Literature Review

https://doi.org/10.1590/2317-6431-2021-2599

Audiology Communication Research
ISSN 2317-6431

Impact of drug treatment on voice, speech, and swallowing in patients with amyotrophic lateral sclerosis: a systematic review

Impacto do tratamento medicamentoso na voz, fala e deglutição de pacientes com esclerose lateral amiotrófica: revisão sistemática

Keila Maruze de França Albuquerque[1], *Leandro Pernambuco*[2], *Leonardo Wanderley Lopes*[2]

ABSTRACT

Purpose: To carry out a systematic review of the literature on the impact of drug treatment on the voice, speech, and swallowing functions of adult individuals with sporadic ALS, measured through scales and their respective scores, concerning the placebo group. **Research strategy:** The search strategy was created based on the PICO strategy. The keywords were selected from a consultation with the health sciences descriptors – DECS and the medical subject headings – MeSH. Two independent researchers searched ASHA, Cochrane, Lilacs, Pubmed, Scopus and Web of Science, in English, Spanish and Portuguese. **Selection criteria:** Randomized clinical trials, carried out on adults, were included, and articles with outcomes related to selfassessment and quality of life, theses, dissertations, abstracts only , case studies, experimental studies, book chapters, encyclopedia and brief communication were excluded. The studies were evaluated using the Robins II and Grade tool. **Results:** Of the 9824 articles found, 5 were selected for analysis and underwent drug intervention. It is noticed the absence of studies aimed at the rehabilitation of bulb functions. The quality of evidence generated varied from high to low risk and the level of evidence low and very low. **Conclusion:** Most studies show a delay in the degeneration of bulbar functions in relation to placebo, although this finding has not been observed in the scores of scales that measure such functions. Studies are at risk of selection bias and very low/low methodological quality makes the findings questionable.

Keywords: Amyotrophic lateral sclerosis; Motor neuron disease; Voice; Speech; Swallowing

RESUMO

Objetivos: Revisar sistematicamente a literatura sobre o impacto do tratamento medicamentoso nas funções de voz, fala e deglutição de indivíduos adultos com esclerose lateral amiotrófica esporádica, mensuradas por meio de escalas e seus respectivos escores, em relação ao grupo placebo. **Estratégia de pesquisa:** A busca foi realizada com base na estratégia PICO (problema/população/paciente; intervenção; comparação/controle; desfecho/*outcome*). As palavras-chave foram selecionadas a partir de consulta aos Descritores em Ciências da Saúde (DeCS) e ao *Medical Subject Headings* (MeSH). Dois pesquisadores independentes fizeram busca na *American Speech-Language-Hearing Association* (ASHA), Cochrane, LILACS, PubMed, Scopus e Web of Science, em inglês, espanhol e português. **Critérios de seleção:** Foram incluídos ensaios clínicos randomizados, realizados em adultos, e excluídos artigos cujos desfechos estavam relacionados à autoavaliação e à qualidade de vida, teses, dissertações, apenas resumos disponíveis, estudos de caso, estudos experimentais, capítulos de livro, enciclopédias e comunicações breves. Os estudos foram avaliados por meio das ferramentas Robins II (*Risk Of Bias In Non-randomized Studies* II) e GRADE (*Grading of Recommendations Assessment, Development and Evaluation*). **Resultados:** dos 9824 artigos encontrados, 5 realizaram a intervenção medicamentosa e foram selecionados para análise. Observou-se ausência de estudos voltados para reabilitação das funções bulbares. A qualidade de evidência gerada variou de alto a baixo risco e o nível de evidência, de baixo a muito baixo. **Conclusão:** a maioria dos estudos demonstra que o tratamento medicamentoso atrasa a degeneração das funções bulbares, com relação ao placebo, embora tal achado não tenha sido observado nos escores de escalas que mensuram tais funções. Os estudos apresentam risco de viés de seleção e muito baixa/baixa qualidade metodológica, limitando a confiança nos achados.

Palavras-chave: Esclerose lateral amiotrófica; Doença do neurônio motor; Voz; Fala; Deglutição

Study carried out at the Universidade Federal da Paraíba - UFPB - João Pessoa (PB), Brasil.
[1] Programa de Pós-graduação (Mestrado) em Fonoaudiologia, Universidade Federal da Paraíba - UFPB - João Pessoa (PB), Brasil.
[2] Departamento de Fonoaudiologia, Universidade Federal da Paraíba - UFPB - João Pessoa (PB), Brasil.
Conflict of interests: No.
Authors' contribution: KMFA contributed to data collection, analysis, and interpretation; LP contributed to study conceptualization and design, data interpretation, and article review; LWL contributed to study conceptualization and design, data interpretation, article review, and approval of the final version.
Funding: None.
Corresponding author: Keila Maruze de França Albuquerque. E-mail: keilamaruze@hotmail.com
Received: November 28, 2021; Accepted: March 02, 2022

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects the cell body of upper motor neurons (in the cortex) and lower motor neurons (in the brainstem and spinal cord). Though rare, ALS is the most common motor neuron disease[1]. It is classified as either sporadic (which corresponds to 90% of cases and can affect anyone, regardless of family history of the disease) or familial (when it is transmitted from one generation to another, corresponding to 10% of cases)[1].

ALS is characterized by paresis until all muscles in the body are paralyzed[2]. Disease progression leads to voice and speech changes (dysarthrophonia), which occur in 80% to 95% of such patients, and swallowing changes (dysphagia), which may occur in practically everyone diagnosed with ALS[3].

There is no cure for ALS. Therefore, its treatment aims to minimize symptoms, which calls for multidisciplinary teamwork. Drug use and/or surgery are two of the main medical approaches to manage the disease, aiming to minimize symptoms and limitations imposed by this health condition. Even though speech-language-hearing (SLH) therapeutic strategies are indicated to manage voice, speech, and swallowing in patients with ALS, drug treatment and surgery may also impact these functions[4,5].

Speech-focused SLH treatment is based on exercises that mobilize the structures of the stomatognathic system (e.g., lips, tongue, mandible, and soft palate) and coordinate articulation and breathing. The objective is to maintain speech intelligible and oral communication active for as long as possible, considering each person's clinical presentation of the disease[4] and speech speed training[4]. In general, the main effects of the SLH rehabilitation strategies for dysarthrophonia in these cases include changes in speech speed, sound pressure level (vocal intensity), resonance (reduced nasality), nasalance score, and sequential movement rate[5].

Concerning dysphagia in ALS patients, SLH rehabilitation strategies can be either indirect or direct. Indirect ones aim to increase the amplitude and force of movements in the swallowing phases and are based on tactile, thermal, and gustatory (sensory) stimulation. They also include myofunctional exercises involving the lips, tongue, cheeks, and palate. Direct strategies are based on offering adapted foods at different paces and in various textures, viscosities, volumes, tastes, and temperatures[6].

A review on the effectiveness of swallowing exercises in neuromuscular diseases found that only one out of the 12 studies analyzed addressed ALS[7]. That study[7] used the Expiratory Muscle Strength Training (EMST) and verified improved swallowing measures in patients with initial symptoms of ALS. The fact that only one article was found addressing patients with ALS shows the scarcity of studies on SLH therapy with this population and reinforces the need for further clinical trials to ground SLH practice in this context.

A survey by ASHA (American Speech-Language-Hearing Association) shows limited evidence of the effects of SLH rehabilitation on voice, speech, and swallowing. Overall, mild- to moderate-intensity exercises in patients in the initial stage of the disease increase survival, preserve the integrity of motor neurons and maintain motor functions related to voice, speech, and swallowing[8]. However, the external evidence available is still limited, which justifies conducting new studies on SLH rehabilitation in patients with ALS.

As for surgical treatment, myotomy of the pharyngoesophageal segment is a possibility when its muscles have hypertonia, compromising the swallowing mechanism. This change affects bolus transportation from the pharynx to the esophagus and may lead to food, liquid, and secretion aspiration[9].

Drug use is one of the possible treatments for people with ALS. This approach aims to increase their survival and help maintain functions related to communication, eating, and so on. Using riluzole, for instance, may increase the survival of ALS patients by up to 6 months[10], although direct and positive consequences on voice, speech and swallowing are not cited in the literature[10]. Another medication, edaravone, proved to be effective to decrease functional limitations in people who are at the beginning of the disease[11]. Nuedexta improved the bulbar function in patients with ALS, including self-perception of speech and swallowing[12].

Thus, considering the limited external evidence of the effects of SLH rehabilitation on voice, speech, and swallowing in patients with ALS and the potential effects of the drug approach on these functions, the research question of this study was: "Do drug treatment strategies in adult patients with either bulbar- or limb-onset sporadic ALS show results in their voice, speech, and swallowing, measured with scales and their respective scores, in comparison with placebo groups?".

PURPOSE

The objective of this study was to systematically review the literature on the impact of drug treatment on voice, speech, and swallowing of adult people with sporadic ALS, measured with scales and their respective scores, in comparison with placebo groups. Considering the severe limitations imposed by ALS on communications and eating, this research is important as it verifies treatment strategies that may improve functional aspects of voice, speech, and swallowing in patients with ALS, either to indicate the need for further studies or clarify which strategies are better to manage these functions.

RESEARCH STRATEGY

Initially, the Cochrane Library, Clinical Trial Register, and Prospero were surveyed for other systematic reviews on this specific topic. Since no other previously conducted or registered systematic review was found, this research was carried out.

The search strategy was based on PICO (population; intervention; comparison; outcome). However, outcome-related terms were not included in the search to avoid restricting it. Keywords were selected by consulting the Health Sciences Descriptors (DeCS) (http://decs.bvs.br) and Medical Subject Headings (MeSH) (http://ncbi.nlm.nih.gov/mesh). Compound descriptors were delimited with quotation marks, and synonym keywords were allocated between parentheses, using the Boolean operator OR – whereas the Boolean operator AND was used for terms without an association.

Generally, the descriptors included the following terms: P - "*amyotrophic lateral sclerosis" OR "Charcot disease" OR "motor neuron disease, amyotrophic lateral sclerosis" OR "Lou Gehrig disease" OR "Gehrig's disease" OR "ALS"; AND* I - "*speech therapies" OR "therapy, speech" OR "myofunctional therapy" OR "voice training" OR "myotherapy orofacial" OR "Dysphagia/therapy" OR "Dysphonia/therapy" OR "Dysarthria/therapy" OR "deglutition disorders/therapy" OR "voice disorders/therapy" OR "speech disorders/therapy" OR "drug therapy" OR "botulinum toxin" OR "velopharyngeal insufficiency/surgery" OR "pharyngeal muscles/surgery" AND* C - "*randomized controlled trial" OR "controlled clinical trial" OR "randomized controlled trials" OR "clinical trial" OR "clinical trials" OR "comparative study" OR "follow-up studies" OR "prospective studies" OR "control*" OR "prospective*".*

Then, the databases were defined for the search, namely: SLH-specific American Speech-Language-Hearing Association (ASHA); Cochrane; Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), via PubMed, Elsevier Scopus, and Web of Science (Institute for Scientific Information Web of Knowledge). Hence, the search strategies were adjusted to meet specificities and conditions in each database.

SELECTION CRITERIA

The criteria to include articles in this systematic review were as follows: primary, intervention, randomized articles on adults with ALS; research including drug treatment strategies with effects on voice, speech, and swallowing parameters, measured with scales and their respective scores; articles in English, Spanish, and Portuguese, with no restrictions on the time of publication.

Article exclusion criteria were as follows: research on associated diseases; other diseases; articles with outcomes related to self-assessment and the quality of life regarding voice, speech, and swallowing; unavailable abstract and article; only abstract available; conference abstracts; case studies/reports; secondary studies; letters; book chapters; encyclopedia; opinion articles; technical articles; guidelines; short communications; theses; dissertations; experimental studies; non-randomized studies; studies that did not assess bulbar functions, bulbar function scales, including those with total or undefined scores.

The articles were selected by two SLH therapists, independent reviewers connected to the laboratory of the institution of origin of this research. They searched the said platforms, and retrievals were exported to the Zotero software, in which the data were managed.

The reviewers selected the articles independently, in two stages: 1) In the first one, titles and abstracts were read, excluding those that did not meet the criteria; 2) in the second stage, the articles were read in full text, selecting them according to the eligibility criteria. The results of both reviewers were compared; in case of divergences on the selection of articles, a third reviewer from the same institution evaluated the study to reach a final decision. The flowchart of article selection is shown in Figure 1.

By the end of the first phase, 9,824 articles had been selected (Figure 1). Then, 439 duplicate ones were excluded, leaving 9,385 for the title and abstract analysis phase. After reading these, 8,975 articles were excluded for not meeting the eligibility criteria defined in this research. Hence, 410 articles were included in the subsequent stage, when they were read in full text. Only five of them met the eligibility criteria and were submitted to methodological quality analysis.

The data of the selected articles were extracted and entered in an Excel spreadsheet for posterior analysis. These data referred to characteristics of the studies (author, year, country of publication, type of study), sample (size, sex, mean age, and type of ALS), intervention (drug, dose, administration, time of treatment, and follow-up), outcome (the measure used to assess bulbar functions and results), and conclusion of the study.

DATA ANALYSIS

Two types of analyses were made in this systematic review: assessment of the risk of bias and assessment of the methodological quality of the selected studies. Two other independent judges (SLH therapists in master's degree programs in the institution of origin) were recruited to analyze the articles. Possible divergences between them were solved by consulting a third judge.

The tool for assessing the risk of bias in randomized clinical trials reviewed by Cochrane – Rob 2.0 – version 2019, was used to assess the risk of bias in the selected articles. Seven domains were assessed: selection, performance, detection, attrition, and report bias, overall random sequence, and other biases. They were classified as low risk, high risk, or uncertain risk.

The methodological quality of the randomized clinical trials was assessed with the Review Manager software, version 5.3. The quality of outcome evidence was assessed with the GRADE system – Grading of Recommendations Assessment, Development, and Evaluation. Its result is classified into four levels, according to the reliability of estimated effects[13]: high, medium, low, and very low.

RESULTS

Five randomized studies that assessed bulbar functions with the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) and the Plaitakis Scale were analyzed. They were published between 1988 and 2018 by North American and European authors. All studies were double-blind, three of them were crossed, and only one was multinational. Their sample sizes ranged from 10 to 867 participants. The characteristics of the selected studies are shown in Table 1.

As for sample characteristics, females predominated in four out of the five studies, with a mean age between 48.5 and 62.07 years. There were more patients with limb-onset ALS than bulbar-onset ALS.

A variety of drug types and doses were used in interventions, most of them administered in capsules. The shortest drug administration lasted 30 days, and the longest, 18 months.

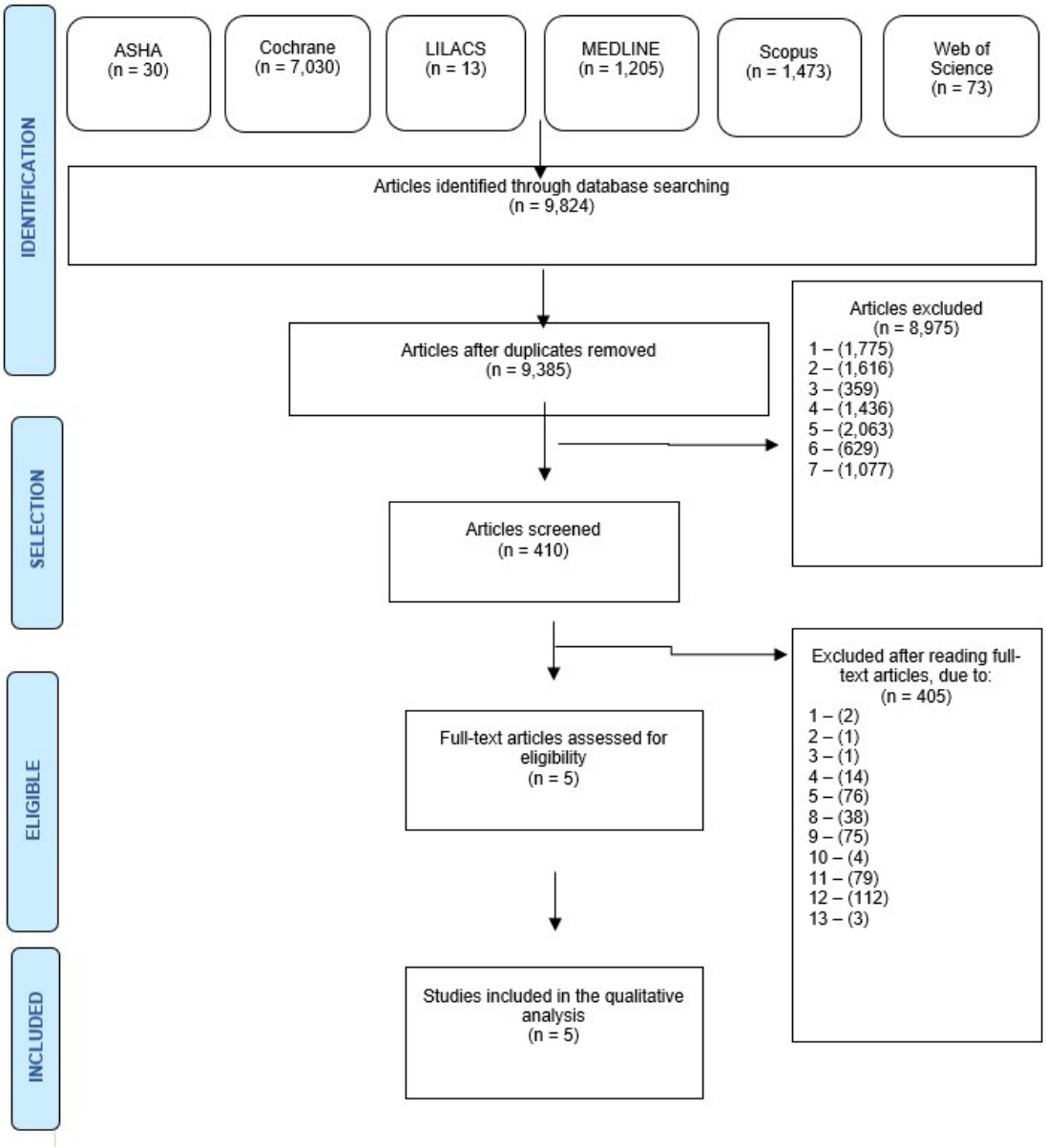

Figure 1. Flowchart of the study search and selections process
Subtitle: n = number of articles; (1) articles with associated diseases; (2) other diseases; (3) with outcomes related to self-assessment and the quality of life regarding the voice, speech, and swallowing; (4) unavailable abstract and article; (5) only abstract available; (6) conference abstracts; (7) case studies/reports; (8) secondary studies; (9) letters, book chapters, encyclopedia, opinion article, technical articles, guidelines, short communications, theses, dissertations; (10) experimental studies in animals; (11) did not assess bulbar functions; (12) bulbar function scales with total scores; (13) scale with undefined score.

Functional assessments were made in the initial, intermediary, and final stages of drug administration. The Plaitakis scale was the most used. The treatments showed that the drugs delay function worsening, though with no statistically significant differences. Despite the absence of statistical significance, there was a trend in the Plaitakis and ALSFRS-R scores throughout the treatments, which may be related to greater impairments in voice, speech, and swallowing functionality.

All selected studies had a low risk of performance, detection, attrition, report, and other biases. As for selection bias (allocation concealment), most studies had an uncertain risk – except for one, which had a low risk. In the overall random sequence, a high risk of bias was detected in only one study (Figure 2).

The quality of evidence was assessed with the GRADE system and ranged from low to very low, as shown in Table 2.

DISCUSSION

This systematic review analyzed the impact of drug treatments on voice, speech, and swallowing in adults with sporadic ALS, measured with scales and their respective scores, in comparison with placebo groups. Considering the eligibility criteria in the study, only five articles were included and analyzed.

The selected studies had adequate methodologies for intervention research, including clinical trials; longitudinal studies

Table 1. Characteristics of the studies

Characteristics of the studies				Characteristics of the sample				Characteristics of the intervention				Characteristics of the outcome			
Author	Year	Country	Type of study	Size	Sex Males/ Females	Age (mean)	Type of ALS	Drug	Dose	Administration	Time of treatment	Follow-up	Assessment measures	Result	Conclusion
Plaitakis et al. [14]	1988	USA	Randomized, placebo controlled, double-blind	22	D = 10/1 P = 9/2	D = 48.5 P = 53.7		Branched-chain amino acids	3.0 g/L-leucine, 2.0 g/L-isoleucine, 1.6 g/L-valine	Powder ingested 4 times a day between meals	1 year	The sample was assessed in months 0, 3, 6, 9, 12	Bulbar scale by Plaitakis et al. [14]	D - 0 month: score 12.5; 3rd month: 10; 6th month: 9; 9th month: 7; 12th month: 8; P - 0 month: score 13.2; 3rd month: 11; 6th month: 9; 9th month: 9; 12th month: 6.	No statistically significant difference was found
Askmark et al. [15]	1993	Sweden	Clinical trial, double-blind, crossed, 2nd phase open clinical trial	14	5/9	62.07	B (5) UMN (1) LMN (8)	Dextromethorphan	150 mg/ day/ 2nd phase 300 mg/ day	Tablet 3 (30 mg) + 1 (60 mg) 4 x day; 2nd phase: 3 (60 mg) + 1 (120 mg)	12 weeks; 2nd phase 3 and 6 months	The sample was assessed in weeks 12, 16, and 28; 2nd phase, 0, 16, and 28	Bulbar scale by Plaitakis et al. [14]	n = 10 concluded the treatment – 3 decreased score, 7 stable; 2nd phase – 3 months n = 8, 6 months n = 6, with unchanged scores.	There were no effects on the parameters assessed
Ryberg et al.[16]	2003	United Kingdom	Double-blind, placebo-controlled, crossed	39	D = 15/5 P = 9/10	D = 53.6 P = 59.2	D = 2 (B), 18 (L) P = 3 (B), 16 (L)	Lamotrigine	300 mg/ day	100-mg tablet taken 3x a day	16 weeks	The sample was assessed in weeks 0, 22, and 44	Bulbar scale by Plaitakis et al. [14]	D 0.35 (n = 17) - P 1.2 (n = 13) p-value = 0.42 (0.017).	There were no effects on the parameters assessed
Meininger et al. [17]	2004	France	Multicentric, multinational, randomized, double-blind, placebo-controlled	867	D 1mg = 176/117 D 2mg = 185/103 P = 168/118	D 1mg = 55.5 D 2mg = 56.8 P = 55.2	D 1mg= 73 (B), 220 (L) D 2mg = 69 (B), 219 (L)	Xaliproden	1 to 2 mg		18 months /568 days	The sample was assessed at the beginning and end of treatment	ALSFRS-R swallowing subscale	Decreased 25%, P = 0.013 and 17%, P> 0.087 for 1 mg and 2 mg.	No statistically significant difference was found
Green et al.[18]	2018	USA	Multicentric, randomized, double-blind, crossed	10	7/3	57.5	(B) 5 (L)	Dextromethorphan/ Quinidine	20 to 10 mg	30 days for active treatment and placebo	The sample was assessed at the beginning and end of treatment	30 days for active treatment and placebo.	ALSFRS-R speech subscale	Active phase: Pre-treatment 2.20 Post-treatment 2.40 p-value 0.50; Placebo: Pre-treatment 2.50 Post-treatment 2.3 p-value 0.50	No statistically significant difference was found

Subtitle: ALS = amyotrophic lateral sclerosis; D = drug; P = placebo; B = bulbar-onset; UMN = upper motor neuron; LMN = lower motor neuron; L = limb-onset; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; n = number of subjects; g/L = grams per liter; mg = milligrams

Table 2. Summary of findings based on the application of the Grading of Recommendations Assessment, Development, and Evaluation

Outcome	Methodological limitations (risk of bias)	Inconsistency (heterogeneity)	Indirect evidence	Imprecision	Publication bias	Methodological quality
Bulbar scale by Plaitakis et al.[14]	Lowered one level (uncertain to high risk of selection bias)	Lowered one level (different time of treatment between studies)	Lowered one level (intervention with different drugs between studies)	Two did not find a statistical difference between the groups		Low
ALSFRS-R	Lowered one level (uncertain risk of selection bias)	Lowered one level (different time of follow-up between studies)	Lowered one level (intervention with different drugs between studies)	Lowered one level (speech and swallowing subscales were assessed in only one study)		Very low

Subtitle: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

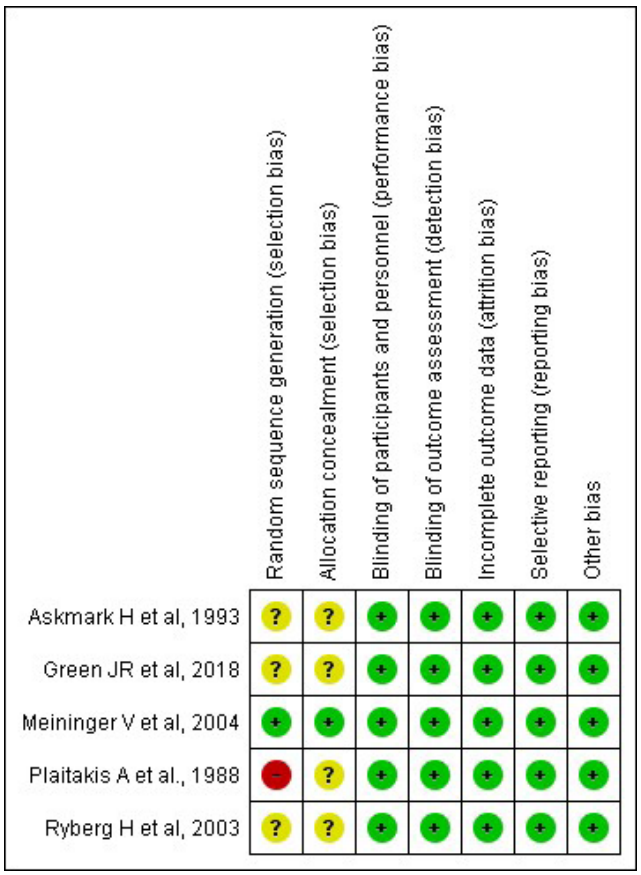

Figure 2. Cochrane Risk of Bias Tool to assess the risk of bias in randomized clinical trials included in this review. Green represents low risk, yellow represents uncertain risk, and red represents high risk

(to investigate drug effectiveness regarding a given objective); controlled studies (in which the groups are as homogeneous as possible and compared with one another – in this case, the placebo); double-blind (in which neither participants nor investigators know in which group they have been allocated); and randomized, to avoid biases, as participants are randomly allocated into the groups.

The sample sizes varied greatly, ranging from 10 to 867 participants. The small number found in four out of the five studies is explained by the fact that ALS is a rare and rapidly progressing disease – which limits patient follow-up in intervention studies. The one with 867 participants was multicentric, which explains the larger sample in a rare disease.

The mean age of the study samples ranged from 48 to 62 years, with a predominance of males[19,20] – especially when the symptoms began in the limbs and the respiratory muscles[21]. It may be more common in males because ALS is characterized by sexual dimorphism[22]. Its proportion between men and women has been decreasing over the years, possibly because of women's exposure to agents that cause ALS – e.g., cigarettes[23]. Exhaustive physical activity seems to be more related to males[24], and female hormones may have protective factors for the disease[25].

As seen in the characteristics of the interventions in the studies, research on ALS drugs has been conducted for more than 30 years. Four[14-16,18] out of the five studies conducted the tests with medications whose expected effects included a reduction in glutamate excitotoxicity. One study was based on neutrophic and neuroprotective factors to maintain skeletal muscle innervation[17]. More specifically, one piece of research on drugs reports that its use improves bulbar functions involved in speech and swallowing[18], as well as the overall functionality of patients with ALS[17].

In the selected studies, no medication was indicated as a standard treatment to minimize the symptoms of the disease. Riluzole is the worldwide recommended drug to manage such symptoms and increase patients' survival[26]. Edaravone, approved in countries such as the United States and Japan, has postponed disease worsening, as verified in studies that used ALSFRS-R to measure the outcome[27]. In the present research, neither of these drugs (riluzole and edaravone) was used in the selected studies. This probably happened because studies on riluzole and edaravone indicate generalized functionality improvements in patients with ALS, not specifying voice, speech, and swallowing parameters.

The dose administered in the studies included in this review varied greatly, as well as the time of treatment. There was no consensus among the studies regarding the dose and time of treatment, which makes intervention comparisons difficult concerning the effectiveness in the researched functions. A systematic review published in Cochrane[28] concluded that there is no evidence of symptom treatment in ALS.

This result[28] is not necessarily due to an absence of evidence but to insufficient statistical power concerning the dose and time of treatment, as well as the verification of outcomes with measures not sensitive to the public and participant selection criteria. ALS is a rare disease, and such population is heterogeneous in terms of symptom manifestation and severity – which makes it difficult to form homogeneous groups to research and reflect on statistical results[28].

The Plaitakis Scale was used in three[14-16] of the studies in this research, and ALSFRS-R was used in two of them[17,18]. These two scales include specific items or domains to verify functions directly or indirectly related to voice, speech and swallowing.

The bulbar domain in the Plaitakis Scale is based on assessments of face, tongue, and palate movement and speech and swallowing aspects. Plaitakis Scale total score ranges from 0 (when there is a severe impairment) to 15 (when all items in the scale are normal)[14]. ALSFRS-R is one of the most used scales in clinical assessments and research of patients with ALS because it is easy to apply and interpret. The bulbar domain in the ALSFRS-R assesses speech, swallowing, and salivation in patients with ALS[29]. ALSFRS-R total score ranges from 4 (the worst function) to 40 (normal). Thus, a low score in both scales is related to greater functionality impairment. Although no statistical significance was found in the five studies, there was a trend toward a stable or decreased score in the Plaitakis and ALSFRS-R scores throughout the drug treatment, indicating greater functionality impairment.

These scales have great clinical and research potential regarding speech and swallowing. Nonetheless, many studies report only the total score, instead of presenting the domain scores related to these functions. This limits the analysis of the intervention effects on specific aspects of voice, speech, and swallowing in the investigated population.

Three studies[14,17,18] found slower worsening of speech and swallowing with drug use, in contrast with the placebo. The other two studies[15,16] did not find effects of drug use on the investigated functions – which may be due to the number of participants in some studies, the scales used to assess overall data on the functions or the progressive nature of the disease.

The outcomes had low methodological quality for the Plaitakis Scale and very low for ALSFRS-R. The low outcome indicates limited effect reliability, while the very low outcome suggests very limited reliability, with an important degree of uncertainty or imprecision in the findings. Therefore, even though the investigated studies reported effects on voice, speech, and swallowing (measured with scales and their scores), no statistically significant differences can be pointed out. This diminishes the reliability of estimates indicated in the conclusion of the studies regarding these effects[13,30].

The result of the GRADE system analysis reinforces the importance of designing research adequately and publishing all relevant information (e.g., total and specific domain scores). This would enable systematic reviews with meta-analyses and recommendations for the management of voice, speech, and swallowing symptoms in patients with ALS.

The assessment of the risk of bias revealed uncertain selection bias in most studies, while one of them[14] had a high risk. These data demonstrate that the most frequent errors in the investigated studies are related to sample selection, random sequence generation, and participant allocation concealment – which may lead to mistaken results. The fact that ALS is a rare disease may influence the small sample sizes, further leading to selection bias.

Allocation sequence generation is the procedure commonly used in clinical trials to randomize the groups that will receive treatment or placebo (or different treatments). Allocation concealment is a strategy used to conceal from participants (volunteers, intervention administrators, or researchers) the allocation sequence into the groups that receive different interventions. These two techniques aim to avoid selection bias, which is a systematic error when creating the intervention groups, possibly influencing the study results.

It must be highlighted that the initial intention of this systematic review was to include the different strategies (SLH rehabilitation, drug treatment, and surgical intervention) to manage voice, speech, and swallowing changes in patients with sporadic ALS. However, no study was found that met the eligibility criteria defined for this research. Such a finding justifies the need for research on this topic to produce external evidence (based on empirical data and robust methods) capable of directing SLH practice and developing recommendations.

It was decided in this research to measure results related to voice, speech, and swallowing with scales widely used in the field to assess people with ALS. Hence, this criterion may explain the exclusion of studies whose main intervention was SLH rehabilitation, as there are more specific measures to monitor the effects of SLH intervention. On the other hand, including scales such as ALSFRS-R in studies focused on SLH rehabilitation would make it possible to compare SLH intervention with other types of interventions and their respective effects on voice, speech, and swallowing.

Conducting a clinical trial in the field of rehabilitation is a great challenge because the etiology is multifactorial and the clinical manifestations are multidimensional, ranging in a wide spectrum of severity. Moreover, it is influenced by factors such as age and environment, which makes it difficult to control variables. ALS, in its turn, is a heterogeneous disease with a usually quick progression, which makes it difficult to form a group with homogeneous characteristics and a representative sample size that would ensure the external validity of the study.

Functional limitations of patients with ALS are traditionally managed with a multidisciplinary approach, mainly including drug treatment and rehabilitation. Drug treatment is symptomatic and may help manage the symptoms of patients with ALS. Rehabilitation, in its turn, aims to maintain the patients' communication and eating functions active, improving their quality of life and participation in society, as they would be able to communicate for longer and eat safely and effectively.

CONCLUSION

Most studies demonstrate that drug treatment delays the degeneration of bulbar functions in experimental groups, in comparison with placebo groups – although this finding was not observed in scale scores that indirectly measure these functions. However, the studies have a risk of selection bias and a low/very low methodological quality, which limits the reliability of the findings.

REFERENCES

1. Chieia MA, Oliveira ASB, Silva HCA, Gabbai AA. Amyotrophic lateral sclerosis: considerations on diagnostic criteria. Arq Neuropsiquiatr. 2010;68(6):837-42. http://dx.doi.org/10.1590/S0004-282X2010000600002. PMid:21243238.
2. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med. 2017;377(2):162-72. http://dx.doi.org/10.1056/NEJMra1603471. PMid:28700839.
3. Makkonen T, Ruottinen H, Puhto R, Helminen M, Palmio J. Speech deterioration in amyotrophic lateral sclerosis (ALS) after manifestation of bulbar symptoms. Int J Lang Commun Disord. 2018;53(2):385-92. http://dx.doi.org/10.1111/1460-6984.12357. PMid:29159848.
4. Sancho PO, Boisson D. What are manegement practices for speech therapy in amyotrophic lateral sclerosis? Rev Neurol. 2006;162(2):273-4. http://dx.doi.org/10.1016/S0035-3787(06)75199-2.
5. Alfwaress FS, Bibars AR, Hamasha A, Maaitah EA. Outcomes of palatal lift prosthesis on dysarthric speech. J Craniofac Surg. 2017;28(1):30-5. http://dx.doi.org/10.1097/SCS.0000000000003167. PMid:27831974.
6. Borges MSD, Mangilli LD, Ferreira MC, Celeste LC. Apresentação de um protocolo assistencial para pacientes com distúrbios da deglutição. CoDAS. 2017;29(5):e20160222. http://dx.doi.org/10.1590/2317-1782/20172016222. PMid:29091113.
7. Troche MS, Mishra A. Swallowing exercises in patients with neurodegenerative disease: what is the current evidence? Perspect ASHA Spec Interest Groups. 2017;2(13):13-20. http://dx.doi.org/10.1044/persp2.SIG13.13.
8. Plowman EK. Is there a role for exercise in the management of bulbar dysfunction in amyotrophic lateral sclerosis? J Speech Lang Hear Res. 2015 Ago 1;58(4):1151-66. http://dx.doi.org/10.1044/2015_JSLHR-S-14-0270. PMid:26091205.
9. Murata KY, Kouda K, Tajima F, Kondo T. Balloon dilation in sporadic inclusion body myositis patients with Dysphagia. Clin Med Insights Case Rep. 2013;6:1-7. http://dx.doi.org/10.4137/CCRep.S10200. PMid:23362370.
10. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;3(3):CD001447. http://dx.doi.org/10.1002/14651858.CD001447.pub3. PMid:22419278.
11. Abe K, Aoki M, Tsuji S, Itoyama Y, Sobue G, Togo M, et al. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505-12. http://dx.doi.org/10.1016/S1474-4422(17)30115-1. PMid:28522181.
12. Smith R, Pioro E, Myers K, Sirdofsky M, Goslin K, Meekins G, et al. Enhanced bulbar function in amyotrophic lateral sclerosis: the nuedexta treatment trial. Neurotherapeutics. 2017 Jul;14(3):762-72. http://dx.doi.org/10.1007/s13311-016-0508-5. PMid:28070747.
13. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Gestão e Incorporação de Tecnologias em Saúde. Diretrizes metodológicas: elaboração de diretrizes clínicas. Brasília: Ministério da Saúde; 2016. 107 p.
14. Plaitakis A, Mandeli J, Smith J, Yahr MD. Pilot trial of branched-chain aminoacids in amyotrophic lateral sclerosis. Lancet. 1988;1(8593):1015-8. http://dx.doi.org/10.1016/S0140-6736(88)91841-7. PMid:2896868.
15. Askmark H, Aquilonius SM, Gillberg PG, Liedholm LJ, Stålberg E, Wuopio R. A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 1993 Fev;56(2):197-200. http://dx.doi.org/10.1136/jnnp.56.2.197. PMid:8437010.
16. Ryberg H, Askmark H, Persson LI. A double-blind randomized clinical trial in amyotrophic lateral sclerosis using lamotrigine: effects on CSF glutamate, aspartate, branched-chain amino acid levels and clinical parameters. Acta Neurol Scand. 2003 Jul;108(1):1-8. http://dx.doi.org/10.1034/j.1600-0404.2003.00111.x. PMid:12807386.
17. Meininger V, Bensimon G, Bradley WR, Brooks B, Douillet P, Eisen AA, et al. Efficacy and safety of xaliproden in amyotrophic lateral sclerosis: results of two phase III trials. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004 Jun;5(2):107-17. http://dx.doi.org/10.1080/14660820410019602. PMid:15204012.
18. Green JR, Allison KM, Cordella C, Richburg BD, Pattee GL, Berry JD, et al. Additional evidence for a therapeutic effect of dextromethorphan/quinidine on bulbar motor function in patients with amyotrophic lateral sclerosis: a quantitative speech analysis. Br J Clin Pharmacol. 2018;84(12):2849-56. http://dx.doi.org/10.1111/bcp.13745. PMid:30152872.
19. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. Clin Epidemiol. 2015;7:181-93. PMid:25709501.
20. Edge R, Mills R, Tennant A, Diggle PJ, Young CA. Do pain, anxiety and depression influence quality of life for people with amyotrophic lateral sclerosis/motor neuron disease? A national study reconciling previous conflicting literature. J Neurol. 2020;267(3):607-15. http://dx.doi.org/10.1007/s00415-019-09615-3. PMid:31696295.
21. Chiò A, Moglia C, Canosa A, Manera U, D'ovidio F, Vasta R, et al. ALS phenotype is influenced by age, sex, and genetics: A population-based study. Neurology. 2020;94(8):e802-10. http://dx.doi.org/10.1212/WNL.0000000000008869. PMid:31907290.
22. Pape JA, Grose JH. The effects of diet and sex in amyotrophic lateral sclerosis. Rev Neurol. 2020;176(5):301-15. http://dx.doi.org/10.1016/j.neurol.2019.09.008. PMid:32147204.
23. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017;3(1):17071. http://dx.doi.org/10.1038/nrdp.2017.71. PMid:28980624.
24. Pupillo E, Messina P, Logroscino G, Beghi E. Long-term survival in amyotrophic lateral sclerosis: a population-based study. Ann Neurol. 2014;75(2):287-97. http://dx.doi.org/10.1002/ana.24096. PMid:24382602.
25. Manjaly ZR, Scott KM, Abhinav K, Wijesekera L, Ganesalingam J, Goldstein LH, et al. The sex ratio in amyotrophic lateral sclerosis: a population based study. Amyotroph Lateral Scler. 2010 Oct;11(5):439-42. http://dx.doi.org/10.3109/17482961003610853. PMid:20225930.

26. Hinchcliffe M, Smith A. Riluzole: real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. Degener Neurol Neuromuscul Dis. 2017;7:61-70. http://dx.doi.org/10.2147/DNND.S135748. PMid:30050378.

27. Heiman-Patterson T, Perdrizet J, Prosser B, Agnese W, Apple S. Real-world evidence of Radicava (edaravone) for amyotrophic lateral sclerosis from a national infusion center database in the United States. Neurology. 2020;94(15, Suppl.):787.

28. Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;1(1):CD011776. http://dx.doi.org/10.1002/14651858.CD011776.pub2. PMid:28072907.

29. Lee M, McCambridge A. Clinimetrics: Amyotrophc Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R). J Physiother. 2018;64(4):269-70. http://dx.doi.org/10.1016/j.jphys.2018.07.005. PMid:30193742.

30. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia. Diretrizes metodológicas: Sistema GRADE: manual de graduação da qualidade da evidência e força de recomendação para tomada de decisão em saúde. Brasília: Ministério da Saúde; 2014. 72 p.