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Riluzole for Amyotrophic Lateral Sclerosis Treatment

Rapid Review

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Abbreviations

AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
EC	expert consensus
EFNS	European Federation of Neurological Associations
FT9	Fine'til 9
HR	hazard ratio
MA	meta-analysis
QALY	quality-adjusted life-year
QoL	quality of life
RC	recurring cost
RCT	randomized controlled trial
RoB	risk of bias
SR	systematic review
TC	transition and/or "tollgate" cost

Key Messages

- Treatment with riluzole may provide clinical benefits for patients with amyotrophic lateral sclerosis, including longer survival time, reduced risk of disease progression, and minor reversible adverse events, compared to no treatment with riluzole or a placebo.
- We did not find any studies meeting our selection criteria on the clinical effectiveness of riluzole for patients with amyotrophic lateral sclerosis compared to alternative pharmacological therapies.
- Riluzole may be cost-effective at generic drug costs for patients with amyotrophic lateral sclerosis. Evidence supporting this finding is limited, and further research is required to inform decision-making.
- Riluzole is recommended for the treatment of amyotrophic lateral sclerosis, except for patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia, and should be initiated promptly following disease diagnosis.
- A patient with lived experience of riluzole treatment for amyotrophic lateral sclerosis was involved in this report. They identified outcomes that are important to patients, including slowing the progression of amyotrophic lateral sclerosis and minimal side effects from the medication.

Context and Policy Issues

Roughly 1,000 individuals in Canada receive a diagnosis of amyotrophic lateral sclerosis (ALS) annually.¹ At any time, around 2,500 to 3,000 people live with this disease in Canada. ALS is a fatal neurodegenerative disease characterized by the progressive degeneration of upper and lower motor neurons.^{2,3} Clinical features of ALS include limb paralysis, muscle atrophy, difficulty speaking or swallowing, shortness of breath, respiratory failure, and weakness.³ The most common presentation involves limb onset, with about 70% of patients experiencing extremity weakness and mobility impairment.² Bulbar onset with oropharyngeal muscle involvement affecting swallowing and speech is observed in 25% of patients.² In addition to motor impairment, up to 50% of patients may experience cognitive or behavioural impairments due to degeneration in the frontal and temporal lobes.^{2,4} Over time, strength progressively declines, and patients typically die from respiratory failure within 5 years of diagnosis.² Despite an increase in research publications in recent years, treatment options for ALS remain limited, and patient care is primarily focused on symptom management and improving function and quality of life (QoL).^{2,5} Ventilation via a tracheostomy may be suitable for patients with ALS. It is estimated that less than 10% of those with ALS receive life-prolonging ventilation via a tracheostomy, specifically those who desire life-prolonging treatment.⁶ According to a study published in 2014 on the economic burden of ALS in Canada, the expenses associated with symptom management and care encompass both direct and indirect costs. Direct costs consist of expenditures on equipment, home renovations, medication, aids, and medical services. Indirect costs, on the other hand, include income loss, early retirement, and caregiver absence. The average annual direct and indirect costs per patient reported in this study were \$32,337 (with 61% being out-of-pocket expenses) and \$56,821, respectively.⁷ However, the average expenses for caring for a single person with ALS have also been reported to range from \$150,000 to \$250,000.¹

Riluzole, a glutamatergic antagonist, is a disease-modifying treatment shown to extend survival time in ALS,⁸ demonstrating reduced mortality⁹ and improved survival time¹⁰ in past studies. A Health Canada Notice of Compliance (dated April 27, 2022) exists for riluzole for patients with ALS.¹¹ According to the product monograph, based on evidence from older clinical trials (last updated July 9, 2012),¹² riluzole is not a cure for ALS, but represents an initial step toward prolonging survival time.¹³ The recommended dosage for achieving a survival benefit, as observed in clinical trials, is 50 mg every 12 hours. There was limited experience with riluzole overdose in humans, but neurologic and psychiatric symptoms have been reported as side effects in isolated cases.¹³

The purpose of this report is to summarize and critically appraise recent available evidence (including observational studies) on the clinical effectiveness and cost-effectiveness of riluzole for patients living with ALS, as well as to summarize evidence-based guidelines regarding the use of riluzole for the treatment of ALS. A current understanding of the clinical effectiveness and cost-effectiveness of riluzole and guidelines for its use may contribute to informed decision-making, particularly in light of the emerging adjunctive and alternative drugs for ALS currently under development.

Research Questions

1. What is the clinical effectiveness of riluzole for patients living with ALS compared to alternative pharmacological therapies?
2. What is the clinical effectiveness of riluzole for patients living with ALS compared to no treatment?
3. What is the cost-effectiveness of riluzole for patients living with ALS?
4. What are the evidence-based guidelines regarding the use of riluzole for the treatment of patients with ALS?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, and a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were riluzole (Rilutek) and amyotrophic lateral sclerosis. Comments, newspaper articles, editorials, letters, and conference abstracts were excluded. Retrieval was limited to the human population. The search was completed on May 5, 2023, and limited to English-language documents published since January 2011. This time frame was chosen as a Cochrane systematic review was published with a literature search completed in 2011.¹⁴

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Table 1: Selection Criteria

Criteria	Description
Population	Patients of any age living with ALS
Intervention	Riluzole (any dose)
Comparator	Q1 and Q3: Any alternative pharmacological therapy (e.g., AMX0035, oral or IV edaravone) Q2 and Q3: Placebo, no treatment (e.g., before and after comparison) Q4: Not applicable
Outcomes	Q1 and Q2: Clinical benefits (e.g., disease progression, health-related quality of life measures, patient satisfaction, Amyotrophic Lateral Sclerosis Functional Rating Scale, survival) and harms (e.g., treatment-related adverse events) Q3: Cost-effectiveness (e.g., cost per QALY gained, ICER) Q4: Recommendations regarding the best use of riluzole for the treatment of patients living with ALS (e.g., recommended dose, treatment settings, treatment delivery, patient populations of interest)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, economic evaluations, evidence-based guidelines

ALS = amyotrophic lateral sclerosis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), were duplicate publications, or were published before January 1, 2011.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included studies. The critical appraisal tools used were a Measurement Tool to Assess Systematic Reviews (AMSTAR-2)¹⁵ for systematic review (SRs) and meta-analyses (MAs), the Downs and Black checklist¹⁶ for randomized controlled trials (RCTs), the Drummond checklist¹⁷ for economic evaluations, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument¹⁸ for guidelines. Summary scores were not calculated for the studies; rather, the strengths and limitations observed among the included studies were summarized and described narratively in [Appendix 3](#).

Patient Engagement

CADTH has adopted the [CADTH Framework for Patient Engagement in Health Technology Assessment](#),¹⁹ which includes standards for patient involvement in individual health technology assessments and is used to support and guide CADTH activities involving patients. For this report, CADTH engaged a patient contributor with lived experience with riluzole treatment for ALS.

Invitation to Participate and Consent

CADTH reached out to a patient advocacy group that supports people living with ALS. The preliminary engagement request included an overview of this project, the purpose of engagement, and the nature of engagement activities. An interested individual was identified, and the CADTH Patient Engagement Officer obtained the person's informed consent to share with CADTH staff their lived experiences with ALS and the use of riluzole.

Engagement Activities

An individual contributor shared their personal experiences via video call during the drafting of the report. Patient perspectives gained through engagement processes were used to understand the relevance of reported outcomes in identified clinical effectiveness studies and to provide insights, background, and context to help inform the conclusion section.

Patient involvement was reported using the Guidance for Reporting Involvement of Patients and the Public (version 2) Short-Form reporting checklist²⁰ ([Table 22](#) in [Appendix 6](#)).

Summary of Evidence

Quantity of Research Available

A total of 519 citations were identified in the literature search. Following the screening of titles and abstracts, 496 citations were excluded and 23 potentially relevant articles from the electronic search were retrieved for full-text review. One potentially relevant publication was identified from the grey literature search for full-text reviews. Of these 24 potentially relevant articles, 12 were excluded because of the irrelevant intervention and/or comparator, and 12^{2-5,14,21-27} met the selection criteria and were included in this report.

[Appendix 1](#) presents the PRISMA²⁸ flow chart of the study selection. Additional references of potential interest are provided in [Appendix 5](#).

Summary of the Study Characteristics

Twelve peer-reviewed publications, including 1 SR with MA,¹⁴ 8 observational studies,^{3-5,21-25} 1 economic evaluation (i.e., cost-effectiveness study),²⁷ and 2 guidelines^{2,26} were included in this report.

Additional details regarding the characteristics of the included publications are provided in [Appendix 2](#) ([Table 2](#), [Table 3](#), [Table 4](#), and [Table 5](#)).

Study Design

Of the 12 peer-reviewed publications that met the selection criteria for this report, 8 were observational studies^{3-5,21-25} (including 5 retrospective studies,^{4,21-25} 2 prospective observational trials,^{3,5} and 1 analysis of a placebo RCT³) comparing patients who received riluzole with patients who did not receive riluzole or who received a placebo. The other 4 publications were 1 SR of RCTs with MA (search date from the databases' inception to April 2011),¹⁴ 1 cost-utility analysis,²⁷ and 2 guidelines.^{2,26} For the study with cost-utility analysis,

costs were quantified based on the health care sector and societal perspectives, and 5-year and 10-year time horizons were examined. A total of 4 reference case models were provided, representing the health care sector and societal perspectives at 5 years and 10 years. The cost-effectiveness threshold was set at \$100,000 per quality-adjusted life-year (QALY) gained in the US context.²⁷

Country of Origin

The authors of 1 SR with MA,¹⁴ 1 economic evaluation,²⁷ and 2 guidelines^{2,26} were based in the US,^{14,27} Sweden,²⁶ and Canada.² Eight observational studies^{3-5,21-25} were conducted in the US,²¹ UK,⁴ Iran,⁵ China,³ Austria,²⁵ Taiwan,²³ and Italy.²⁴

Patient Population

In 1 SR with MA¹⁴ on patients who were diagnosed with ALS, of the 4 RCTs included, 1 study involved adults aged older than 75 years.²⁹ The age range in other studies and the sex ratio in all included studies were not reported.

All 8 primary studies^{3-5,21-25} were carried out on male and female adults with a probable or definite ALS diagnosis. The studies had variable patient inclusion criteria related to age,^{21,22} riluzole use,^{3-5,21-25} Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) score at baseline,^{21,22} and time from onset to enrolment.^{21,22} The exclusion criteria were not reported in the studies.

In 1 economic evaluation study,²⁷ a cost-utility analysis was conducted on the information of patients with ALS treated with riluzole in the authors' institution.

Both guidelines^{2,26} included in this report were focused on patients diagnosed with ALS.

Interventions and Comparators

In 1 SR with MA,¹⁴ the intervention and comparator were treatment with oral riluzole and a placebo, respectively.

In all 8 primary studies,^{3-5,21-25} the intervention was riluzole and the comparators were no treatment with riluzole^{3,5,21-25} or a placebo.⁴

In the economic evaluation study,²⁷ the intervention was riluzole and the comparator was usual supportive care for ALS, without riluzole use.

In the revised guideline of the European Federation of Neurological Associations (EFNS) on the clinical management of ALS,²⁶ among a wide range of controlled therapeutic interventions, riluzole was the drug intervention relevant to this report. In the guideline on Canadian best practice recommendations for the management of ALS, among a variety of interventions included in the guideline (such as disease-modifying therapies; multidisciplinary care; respiratory management; nutritional management; medication alignment; interventions to manage venous thromboembolism, difficulty speaking, and other symptoms; exercise; cognition and behaviour management interventions; caregiver support, and palliative care), riluzole was 1 of the disease-modifying therapies relevant to this report.²

Outcomes

In 1 SR and MA,¹⁴ the primary outcome was a pooled hazard ratio (HR) based on percent mortality (or tracheostomy) for riluzole versus a placebo over all time points up to 12 months. Secondary outcomes were survival at 12 months and muscle strength and function evaluated by modified Norris Scales and adverse events (AE).

Outcome measures reported in the primary studies were survival rate,^{4,21,23-25} stage-specific risk of progression based on King and Fine'til 9 (FT9) staging methods,²² long-term (e.g., ranged from 36 months²¹ to 200 months^{3,25}) riluzole effectiveness based on ALSFRS,³ and QoL using the ALS Assessment Questionnaire (ALSAQ-40).⁵

The ALSAQ-40 is a 40-item questionnaire, specifically designed to evaluate QoL in patients with ALS. The questionnaire contains 40 items divided into 5 sections, representing 5 distinct areas of health: mobility (10 items), activities of daily living (10 items), eating and drinking (3 items), communication (7 items), and emotional functioning (10 items). The questions refer to the patient's condition during the past 2 weeks and the answers are given on a 5-point Likert scale, providing a summary score from 0 (best health status) to 100 (worst health status).³⁰

In the economic evaluation study,²⁷ the primary outcome was to examine the cost-effectiveness of riluzole in the treatment of ALS in regard to recent advances in disease staging and understanding of stage-specific drug effects. The authors used the FT9 staging method of ALS for estimating costs and utilities, and health states were described using the 3-Level EQ-5D.

Costs at 2018 prices obtained at the author's institution from patients with ALS were disaggregated into recurring costs (RCs) and "one-off" transition and/or "tollgate" costs (TCs). Distributions of transition probabilities and utility weights were informed by direct estimation, whereas lognormal distributions were used for stage-specific RCs and TCs.

In the revised report of the EFNS task force on the clinical management of ALS,³¹ updating EFNS's guidelines on the clinical management of ALS and identifying areas for further research were the main outcomes. In the guideline on Canadian best practice recommendations for the management of ALS,² the primary outcome was to summarize best practice recommendations for the care and management of patients living with ALS in Canada, including all stages of the disease. This guideline aimed to establish a national standard to improve the quality of care for patients, families, and caregivers living with ALS.

Summary of the Critical Appraisal

Systematic Reviews

Of the 12 studies included in this report, 1 was an SR with MA to examine the efficacy of riluzole in prolonging survival, in delaying the use of tracheostomy to sustain survival, and to assess the efficacy of riluzole upon functional health.¹⁴ We used the a Measurement Tool to Assess Systematic Reviews (AMSTAR-2) checklist¹⁵ to evaluate the quality of the SR and determine whether the most important elements of the SR methodology were reported ([Table 6](#)).

The strengths of the SR were in defining the research question and inclusion and exclusion criteria, describing the study design of the selected primary studies, using a comprehensive literature search strategy, conducting study selection and data extraction in duplicate, using a satisfactory tool for assessing the risk of bias (RoB) in primary studies (based on the Cochrane Handbook for Systematic Reviews of Interventions) and reporting potential sources of conflict of interest. The methods for data synthesis to evaluate the time-to-tracheostomy primary outcome, which involved pooling weighted average HRs for each primary study, were appropriate. The authors applied life table methods to obtain summary survival curves for combined treated and combined control participants across different studies and doses, and the median survival for treated and control participants was estimated by interpolation from the survival curves. However, the SR did not include an explicit statement showing that the systematic search protocol was established before the conduct of the review and did not provide a list of excluded studies and justify the exclusions. The authors also did not describe the selected primary studies in detail, investigate publication bias (small study bias) in individual studies, and discuss its potential impact on the results of MA. Thus, the potential impact of studies with low sample sizes (which could result in more extreme treatment effects)³² on the findings was unclear. In addition, the SR did not report the sources of funding for the primary studies included in the review. Sources of funding for included primary studies are important for understanding the extent to which these may contribute to RoB in the findings, and the interpretation of their results (e.g., studies funded by private industry are at a higher RoB in favour of the intervention under study³³).

Primary Studies

The Downs and Black Checklist used for critical appraisal of the included primary studies consists of 5 sections ([Table 7](#)): reporting, external validity, internal validity, confounding, and power. In the following paragraphs, the strengths and weaknesses of the included primary studies are described for each of the 5 sections.

Reporting: The items clearly described or reported in the 8 observational, nonrandomized studies^{3 to 5,21 to 25} (i.e., 5 retrospective studies,^{4,21-25} 2 prospective observational trials,^{3,5} and 1 analysis of a placebo RCT³) included in this report were study objectives, characteristics of the patients (except 1 study⁵), interventions, estimated random variability in data for main outcomes (except 1 study²⁵), actual P values for the main outcomes (except 1 study⁵), and characteristics of patients lost to follow-up. The main findings were not clearly described in 4 studies,^{4,5,21,22} and the distribution of potential confounders (e.g., sex, age, and disease characteristics) were not reported in 5 studies.^{3-5,23}

External validity: Staff, places, and facilities described in the studies were representative of the procedures provided to patients, and funding sources were reported in most studies (except 3 studies).^{5,23,24} The primary studies included in this report were unclear if the patients who were asked to participate in the studies were representative of the entire population recruited (i.e., poor reporting of the source of the population).

Internal validity: The main outcome measures and statistical tests used for data analysis were clearly described in the studies (except for the unclear appropriateness of analyses in 2 studies).^{5,23} However, the studies did not report any information about adherence to medications. Thus, the number of patients who did not follow the prescribed regimen was unknown.

Confounding: In all studies it was unclear if losses of patients to follow-up were considered in statistical analyses, and it was unclear in most studies^{3-5,22,24} whether statistical analyses were adequately adjusted for potential confounding factors.

Power: Sample size and power calculation were not reported in the studies, and it was unclear if they were sufficiently powered to detect clinically significant effects, such as the survival advantage of riluzole in later stages of the disease²⁵ and its impact on QoL.⁵

Additional details regarding the strengths and limitations of the included publications are summarized in [Appendix 3](#).

Economic Evaluation

The 36-item Drummond checklist¹⁷ ([Table 8](#)) was used for critical appraisal of 1 study on the cost-effectiveness of riluzole for ALS included in this report.²⁷ The areas questioned in the reporting checklist are related to the research question, description of the study and intervention, study design, measurements, valuation of costs and consequences, potential discounting, incremental analysis, presentation of results with uncertainty and sensitivity analyses, and discussion of results in the context of policy relevance and existing literature. The authors used appropriate self-reported measures of patients' physical function (specifically, ALSFRS-Revised [ALSFR-R] scores) and QoL (EQ-5D scores) over time, along with the FT9 staging of ALS, to estimate costs and utilities using Markov models. The time horizons considered for these estimates were 5 years and 10 years, and the main model assumptions appeared to be appropriate;²⁷ however, they did not provide adequate details of the patients from whom valuations were obtained, and productivity changes and their relevance to the study question. Productivity changes (losses) may contribute to a large proportion of costs of health conditions in an economic evaluation from a societal perspective,³⁴ and using an appropriate methodology for measuring and valuing these productivity costs is essential.³⁵ However, there is currently a lack of methodological consensus on how productivity losses should be measured and valued.³⁴

Guidelines

The Appraisal of Guidelines for Research and Evaluation (AGREE) II Reporting Checklist¹⁸ ([Table 9](#)) was used for the critical appraisal of the 2 guidelines^{2,26} included in this report. The checklist is a tool to improve the completeness of reporting in clinical practice guidelines and is intended to provide guidance to guideline developers, guideline users, guideline funders, peer reviewers, and journal editors about the essential components of a high-quality practice guideline.³⁶ The checklist entails 6 quality domains (scope and purpose, stakeholder involvement, rigour and development, clarity of presentation, applicability, and editorial independence) and 23 key items.³⁶ The areas clearly described or reported in the 2 guidelines^{2,26} were overall objectives; main questions; target patients; the guideline development groups, including individuals from relevant health care professionals; the target users of the guidelines; the methods for formulating the recommendations; and the consideration of health benefits, side effects, and risks in formulating the recommendations. In both guidelines, key recommendations were easily identifiable, recommendations were specific and unambiguous, and different options for the management of patients with ALS were clearly presented. In addition, both guidelines included statements demonstrating that the views of the funding

bodies have not influenced the content of the guideline, and competing interests of guideline development group members were mentioned. However, facilitators and barriers to the applications and monitoring and/or auditing criteria were the areas not covered in the guidelines. In the guideline developed by Shoesmith et al. (2020),² it was unclear if a systematic method was used to search for evidence, and both guidelines were uncertain if the views of patients with ALS were sought. The guideline developed by Andersen et al. (2012)²⁶ was unclear in several aspects, such as explaining how the quality of evidence supporting the recommendations was assessed and providing a link between the recommendations and their supporting evidence to ensure transparency and support the credibility of the recommendations. In addition, the guideline did not specify a procedure for updating its recommendations and did not indicate whether it underwent external expert review before publication. External review by subject matter experts is important to ensure the guideline's rigour, accuracy, and relevance to the field.³⁷

Summary of Findings

We identified 12 studies, including 1 SR with MA¹⁴ and 8 observational studies^{3-5,21-25} (5 retrospective studies,^{4,21-25} 2 prospective observational trials,^{3,5} and 1 analysis of a placebo RCT³) on the clinical effectiveness of riluzole for patients with ALS, 1 study²⁷ on the cost-effectiveness of riluzole for patients with ALS, and 2 evidence-based guidelines^{2,26} regarding the use of riluzole for the treatment of patients with ALS.

[Appendix 4](#) presents the main outcomes of the included studies.

Clinical Effectiveness of Riluzole for Patients With ALS

Tracheostomy-Free Survival

In 1 SR with MA¹⁴ that reported pooled HRs, riluzole 100 mg per day was associated with a 9% gain in the probability of 1-year tracheostomy-free survival (49% in the placebo group and 58% in the riluzole group) and increased median tracheostomy-free survival from 11.8 months to 14.8 months compared to a placebo ([Table 10](#)). Improved survival time from disease onset to death or tracheostomy was not statistically significant in the Georgouloupoulou et al. (2013) study ([Table 14](#)).²⁴

Survival

In the SR with MA,¹⁴ the pooled HR of mortality at 12 months with riluzole 100 mg was lower in patients who received riluzole than in those who received placebo. In the Thakore et al. (2022) study,²¹ median survival was significantly longer (i.e., 2 months) in patients treated with riluzole than in patients who did not receive riluzole, and 1-year treatment was associated with improved median survival by 1.9 months ([Table 11](#)). In the Georgouloupoulou et al. (2013) study,²⁴ a significantly longer median survival time from onset to death (43 months versus 31 months) was reported in patients receiving riluzole than in patients not receiving riluzole ([Table 14](#)). A higher survival time²³ ([Table 13](#)) and a survival advantage only for the initial treatment period or the early stage of the disease²⁵ ([Table 12](#)) compared to no treatment with riluzole were reported in 2 other studies. In summary, the identified studies all reported a survival advantage for patients who received treatment with riluzole compared with those who did not.

Stage-Specific Risk of Progression

In the Thakore et al. (2020) study,²² adjustments were made for age and ALSFRS-R slope at the initial visit, and the probability of progression (represented by the transition from early to late stages and death based on the King and FT9 staging methods) with and without riluzole was evaluated. The reported HRs for both staging methods suggested the effectiveness of riluzole in reducing the risk of transitioning between different stages of ALS; however, the statistical significance of these findings was not reported (Table 15). Likewise, in the Fang et al. (2018) study,⁴ the time at stage 4 was significantly longer for patients receiving riluzole than for those receiving a placebo (Table 16).

Function and Muscle Strength

In 1 SR with MA,¹⁴ there was a small beneficial effect (i.e., a statistically significantly slower rate of decline) for riluzole versus a placebo on both bulbar and limb function (Table 10), but not on muscle strength (mean difference for rate of decline of muscle strength = -1.88; 95% confidence interval, -5.79 to 2.03).

Functional ability rated by ALSFRS and ALSFRS-R in 1 study³ showed significantly higher scores, which represented better functional ability, in patients treated with riluzole compared to patients not treated with riluzole (Table 17).

Adverse Events

In 1 SR with MA,¹⁴ there were increases in a few nonserious AEs (i.e., nausea, asthenia, and a 3-fold increase in serum alanine transferase), which were mostly reversible after stopping the drug (Table 10).

Quality of Life

QoL was assessed in 1 study⁵ in which no significant differences were found between patients treated with riluzole and patients not treated with riluzole from baseline to 12 months (Table 18).

Cost-Effectiveness of Riluzole for Patients With ALS

In the economic evaluation study,²⁷ from the health care sector perspective at the 5-year horizon, riluzole use contributed to 0.182 QALY gained at a cost difference of \$12,348 (\$5,403 riluzole cost; \$8,870 RC and -\$1,925 TC differences), demonstrating an incremental cost-effectiveness ratio of \$67,658 per QALY. The study findings supported the cost-effectiveness of riluzole to treat ALS at the \$100,000 per QALY threshold at generic drug costs (Table 19), and a conclusion of cost-effectiveness was maintained for analyses with a 10-year time horizon and from the societal perspective. Table 20 demonstrates the health state utility weights and costs (in dollars per month) by stage reported in this study.

Guidelines Regarding Riluzole Use for Patients With ALS

The authors of the 2 guidelines included in this report recommend that (Table 21):

- Patients with ALS should be offered treatment with riluzole 50 mg twice daily (based on evidence from RCTs), except for patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia (based on expert consensus [EC]).²⁶
- Treatment with riluzole is recommended soon after the diagnosis of ALS (based on EC), given its effectiveness in enhancing survival time by a median duration of 3 months.²

- Patients taking riluzole should be monitored for AEs (based on EC). In cases where patients experience fatigue while taking riluzole, the consideration of reducing or discontinuing the medication may be appropriate (based on EC and evidence from observational, nonrandomized studies).²

Limitations

The primary studies^{3-5,21-25} included in this report were at RoB from several aspects, such as not reporting the distribution of potential confounders (e.g., sex, age, and disease characteristics),^{3-5,23,27} compliance with the medications (riluzole), if losses of patients to follow-up were considered in statistical analyses,^{3-5,21-25} if the statistical analyses were adequately adjusted for potential confounding factors,^{3-5,22,24,27} and if statistical analyses were sufficiently powered to detect clinically significant effects. We did not find any studies that compare riluzole's clinical effectiveness with alternative pharmacological drugs in patients with ALS.

In terms of the cost-effectiveness of riluzole for ALS, we did not identify any Canadian economic analyses that met the inclusion criteria for this review. In addition, the cost evaluation study included in this report²⁷ was based on US health care perspectives, and the relevance of the information reported in this study to the Canadian health care system is unclear.

Conclusions and Implications for Decision- or Policy-Making

We reviewed a total of 9 studies (1 SR with MA¹⁴ and 8 primary studies^{3-5,21-25}) on the clinical effectiveness of riluzole in patients with ALS compared to those not receiving riluzole^{3,21-25} or those who received a placebo.^{4,5,14} According to the SR with MA published in 2012,¹⁴ riluzole 100 mg was associated with 3 months longer median tracheostomy-free survival time than a placebo. Additionally, 6 studies published between 2013 and 2022 reported improved survival time^{21,23-25} and reduced risk of disease progression at different stages^{4,22} in patients treated with riluzole compared to those not receiving treatment²² or receiving a placebo.⁴

The SR and MA included in this report¹⁴ found that the AEs associated with riluzole were generally minor and reversible, such as nausea, asthenia, and an increase in serum alanine transferase. In addition, CADTH sought input from 1 patient with lived experience of early treatment with riluzole, who identified slowing disease progression and minimal side effects as priority outcomes for ALS treatment, which were aligned with the findings reported in this review.

Regarding functional ability, limited evidence suggests a small beneficial effect of riluzole compared to placebo on both bulbar and limb function,¹⁴ as well as improved functional ability compared to no treatment.³ In addition, we identified 1 study that reported no significant difference in QoL between treatment with riluzole and a placebo.⁵

We did not find any studies on the clinical effectiveness of riluzole for patients with ALS compared to alternative pharmacological therapies.

The findings of 1 economic evaluation study published in 2020²⁷ showed riluzole's cost-effectiveness to treat ALS at the \$100,000 per QALY threshold at generic drug cost, from a US health care system perspective.

According to 2 evidence-based guidelines,^{2,26} treatment with riluzole (50 mg twice daily) is recommended to treat ALS and should be initiated upon diagnosis,^{2,26} except for patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia.²⁶ While the guidelines did not comment on treatment delivery or implementation considerations in detail, the patient contributor to this report expressed a preference for the oral medication form due to its convenience (compared to infusions). The patient also highlighted potential barriers to access, such as the risk of losing medication access when requiring full-time continuous positive airway pressure (CPAP) therapy due to declining health.

The findings of the studies included in this report support the clinical effectiveness (i.e., longer survival time; reduced risk of disease progression; and minor, reversible AEs) of riluzole versus no treatment or a placebo for patients with ALS and suggest early treatment soon after disease diagnosis. Also, riluzole might be cost-effective at generic drug costs,²⁷ though additional economic evaluation studies from a Canadian health care perspective are required to reach firm conclusions about the cost-effectiveness of riluzole for ALS and to facilitate informed decision-making. Furthermore, it is important to note that there are ongoing trials investigating the use of add-on drugs in conjunction with riluzole ([Appendix 5](#)) that have the potential to influence the role of riluzole in the treatment approach for ALS in the future. These additional interventions and the ongoing research highlight the dynamic nature of ALS treatment and the possibility of evolving treatment strategies beyond riluzole monotherapy.

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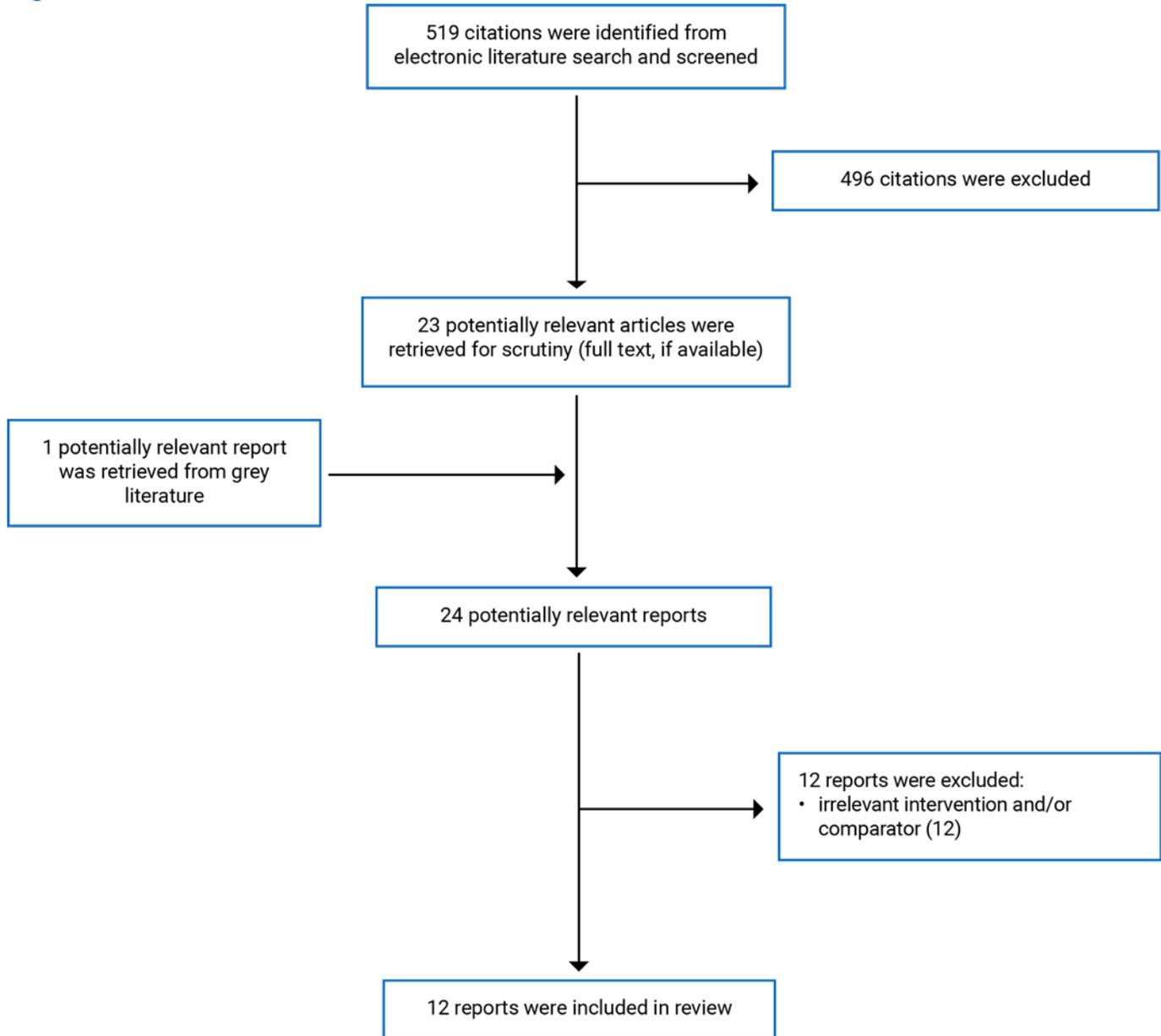
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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of the Included Systematic Review

Study citation, country, objective, funding source	Study designs and the number of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Miller et al. (2012) ¹⁴ US Funding source: <ul style="list-style-type: none"> Motor Neuron Disease Association MRC Centre for Neuromuscular Diseases 	Design: Systematic review and MA Total studies included: 4 RCTs Total studies relevant to this review: 4 RCTs	Population included: Adults diagnosed with amyotrophic lateral sclerosis Age in all included studies: Older than 75 yrs in 1 study and NR in 3 studies Total number of patients: 1477 <ul style="list-style-type: none"> Riluzole: 974 Placebo: 503 Sex: NR Exclusion criteria: <ul style="list-style-type: none"> Non-RCT studies Studies without a control group, or a control group other than a placebo 	Interventions included: Riluzole (100 mg) Comparator: Placebo	Outcome measure: Primary outcome: Tracheostomy-free survival over all time points with riluzole vs. placebo Secondary outcome: <ul style="list-style-type: none"> Survival at 12 months Function and muscle strength evaluated by modified Norris Scales Adverse events Follow-up: 12 months in 4 RCTs included in MA

MA = meta-analysis; NR = not reported; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, design, country, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Thakore et al. (2022) ²¹ Design: Retrospective Country: US Funding source: No funding.	Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 4,778, NR, NR <ul style="list-style-type: none"> On riluzole: 3,446, 55.73 (11.24), NR Not on riluzole: 1,332, 55.95 (11.74), NR Sex: number of males, n (%) Total: 2,997 (75.44) <ul style="list-style-type: none"> On riluzole: 2,179 (63.20) Not on riluzole: 818 (61.40) Inclusion criteria: Patients with information on <ul style="list-style-type: none"> ALSFRS or revised ALSFRS (ALSFRS-R) scores Time from onset to enrollment (TFOE) Riluzole us Exclusion criteria: NR	Intervention: Riluzole Comparator: No treatment with riluzole	Outcomes: Survival rate Follow-up: 36 months

Study citation, design, country, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
<p>Thakore et al. (2020)²² Design: Retrospective Country: US Funding source: No funding.</p>	<p>Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 1,903, NR, NR <ul style="list-style-type: none"> On riluzole: 1587, 55.80 (11.40), NR Not on riluzole: 316, 56.10 (12.10), NR Sex: number of males, n (%) Total: 1,032 (64.74) <ul style="list-style-type: none"> On riluzole: 1,031 (65.00) Not on riluzole: 201 (63.60) Inclusion criteria: Patients with information on <ul style="list-style-type: none"> Age onset date Riluzole use ALSFRS-R sub-scores Exclusion criteria: NR</p>	<p>Intervention: Riluzole Comparator: No treatment with riluzole</p>	<p>Outcomes: Stage-specific risk of progression based on King and FT9 (Fine'til 9) staging methods Follow-up: 36 months</p>
<p>Fang et al. (2018)⁴ Design: Retrospective analysis of a randomized controlled trial (RCT) Country: UK Funding source: NIHR Maudsley Biomedical Research Centre, The European Union Joint Programme on Neurodegeneration, and the King's Summer Undergraduate Studentship.</p>	<p>Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 959, NR, NR <ul style="list-style-type: none"> Riluzole 50 mg: 237, NR, NR Riluzole 100 mg: 236, NR, NR Riluzole 200 mg: 244, NR, NR Placebo: 242, NR, NR Sex: number of males, n (%) NR Inclusion criteria: Patients with probable or definite ALS diagnosis Exclusion criteria: NR</p>	<p>Intervention: Riluzole (100 mg per day) Comparator: Placebo</p>	<p>Outcomes: Survival rate Follow-up: 800 days</p>
<p>Chen et al. (2016)³ Design: Prospective observational study Country: China Funding source: National Natural Science Foundation of China</p>	<p>Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 1,540, NR, NR <ul style="list-style-type: none"> On riluzole: 415, 51.10 (NR), 50.00 to 52.20 Not on riluzole: 1,125, 49.50 (NR), 48.80 to 50.20 Sex: number of males, n (%) Total: NR <ul style="list-style-type: none"> On riluzole: Male to female ratio = 1.55 Not on riluzole: Male to female ratio = 1.76 Inclusion criteria: <ul style="list-style-type: none"> Patients diagnosed with ALS Treatment with riluzole (50mg) twice per day </p>	<p>Intervention: Riluzole (50 mg, twice per day) Comparator: Patients not on riluzole</p>	<p>Outcomes: <ul style="list-style-type: none"> Stage-specific survival rate ALSFRS-R Follow-up: Every 3 month follow-up up to 200 months</p>

Study citation, design, country, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	for longer than 2 weeks Exclusion criteria: NR		
Shamshiri et al. (2016) ⁵ Design: Prospective observational study Country: Iran Funding source: NR	Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 132, NR, NR <ul style="list-style-type: none"> • On riluzole: NR, NR, NR • Not on riluzole: NR, NR, NR Sex: number of males, n (%) NR Inclusion criterion: Patients with probable or definite ALS diagnosis Exclusion Criteria: NR	Intervention: Riluzole Comparator: Patients not on riluzole	Outcomes: Quality of life (QoL) assessed by ALS Assessment Questionnaire (ALSAQ-40) Follow-up: 1 year
Cetin et al. (2015) ²⁵ Design: Retrospective Country: Austria Funding source: No funding.	Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 911, 64.50, NR <ul style="list-style-type: none"> • On riluzole: 528, NR, NR • Not on riluzole: 383, NR, NR Sex: number of males, n (%) Total: NR <ul style="list-style-type: none"> • On riluzole: Male to female ratio = 1.13 • Not on riluzole: Male to female ratio = 1.17 Inclusion criteria: <ul style="list-style-type: none"> • The main diagnosis of ALS • Riluzole use Exclusion criteria: Age below 20 years	Intervention: Riluzole (100 mg per day) Comparator: Patients not on riluzole	Outcomes: Survival rate Follow-up: 200 months
Georgouloupoulou et al. (2013) ²⁴ Design: Retrospective Country: Taiwan Funding source: NR	Patients with ALS. Number of patients (n), Age in year, mean (SD), range: Total: 193, NR, NR <ul style="list-style-type: none"> • On riluzole: 133, 63.65 (10.18), NR • Not on riluzole: 60, 72.99 (10.21), NR Sex: number of males, n (%) Total: 102 (52.84) <ul style="list-style-type: none"> • On riluzole: 76 (57.14) • Not on riluzole: 26 (43.33) Inclusion criteria: Patients diagnosed with ALS Exclusion criteria: NR	Intervention: Riluzole Comparator: Patients not on riluzole	Outcomes: Survival rate Follow-up: 168 months
Lee et al. (2013) ²³ Design: Retrospective	Patients with ALS. Number of patients (n), Age in year, mean (SD), range:	Intervention: Riluzole (100 mg per day) Comparator:	Outcomes: Survival rate Follow-up: 120 months

Study citation, design, country, funding source	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Country: Taiwan Funding source: NR	Total: 1,149, 56.27 (14.15), NR <ul style="list-style-type: none"> On riluzole: 698, NR, NR Not on riluzole: 451, NR, NR Sex: number of males, n (%) Total: 715 (62.23) <ul style="list-style-type: none"> On riluzole: NR Not on riluzole: NR Inclusion criteria: Patients diagnosed with ALS Exclusion criteria: NR	Patients not on riluzole	

ALS = amyotrophic lateral sclerosis; ALSFRS = amyotrophic lateral sclerosis functional rating scale; ALSFRS-R = revised amyotrophic lateral sclerosis functional rating scale; NR = not reported; SD = standard deviation.

Table 4: Characteristics of the Included Economic Evaluation

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in the analysis	Main assumptions
Thakore et al. (2020) ²⁷ US Funding source: Internal NICORE (Neurologic Institute Center for Outcomes Research and Evaluation, Cleveland Clinic) grant	^aAnalysis: cost-utility analysis Time horizon: 5 and 10 years Perspective: US Health care sector and societal perspectives with a willingness to pay threshold of USD \$100,000 per QALY.	Patients treated with riluzole in a prospective cohort study	Intervention: Riluzole Comparator: Usual supportive care for ALS, without riluzole use.	A cost-effectiveness framework using Markov models with 1 month cycles by FT9 ^a stage (stage 0 to 4) State transition probability matrices were estimated from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.	Self-reported measures of patients' physical function over time (ALSFRS-R) and quality of life (EQ-5D) ^b were obtained at the authors' institution from patients with ALS. FT9 staging of ALS was used for the estimation of costs and utilities based on ALSFRS-R data ^a Cost inputs included physician, outpatient facility, and home health care costs.	For analyzing treatment cost, the efficacy of all (bioequivalent) formulations of riluzole was assumed to be identical. Because an early diagnosis was unlikely (FT9 stage 0), treatment was assumed to start in FT9 stage 1.

ALS = amyotrophic lateral sclerosis; ALSFRS-R = revised ALS functional rating scale; EQ-5D = European Quality of Life 5 Dimension scale; FT9 = Fine'til 9; QALY = quality-adjusted life-year.

^aFT9 is a novel staging method derived from the revised ALS functional rating scale (ALSFRS-R). It is a widely used 12-question, 5-level instrument comprised of 4 sub-scores (bulbar, fine motor, gross motor, and respiratory; 3 questions each). FT9 counts the number of ALSFRS-R sub-scores that are 9 or less (12 is normal).³⁸

^bThe EQ-5D is a brief, multi-attribute, preference-based health status measure. This measure consists of five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with each dimension specifying either three (EQ-5D-3L) or five levels (EQ-5D-5L) of severity, and is completed by a patient or respondent.³¹

Table 5: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations for development and evaluation	Guideline validation
Andersen et al. (2012)²⁶						
Intended users: Clinicians Target population: Patients with ALS	Existing management options for ALS Interventions relevant to this report: Riluzole	Updating European Federation of Neurological Associations (EFNS) guidelines on the clinical management of ALS Identifying areas where further research is needed.	A literature search in 14 databases with no constraints on language or publication status.	NR	Recommendations were reached by consensus. Each pair of investigators prepared a written analysis that was communicated and discussed by email with the other members of the task force. A combined draft was then written by the chairman and circulated to the task force for further discussions. All recommendations had to be agreed by all members of the task force unanimously.	NR
Shoesmith et al. (2020)²						
Intended Users: Clinicians, allied health professionals, and primary care providers Target Population: Patients with ALS	Existing management options for ALS Interventions relevant to this report: Riluzole	Outlining best practice recommendations for the care and management of patients living with ALS in Canada, including all stages of the disease.	A literature search in 4 databases. Forty-seven clinical questions were selected based on ranking by experts.	The quality of evidence was orderly classified from 1 to 4 by the working group.	Recommendations were reached by consensus. The working group met regularly at face-to-face meetings and through regular group teleconferences. Each topic group drafted preliminary guideline statements for each clinical question. The draft statements were reviewed by the working group and refined on an iterative basis, ideally until consensus was obtained. There was consensus on all statements and no vote was held.	In the first round, the executive draft summary was reviewed and commented on by the Canadian ALS Research Network (including all multidisciplinary ALS clinics in Canada) and topic experts external to the working group representing gastroenterology, respiratory, palliative care, and psychiatry. In the second round, key stakeholders within each provincial ALS Society were asked to review and comment on the revised executive draft summary.

ALS = amyotrophic lateral sclerosis; NR = not reported.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 6: Strengths and Limitations of the Included Systematic Review Using a Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)¹⁵

Checklist's Items	Miller et al. (2012) ¹⁴
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes
#10. #Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for the statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Unclear
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

NA = not applicable; PICO = population, intervention, comparator, outcome; RoB = risk of bias.

Table 7: Strengths and Limitations of Primary Clinical Studies Using the Downs and Black Checklist¹⁶

Checklist's Items	Thakore (2022) ²¹	Thakore (2020) ²²	Fang (2018) ⁴	Chen (2016) ³	Shamshiri (2016) ⁵	Cetin (2015) ²⁵	Lee (2013) ²³	Georgoulou (2013) ²⁴
1. Is the objective of the study clear?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
4. Are the interventions clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects clearly described?	No	No	No	No	No	No	No	No
6. Are the main findings of the study clearly described?	No	No	No	Yes	No	Yes	Yes	Yes
7. Does the study estimate random variability in data for main outcomes?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
8. Have all the important adverse events consequential to the intervention been reported?	No	No	No	No	No	No	No	No
9. Have characteristics of patients lost to follow-up been described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Have actual P values been reported for the main outcomes except for probability < 0.001?	Yes	Partially	Yes	Yes	No	Yes	Yes	Partially
11. Is the source of funding clearly stated?	Yes	Yes	Yes	Yes	No	Yes	No	No
12. Were subjects who were asked to participate in the study representative of the entire population recruited?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
13. Were those subjects who were prepared to participate representative of the recruited population?	NA	NA	NA	Unclear	Unclear	NA	NA	NA
14. Were staff, places, and facilities where patients were treated representative of the treatment most received?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Checklist's Items	Thakore (2022) ²¹	Thakore (2020) ²²	Fang (2018) ⁴	Chen (2016) ³	Shamshiri (2016) ⁵	Cetin (2015) ²⁵	Lee (2013) ²³	Georgoulopoulou (2013) ²⁴
15. Was an attempt made to blind study subjects to the intervention?	NA	NA	NA	NA	NA	NA	NA	NA
16. Was an attempt made to blind those measuring the main outcomes?	NA	NA	NA	NA	NA	NA	NA	NA
17. If any of the results of the study were based on data dredging was this made clear?	No	No	No	No	No	No	No	No
18. Was the time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
19. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Partially	Yes	Unclear	Yes
20. Was compliance with the interventions reliable?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
21. Were the main outcome measures used accurate (Valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22. Were patients in different intervention groups recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
24. Were study subjects randomized to intervention groups?	No	No	No	No	No	No	No	No
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	NA	NA	NA	NA	NA	NA	NA	NA
26. Was there an adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No
27. Were losses of patients to follow-up taken into account?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
28. Was the study sufficiently powered to detect clinically important effects where the P value for a difference due to chance is < 5%?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

NA = not applicable.

Table 8: Strengths and Limitations of the Included Economic Evaluation Study Using the Drummond Checklist¹⁷

Checklist's Items	Thakore et al. (2020) ²⁷
1. The research question is stated.	Yes
2. The economic importance of the research question is stated.	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified.	Yes
4. The rationale for choosing alternative programs or interventions compared is stated.	Unclear
5. The alternatives being compared are clearly described.	Yes
6. The form of economic evaluation used is stated.	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes
Data collection	
8. The source(s) of effectiveness estimates used are stated.	Yes
9. Details of the design and results of the effectiveness study are given (if based on a single study).	Yes
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes
12. Methods to value benefits are stated.	Yes
13. Details of the subjects from whom valuations were obtained were given.	No
14. Productivity changes (if included) are reported separately.	Partially
15. The relevance of productivity changes to the study question is discussed.	No
16. Quantities of resource use are reported separately from their unit costs.	Yes
17. Methods for the estimation of quantities and unit costs are described.	Yes
18. Currency and price data are recorded.	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given ^a	Yes
20. Details of any model used are given.	Yes
21. The choice of model used and the key parameters on which it is based are justified.	Yes
Analysis and interpretation of results	
22. Time horizon of costs and benefits is stated.	Yes
23. The discount rate(s) is stated.	Yes
24. The choice of the discount rate(s) is justified ^a	Yes
25. An explanation is given if costs and benefits are not discounted.	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	Yes
27. The approach to sensitivity analysis is given.	Yes
28. The choice of variables for sensitivity analysis is justified.	Yes
29. The ranges over which the variables are varied are justified.	partially
30. Relevant alternatives are compared.	Yes

Checklist's Items	Thakore et al. (2020) ²⁷
31. Incremental analysis is reported.	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form ^b	Yes
33. The answer to the study question is given.	Yes
34. Conclusions follow from the data reported.	Yes
35. Conclusions are accompanied by the appropriate caveats.	Yes

NA = not applicable.

^aAnnual discount was set at 3% for expenses and utilities. Costs were adjusted to the year 2018 using the Health care Personal Consumption Expenditures chain-type price index.

Table 9: Strengths and Limitations of Guidelines Using the AGREE II Checklist¹⁸

Checklist's Items	Andersen et al. (2012) ¹⁴	Shoesmith et al. (2020) ²
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Unclear
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	No	Partially
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Unclear	Yes
13. The guideline has been externally reviewed by experts before its publication.	Unclear	Yes
14. A procedure for updating the guideline is provided.	Partially	NA
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for the management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes

Checklist's Items	Andersen et al. (2012) ¹⁴	Shoesmith et al. (2020) ²
Domain 5: Applicability		
18. The guideline describes the facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	Yes
20. The potential resource implications of applying the recommendations have been considered.	No	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

NA = not applicable.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 10: Summary of Evidence for Riluzole in Amyotrophic Lateral Sclerosis (ALS) in a Systematic Review and Meta-analysis by Miller et al. (2012)¹⁴

Outcomes	Assumed risk ^a	Corresponding risk	Relative effect, (95% confidence interval)	Total number of patients (studies)	Quality of the evidence	Comments
	Placebo	Riluzole (95% CI)				
Pooled HR of mortality or tracheostomy at 12 months with riluzole 100 mg	510 events per 1000 patients	419 per 1000 (367 to 475)	HR = 0.83 (0.70 to 1.00)	1282 (3)	High	The relative effect showed a 3-month increase in median survival from 11.80 to 14.80 months.
The mortality rate at 12 months with riluzole 100 mg	440 events per 1000 patients	343 per 1000 (286 to 405)	RR = 0.78 (0.65 to 0.92)	799 (3)	High	–
Rate of decline of Norris Scale ^b - Norris Limb with riluzole 100 mg and 12-month follow-up	23.10 point per year the weighted mean rate of decline	The mean rate of decline in the intervention groups was 3.94 point slower (7.25 to 0.64 slower)	NR	731 (3)	High	The pooled data showed a slower decline of limb function in the riluzole group.
Rate of decline of Norris Scale - Norris bulbar with riluzole 100 mg and 12-month follow-up	11.10 point per year weighted mean rate of decline	The mean rate of decline in the intervention groups was 2.06 slower (3.86 to 0.27 slower)	NR	742 (3)	High	The pooled data showed a slower decline of bulbar function in the riluzole group.
AE: nausea	91 events per 1000 patients	142 per 1000 (96 to 207)	RR = 1.55 (1.06 to 2.28)	801 (3)	High	–
AE: asthenia	116 events per 1000 patients	175 per 1000 (124 to 246)	RR = 1.5 (1.07 to 2.12)	801 (3)	High	–
AE: three-fold increase in alanine transferase	49 events per 1000 patients	129 per 1000 (78 to 211)	RR = 2.62 (1.59 to 4.31)	801 (3)	High	–

AE = adverse event; HR = hazard ratio; NR = not reported; RR = risk ratio.

^aAssumed risk refers to the median control group risk across studies. The corresponding risk (and its 95% confidence interval) was based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).¹⁴

^bThe Norris Scale is a comprehensive tool used for assessing the functional capacity of individuals with ALS, encompassing two distinct sections. The first section is known as the Norris Limb Scale, which comprises 21 items focused on activities of daily living (ADLs) pertaining to the extremities. These items encompass tasks such as gripping, buttoning, zipping, and standing up. The second section, known as the Norris Bulbar Scale, consists of 13 items specifically designed to evaluate bulbar function, which includes speech and swallowing abilities. Each item is assigned an ordinal 4-point scale, with corresponding values and functional scores of “normal” (3 points), “somewhat impaired” (2 points), “inadequate” (1 point), and “cannot do at all” (0 points). The maximum score achievable for the Norris Limb Scale and Norris Bulbar Scale is 63 and 39, respectively.³⁹

Table 11: Summary of Findings by Outcome – Impact of Early Initiation of Riluzole on Median Survival in Thakore et al. (2022)²¹

Outcomes	Riluzole (n = 3,446)	No riluzole (n = 1,332)	P value
Median survival period (months)	22.60	20.20	< 0.001
The impact of delayed riluzole initiation by 1 year	Reduced median survival from the onset by 1.90 months (40.10 to 38.20 months)		

Table 12: Summary of Findings by Outcome – Survival Time (day) in Cetin et al. (2015)²⁵

Outcomes	Riluzole (n = 1,125) mean (CI 95%)	No riluzole (n = 415) mean (CI 95%)	P value
Group 1 (≤ 0.20) ^a	1,255 (1,105 to 1,404)	908 (829 to 987)	0.010 ^b
Group 2 (0.21 to 0.40)	1,089 (910 to 1,268)	908 (829 to 987)	0.09
Group 3 (0.41 to 0.60)	794 (240 to 1,348)	829 (449 to 1,209)	0.77
Group 4 (0.61 to 0.80)	582 (433 to 731)	829 (449 to 1,209)	0.28
Group 5 (≥ 0.81)	601 (518 to 684)	829 (449 to 1,209)	0.026

^aTo evaluate a possible time-dependent effect of riluzole therapy, the patients were classified into five groups according to their therapy ratio. The groups were defined as the duration of riluzole therapy in days divided by the survival time from diagnosis in days. The duration of riluzole therapy was calculated as the total dosage of prescribed pills divided by the defined daily dose for riluzole (i.e., 100 mg).

^bRiluzole therapy was associated with a survival advantage only for the initial treatment period.

Table 13: Summary of Findings by Outcome – Survival Time in Lee et al. (2015)²³

Outcomes	Riluzole (n = 698) OR (CI 95%)	No riluzole (n = 451) OR (CI 95%)	P value
Survival time (months)	0.457 (0.297 to 0.748)	1.00	0.002

CI = confidence interval; OR = odds ratio.

Table 14: Summary of Findings by Outcome – Survival Time in Georgouloupoulou et al. (2013)²⁴

Outcomes	Riluzole (n = 133) Median (CI 95%)	No Riluzole (n = 60) Median (CI 95%)	P value
Survival time (months to death)	43 (37 to 51)	31 (25 to 46)	< 0.01
Survival time (months to tracheostomy)	38 (35 to 43)	31 (25 to 46)	0.11

CI = confidence interval.

Table 15: Summary of Findings by Outcome – Stage-Specific Riluzole Effect in Thakore et al. (2020)²²

Outcomes	HR	Outcomes	HR
Transition in King's stages ^a		Fine'til 9 (FT9) stages ^b	
Stages 1 to 2	0.81	Stages 1 to 2	0.84
Stages 2 to 3	0.82	Stages 3 to 4	0.71
Stage 4 to death	0.57	Stage 4 to death	0.67

HR = hazard ratio.

^aThe King's staging system consists of 5 disease stages, with stage 5 being death. Stages 1 to 3 are based on the number of brain regions involved in the disease, measured by symptoms of weakness, wasting, spasticity, dysphagia, or dysarthria. Stage 4 is a nutritional failure, defined by the requirement for gastrostomy, or respiratory failure, defined by the requirement for non-invasive ventilation (NIV).⁴⁰

^bFine'til 9 (FT9) is a novel staging method derived from the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R). It is a widely used 12-question, 5-level instrument comprised of 4 sub-scores (bulbar, fine motor, gross motor, and respiratory; 3 questions each). Each function is scored from 4 (normal) to 0 (no ability), with a maximum total score of 48 and a minimum total score of 0. FT9 sums the number of ALSFRS-R sub-scores that are 9 or less (12 is considered normal).²⁷

Table 16: Summary of Findings by Outcome – Stage at Which Riluzole Treatment Prolongs Survival in Fang et al. (2018)⁴

Outcomes	Hazard ratio	P value
A longer stage 4 in patients with 100 mg per day riluzole compared to a placebo	0.55, 95% CI, 0.36 to 0.83	0.037
A longer stage 4 in multistate outcome analysis of treatments (MOAT) ^a with 100 mg per day riluzole compared to a placebo	0.638, 95% CI, 0.464 to 0.878	0.006

^aMulti-state Outcome Analysis of Treatments (MOAT) is a method for survival analysis that partitions total survival time into clinically distinct periods operationally defined by cut points on rating scales.⁴¹

Table 17: Summary of Findings by Outcome – Long-Term Riluzole Effectiveness in Chen et al. (2016)³

Outcomes	Riluzole (n = 1,125)	No Riluzole (n = 415)	P value
Body-mass index (BMI) (mean, 95% CI, Kg/m ²)	23.3, 23.0 to 23.6	22.6, 22.4 to 22.9	< 0.0005
ALSFRS score	34.0 (7.0)	32.0(9.0)	< 0.0005
ALSFRS-R score	42.0 (7.0)	40.0 (9.0)	< 0.0005

ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; IQR = Interquartile range.

Table 18: Summary of Findings by Outcome – Quality of Life in Shamshiri et al. (2016)⁵

Outcomes ^a	Riluzole (n = NR)	No riluzole (NR)	P value
Baseline	88.62 (43.74)	83.79 (37.840)	> 0.05 ^b
Month 6	95.73 (44.65)	96.70 (36.70)	> 0.05
Month 12	108.16 (43.04)	114.15 (34.81)	> 0.05

NR = not reported.

^aQuality of life was assessed using Amyotrophic Lateral Sclerosis (ALS) Assessment Questionnaire (ALSAQ-40). This 40-item questionnaire has been specifically designed to evaluate the quality of life of ALS patients.

^bActual P values were not reported.

Table 19: Summary of Findings of the Economic Evaluation Study – Cost-Effectiveness of Riluzole for Amyotrophic Lateral Sclerosis by Thakore et al. (2020)²⁷

Outcomes	Treatment	Residual QALYs	Treatment cost	Health care sector perspective			Societal perspective		
				Cumulative recurrent costs ^a	Cumulative transition/tollgate costs ^b	ICER (cost/QALY)	Cumulative recurrent costs	Cumulative transition/tollgate costs	ICER (cost/QALY)
Cost-effectiveness				Model I			Model II		
5-year horizon	Riluzole	1.671	\$5,403	\$73,206	\$36,776	\$67,658	\$234,527	\$50,189	\$59,756
	No riluzole	1.488	\$0	\$64,335	\$38,702		\$226,075	\$53,138	
	Difference	0.182	\$5,403	\$8,870	-\$1,925		-\$8,452	-\$2,949	
–				Model III			Model IV		
10-year horizon	Riluzole	1.889	\$6,145	\$85,057	\$40,745	\$70,258	\$393,005	\$56,236	\$69,217
	No riluzole	1.608	\$0	\$70,716	\$41,512		\$378,557	\$57,402	
	Difference	0.281	\$6,145	\$14,541	-\$767		\$14,448	-\$1,166	

ICER = indicates incremental cost-effectiveness ratio; QALY = quality-adjusted life-years.

“Recurring costs” (RCs) refer to ongoing expenses that are incurred on a regular basis, typically at fixed intervals. These costs are repeated periodically, such as monthly, quarterly, or annually.⁴²

“One-off” transition or “tollgate” costs (TCs) are expenses associated with a specific event or milestone during a project’s lifecycle. These costs are typically incurred during the transition from one phase to another or at key checkpoints within a project.⁴²

Table 20: Summary of Findings of the Economic Evaluation Study – Health state utility weights and costs (\$ per month) by stage in Thakore et al. (2020)²⁷

Outcomes	Stage 1	Stage 2	Stage 3	Stage 4	Comments
Health state utilities EQ-5D weights (standard error)	0.743 (0.013)	0.629 (0.009)	0.541 (0.012)	0.464 (0.015)	Stage 0 weight = 0.789 (Estimates from 1868 observations obtained from 678 patients.)
Total health care sector RC	1,232	1,808	2,464	3,350	–
Total societal monthly RC (HCA)	2,531	4,336	5,787	7,469	Absenteeism included in RC, not under TC by HCA. Absenteeism cost of \$3,031 per month was incurred even after death.
Total societal monthly RC by (FCM)	1,232	2,171	3,189	4,438	Absenteeism included in TC, not under RC by FCM.
Total cumulative health care sector TC	491	10,073	22,656	44,479	Costs applied to stages 0 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to death transitions were 245.5; 5,036.5; 11,082.5; 17,203.0; 10,911.5; respectively.
Total cumulative societal TC (HCA)	491	10,073	27,758	54,683	Costs applied to stages 0 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to death transitions were 245.5; 5,036.5; 13,633.5; 22,305.0; 20,462.5; respectively.

Outcomes	Stage 1	Stage 2	Stage 3	Stage 4	Comments
Total cumulative societal TC (FCM)	4,388	16,568	35,552	63,776	Costs applied to stages 0 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to death transitions were 2,194; 8,284; 15,582; 23,604; 21,112; respectively.

ALS = amyotrophic lateral sclerosis; DME = durable medical equipment; FCM = friction cost method; GT = gastric tube; HCA = human capital approach; RC = recurring costs; TC = transition/tollgate cost.

Table 21: Summary of Recommendations in the Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
^aAndersen et al. (2012)²⁶	
"Patients with ALS should be offered treatment with riluzole 50 mg twice daily (p. 366)".	Level A
"Irrespective of familial disposition, all patients with symptomatic progressive motor neuron disorders (MND) and carrying a superoxide dismutase type 1 (SOD1) gene mutation should be offered treatment with riluzole (p. 366).	GCPP
"Patients with progressive muscular atrophy, primary lateral sclerosis or hereditary spastic paraplegia should as a rule not be treated with riluzole (p. 366)".	GCPP
^bShoesmith et al. (2020)²	
Riluzole prolongs survival by a median duration of 3 months.	Level A
Riluzole should be initiated soon after the diagnosis of ALS.	Level EC
"Regular monitoring of potential adverse effects of riluzole is important (p. E1454)."	Level EC
In patients developing fatigue while taking riluzole, reducing or discontinuing the drug may be considered.	Level C
Riluzole is effective with the progression of the disease, including the development of respiratory insufficiency.	Level EC
"Patients and healthcare authorities should be educated on the rationale for patient attendance at a multidisciplinary clinic (page E1454)."	Level B
The education contributes to increased use of riluzole, percutaneous feeding tubes, and non-invasive ventilation (NIV) support.	

ALS = amyotrophic lateral sclerosis; EC = expert consensus; GCPP = good clinical practice point.

^aExisting evidence was evaluated according to the recommendations of the European Federation of Neurologic Societies (EFNS) resulting in level A, B, or C recommendations.⁴³ Where there was a lack of evidence but consensus was clear, the authors stated their opinion as "good clinical practice points" (GCPP).¹⁴

^bCriteria developed for rating levels of evidence in guideline recommendations by Shoesmith et al. (2020)²: A = at least 2 consistent class I studies; B = at least 1 class I study or 2 consistent class II studies; C = at least 1 class II study or 2 consistent class III studies; EC = expert consensus among Canadian ALS clinical experts where evidence meeting criteria for Level A through Level C is lacking. The authors applied the following criteria for rating therapeutic studies: Class I – randomized controlled clinical trial (RCT) in a representative population; masked or objective outcome assessment; relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is an appropriate statistical adjustment for differences; also required are concealed allocation, primary outcome(s) clearly defined, exclusion and inclusion criteria clearly defined, adequate accounting for dropouts (with at least 80% of enrolled participants completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias. Class II – cohort study meeting criteria a–d (see class I) or an RCT that lacks 1 or 2 criteria b–d (see class I); all relevant baseline characteristics are presented and substantially equivalent among treatment groups, or it is appropriate; statistical adjustment for differences; masked or objective outcome assessment. Class III – controlled studies (including well-defined natural history controls or patients serving as their own controls); a description of major confounding differences between treatment groups that could affect the outcome; outcome assessment masked, objective, or performed by someone who is not a member of the treatment team. Class IV – did not include patients with the disease; did not include patients receiving different interventions; undefined or unaccepted interventions or outcome measures; no measures of effectiveness or statistical precision were presented or calculable.

Appendix 5: References of Potential Interest

The following publications were identified because they may provide additional information associated with this report.

Primary Studies

Alternative Intervention and/or Comparator

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Appendix 6: Guidance for Reporting Involvement of Patients and the Public (Version 2) Short-Form Reporting Checklist

Note that this appendix has not been copy-edited.

Table 22: Patient Involvement in Riluzole for the Treatment of ALS

Section and topic	Items	Reported in section
Aim	A patient living with ALS, who is currently taking riluzole, was engaged during the writing of this report. He shared his experience, thoughts, perspectives, and priorities to help contextualize the information gathered from the literature search. The purpose of the engagement was to offer a unique perspective of the treatment to allow for a more nuanced understanding of the literature and to add context to the findings reported in the literature.	Key Messages
Methods	<p>A request for engagement was disseminated through a relevant patient advocacy group, and an individual responded expressing interest.</p> <p>After giving informed consent, the patient participated in a semi-structured dialogue with a Patient Engagement Officer and the Research Officer authoring this report via a one-hour video call.</p> <p>A summary of the engagement discussion was prepared by the Patient Engagement Officer and shared with the patient, who confirmed that the contents reflected his experience and the discussion. This summary was subsequently shared with the Research Officer, who was able to refer to it while considering the evidence compiled during the literature search.</p>	Methods
Results of engagement	The researchers were made aware of the importance of two specific outcomes that mattered to the patient. In particular, the patient identified the need for minimal and manageable side effects and an effective slowing of disease progression.	Key Messages
Discussion and conclusions	<p>The patient contributor was highly engaged in the dialogue, openly sharing his personal experience living with ALS, his diagnosis and symptoms, treatment experience, and perspectives on riluzole.</p> <p>He reported a high degree of satisfaction with riluzole, stating that he did not experience noticeable side effects. He reported that it is not causing harm and has the potential to be offering a benefit, so is a wise decision to take. He recommended that other people with ALS could benefit from riluzole.</p> <p>He appreciates that riluzole is an oral medication, preferring that to an infusion for convenience. He prefers minimizing time spent in the hospital or clinic whenever possible.</p> <p>The patient reported barriers to access, including losing access to the medication if there is a decline in health to the point of requiring full-time continuous positive airway pressure (CPAP) therapy.</p>	Conclusions and Implications for Decision- or Policy-Making
Reflections/critical perspective	The success of patient engagement in the review is related to several factors. First, the patient was supported by a Patient Engagement Officer. Second, the Research Officer was receptive to patient involvement and consulted the summary of the engagement during their consideration of the clinical evidence. Finally, compensation was offered for patient collaborators' time and expertise.	Conclusions and Implications for Decision- or Policy-Making

Section and topic	Items	Reported in section
	<p>Limitations to our approach include our method of engagement through video calls. ALS can impact the ability to speak or write, making it difficult to communicate. This was mitigated by offering the patient different ways to engage, including by video call or in writing via email. In this instance, the individual chose a video call as his preferred method of engagement.</p> <p>Another limitation of our approach is that people need reliable internet access and access to a phone, computer, or tablet to contribute to CADTH's work, which may exclude some voices.</p>	

ALS = amyotrophic lateral sclerosis.