
</tr>
<tr>
<td>Yanagisawa et al., 1997&lt;sup&gt;25&lt;/sup&gt;</td>
<td>RCT, DB, PC</td>
<td>97/98</td>
<td>Riluzole 100 mg daily or placebo</td>
<td>• Probable or definite ALS&lt;br&gt;• Age 20 to 75 years&lt;br&gt;• FVC deterioration less than 40% in last two months&lt;br&gt;• Tracheostomy not expected in next six months</td>
<td>Progression-free survival (time to death, tube nutrition, dependence on respirator, loss of upper extremity function, independent ambulation, tracheostomy)&lt;br&gt;Tracheostomy-free survival (time to death, tracheostomy or dependence on respirator)&lt;br&gt;Overall survival</td>
<td>3</td>
</tr>
<tr>
<td>Bensimon et al., 2002&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RCT, DB, PC</td>
<td>86/82</td>
<td>Riluzole 50 mg bid or placebo</td>
<td>Probable or definite ALS One or more of the following:&lt;br&gt;• Age over 75 years&lt;br&gt;• ALS greater than five years duration&lt;br&gt;• FVC below 60% of theoretical maximum value, or not assessable</td>
<td>Time to failure (considered to be death, tracheostomy or intubation with artificial ventilation)</td>
<td>3</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, DB: double-blind, PC: placebo-controlled, bid: twice daily, ALS: amyotrophic lateral sclerosis, FVC: forced vital capacity
Table 2: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Riluzole/Placebo</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration of Disease (yr)</th>
<th>Forced Vital Capacity*</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensimon et al., 1994</td>
<td>Riluzole 50 mg bid</td>
<td>45/32</td>
<td>56.8±11</td>
<td>66.0±12</td>
<td>2.2±1.7</td>
<td>0.92±0.17</td>
<td>Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>46/32</td>
<td>58.1±11</td>
<td>65.1±12</td>
<td>2.3±1.8</td>
<td>0.86±0.18</td>
<td></td>
</tr>
<tr>
<td>Lacomblez et al., 1996</td>
<td>Riluzole 50 mg daily</td>
<td>144/93</td>
<td>57.1±10.7</td>
<td>67.6±13.0</td>
<td>1.9±1.2</td>
<td>88.6±18.9</td>
<td>Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td></td>
<td>Riluzole 100 mg daily</td>
<td>143/93</td>
<td>56.9±10.9</td>
<td>68.1±13.4</td>
<td>1.7±1.2</td>
<td>88.4±19.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riluzole 200 mg daily</td>
<td>136/108</td>
<td>56.8±10.8</td>
<td>67.1±11.5</td>
<td>1.8±1.2</td>
<td>88.2±19.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>152/90</td>
<td>56.0±11.5</td>
<td>68.1±13.1</td>
<td>1.8±1.4</td>
<td>87.6±18.2</td>
<td></td>
</tr>
<tr>
<td>Yanagisawa et al., 1997</td>
<td>Riluzole 100 mg daily</td>
<td>53/45</td>
<td>59.6±9.1</td>
<td>NR</td>
<td>2.1±2.0</td>
<td>2218±975</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>56/41</td>
<td>58.4±10.1</td>
<td>NR</td>
<td>2.5±2.1</td>
<td>2167±895</td>
<td></td>
</tr>
<tr>
<td>Bensimon et al., 2002</td>
<td>Riluzole 100 mg daily</td>
<td>34/48</td>
<td>57.8±1.4**</td>
<td>59.7±1.4</td>
<td>3.4±0.2</td>
<td>51.9±3.1</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>48/38</td>
<td>62.8±1.4</td>
<td>61.8±1.4</td>
<td>3.9±0.4</td>
<td>55.1±2.6</td>
<td></td>
</tr>
</tbody>
</table>

*Forced vital capacity is expressed as the fraction of normal in the Bensimon et al. 1994 trial, percentage of predicted in the Lacomblez et al. 1996 trial, in millilitres in the Yanagisawa et al. 1997 trial and as the vital capacity ratio in the Bensimon et al. 2002 trial.
NR = not reported
** significantly different from placebo
4.2 Assessment of Clinical Efficacy

The following outcomes were examined:

- all-cause mortality and tracheostomy-free survival (those who had survived without tracheostomy)
- all-cause morbidity
- patient withdrawals due to adverse events
- number of patients experiencing adverse events
- quality of life
- time to tracheostomy.

Statistical heterogeneity was assessed by performing a chi-square test procedure and publication bias was assessed by visually inspecting the funnel plot. Given the small number of RCTs included in this review, however, the measurements of heterogeneity and publication bias may be misleading.

4.2.1 All-cause mortality

All-cause mortality was not broken down according to death alone in any of the trials. Only for the Bensimon et al. 1994 and the Lacomblez et al. 1996 trials was it possible to identify, at the end of the period of observation, the number of patients alive or dead and with or without a tracheostomy. The breakdown of patients in the placebo or riluzole 100 mg groups is shown in Table 3:

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Placebo</th>
<th>Riluzole 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total patients alive with tracheostomy/Total patients with tracheostomy</td>
<td>Total patients alive with no tracheostomy/Total patients with no tracheostomy</td>
</tr>
<tr>
<td>Bensimon et al., 1994</td>
<td>3/6</td>
<td>42/72</td>
</tr>
<tr>
<td>Lacomblez et al., 1996</td>
<td>4/10</td>
<td>122/232</td>
</tr>
<tr>
<td>Yanagisawa et al., 1997</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bensimon et al., 2002</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported
Since information on the number of people who had died, with or without a tracheostomy, could only be determined at the end of trial period, the results could not be combined because the end of trial period was 12 months for the 1994 Bensimon et al. trial and 18 months for the 1996 Lacomblez et al. trial. When the risk differences due to death and due to death plus tracheostomy for each trial were compared, a similar risk difference was found. A trend towards increased survival for the riluzole group was demonstrated in both trials.

Table 4: Risk difference in mortality attributed to death alone compared with death plus tracheostomy combined

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Risk difference in death at the end of follow-up</th>
<th>Risk difference in death or tracheostomy at the end of follow up</th>
<th>Chi-square test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensimon et al., 1994</td>
<td>-19% (-34%, -4%)</td>
<td>-17% (-31%, -2%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Lacomblez et al., 1996</td>
<td>-8% (-17%, 1%)</td>
<td>-6% (-15%, 3%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Yanagisawa et al., 1997</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bensimon et al., 2002</td>
<td>NA</td>
<td>-1% (-15%, 12%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available

4.2.2 Tracheostomy-free survival

Tracheostomy-free survival was investigated in the Cochrane and NICE reviews. Both reviews combined tracheostomy-free survival data (time to death or tracheostomy) for all trials excluding the Yanagisawa et al. trial, and found similar results. The reports describe survival using the hazard ratio (HR), which represents the overall relative risk of death over the period of observation, rather than using other measures (such as odds ratios), which look only at fixed time points.

The Cochrane review determined from the combination of three studies [Bensimon et al. 1994, Lacomblez et al. 1996 and Meininger 1996 (unpublished) now published under Bensimon et al. 2002]\(^{23,24,26}\) that riluzole provided some benefit at close to statistically significant values (HR=0.84, p=0.056, 95% CI: 0.70 to 1.01). There was also evidence of heterogeneity (p<0.0001). Similarly, the meta-analysis of the same three trials in the NICE review showed that riluzole provided a benefit that was statistically significant (HR=0.83, 95% CI: 0.69 to 0.99). There was no evidence of heterogeneity (p=0.39). The NICE review included all doses of riluzole from the Lacomblez et al. trial, whereas the Cochrane report only included the 100 mg dose. This may account for some differences.

In an update to the NICE review, tracheostomy-free survival information from the Yanagisawa et al. trial was added, changing the estimated HR to 0.89, 95% CI: 0.75 to 1.05. This also increased the level of heterogeneity (p=0.09). It was concluded in the report that the estimate of benefit was reduced when the patients from the Yanagisawa et al. trial were added, and that the estimate no longer achieved statistical significance.
Ultimately, both the Cochrane and NICE reviews concluded that riluzole extends tracheostomy-free survival by two to three months with borderline significance. Furthermore, both meta-analyses detected heterogeneity for this outcome ($p<0.1$).

### 4.2.3 All-cause morbidity

There was limited information about morbidity in the four included RCTs. There was no information regarding serious adverse events or hospitalization provided in the Bensimon et al. 1994 or Lacomblez et al. 1996 trials. The 2002 Bensimon et al. trial reported that 127 patients (75.6%) experienced serious adverse events; 68 patients (79.1%) in the placebo group and 59 patients (72.0%) in the riluzole group. In the Yanagisawa et al. 1997 RCT, three patients experienced a serious adverse event; one (1.0%) in the placebo group and two (2.0%) in the riluzole group. The types of serious adverse events were not discussed in either trial. The considerable differences between patient groups and statistical heterogeneity detected ($p=0.025$) for this outcome do not allow these results to be combined to produce a meaningful outcome.

### 4.2.4 Patient withdrawals due to adverse events

Withdrawals due to adverse events were described in each of the included RCTs (Table 5). In the Bensimon et al. 1994 trial, 9 patients (11.5%) in the placebo group and 19 patients (24.7%) in the riluzole group withdrew from the trial due to adverse events. Common reasons for discontinuation in the placebo group were asthenia (weakness), respiratory disorders and increases in the liver enzymes ALT or AST [n=6 (2 for each reason)]. Stiffness, nausea and dysphagia (difficulty swallowing) were other reasons for withdrawal [n=3 (1 for each reason)]. Of the patients in the riluzole group, the most common reasons for discontinuation were asthenia (n=8), increase in ALT or AST (n=5), and stiffness, nausea and abdominal pain [n= 6 (2 for each reason)]. Other reasons for withdrawal in the treatment group included lack of coordination, fracture, respiratory disorder, rhinitis, pain and fasciculations (involuntary muscle contraction or twitching) [n=6 (1 for each reason)].

In the Lacomblez et al. RCT, 120 patients withdrew from the trial due to adverse events. Twenty-seven patients (11.2%) in the placebo group withdrew from the trial due to adverse events compared with 23 patients (9.7%), 34 patients (14.4%) and 36 patients (14.8%) in the 50 mg, 100 mg and 200 mg groups respectively. Common adverse events causing withdrawal included digestive system disorders (e.g. nausea, dysphagia), respiratory system disorders (e.g. decreased lung function, bronchitis) and increased liver function tests.²⁸

In the 1997 RCT by Yanagisawa et al., 6 patients (6.2%) in the placebo group withdrew due to adverse events compared to 5 patients (5.1%) in the riluzole group. No specific information was provided regarding the types of adverse events causing withdrawal.

In the 2002 Bensimon et al. RCT, most of the clinical and laboratory withdrawals – 8 patients (9.3%) from the placebo group and 15 patients (18.3%) from the treatment group – were due to adverse events. Common adverse events causing withdrawal from the trial were related to respiratory function and liver enzyme elevation.
Table 5: Total patient withdrawals and patient withdrawals due to adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Withdrawals</th>
<th>Withdrawals Due to Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Riluzole</td>
</tr>
<tr>
<td>Bensimon et al., 1994</td>
<td>17/78 (21.8%)</td>
<td>27/77 (35.1%)</td>
</tr>
<tr>
<td>Lacomblez et al., 1996</td>
<td>50/242 (20.7%)</td>
<td>50 mg: 48/237 (20.3%)</td>
</tr>
<tr>
<td></td>
<td>100 mg: 54/236 (22.9%)</td>
<td>100 mg: 34/236 (14.4%)</td>
</tr>
<tr>
<td></td>
<td>200 mg: 53/244 (21.7)</td>
<td>200 mg: 36/244 (14.8%)</td>
</tr>
<tr>
<td>Yanagisawa et al., 1997</td>
<td>48/97 (49.5%)</td>
<td>57/98 (58.2%)</td>
</tr>
<tr>
<td>Bensimon et al., 2002</td>
<td>13/86 (15.1%)</td>
<td>22/82 (26.8%)</td>
</tr>
</tbody>
</table>

The pooled results of the Bensimon et al. 1994, Lacomblez et al. 1996 and Bensimon et al. 2002 trials show that 6% more patients in the treatment group withdrew due to an adverse event compared with those in the control group (95% CI: 2% to 11%) (Figure 2). A more conservative estimate provided by a random effects model is 7% (95% CI: 1% to 12%) (Figure 3). When the Yanagisawa et al. 1997 trial is combined with the other three trials, the estimate is 5% more patient withdrawals in the riluzole group due to an adverse event compared with those in the control group (95% CI: 1% to 9%). Applying the random effects model shows similar results.

Figure 2: Patient withdrawals due to adverse events (fixed effects model)
### 4.2.5 Number of patients with adverse events

In the 1994 Bensimon *et al.* trial, the number of patients experiencing an adverse event was similar in both groups: 71/78 (91.0%) in the control group and 71/77 (92.2%) in the treatment group. More patients, however, experienced more than one adverse event in the treatment group. Common adverse events in both groups included respiratory disorders, asthenia, increased liver function tests and dysphagia.

In the 1996 Lacomblez *et al.* trial, clinical and laboratory adverse events were reported separately. Clinical adverse events were reported by 862 patients: 216 (89.3%) in the placebo group, 207 (87.3%), 216 (91.5%) and 223 (91.4%) in the 50 mg, 100 mg and 200 mg groups respectively. Also, 348 patients reported adverse events in laboratory values: 56 (23.1%), 69 (29.1%), 114 (48.3%) and 109 (44.7%) in the placebo, 50 mg, 100 mg and 200 mg treatment groups. Common adverse events in both groups were digestive system disorders (e.g. dysphagia, nausea), asthenia and respiratory system disorders (decreased lung function).

The 2002 Bensimon *et al.* trial reported the total number of patients experiencing at least one adverse event. These numbers were similar in the two groups, 74/82 (90.2%) in the placebo group and 78/86 (90.7%) in the treatment group. Common adverse events in both groups included decreased lung function, dysphagia, bronchitis and respiratory disorders.

In the trial by Yanagisawa *et al.* it was reported that 17 of 97 patients (17.5%) in the control group and 23 of 98 patients (23.5%) in the riluzole group experienced adverse events. Common adverse events in both groups included headache, “heavy head,” apathy, spasm and muscle stiffness.

Since the number of patients experiencing adverse events in the Lacomblez *et al.* 1996 trial was divided into those experiencing clinical and laboratory adverse events, it was impossible to determine the total number of patients experiencing adverse events (clinical and laboratory). Thus, this trial was excluded in the meta-analysis of this outcome. When the two Bensimon trials were combined, it showed that adverse events were equal in the treatment and placebo groups.
(Figure 4). When the 1997 Yanagisawa et al. trial was added to the meta-analysis, the estimate changed slightly and was not significant.

**Figure 4:** Number of patients with adverse events (fixed effects model)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n</th>
<th>Control n</th>
<th>RD (95%CI Fixed)</th>
<th>Weight %</th>
<th>RD (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benaron</td>
<td>71 (77)</td>
<td>71 (78)</td>
<td>0.0 (0.0; 0.0)</td>
<td>48.0</td>
<td>0.0 (0.0; 0.0)</td>
</tr>
<tr>
<td>Benaron, 2002</td>
<td>74 (82)</td>
<td>78 (88)</td>
<td>0.0 (0.0; 0.0)</td>
<td>52.0</td>
<td>0.0 (0.0; 0.0)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145 (159)</td>
<td>149 (166)</td>
<td>0.0 (0.0; 0.0)</td>
<td>100.0</td>
<td>0.0 (0.0; 0.0)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-squared 0.07, df 1, p = 0.8
Test for overall effect: z = 0.10, p = 0.9

---

4.2.6 **Quality of life**

There was no information in the included trials regarding quality of life in patients with ALS treated with riluzole.

4.2.7 **Time to tracheostomy**

There was no information in the included trials regarding time to tracheostomy.
5 DISCUSSION

ALS is a severe MND that results in death usually within three to five years. Several clinical reviews of riluzole for the treatment of patients with ALS have been conducted, but they do not provide adequate information on the drug’s safety. For this reason, CCOHTA performed a systematic review on the efficacy of treating ALS patients with riluzole, and mainly focused on morbidity.

A literature search and prospective screening procedure identified four RCTs eligible for inclusion. All included comparisons of 100 mg riluzole to placebo in patients with ALS. The patient populations in the Bensimon et al. 1994 RCT and the Lacomblez et al. 1996 dose-ranging RCT were identical. The 1997 RCT by Yanagisawa et al. was similar but it included patients with greater respiratory compromise. The trial conducted by Bensimon et al. in 2002 enrolled types of patients who may have been excluded from the other three trials.

All four RCTs were of moderate quality according to the Jadad scale. Allocation concealment was evaluated to detect possible influence of bias. The trials conducted by Bensimon et al. in 1994 and 2002 were considered to have adequately concealed randomized treatment allocations. The trials by Lacomblez et al. and Yanagisawa et al. did not clearly describe a method of allocation concealment.

5.1 Efficacy and Safety

The aim of our report was to identify all-cause mortality, but this outcome was combined with tracheostomy in all the included trial reports. Since the decision to perform a tracheostomy was made at the treating physician’s clinical discretion, this outcome could be potentially influenced by performance or detection bias. Data describing all-cause mortality could only be obtained from the Bensimon et al. 1994 trial and the Lacomblez et al. 1996 trial. These results could not be combined because of differing trial lengths. The risk difference due to death and due to death and tracheostomy, however, were similar in each trial. Thus, the possible influence of bias from the decision to perform a tracheostomy did not appear to play a role in the estimate of survival. If more tracheostomies had been performed, analyses using death alone would have been warranted, and the effect of riluzole on the time to tracheostomy particularly interesting. Perhaps of more clinical relevance would be the time to permanent ventilation, as many patients can survive for years with a tracheostomy or artificial ventilation.

Tracheostomy-free survival (i.e. time to death or tracheostomy) was estimated in the NICE and Cochrane reviews. Both identified the same four RCTs included in this review. Based on data from three of the RCTs, the Cochrane review concluded that there was a benefit of about two to three months in tracheostomy-free survival derived from the use of riluzole, and that this was very close to attaining statistical significance. Statistical heterogeneity was also detected, but this was expected given the different patient populations in one included trial. The NICE review included data from all four RCTs and arrived at similar conclusions. The inclusion of the fourth trial decreased the benefit of riluzole only slightly and was not statistically significant. Statistical heterogeneity was borderline among the studies.
Both reviews concluded that riluzole increased tracheostomy-free survival by two to three months and both obtained borderline significant results using 95% CIs. Both reviews caution that trial data are heterogeneous and thus, robust conclusions about effects cannot be drawn. Less stringent criteria (i.e. 90% CI) may lead to other interpretations.

Available systematic reviews and meta-analyses regarding riluzole for patients with ALS provide little information on safety, as most of them focus on efficacy and effectiveness. Since substantial morbidity is involved, safety information is needed to complete the clinical picture of riluzole treatment for ALS.

Safety was partially reported in each included RCT. The 1997 Yanagisawa et al. RCT described rates that differed from those in the other included RCTs. One explanation could be cultural differences in the reporting of outcomes. To reduce confounding and possible bias when estimating these outcomes, meta-analyses were undertaken with or without the data from the 1997 Yanagisawa et al. trial.

Serious adverse event data were only reported in the 2002 Bensimon et al. trial and the 1997 Yanagisawa et al. trial. In the 2002 Bensimon et al. trial, there were more serious adverse events occurring in the placebo group; but the types of events were not described. Adverse events were reported in both 1994 and 2002 Bensimon et al. trials. When these results were combined, the adverse events were equal in incidence in the placebo and riluzole groups. Because of the nature of the disease, however, it is difficult to determine whether the serious adverse events or adverse events occurred because of the drug or the disease progression. Regardless of what may be causing this, patients with ALS are concerned about improving their health and not necessarily about the cause of a serious adverse event or adverse event. If riluzole were to prolong survival, however, the incidence of adverse events would likely increase because of disease progression. It may be unrealistic to expect a decrease in adverse events in a progressive neuromuscular disease.

Information about the number of patient withdrawals due to adverse events was included in all RCTs. To avoid introducing potential bias, however, the results from the 1997 Yanagisawa et al. trial were excluded in this particular meta-analysis. The remaining three RCTs were combined to determine that more people withdrew from the trials due to adverse events in the riluzole group. Although these findings reflect patient and physician reported adverse events and laboratory findings, they also indicate that certain patients may be unable to continue therapy.

There were no data on quality of life or time to tracheostomy in any of the included studies. Given the limited data, speculating about the safety and effectiveness of riluzole for patients with ALS is difficult. It is unknown whether a proportional benefit would occur among individuals who survive longer.

5.2 Limitations

The findings in this report are limited because of several factors that relate to the lack of available data. To our knowledge, only four RCTs have been conducted in this area.
• The lack of reporting about serious adverse events and adverse events prevents the formation of robust conclusions regarding the safety of riluzole for patients with ALS. A more adequate reporting of adverse events is desirable to complete the clinical picture.

• The included trials were relatively short (12 to 18 months). There are 50-month survival data, but these data are unavailable.

• RCTs involving information on quality of life and time to tracheostomy were not performed.

• The generalizability of the findings is uncertain: 363 of the 1477 patients (25%) in the RCTs were either older, had more advanced disease or were Japanese. The remaining patients were mainly from France or Belgium; few North American patients were included.

5.3 Generalizability

The generalizability of findings to the North American ALS population is uncertain. Of the four RCTs included in this review, most were conducted in Europe. Both Bensimon et al. trials included patients from France and Belgium. The Yanagisawa et al. trial only included patients in Japan. The 1996 Lacomblez et al. trial was the only international trial that included patients from North America (188/959 or 20%).

In a post hoc analysis performed by the FDA, the difference in mortality rates for French patients compared with non-French patients was investigated. The difference among French patients was greater (61% versus 52% in the placebo and riluzole groups), compared with patients outside France (39% versus 36% respectively). The reasons for this are unclear. The centres outside France enrolled patients later than those in France, so median follow-up was shorter for centres outside France. There is, however, greater mortality outside France. The survival of patients receiving riluzole and placebo in French centres were compared with those from outside France in the Lacomblez et al. trial. Although the Kaplan-Meier curves show that survival is greater in the non-France centres, the curves tend to meet around 18 months, whereas the Kaplan-Meier curves stay separate for the French centres. Thus, the homogeneity and generalizability of the trials may be questioned.

5.4 Non-RCT Findings

Although only RCTs were considered in this report, many retrospective studies, open-label studies and database analyses have been conducted in this area.

To assess the functional status of patients with ALS over time, a clinical classification system called the ALS Health State Scale (ALS/HSS) was developed. This was based on a patient’s ability to speak, ambulate and perform upper extremity activities of daily living. The ALS/HSS includes five distinct states: mild, moderate, severe, terminal and death.

A post-hoc analysis involving the patients from the Lacomblez et al. trial was conducted to determine whether riluzole could favourably influence the time spent in the different stages of
ALS. The length of time spent in the mild state was similar in the riluzole and placebo groups. Patients receiving riluzole in the moderate, severe and terminal health states demonstrated a decreased risk for progress to the next health state when compared with placebo. Only patients in the moderate health state demonstrated a significant decrease compared with placebo (relative risk=0.81, p=0.03). When the two lower states were combined (health state A) and compared with the two higher states combined (health state B), it was found that the time spent in health state A was longer in patients treated with riluzole compared with placebo (317 versus 242 days). There was no benefit from riluzole demonstrated in patients with more advanced ALS. This may have been due to a small number of patients originally in health state B (n=150) or a short 18-month follow-up.32,33

During regulatory review of riluzole, the drug manufacturer launched a program to let patients with ALS have broader access to the drug and to monitor its safety in a large population. The Riluzole Early Access Program (EAP) began in June 1995 as a multicentre, multinational, open-label, uncontrolled study of riluzole. All patients were instructed to take riluzole 50 mg twice daily and monitored monthly for the first three months, then every three months thereafter. A total of 8,383 patients from 44 countries were enrolled. The types of adverse events in this study were similar to those experienced in the previous RCTs. The overall frequency of adverse events in the open-label trial was lower than in the comparable groups of the RCTs.34-36 This may be due to the under-reporting of adverse events in the open-label trials.

An international, open-label, multicentre extension of riluzole pivotal studies was conducted to assess long-term safety for ALS patients. The extension study enrolled 156 patients from the Bensimon et al. 1994 and Lacomblez et al. 1996 studies. The mean duration of the study was 28.7 months (range 0 to 81 months). The analyses of adverse events and serious adverse events showed results that were similar to those obtained in the RCTs. It is difficult to compare the two populations, however, as the baseline characteristics differ somewhat.37

An ALS patient-care database focusing on physician practices and patient outcomes was established for North American patients. Information about baseline characteristics, health-related quality of life, therapy, patient satisfaction and end of life issues were collected from neurologists and patients. One concern is the generalizability of data interpretation. Differences between treatment groups and treatment strategies and information on adverse events may be reported inconsistently, thus leading to bias.38,39

Although RCTs suggest an increase in tracheostomy-free survival of about two to three months, there are patients who demonstrate a considerable benefit, but this population has not been identified yet. In the meantime, as it is the only drug available for treatment, most patients with ALS receive riluzole.

Research is being done to develop new drugs and technologies (e.g. insulin like growth factor-1, stem cell therapy), to find a use for drugs that are already approved for other indications (e.g. nimesulide, various AIDS medications) and to combine riluzole with other drugs (e.g. minocycline and nimodipine).40-42
6 CONCLUSIONS

Riluzole has the potential to reduce serious morbidity in certain patients at the cost of causing some drug intolerance (withdrawals due to adverse events). No information is available describing its impact on quality of life or time to tracheostomy alone.
7 REFERENCES


## Appendix 1: Literature Search Strategy

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<td>ToxFile</td>
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**AND**

BIOSIS: Amyotrophic lateral sclerosis/de OR motor neuron disease/de

EMBASE: motor neuron disease!/de
MEDLINE/ToxFile:
Amyotrophic lateral sclerosis/de OR motor neuron disease/de

PASCAL:
Amyotrophic lateral sclerosis/de OR motor neuron disease/de

All databases:
“lateral sclerosis” OR “gehrig? disease?” OR ALS/ti,ab OR “motor neuron disease?” OR MND/ti,ab

\[ \text{AND} \]

EMBASE:
major clinical study/de OR multicenter study/de OR controlled study!/de OR randomized controlled trial/de OR drug comparison!/de OR evidence based medicine!/de

BIOSIS:
multicenter study/de OR randomized controlled trial/de OR randomized clinical trial/de OR randomized trial/de OR evidence-based medicine/de OR meta-analysis/de

MEDLINE/ToxFile:
controlled clinical trials!/de OR epidemiologic research design!/de OR comparative study/de OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial

All Databases:
random* OR “single (blind* OR dumm* OR mask*)” OR “double (blind* OR dumm* OR mask*)” OR “triple (blind* OR dumm* OR mask*)” OR “treble (blind* OR dumm* OR mask*)” OR placebo* OR “meta analy*” OR metaanaly* OR “quantitative* (review* OR overview*)” OR “systematic* (review* OR overview*)” OR “methodologic* (review* OR overview*)” OR “control* (study OR studies OR trial*)” OR RCT? OR “control* clinical (study OR studies OR trial*)” OR “multicent* (study OR studies OR trial*)” OR “comparative (study OR studies)” OR (drug OR drugs)(3n)comparison*

Performed 19 April 2002
125 unique records (excludes 5 additional duplicates detected when importing to Reference Manager)

BIOSIS – 2 records
EMBASE® - 80 records
MEDLINE® - 39 records
PASCAL – 4 records
ToxFile - 0 records
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<td>Same descriptors and keywords as per original search</td>
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<td>Human</td>
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<td>Human</td>
<td>MEDLINE/ToxFile: dt=review</td>
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<td>Updated 25 February 2003 – 4 records</td>
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AND  
motor neuron disease!/de OR “motor neuron* disease*” OR “amyotrophic lateral sclerosis” OR ALS OR “lou gehrig*”  
*The Cochrane Database of Systematic Reviews = 2 complete reviews, 2 protocols; The Database of Abstracts of Reviews of Effectiveness = 1 record; The Cochrane Controlled Trials Register = 22 references; Abstracts by INAHTA and other healthcare technology agencies = 6 records; The NHS Economic Evaluation Database = 3 records* |
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**Alerts:**  
BIOSIS Previews®  
EMBASE® Alert  
MEDLINE®  
PASCAL  
Pharmaceutical News Index (PNI®)  
*Same descriptors and keywords as per DIALOG® (all searches run separately)* |
| Human (BIOSIS, MEDLINE® only) |  
Web sites of health technology assessment and related agencies; clinical trial registries; other databases  
e.g. NZHTA, AHRQ, National Research Register, University of York NHS Centre for Reviews and Dissemination – CRD databases |
Appendix 2: World Federation of Neurology Requirements for the Diagnosis of ALS

A) the presence of A:1, A:2, and A:3
   (A:1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination
   (A:2) evidence of upper motor neuron (UMN) degeneration by clinical examination
   (A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination

with

B) the absence of B:1 and B:2
   (B:1) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN or UMN degeneration
   (B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

(taken from web site http://www.wfnals.org/oldsite/Articles/elescorial1998criteria.htm)
# Appendix 3: Trial Eligibility Form

## Inclusion/Exclusion Form: Project #173

Reference ID #: _______________________

Author: ______________________________

Title: _______________________________________________________________________

Citation: ______________________________________________________________________

Reviewer: KG ____ DRH ____

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<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unsure</th>
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<tr>
<td>1. Study Design</td>
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<td></td>
<td></td>
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<tr>
<td>a. Randomized controlled trial</td>
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<td></td>
<td></td>
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<tr>
<td>2. Patient Population</td>
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<td></td>
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</tr>
<tr>
<td>a. Amyotrophic lateral sclerosis</td>
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<tr>
<td>3. Intervention</td>
<td></td>
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<tr>
<td>a. Riluzole</td>
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<tr>
<td>4. Outcome Measures (at least one of the following)</td>
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<tr>
<td>a. All-cause mortality</td>
<td></td>
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</tr>
<tr>
<td>b. All-cause morbidity</td>
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<tr>
<td>c. Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Quality of life</td>
<td></td>
<td></td>
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<tr>
<td>e. Time to tracheostomy</td>
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</tr>
</tbody>
</table>

If “yes” to questions 1 to 4, include study
If “no” to any question, exclude study and give explanation

___YES (include study)       ___NO (exclude study)

Reasons for exclusion:

___ Not RCT
___ No control group
___ Study excludes outcome measures of interest
___ Review article
___ Retrospective study
___ Other
Appendix 4: Quality Assessment Form

1. **Randomization:** Was the study described as randomized (i.e. including words such as randomly, random, randomization)?
   Yes = 1  No = 0                   =_____
   A trial that is “randomized” is to receive one point. Trials describing an appropriate method of randomization (table of random numbers, computer generated) are to receive an extra point.
   Appropriate = 1  Not appropriate = 0                   =_____
   If the report describes the trial as randomized and uses an inappropriate method of randomization (e.g. date of birth, hospital numbers), a point is deducted.
   Total Points  0 1 2     SCORE=_____  

2. **Double-blinding:** was the study described as double-blind?
   Yes = 1  No = 0                   =_____
   A trial that is “double-blind” is to receive one point. Trials describing an appropriate method of double-blinding (identical placebo: colour, shape, taste) are to receive an extra point.
   Appropriate = 1  Not appropriate = 0                   =_____
   If the report describes the trial as double-blind and uses an inappropriate method of double-blinding (e.g. comparison of tablets versus injection with no dummy), a point is deducted.
   Total Points  0 1 2     SCORE=_____  

3. **Withdrawals and dropouts:** was there a description of withdrawal and dropouts?
   Yes = 1  No = 0                   =_____
   A trial reporting the number of and reasons for withdrawals or dropouts is to receive one point. If there is no description, no point is given.
   OVERALL SCORE=______
   Low = 0 to 2 points
   Moderate = 3 to 4 points
   High = 5 points (maximum)

4. **Adequacy of allocation concealment:** (circle one)
   • Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes = ADEQUATE
   • Alteration; reference to case record number or date of birth = INADEQUATE
   • Allocation concealment is not reported or fits neither category = UNCLEAR
## Appendix 5: Data Abstraction Form

### Part A: Trial Information

Extractor: KG DH  
Review Title: ____________________________________________________________  
Paper Title: ______________________________________________________________  
Paper ID: _______________________________________________________________  
(Surname of first author, publication year)  
Reference Manager Number: ________________________________________________  
Other references to which this trial may link with: ____________________________

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<td>Type</td>
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<tr>
<td>Additional Notes</td>
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<table>
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<tr>
<td>Method of Concealment of Randomization</td>
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<tr>
<td>Was this concealment adequate, inadequate or unclear?</td>
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<td>Blinding</td>
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<td>Investigator</td>
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<tr>
<td>Assessor</td>
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<td>Description of Withdrawals or Drop-outs</td>
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## Participants

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<td></td>
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<tr>
<td>Total Number Enrolled into Trial</td>
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<tr>
<td>Number of Patients</td>
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<td>Diagnosis (definite or probable ALS)</td>
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<td>% FVC, mean</td>
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## Adverse Events

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<td>Total Number of Serious Adverse Events</td>
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<td>Total Number of Patients with Serious Adverse Events</td>
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### Part B: Outcomes

(Use one form per outcome)

Extractor: KG DH

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*give formulae used for calculating data:

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<th>Is further statistical advice needed?</th>
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<tr>
<td>Is authors to be contacted?</td>
<td>Yes or No</td>
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### Questions for Authors

### Additional Notes
Appendix 6: Excluded Studies

A) **Review Articles**


B) Does Not Measure Outcome of Interest


C) No Control Group


D) Not a Randomized Controlled Trial


E) Other - Miscellaneous


F) Other - Letter


G) Other - News Item


H) **Other - Not ALS**

I) **Other - Pharmacoeconomic Studies**

J) **Other - Commentary**

K) **Other - Retrospective Study**