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A SYSTEMATIC REVIEW WITH META-ANALYSIS ON THE EFFICACY OF RANDOMIZED CLINICAL TRIALS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS USING THE FINAL SCORE ON THE AMYOTROPHIC LATERAL SCLEROSIS FUNCTIONAL RATING SCALE-REVISED AS THE OUTCOME MEASURE.

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ABSTRACT

In recent years there has been a significant increase in clinical trials to discover new medications that can slow the progression of Amyotrophic Lateral Sclerosis. The objective of this study was to carry out a systematic review with meta-analysis of randomized clinical trials lasting six or more months to evaluate the efficacy of treatments in patients with Amyotrophic Lateral Sclerosis carried out between 2016 and 2021, using the final score on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. The search for articles covered the main databases in addition to the ClinialTrials.gov website and in the end, 18 studies were selected for analysis. In total, 4.214 participants were enrolled, 1.880 received the drug and 1.933 received the placebo, and about 30,0% discontinued over the course of the studies. The average age was 57 years old, with a predominance of males (65,0%) and 21,4% of participants had the onset of symptoms in the bulbar region and 77,0% in the spinal region. Reading the articles also revealed great clinical variability between patients. Of the 15 drugs that were tested, Edaravone, Relyvrio and Masitinib showed positive effects if they were administered before severe functional impairment. However, a recent study failed to achieve Relyvrio's primary goal of slowing the decline in ALSFRS-R scores compared with placebo. In the methodological analysis, two studies presented some concerns due to blinding, including only patients and investigators, and had high discontinuation rates. The funnel plot and Egger's regression test showed no publication bias. Subgroup analysis showed that substantial heterogeneity of the studies included in the analysis was significantly greater in the group of published articles as opposed to the unpublished studies.

Keywords: Amyotrophic Lateral Sclerosis. Clinical Trial. Randomized Double-Blind Study. Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

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INTRODUCTION

In recent years there has been a significant increase in clinical trials to discover new drugs that can slow the progression of Amyotrophic Lateral Sclerosis (ALS), a degenerative disease caused by the death of motor neurons. One of the most used measures to assess the efficacy of these treatments is the ALS Functional Rating Scale-Revised (ALSFRS-R) score, which consists of 12 questions that can be scored from 0 to 4. A score of 0 on a question indicates absence of function, while a score of 4 indicates complete function. The final score ranges from 0 to 48, the higher the score, the greater the degree of functionality [1]. Riluzole, with antiglutamatergic action, was the first drug approved for the treatment of ALS [2]. Despite the increase in Randomized Clinical Trials (RCTs), there are some challenges in generalizing their results due to the duration of each study, selection of patients with great clinical variability and different clinical outcomes analyzed.

OBJECTIVE

The objective of this study was to carry out a systematic review with meta-analysis of RCTs lasting six or more months to investigate the efficacy of treatments in patients with ALS carried out between 2016 and 2021 using the final score of ALSFRS-R as measure.

METHODOLOGY

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [3] and was published on the PROSPERO Platform (CRD42023434501).

ELIGIBILITY CRITERIA

The PICOT strategy (population, intervention, control, results, and type of study) was used to establish the eligibility criteria: (1) population: patients diagnosed with ALS or probable ALS; (2) intervention: medication; (3) control: placebo; (4) results: final score on the Revised ALS Functional Assessment Scale; (5) type of study: Randomized Clinical Trial. Review articles, letters and case reports were excluded. Studies that did not report data/results or the data/results reported were insufficient were also excluded. Furthermore, observational studies were not included.

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DATABASES AND SEARCH STRATEGY

The search for articles was carried out on January 20, 2022 in the Databases: MEDLINE via PubMed (https://pubmed.ncbi.nlm.nih.gov), ELSEVIER via Embase (https://www.embase.com) and Scopus (https://www.scopus.com), LILACS via Virtual Health Library (VHL) (https://lilacs.bvsalud.org) and the Cochrane Central Register of Controlled Trials (CENTRAL) (https://www.cochranelibrary.com/central), published in English using the English-language medical metadata system (MeSH) (https://www.ncbi.nlm.nih.gov/mesh), and records of completed RCTs that had their first results posted on the website https://clinicaltrials.gov in the period 2016 to 2021. The search strategy involved the following terms and Boolean characters:

- ("amyotrophic lateral sclerosis" OR “Lou Gehrig Disease”) AND ("randomized controlled trial" OR "double-blind method" OR phase AND "clinical trial") AND (experimental AND "control group" OR placebo) AND functional AND rating AND scale.

STUDY SELECTION

The identification of duplicate articles and the selection of studies were carried out using the Rayyan software (https://www.rayyan.ai/) [4]. Full texts were selected by 2 independent reviewers who searched for potentially relevant studies based on titles and abstracts. Relevant studies were read in full, included in the meta-analysis according to the eligibility criteria, and disagreements were resolved by consensus or by a third reviewer.

DATA EXTRACTION AND SYNTHESIS

The information obtained regarding the study population, intervention, follow-up period, data loss rate and results were tabulated in an Excel spreadsheet. Quality assessment was performed independently by reviewers using the Cochrane risk of bias tool. The meta-analysis was based on the random effects model and in evaluating the effectiveness of treatments, the standardized difference in means, adjusted difference in least squares means and confidence intervals (CI) were calculated. The forest plot was used to graphical representation of effect sizes and CI (95%). Values of $p < 0.05$ in a two-tailed analysis were considered statistically significant. The statistical heterogeneity index was used to estimate the inconsistency between studies (I^2) [5]. The evaluation of publication

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bias was carried out using the funnel scatterplot and the Egger regression test. Data analysis was performed using Meta Essentials software [6].

RESULTS

The database search identified 465 studies. Additionally, 39 RCTs were identified on the clinicaltrials.gov website. The process continued with the removal of duplicate articles (n = 152), with the exclusion of articles in the title and summary phases (n = 285) and, finally, with the removal of 49 studies in the reading phase of full articles. according to the eligibility criteria, leaving 18 studies for analysis of methodological quality and meta-analysis. The entire process is illustrated in Figure 1. Table 1 presents 12 studies published in scientific journals (studies 1 to 12) and 6 RCTs. The first four studies were carried out with the drug Edaravone (MCI-186) from Mitsubishi Tanabe Pharma Corporation and studies 13, 14 and 15 were carried out with the drug Tirasemtive from Cytokinetics at dosages of 250, 375 and 500 mg, respectively. In all studies, patient allocation occurred randomly, and the intervention model used was parallel allocation. In studies 7, 8 and 19 the blinding was of patients and researchers, while in studies 10, 12, 13, 14 and 15 the blinding was of patients, care providers and researchers, and in the other studies the blinding was of patients, providers care providers, researchers, and evaluators. The study 9 had the primary objective of evaluating the safety of DM1003 (Biotin) by monitoring serious adverse effects, disease-related events, routine laboratory tests and vital signs. The main objective of study 16 was to evaluate the dosage of pharmacodynamic biomarkers and study 20, the safety and efficacy of TRO19622 (Olesoxime) evaluated by the 18-month survival rate. We chose to include these three studies in the analysis because we had ALSFRS-R score data available. The other studies had as main objective the intention to treat. In total, 4.214 participants were enrolled, but 3.813 began the studies with 1.880 receiving the drug and 1.933 receiving the placebo and 1.222 patients were discontinued (29,0%) throughout the studies. Sample sizes ranged from 16 to 942, with a median of 171 participants. The average age of participants was 57 years old, with a predominance of males (65%). Based on the first twelve studies, 21,4% of participants had onset of symptoms in the bulbar region and 77,0% in the spinal region. Thirteen studies presented data on the use of Riluzole, and the average was 80.0% for the placebo and medication groups. The risk of bias analysis for studies with intention to treat revealed some concerns for studies 8 and 11 and for the other studies, low risk (Figure 2). The effect sizes of each

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study with their respective CI (95%) and weight are represented in Figure 3. The combined effect size of the twenty studies was 0,35 (95% CI –0,44 – 1,14). This value was not considered statistically significant (valor de Z = 0,94; p = 0,350). Heterogeneity (I^2) between studies was 52.58%, a value considered substantial (Table 2).

Figure 1. Flow chart of the selection process.

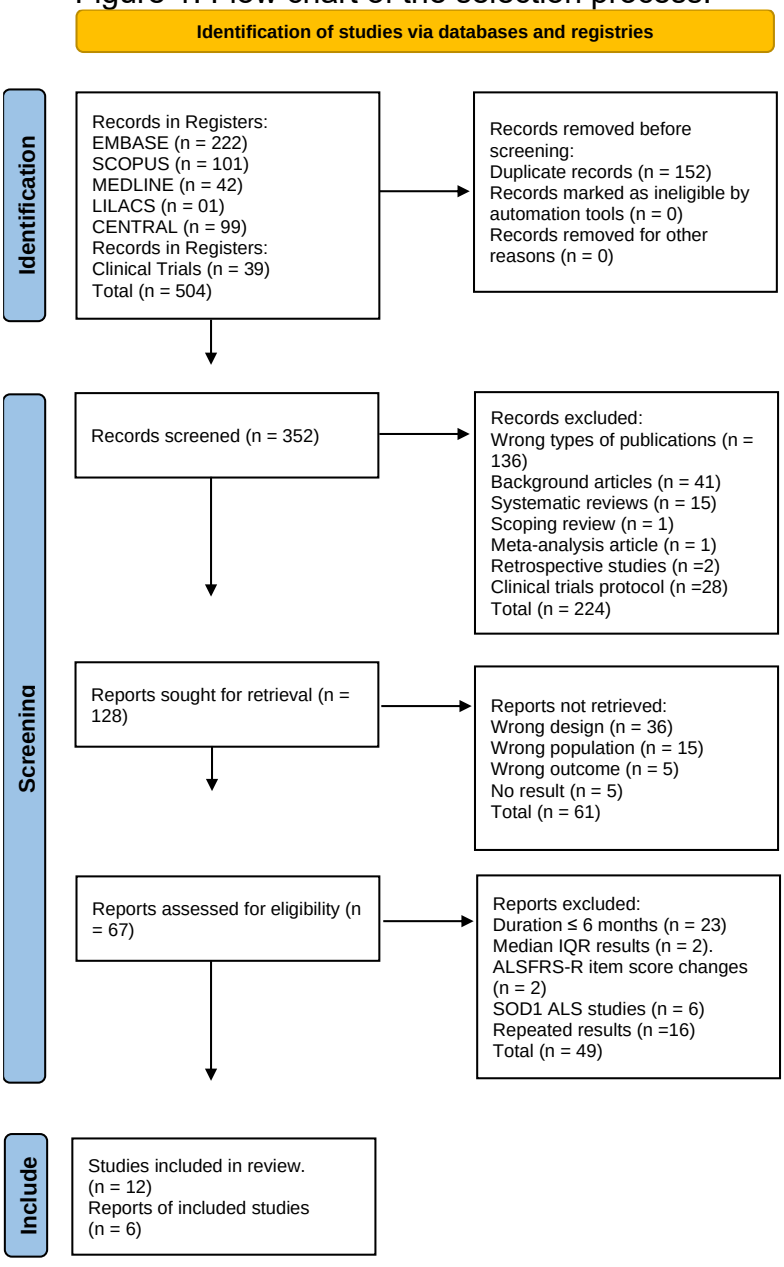

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Table 1. Studies selected for meta-analysis.

Studie	Reference	Clinical Trial*	Interventions	Enrollment	Experimental	Placeb	Discontinuation
Study 1	[7]	NCT00330681	Edaravone Placebo	72	40	32	4
Study 2	[8]	NCT00424463	Edaravone Placebo	52	27	25	5
Study 3	[9]	NCT00415519	Edaravone Placebo	25	13	12	4
Study 4	[10]	NCT01492686	Edaravone Placebo	137	69	68	10
Study 5	[11]	NCT03127514	PB-TURSO Placebo	90	56	34	-
Study 6	[12]	NCT03280056	NurOwn Placebo	196	95	94	7
Study 7	[13]	NCT02588677	Masitinib (4.5) Placebo	107	45	62	8
Study 8	[14]	ACTRN1261800 34280#	dimethyl fumara Placebo	109	72	35	32
Study 9	[15]	NCT03114215	Biotin Placebo	30	20	10	3
Study 10	[16]	NCT01786603	Rasagiline Placebo	80	60	20	30
Study 11	[17]	2017-001983-39	PenGH Placebo	16	10	6	10
Study 12	[18]	NCT01753076	Ozanezumab Placebo	303	152	151	95
Study 13	[19]	NCT02496767	Tirasemtiv (250 mg) Placebo	314	126	188	102
Study 14	[19]	NCT02496767	Tirasemtiv (375 mg) Placebo	314	125	188	117
Study 15	[19]	NCT02496767	Tirasemtiv (500 mg) Placebo	313	122	188	122
Study 16	[20]	NCT03456882	RNS60 Placebo	147	74	73	37
Study 17	[21]	NCT02118727	Memantine Placebo	89	54	29	36
Study 18	[22]	NCT01281189	Dexpramipexole Placebo	942	331	321	290
Study 19	[23]	NCT00326625	Glatiramer Acetate Placebo	366	130	144	92
Study 20	[24]	NCT00868166	Olesoxime Placebo	512	259	253	226

* Except for studies 8 and 11, all others were registered on the clinicaltrials.gov website.
# Registered on the Australian and New Zealand Clinical Trials Registry website.
§ Registered on the European Union Medicines Regulatory Authorities Clinical Trials Database website.

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Figure 2. Risk of Bias of Selected Studies.

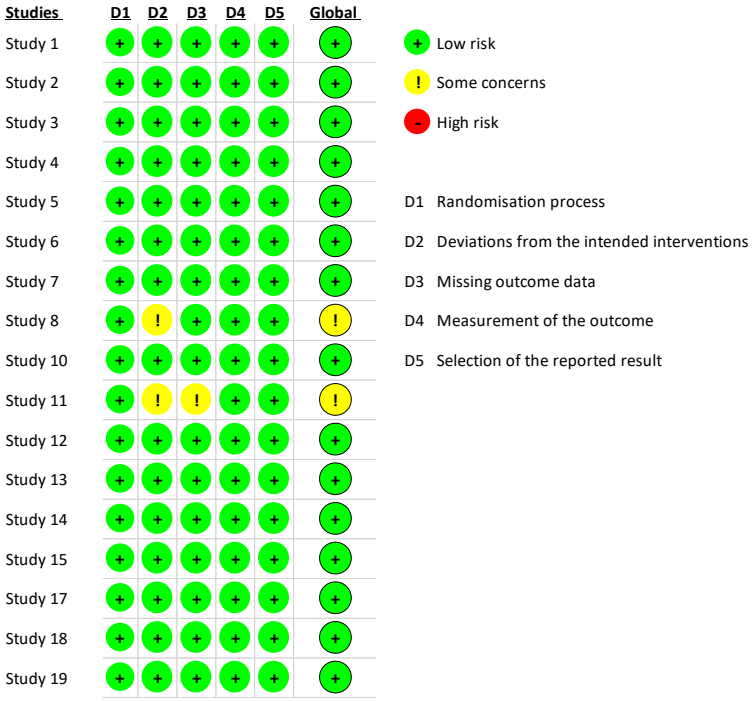

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Figure 3. Forest plot of studies performed to treat ALS. The x-axis forms the effect size scale, plotted on the top of the plot. The studies on the positive side of zero favoring treatment, and on the negative side are studies favoring placebo. The bottom row (or "summary row") turns the plot into a "meta-analysis." This meta-analytic result consists of two intervals, both around the same bullet. This bullet represents the weighted average effect (combined effect size). The smaller, black, interval is a confidence interval. The larger, green, interval is the prediction interval.

Studies	Effect Size	CI Lower Limit	CI Upper Limit	Weight
Study 1	3,01	0,36	5,66	3,96%
Study 2	1,85	-0,44	4,14	4,89%
Study 3	-0,52	-5,60	4,56	1,45%
Study 4	2,49	0,99	3,99	7,63%
Study 5	4,23	0,51	7,95	2,34%
Study 6	0,37	-1,46	2,20	6,24%
Study 7	4,68	0,81	8,55	2,18%
Study 8	-1,12	-3,78	1,54	3,92%
Study 9	-3,60	-9,53	2,33	1,08%
Study 10	3,12	-2,35	8,59	1,19%
Study 11	-6,30	-12,72	0,12	1,01%
Study 12	-1,30	-3,05	0,45	6,54%
Study 13	0,00	-2,17	2,17	5,10%
Study 14	-0,80	-3,04	1,44	4,90%
Study 15	-0,60	-2,89	1,69	4,75%
Study 16	0,48	-1,42	2,38	6,02%
Study 17	-0,09	-1,34	1,16	8,88%
Study 18	0,08	-1,12	1,27	9,09%
Study 19	-0,78	-2,90	1,34	5,24%
Study 20	0,08	-0,16	0,32	13,58%
Combined Effect Size				

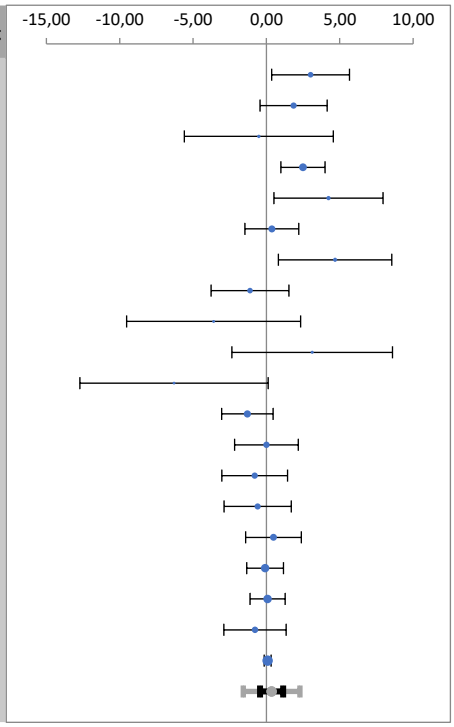

Table 2. Combined Effect Size and Heterogeneity of studies.

Combined Effect Size	
Effect Size	0,35
Standard error	0,38
CI Lower limit	-0,44
CI Upper limit	1,14
PI Lower limit	-1,58
PI Upper limit	2,28
Z-value	0,94
One-tailed p-value	0,175
Two-tailed p-value	0,350
Heterogeneity	
Q	40,07
Pq	0,00
I^2	52,58%
T^2	0,71
T	0,84

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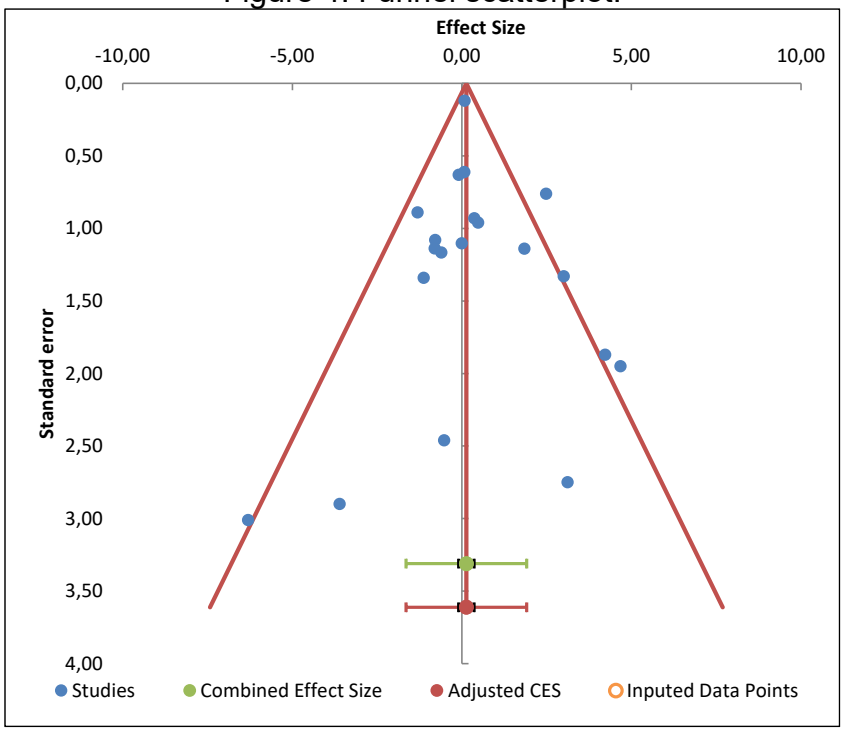
The publication bias analysis based on the funnel scatterplot revealed symmetry in the distribution of studies (Figure 4) and the result of the Egger regression test was not statistically significant (t = 0,64 (df = 19); p = 0,528).

Figure 4. Funnel scatterplot.



DISCUSSION

One of the challenges in analyzing studies carried out in patients with ALS is due to the clinical variability between them. This study focused on cases of sporadic ALS, leaving aside cases of familial ALS. Fifteen medications were evaluated for the treatment of sporadic ALS. In the case of Edaravone, an antioxidant drug indicated for the treatment of acute cerebral infarction in Japan since 2001, it was not possible to demonstrate its efficacy in the first phase III study in comparison with placebo in the treatment of ALS using the ALSFRS-R score [25]. A post-hoc subgroup analysis was performed to identify a subgroup in which Edaravone could be expected to show efficacy. The full analysis set (FAS) consisted of all patients who received at least one dose of Edaravone or placebo and who had efficacy data available. The subgroup with the highest expected efficacy within the FAS, identified as EESP, had a forced vital capacity (FVC) equal to or greater than 80% and 2 or more points for all ALSFRS-R items before treatment. The subgroup with the highest expected efficacy within the EESP group, identified as dpEESP2y, had a diagnosis of "definite" or "probable" ALS according to the Airlie House de El Escorial criteria

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and disease onset within two years. The differences between the groups receiving Edaravone and placebo for the change in the least squares mean in the ALSFRS-R score ± standard error was 0,65 ± 0,78 (p = 0,4108) in the FAS, 2,20 ± 1,03 (p = 0,0360) in EESP and 3,01 ± 1,33 (p = 0,0270) in dpEESP2y. In this meta-analysis we included the results of the dpEESP2y group. The second study conducted to evaluate the long-term efficacy and safety of Edaravone in the FAS and EESP groups [8] and the third study involving patients with ALS severity classification in Japan Grade 3, definite, probable, or probable-laboratory supported ALS (El Escorial/revised Airlie House), FVC ≥ 60%, disease duration ≤ 3 years at the time of consent and change in ALSFRS-R score from –1 to –4 points during the 12-week pre-observation period [9] did not show statistically significant results compared with placebo, and in the fourth study, Edaravone exhibited efficacy in the dpEESP2y group [10]. Another medication that showed positive results was Sodium Phenylbutyrate-Taurursodiol (PB-TURSO) (study 5) also known as AMX0035 and Relyvrio. Sodium Phenylbutyrate is a histone deacetylase inhibitor that positively regulates heat shock proteins by decreasing oxidative stress in the endoplasmic reticulum [26]. Taurursodiol prevents the translocation of the Bax protein to the mitochondrial membrane, thus reducing mitochondrial permeability and increasing the cell's apoptotic threshold [27]. The first study conducted to evaluate the efficacy of PB-TURSO over a 24-week period involving patients with definite ALS who had symptom onset within the last 18 months revealed a mean rate of change in the ALSFRS-R score of −1,24 points per month with the active drug and −1,66 points per month with placebo (difference of 0,42 points per month; 95% CI 0,03 – 0,81; p = 0,03) [28]. Subsequently, a study carried out to evaluate the long-term efficacy and safety (48 weeks) of PB-TURSO revealed a difference of 4,23 ± 1,87 (p = 0,02) compared to placebo [11]. In this meta-analysis we included the long-term results of the study. Although early results reported based on data from the Phase 2 CENTAUR study (NCT03127514) were in favor of PB-TURSO, the Phase 3 PHOENIX study (NCT05021536) was recently launched to confirm the efficacy of PB-TURSO over one year, enrolling 664 people with early ALS. However, the data showed that the study failed to meet its primary goal of slowing the decline in ALSFRS-R scores compared to placebo. These results were a key factor in the decision to remove Relyvrio (PB-TURSO) from the market [29]. Another drug with promising results is Masitinib (study 7), a selective tyrosine kinase inhibitor that plays a protective role in the central and peripheral nervous systems. Long-term survival analysis (median follow-up of 75 months from diagnosis) indicated that oral Masitinib (4,5 mg/kg/day) can prolong

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survival by more than 2 years compared to placebo if treatment is started before severe impairment of functionality [13]. It is worth highlighting that in the trial carried out with Penicillin G/hydrocortisone (PenGH) (study 11), 56,0% of patients had Bulbar-onset ALS, a number well above other studies and a disease progression rate of 2,2 (95% CI 1,1 – 3,3) ALSFRS-R points/month, which is almost twice as fast as observed in previous clinical trials [17]. In all studies, the concomitant use of Riluzole was reported, but only thirteen studies presented data on the use of the medication, which averaged 80.0%. In the methodological analysis, the risk of bias in studies 8 and 11 presented some concerns due to the blinding including only patients and researchers leaving aside caregivers and evaluators, in addition to presenting high discontinuation rates of 30,0 and 60,0%, respectively. The publication bias analysis based on the funnel scatterplot (Figure 4) showed no asymmetry, that is, there was no publication bias. The result of Egger's linear regression test corroborated the non-asymmetry of the first analysis (t = 0,64 (df = 19); p = 0,528). The Combined Effect Size of the twenty studies was not statistically significant, with the null hypothesis prevailing, indicating the absence of effect for the set of studies. However, as shown in Figure 3, studies 1, 4, 5 and 7 had a statistically significant effect favoring the drugs and a substantial heterogeneity of 52,58% led us to perform a subgroup analysis to better explore these results. We divided the studies into three subgroups, the first subgroup formed by studies published in scientific journals whose results were not statistically significant (studies 2, 3, 6 and 8 to 12), the second subgroup formed by studies with statistically significant effect sizes (studies 1, 4, 5 and 7) and the third subgroup formed by RCTs whose results were posted on the clinicaltrials.gov website, but were not published in scientific journals (studies 13 to 20). The effect size of the first subgroup was –0,41 (95% CI –2,26 – 1,45), of the second subgroup it was 2,97 (95% CI 1,58 – 4,36) and of the third subgroup was 0,05 (95% CI –0,08 – 0,19). The result also revealed heterogeneity of 44,15% for the first subgroup while in the others the heterogeneity was 0,0% (p = 0,013). The variation in the results of the studies included in the analysis, therefore, was significantly greater in the group of published articles as opposed to unpublished studies.

CONCLUSIONS

This study aimed to evaluate the efficacy of RCTs of medications used to treat patients with ALS during the period 2016 to 2021. The search for articles covered the main

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databases in addition to the ClinialTrials.gov website. 18 studies were selected for methodological evaluation and meta-analysis. In total, 4.214 participants were enrolled, 1.880 received the drug and 1.933 received the placebo, and about 30,0% of participants discontinued over the course of the studies. The average age was 57 years old, with a predominance of males (65,0%) and 21,4% had onset of symptoms in the bulbar region and 77,0% in the spinal region. Reading the articles also revealed great clinical variability between patients. Of the 15 drugs that were tested, Edaravone, Relyvrio and Masitinib showed positive effects if they were administered before severe functional impairment. However, a recent study showed that Relyvrio failed to achieve its primary goal of slowing the decline in ALSFRS-R scores compared with placebo. In the methodological analysis, two studies presented some concerns due to blinding, including only patients and investigators, and had high discontinuation rates. The funnel plot and Egger regression test showed no publication bias. Subgroup analysis showed that substantial heterogeneity of the studies included in the analysis was significantly greater in the group of published articles as opposed to the unpublished studies.

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