Efficacy of alpha-lipoic acid in patients with burning mouth syndrome compared to that of placebo or other interventions: a systematic review with meta-analyses

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Burning mouth syndrome (BMS) is a chronic oral disorder of unknown etiology which presents therapeutic challenges. Alpha-lipoic acid (ALA) has been studied as a potential treatment for BMS. The objective of this systematic review and meta-analysis was to evaluate the effectiveness of ALA compared to that of placebo or other interventions in individuals with BMS. Randomized controlled trials (RCT) using ALA to treat BMS were identified from MEDLINE, Cochrane Library, EMBASE, and Web of Science up to February 3, 2021. The assessment of the risk of bias in the included studies was based on the Cochrane guidelines. The primary outcome evaluated was the visual analog scale (VAS) pain intensity. ALA was compared with placebo, clonazepam, gabapentin, pregabalin, ALA plus gabapentin, capsaicin, Biotène®, and laser therapy. Altogether, 137 records were scanned for inclusion/exclusion, and nine RCTs (two unclear and seven at high risk of bias) were included in the qualitative and quantitative analyses, with a total of 594 patients with BMS included in this review. All studies reported an improvement in VAS pain scores ranging from -0.72 to -2.77. Meta-analysis results showed a non-significant reduction in pain intensity for ALA (P = 0.616) compared to that of placebo on a VAS of 0–10. Patients taking ALA were 1.923 times more likely to show an improvement in self-reported BMS symptoms (P = 0.031) than those in the placebo group. Clonazepam and pregabalin showed a significant VAS pain reduction of 4.08 and 4.68 (P < 0.001), respectively, compared to that with ALA. Although ALA intervention provided a non-significant improvement in the pain score and was more likely to produce a reduction in BMS symptoms, the evidence was of low quality. Further research is needed to establish clear guidelines for the use of ALA for BMS treatment.

Keywords: Alpha-lipoic acid; Burning Mouth Syndrome; Clonazepam; Meta-Analysis; Systematic Review.

INTRODUCTION

Burning mouth syndrome (BMS) is a chronic oral cavity disorder characterized by an intraoral burning sensation without any known dental or medical causes [1]. Predominant symptoms may be localized to the tongue and/or lips or may be more diffuse and involve the entire oral mucosa [1]. BMS is most prevalent in older adults, particularly women aged 50–70 years [2].

Comorbid conditions include xerostomia, dysgeusia, psychological conditions such as anxiety and depression, and nutritional deficiencies [3]. While BMS has classically been attributed to multiple factors, recent evidence hints at a link to peripheral small fiber neuropathy, trigeminal neuropathy, and/or centrally mediated pain, possibly related to dysfunctional dopaminergic neurons in the basal ganglia, which may result in dysesthesia, hyperalgesia, and allodynia [4]. BMS is a diagnosis of exclusion once other possible burning causes have been ruled out. These include vitamin/iron deficiencies, oral candidiasis, nerve trauma, tumors, and other immune-related diseases [1].

Alpha-lipoic acid (ALA) is a dietary supplement designated as an antioxidant that does not require prescription [5]. ALA contains sulfur and is produced in plants, animals, and humans [6]. It acts as a coenzyme in the Krebs cycle and as a cofactor in energy production in the cell [7]. Glutamate toxicity is a major contributor to pathological death in the nervous system. ALA protects against glutamate toxicity by reducing cellular levels of glutathione (GSH). When GSH is present at low levels in cells, oxidative stress, inflammation, and nerve damage occur, causing peripheral neuropathy [8]. ALA exerts its effect on the BMS by scavenging free radicals and may play a role in nerve repair [9]. Multiple randomized controlled trials (RCTs) have investigated its effects on reducing symptoms and providing relief to patients with BMS [10–12].

The exact etiology of BMS is unknown, but a likely cause is related to the reduction in the density of small fibers in the painful areas [13]. BMS is difficult to diagnose and is typically diagnosed by exclusion [14]. Currently, there are no comprehensive recognized guidelines for managing BMS, and we lack effective, proven treatment regimens as no treatment delivers a cure [14]. ALA has been shown in a meta-analysis [15] to have favorable outcomes for the treatment of diabetic neuropathy. Utilization of ALA to treat BMS could be beneficial owing to its similar etiologies [16]. ALA is readily found in food and can be purchased over the counter as a supplement or remedy. Evaluation of ALA as a possible treatment for BMS would be beneficial, especially for patients with pharmacophobia [17]. Pharmacophobia is the fear of taking medication and has been associated with the improper use of medications, refusal to take medication as prescribed, and relapse of a disorder or disease [17]. This systematic review was designed to analyze RCTs regarding the efficacy of ALA in the management of primary BMS, compared with placebo or other interventions in improving clinical outcomes.

METHODS

1. Research question

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) were followed [18], and the full protocol was registered with the international prospective registration system PROSPERO (CRD42021290489).

The research question understudy was as follows:

- Study Type: RCTs
- Population: adult patients with BMS
- Intervention: ALA
- Comparison: placebo intervention or other active interventions (ALA combined with vitamins, laser, and anticonvulsants)
- Outcomes: primary: pain intensity; secondary: BMS symptoms, pain frequency, quality of life outcomes, number of responders, and side effects and adverse events
- Setting: university medical/dental school

2. Included/excluded studies

Inclusion criteria: RCTs published in the English language on the efficacy of ALA compared with placebo or other active interventions.

Exclusion criteria: pilot studies, open-label studies, editorials, reviews, systematic reviews, meta-analyses, and practice guidelines.

Table 1. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed searched up to 2/3/2021 search strategy:	((alpha-lipoic acid) OR (alpha-lipoic acid)) AND ("Burning Mouth Syndrome/therapy"[Mesh] OR "burning mouth syndrome" OR (oral dysesthesia) OR glossodynia OR stomatodynia OR stomatalgia OR glossopyrosis)
	Results: 44 records
The Web of Science searched up to 2/3/2021 search strategy:	(alpha-lipoic acid) OR (alpha-lipoic acid) AND ("Burning Mouth Syndrome/therapy"[Mesh] OR "burning mouth syndrome" OR (oral dysesthesia) OR glossodynia OR stomatodynia OR stomatalgia OR glossopyrosis)
	Results: 71 records
Cochrane searched up to 2/3/2021 search strategy:	#1 (alpha-lipoic acid) OR (alpha-lipoic acid) #2 ((burning AND mouth AND syndrome) OR (oral AND dysesthesia) OR glossodynia OR stomatodynia OR stomatalgia OR glossopyrosis) #1 and #2
	Results: 3 Cochrane reviews, 1 protocol, 16 trials
EMBASE searched up to 2/3/2021 search strategy:	#1' thiotic acid' exp OR 'thiotic acid' #2 burning AND mouth AND syndrome #3 #1 AND #2
	Results: 92 results

3. Search strategies

In this systematic review, PubMed, EMBASE, Web of Science, and the Cochrane Library were searched up to February 3, 2021, using the search strategies described in Table 1.

4. Data collection and management

Three authors (S.N., J.C., and F.S.) screened all the results of the search strategy (Table 1), reviewed the title and abstract of all references, and decided on the relevance of the reference based on the inclusion/exclusion criteria. In the event of disagreement, the article was fully reviewed (PDF) by the three authors, and the final inclusion/exclusion was decided by consensus with another author (R.E.). The same three authors scanned the reference sections of all included studies (manual search), literature and systematic reviews, meta-analyses, and practice guidelines for further relevant records. The authors reviewed any new relevant references using the same inclusion and exclusion criteria. A fourth author (R.E.) made the final decision after reviewing the full-text if a disagreement arose.

Using a standardized form for data extraction, three authors (S.N., J.C., and F.S.) independently extracted the following from each eligible RCT: study design, funding, recruitment period, criteria for inclusion and exclusion, age and sex of participants in each group, details of the interventions, sample size per group, and outcomes reported in each study with results (means, standard deviations, standard error of the mean, etc.). A fourth reviewer (R.E.) curated and validated the data.

5. Risk of bias assessment

Three authors (S.N., J.C., and F.S.) independently analyzed the risk of bias for each study, which was then reviewed by the fourth author (R.E.). This procedural approach followed the methods described in the Cochrane handbook [19].

6. Statistical analyses

Only RCTs on the efficacy of ALA for the treatment of BMS compared with placebo or other interventions were included.

Barbosa et al. [20] reported the interquartile range (Q1, Q3) and the median (M). The review authors calculated the average = (Q1 + M + Q3) / 3 and standard deviation = (Q3 − Q1) / 1.35. Pain intensity was reported on a 0−10
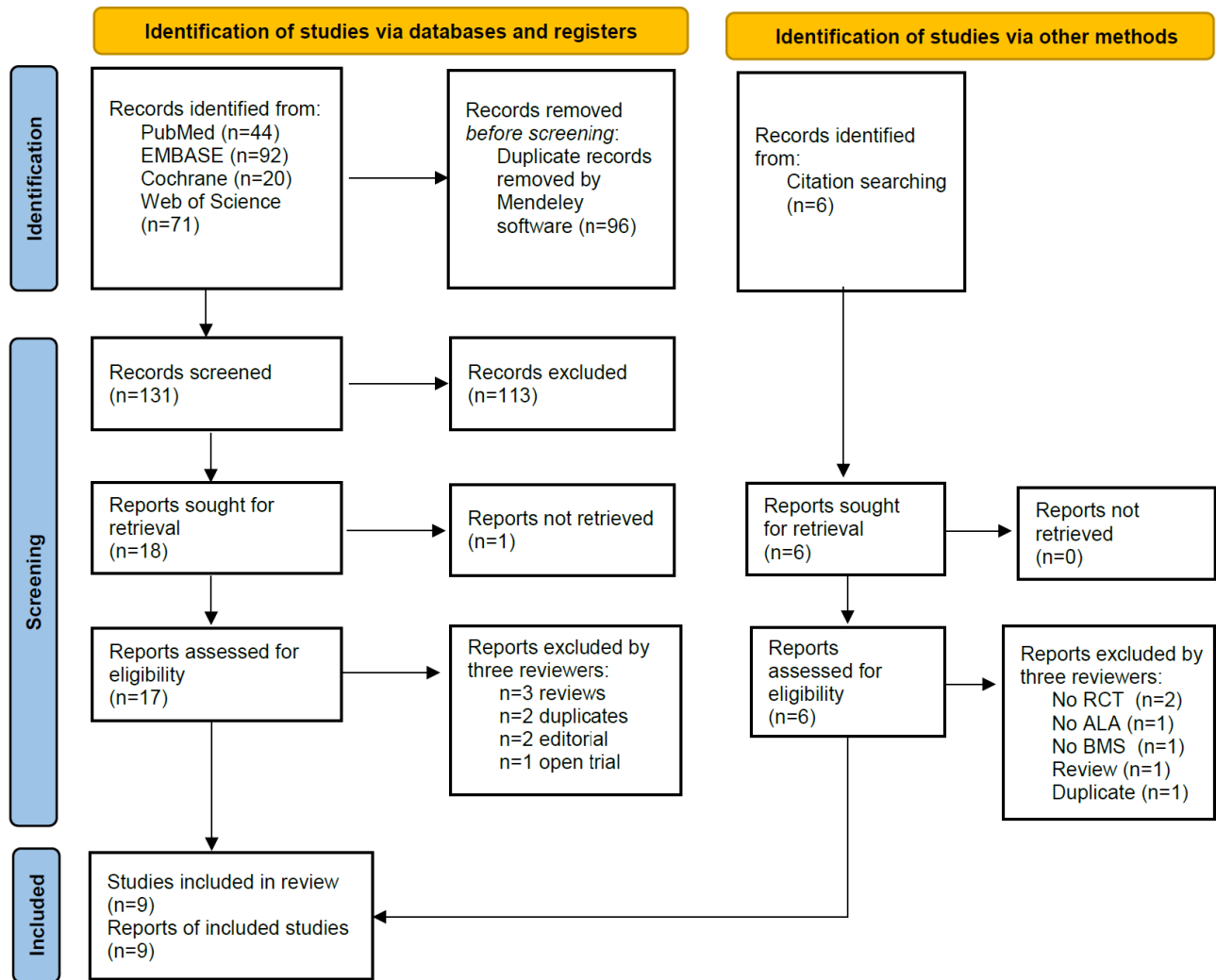
Fig. 1. PRISMA 2020 flow diagram with included searches of databases and other sources [18]. Abbreviations: ALA, alpha-lipoic acid; BMS, burning mouth syndrome; n, number; RCT, randomized controlled trial.

or 0–100 visual analog scale (VAS). When more than one time point was reported, such as in Carbone et al. [5], for 2 and 4 months, the later measurement was used for the meta-analyses. For pain intensity, we reported the difference in the mean (DM) of the change in pain intensity from baseline with 95% confidence intervals (CI). We reported the risk ratios (RR) with 95% CI for the number of participants with improvement in pain or relief.

The Comprehensive Meta-Analysis v3 software (Biostat, Englewood, NJ, USA) was used in this study. Both Cochran's Q test [21] and the I2 statistic [22] were used to test for heterogeneity. Effect estimates were

combined with a random-effects model, if heterogeneity was present (Q-test P < 0.10), or with the fixed-effect model, if not present.

7. Subgroup and sensitivity analyses

Subgroup analyses for each comparison group (placebo, ALA + vitamins, Biotène, capsaicin, clonazepam, laser, and pregabalin) were conducted for pain intensity (VAS 0–10) to assess the effect of each intervention compared to that for ALA groups. Sensitivity analyses comparing the results, including only low risk of bias studies, were not conducted due to the small number of studies in each meta-analysis; for the same reason, a funnel plot could

Table 2. Summary of included studies: Sample size, interventions, age, gender and study design

Reference	Recruitment year, country, sample size	Interventions & sample size per group	Gender (M/F)	Mean age ± SD or median (range in yr or Interquartile Range)	Study design/ overall risk of bias
Barbosa, et al. 2018 [20]	2015 Brazil N = 15	• ALA 600 mg/day (n = 5) • Laser (n = 10)	6M/9F	Median 45.0 (Q25 = 40; Q75 = 52)	Not blinded RCT/HIGH
Carbone, et al. 2009 [5]	2009 Italy N = 66	• ALA 400 mg/day (n = 22) • ALA 400 mg + Vitamins C/PP/E/B6 • /B2/B1/B12/Folic Acid (n = 22) • Placebo (n = 22)	54F/12M	67.3 ± 11.9	DBRPCT/ UNCLEAR
Cavalcanti & da Silveira, 2009 [24]	2005-7 Brazil N = 38	• Crossover • ALA 600 mg/day then Placebo (n = 19) • Placebo then ALA 600 mg/day (n = 19)	4M/34F	Median 63.1 (range 36-78)	DBRPCT Crossover /HIGH
Çinar, et al. 2018 [25]	2015-17 Turkey N = 75	• ALA 600 mg (n = unknown) • Clonazepam 2 mg (n = unknown) • Pregabalin 150 mg (n = unknown)	ALA 15F Clonazepam: 16F Pregabalin: 17F (unknown number of males)	ALA: 42 ± 2.75 Clonazepam: 43 ± 2.25 Pregabalin: 45 ± 2.75	Not blinded RCT/ HIGH Open label RCT
Femiano & Scully, 2002 [10]	Italy N = 60	• ALA 600 mg/day X 2 mo (n = 30); • Placebo starch (n = 30)	18M/42F	median 45 (22–68)	DBRPCT / UNCLEAR
López-D'alessandro & Escovich, 2011 [26]	2003-2008 Argentina N = 120	• ALA 600 mg/day x 2 mo (n = 20) • 300 mg/day Gabapentin x2 mo. (n = 20) • ALA + gabapentin (n = 20) • Placebo starch (n = 60)	26M/94F	mean 57.5 ± 14.1 median: 57	DBRPCT/ UNCLEAR Double blinded RCT
Lopez-Jornet, et al. 2009 [11]	2007 Spain N = 60	• ALA 800 mg/day x 2 mo (n = 30) • Placebo (n = 30)	56F/6M 2 dropouts	64.37 ± 11.61	DBRPCT/ HIGH
Marino, et. al. 2010 [27]	2008 Italy N = 56	• ALA 800 mg/day 400 mg 2xday (n = 14) • 250 mg capsaicin 3xday (n = 14) • Biotène®oral rinse 5xday (n = 14) • Control − boric acid 3xday (n = 14)	10M/46F	62 ± 9.8	Single- blind open label RCT/ HIGH
Palacios-Sanchez, et al. 2015 [12]	2014 Spain N = 60	• ALA 600 mg/day x 2mo. (n = 30) • Placebo (n = 30)	5M/55F	62.13years (Range 36-86)	DBRPCT/ HIGH

Abbreviations: ALA, alpha-lipoic acid; DBRPCT, double-blinded randomized placebo-controlled trial; F, female gender; M, male gender; mo, month(s); N, total sample size; n, sample size per group; RCT, randomized controlled trial; SD, standard devation.

not be created to assess publication bias.

8. Quality of the evidence (GRADE)

The review authors produced a summary of the findings for the quality of evidence assessment using the GRADE pro software developed by the working group named Grading of Recommendations Assessment, Development and Evaluation (GRADE) [23].

RESULTS

1. Results of the search

The search strategy initially yielded 227 references,

which was reduced to 131 after removing duplicates. Three review authors independently assessed 131 records and reduced them to 18 relevant manuscripts based on the titles and abstracts. Of these, one record could not be retrieved and only nine RCTs were included. The main reasons for exclusion were review articles (n = 3), duplicates (n = 2), editorials (n = 2), and open trials (n = 1). Six additional records were identified by scanning the reference sections of the included studies (hand search); however, after a full review of the reports, six were excluded due not being an RCT (n = 2), no ALA intervention (n = 1), no BMS (n = 1), being a literature review (n = 1), and being a duplicate (n = 1). A summary of our results is presented in the PRISMA 2020 flowchart

Table 3. Summary of inclusion criteria

Reference	Inclusion Criteria
Barbosa, et al. 2018 [20]	• Dx of BMS based on diagnostic criteria established by the IHS (sensation of burning or numbness in the oral mucosa thatoccurs for more than 2 h per day over more than 3 months in the absence of clinical alterations) [31]
Carbone, et al. 2009 [5]	• Presence of an isolated complaint of chronicpain in the oral mucosa with a normal clinical examination, and pain present for more than 4 months, which was continuous throughout all or part of the day, with no paroxysms and not following a nerve trajectory
Cavalcanti & da Silveira, 2009 [24]	• History of oral burning pain for more than 6 months and absence of oral finding
Çinar, et al. 2018 [25]	• Patients aged >18 years • BMS was diagnosed after ruling out all possible organic causes
Femiano & Scully, 2002 [10]	• Diagnosed with BMS from a history of constant burning discomfort in the anterior tongue, lower lip or hard palate, for more than two months, with no relevant drug or medical history
López-D'alessandro & Escovich, 2011 [26]	• Patients with BMS who have been treated at our service without responding to the applied treatment. • Idiopathic BMS of more than three months duration that wanted to participate voluntarily were included
Lopez-Jornet, et al. 2009 [11]	• Presentation of a clinical history of continuous symptomatology of oral burning or pain, daily or almost daily, during all or part of the day for more than 6 months evolution, without paroxysms, and independent of the nervous pathway; likewise, no clinical abnormality that would justify the symptomatology • had to present a normal blood analysis
Marino, et. al. 2010 [27]	• Symptoms of diffuse burning pain of the tongue and / or oral mucosa associated or unassociated with subjective oral dryness or loss or alteration of taste or sensation • Burning pain almost every day • Normal-looking mucosa in the region of burning • Absence of systemic disorders or laboratory alterations known to be associated with orofacial pain • Daily bilateral oral burning (or pain-like sensation) • Pain is unremitting for at least 4–6 months' • Pain never worsens, but may be relieved, by eating and drinking painseldom interfere with the sleep
Palacios-Sanchez, et al. 2015 [12]	• > 18 years of age • clinically diagnosed with BMS who reported a history of continuous oral burning pain for more than 4 months with no clinical signs that could justify the syndrome

BMS, burning mouth syndrome; Dx, Diagnosis; IHS, International Headache Society; RCT, randomized controlled trial.

[18] (Fig. 1).

2. Included studies

A total of nine publications [5,10–12,20,24–27] comparing ALA to placebo or other active interventions (laser, vitamins, clonazepam, pregabalin, gabapentin, capsaicin, Biotène, ALA and vitamins, and ALA and gabapentin) used to treat BMS were eligible for qualitative analysis, as shown in Table 2.

1) Study design

This systematic review included five double-blind RCTs [5,10–12,26], one single-blind open-label RCT [27], one crossover double-blind RCT [24], and two unblinded RCTs [20,25].

2) Diagnosis of BMS

The population enrolled in the included RCTs was all adult patients (> 18 years) who had BMS. The diagnostic criteria for BMS for each study included in this review were clinical symptoms of burning or numbness of mouth (without any other pathological condition) for more than 2 months [10], 3 months [20,26], 4–6 months [5,12,27], or 6 months [11,24], with one study not being specific [25] (Table 3).

3) Demographics and setting

The participants ranged in ages from 22 to 86 years. The frequency of participants in each study ranged from 15 [20] to 120 [26]. In all the studies, women constituted the majority of the participants. All studies were conducted at university medical/dental schools in Brazil [20,24], Italy [5,10,27], Spain [11,12], Argentina [26], and Turkey [25].

4) Interventions

The interventions analyzed in this review included ALA

Table 4. Risk of bias analyses

Study	Random Seq. Generation	Allocation Concealment	Blinding Participants/ Researcher	Blinding Outcome Assessors/ Statistician	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Barbosa, et al. 2018 [20]	-	+	+	?	+	-	+	+
Carbone, et al. 2009 [5]	-	-	-	?	+	-	?	+
Cavalcanti & da Silveira, 2009 [24]	-	-	-	?	?	-	+	+
Çinar, et al. 2018 [25]	?	+	+	+	+	-	?	+
Femiano & Scully, 2002 [10]	?	-	-	?	-	-	?	?
López-D'alessandro & Escovich, 2011 [26]	-	-	-	?	-	-	?	?
Lopez-Jornet, et al. 2009 [11]	-	-	-	?	+	+	+	+
Marino, et. al. 2010 [27]	-	+	+	+	-	-	?	+
Palacios-Sanchez, et al. 2015 [12]	?	-	?	?	?	-	+	+

KEY: +, High risk of bias; −, Low risk of bias; ?, Unclear risk of bias.

at various doses and durations. The total daily dose was 400 mg [5], 600 mg [10,12,20,24–26], and 800 mg [11,27] (Table 2). The study duration varied from 1 month [20], 2 months [10,12,24,26], to 4 months [5,25, 27]. One study analyzed the outcomes at both 1 and 2 months [11], and another at 2 and 4 months [5].

Comparison groups varied from:
- The placebo group included matched placebo tablets composed of cellulose starch 100 mg [10–12,24,26]; boric acid (0.05 g) dissolved in distilled water (100 ml) as a mouth rinse[27]; or dicalcium phosphate, microcrystalline cellulose, hydroxypropylmethyl cellulose, silicon dioxide, vegetal magnesium stearate, shellac, and stearic acid [5].
- ALA 400 mg plus vitamins C, B3, E, B6, B2, B1, B12, and folic acid daily [5].
- Anticonvulsants included gabapentin 300 mg/day [26], pregabalin 150 mg/day [25], and clonazepam (2 mg/day) [25]. One study compared the 600 mg ALA group to 300 mg gabapentin combined with 600 mg ALA per day [26].
- Biotène® mouthwash five times a day [27].
- Capsaicin (250 mg) was emulsified in 50 ml of water, with no mention of the frequency of use [27].
- The laser was delivered as a weekly session of 10 s for 4 weeks [20].

5) Rescue medications

Three studies noted the use of co-interventions by patients [12,20,24]. In one trial, 45 patients were treated with antihypertensive agents, statins, anxiolytics, anti-ulcerogenic agents, antidiabetic agents, thyroid hormones, oral bisphosphonates, antidepressants, antipsychotics, nonsteroidal anti-inflammatory drugs, and muscle relaxants [20]. In another study, 19 patients had ongoing medications, including antidepressants with tranquilizers, antihypertensive medications, and hormonal repositioning [24]. A third study included participants taking anti-depressants, anxiolytics, antihypertensives, thyroid medications, analgesics, antidiabetics, and antacids [12]. Multiple RCTs did not specify whether rescue medications were discontinued prior to the interventional therapy being administered to the study participants [5,10, 11,25–27].

3. Risk of bias in included studies

Table 4 presents the assessment of the risk of bias. Two studies were assigned an unclear overall risk of bias [10,26] and six studies had a high overall risk of bias [5,11,12,20,24,25,27] (Fig. 2).

4. Adverse events

Several studies have reported on adverse events. These events included nausea and headaches, which led to

Graph of Risk of Bias
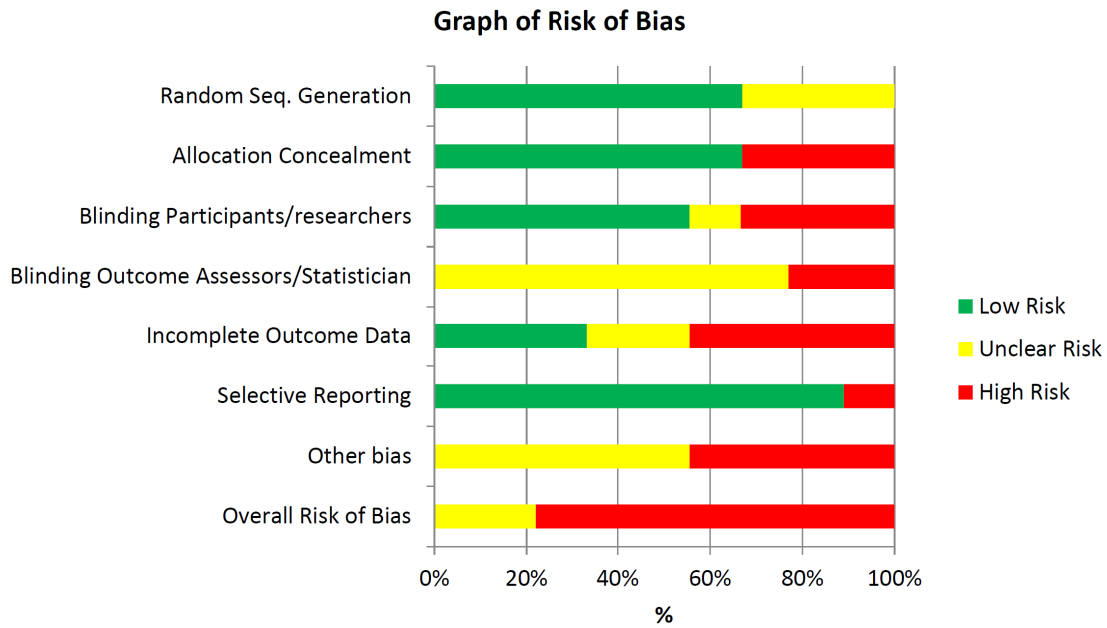
Fig. 2. Summary of risk of bias of eligible. RCT, randomized controlled trial.
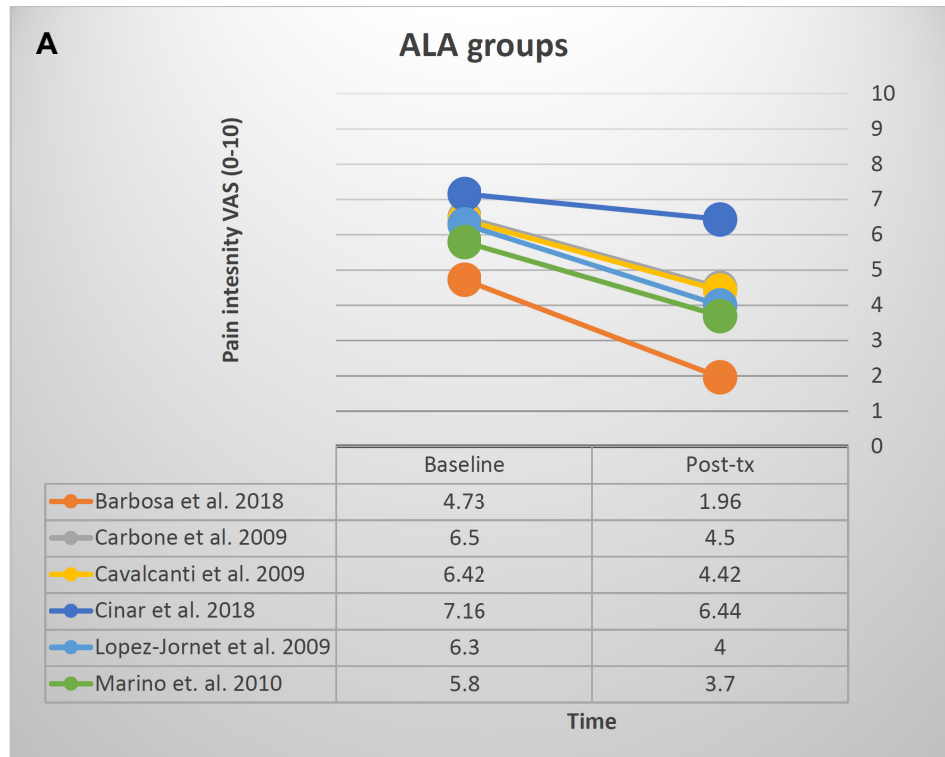
Fig. 3. Pre- and post-VAS pain intensity reported in ALA groups (A), placebo groups (B), and other active interventions (C). Abbreviations: ALA, alpha-lipoic acid; Post-Tx, post-treatment; VAS, visual analog scale.

discontinuation of treatment for one patient [20]; strong headache caused discontinuation of treatment for one patient [24]; one patient abandoned the treatment in another study because of gastrointestinal upset [11]; and mild nausea and myalgia were also reported in the ALA group [25]. Studies reporting adverse events were

B Placebo groups

Pain intensity VAS (0-10)

	Baseline	Post-tx
Carbone et al. 2009 (placebo)	6.65	5.4
Cavalcanti et al. 2009 (placebo)	7.89	5.2
Lopez-Jornet et al. 2009 (placebo)	6.6	2.8
Marino et. al. 2010 (boric acid)	4.8	5.3

Time

C Active interventions (comparison group)

Pain intensity VAS (0-10)

	Baseline	Post-tx
Barbosa et al. 2018 (Laser)	3.16	1.5
Carbone et al. 2009 (ALA + vitamins)	6.89	5.11
Cinar et al. 2018 (clonazepam)	8.04	3.96
Cinar et al. 2018 (pregabalin)	8.12	3.44
Marino et. al. 2010 (capsaicin)	6.1	2.9
Marino et. al. 2010 (Biotene	5.3	3.6

Time

(Fig. 3. continued)

generally categorized as mild or minimal [10,11,25]. Four studies reported no adverse events [5,12,26,27]. Concerning other interventions excluding ALA, the authors reported dizziness (n = 4), transient diarrhea (n = 2), and myalgia (n = 2) with clonazepam; and increased appetite (n = 3), transient vertigo (n = 1), mild nausea (n = 1), and diarrhea (n = 1) in the pregabalin group [25].

A

Change in pain intensity from baseline (VAS 0-10)

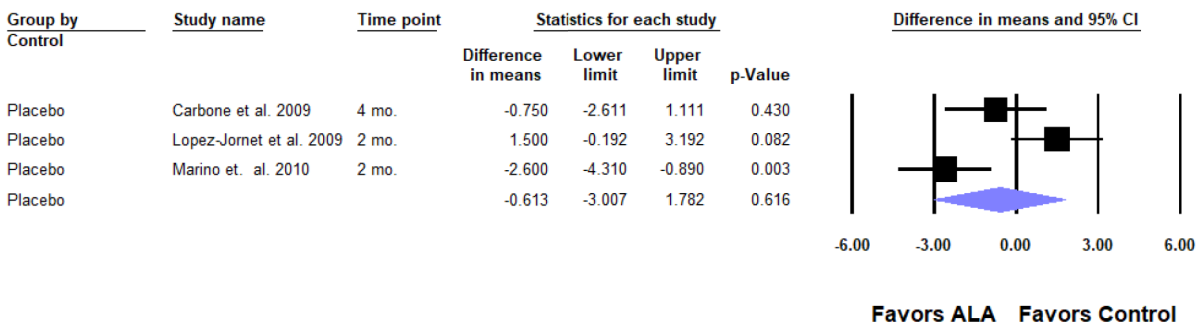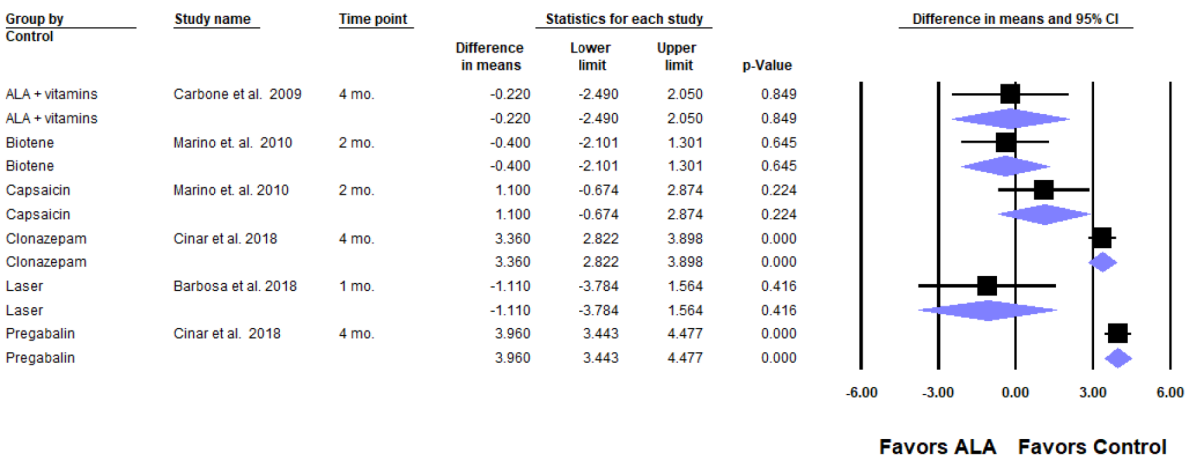| Group by Control	Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value	
Placebo	Carbone et al. 2009	4 mo.	-0.750	-2.611	1.111	0.430	
Placebo	Lopez-Jornet et al. 2009	2 mo.	1.500	-0.192	3.192	0.082	
Placebo	Marino et. al. 2010	2 mo.	-2.600	-4.310	-0.890	0.003	
Placebo			-0.613	-3.007	1.782	0.616	

Difference in means and 95% CI

-6.00 -3.00 0.00 3.00 6.00

Favors ALA   Favors Control

Random-effects model

B

Change in pain intensity from baseline (VAS 0-10)

Group by Control	Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value	
ALA + vitamins	Carbone et al. 2009	4 mo.	-0.220	-2.490	2.050	0.849	
ALA + vitamins			-0.220	-2.490	2.050	0.849	
Biotene	Marino et. al. 2010	2 mo.	-0.400	-2.101	1.301	0.645	
Biotene			-0.400	-2.101	1.301	0.645	
Capsaicin	Marino et. al. 2010	2 mo.	1.100	-0.674	2.874	0.224	
Capsaicin			1.100	-0.674	2.874	0.224	
Clonazepam	Cinar et al. 2018	4 mo.	3.360	2.822	3.898	0.000	
Clonazepam			3.360	2.822	3.898	0.000	
Laser	Barbosa et al. 2018	1 mo.	-1.110	-3.784	1.564	0.416	
Laser			-1.110	-3.784	1.564	0.416	
Pregabalin	Cinar et al. 2018	4 mo.	3.960	3.443	4.477	0.000	
Pregabalin			3.960	3.443	4.477	0.000	

Difference in means and 95% CI

-6.00 -3.00 0.00 3.00 6.00

Favors ALA   Favors Control
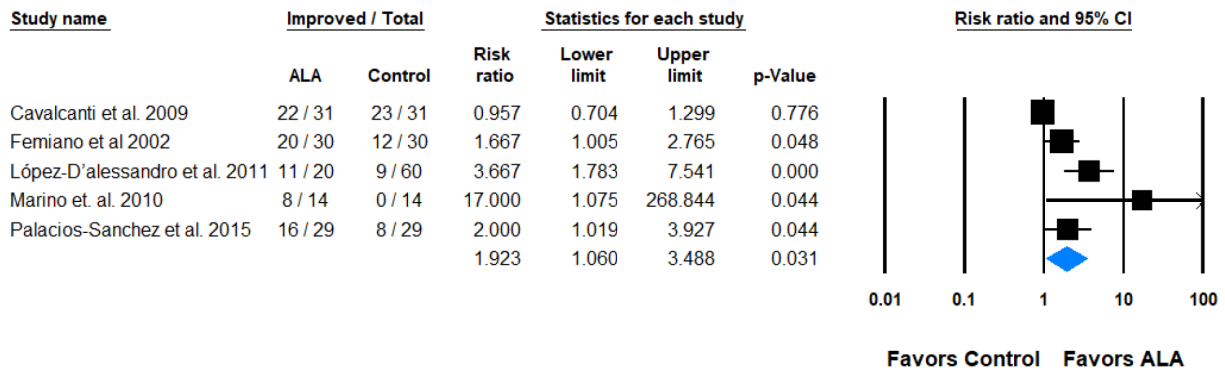
Fixed-effects model

Fig. 4. Meta-analyses and subgroup analyses. (A) Change in pain intensity from baseline (VAS 0-10) with ALA compared to that with placebo. (B) Change in pain intensity from baseline (VAS 0-10) with ALA compared to that with other active interventions. (C) Risk of any improvement in BMS with ALA versus placebo groups. (D) Risk of any improvement in BMS with ALA versus other active interventions.
Abbreviations: ALA, alpha-lipoic acid; CI, confidence interval; VAS, visual analog scale.

5. Primary outcome: pain Intensity

The primary outcome was pain intensity measured on a VAS 0–10, numerical rating scale (NRS) 0–10 [5,11, 20,25,27]. or 0–100 VAS [24]. For the ALA groups (Fig. 3A), all studies reported a pain intensity improvement from baseline, ranging from -0.72 to -2.77 (0-10 scale). Barbosa et al. [20] reported the greatest difference at -2.77, and Çinar et al. [25] reported the least improvement in pain inten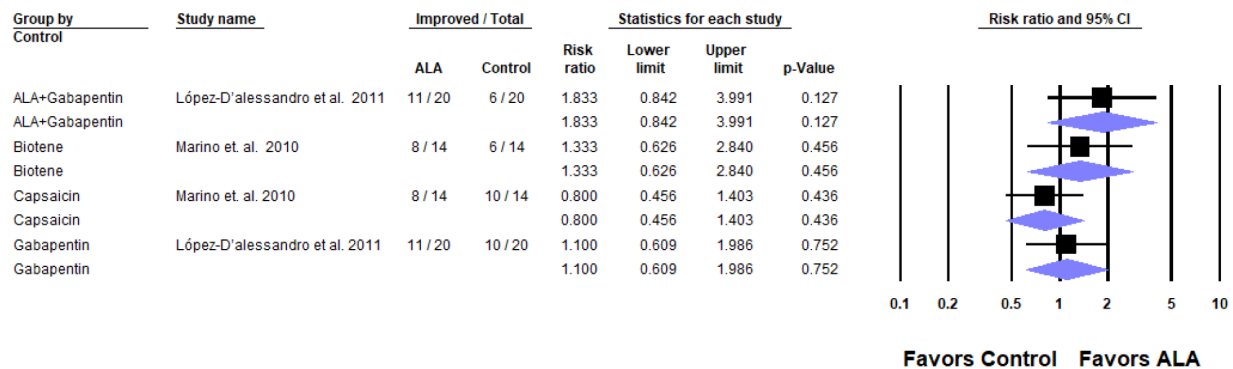sity at -0.72. However, the placebo group showed mixed results. Three studies [5,11,24] showed a decrease in pain intensity from baseline in the placebo groups, ranging from - 1.25 to - 3.8 units (Fig. 3B), and Marino et al. [27] showed an increase of 0.5. Other active interventions (clonazepam, pregabalin, laser, capsaicin, Biotène®, and ALA and vitamins) also showed a decrease in VAS from baseline, ranging from a decrease of - 1.66 to - 4.68. Pregabalin showed the most remarkable improvement in VAS at - 4.68, while laser showed the least at - 1.66 (Fig. 3C).

C — Risk of any improvement

Study name	Improved / Total		Statistics for each study				Risk ratio and 95% CI
	ALA	Control	Risk ratio	Lower limit	Upper limit	p-Value	
Cavalcanti et al. 2009	22 / 31	23 / 31	0.957	0.704	1.299	0.776	
Femiano et al 2002	20 / 30	12 / 30	1.667	1.005	2.765	0.048	
López-D'alessandro et al. 2011	11 / 20	9 / 60	3.667	1.783	7.541	0.000	
Marino et. al. 2010	8 / 14	0 / 14	17.000	1.075	268.844	0.044	
Palacios-Sanchez et al. 2015	16 / 29	8 / 29	2.000	1.019	3.927	0.044	
			1.923	1.060	3.488	0.031	

Favors Control   Favors ALA

Random-effects model

D — Risk of any improvement

Group by Control	Study name	Improved / Total		Statistics for each study				Risk ratio and 95% CI
		ALA	Control	Risk ratio	Lower limit	Upper limit	p-Value	
ALA+Gabapentin	López-D'alessandro et al. 2011	11 / 20	6 / 20	1.833	0.842	3.991	0.127	
ALA+Gabapentin				1.833	0.842	3.991	0.127	
Biotene	Marino et. al. 2010	8 / 14	6 / 14	1.333	0.626	2.840	0.456	
Biotene				1.333	0.626	2.840	0.456	
Capsaicin	Marino et. al. 2010	8 / 14	10 / 14	0.800	0.456	1.403	0.436	
Capsaicin				0.800	0.456	1.403	0.436	
Gabapentin	López-D'alessandro et al. 2011	11 / 20	10 / 20	1.100	0.609	1.986	0.752	
Gabapentin				1.100	0.609	1.986	0.752	

Favors Control   Favors ALA

Fixed-effects model

(Fig. 4. continued)

6. Meta-analyses results

1) ALA vs. placebo

Pre- and post-pain intensity (VAS 0–10) for the ALA groups compared to those of placebo were reported in three studies [5,11,27]. Pain intensity was not significantly different between the two groups (P = 0.616; Fig. 4A). Patients receiving ALA were 92.3% more likely to have an improvement in BMS self-reported symptoms than those in the placebo group (RR = 1.923; 95% CI = 1.060–3.488; P = 0.031; Fig. 4C) in five studies [10, 12,24,26,27].

2) ALA versus other active interventions

One study [25] reported significant improvements in pain intensity from baseline with clonazepam compared to that with placebo (DM = 3.360; 95% CI = 2.822–3.898; P < 0.001; Fig. 4B) in one arm and improvements with pregabalin compared to that with placebo in another arm of the study (DM = 3.960; 95% CI = 3.443–4.477; P < 0.001; Fig. 4B). There were no significant differences in the change in pain intensity with ALA and vitamins (P = 0.849), Biotène® (P = 0.645), laser (P = 0.416), or capsaicin (P = 0.224) compared to that with placebo (Fig. 4B).

Patients receiving ALA and gabapentin were 83.3%

Table 5. GRADE assessment of the quality of the evidence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
ALA compared to placebo for BMS					
				Risk with Placebo	Risk difference with ALA (95% C I)
Change in pain intensity from baseline VAS0-10	144 (3studies) 1-4 months	$\oplus\oplus\ominus\ominus$ LOW*, † due to risk of bias, inconsistency	----	----	The mean change in VAS pain intensity from baseline in the intervention groups was 0.613 units lower (3.007 lower to 1.782 higher)
Risk of any improvement in BMS symptoms	288 (5studies) 2-4months	$\oplus\oplus\oplus\ominus$ MODERATE* due to risk of bias	RR 1.923 (1.060 to 3.488)	317 per 1000	293 more per 1000 (from 19 more to 789 more)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

* All studies at unclear/high risk of bias
† Minimal or no overlap of confidence intervals

Abbreviations: BMS, burning mouth syndrome; CI, confidence interval; GRADE, grading of recommendations, assessment, development, and evaluation; RR, risk ratio; VAS, visual analog scale.

more likely to have an improvement compared to those receiving ALA alone, although this result was not statistically significant (RR = 1.833; 95% CI = 0.842–3.991; P = 0.127; Fig. 4D).

7. Results for secondary outcomes reported in the included studies

1) ALA versus placebo

One study [5] reported a number of responders with an improvement of 50% in their symptoms of BMS from baseline to 8 and 16 weeks, measured using VAS scores of 0–10. There were no statistically significant differences in the number of responders between ALA and ALA combined with vitamins or placebo at 8 weeks (P = 0.126) and 16 weeks (P = 0.772) [5].

2) ALA versus laser

One RCT [20] reported an unstimulated salivary flow rate (ml/min) before and after the treatment. The increase in the ALA group of 0.1 ml/min from baseline was not statistically significant (P = 0.414). However, the laser therapy group showed a statistically significant improvement from the baseline (P = 0.034), with an

increase of 0.2 ml/min [20]. The same study also reported TNF-α concentration levels before and after treatment, with a non-significant increase of + 8.0 pg/ml from baseline in the ALA group (P = 0.465) and a non-significant decrease of -1.8 in the laser group (P = 0.686) [20].

8. Quality of the evidence (GRADE)

In summary, due to an unclear or high risk of bias and the lack of overlap of confidence intervals (unexplained heterogeneity), the quality of the evidence was low (Table 5) for ALA compared to that for the placebo groups regarding the change in VAS pain from baseline (Fig. 4A), and moderate quality (Table 5) for the risk of any improvement in BMS symptoms (Fig. 4C). As shown for visual reference (Fig. 4B and 4D), other subgroup analyses included only one study; therefore, quality of the evidence (GRADE) could not be validated.

DISCUSSION

1. Summary of main findings and discussion

This systematic review investigated the effectiveness

of ALA as a therapeutic agent for the treatment of BMS at different dosages (400 mg, 600 mg, and 800 mg daily) versus placebo, other active interventions (clonazepam, pregabalin, gabapentin, laser, capsaicin, and Biotène®), and combination therapies (ALA plus gabapentin and ALA combined with vitamins).

1) ALA vs. placebo

Three studies [5,11,27] compared ALA versus placebo for BMS treatment, with two studies [5,27] showing a positive improvement in pain intensity from baseline in the ALA groups. However, the overall meta-analysis result, including these three studies, was insignificant (P = 0.616). The third study [11] had a high dropout rate, with only 39 of the 60 patients completing the study.

The risk of any improvement in symptoms with ALA was favorable in four of the studies versus placebo [10,12, 26,27] and unfavorable to ALA in one study [24]. The pooled results showed that patients receiving ALA were 92% more likely to have an improvement in BMS symptoms (P = 0.031). These results are consistent with reviews by De Souza et al. [28], Liu et al. [14], and Phan et al. [29].

De Souza et al. [28] reported that 6 of 7 studies showed improvement in symptoms, although only four studies found ALA superior to placebo. Liu et al. [14] reported that five of six studies showed an improvement, with no significant differences in pain scores between ALA and placebo. Phan et al. [29] reported that ALA showed no significant difference in pain reduction from placebo (P = 0.713) and that ALA significantly improved patients' symptoms in four studies (RR = 2.676; P < 0.001).

2) ALA vs. clonazepam

Çinar et al. (2018) [25] evaluated clonazepam for the treatment of BMS and reported a significant improvement in pain intensity compared to that with ALA (P < 0.001). Reyad et al. [30] also reviewed topical and systemic clonazepam for BMS compared with placebo and reported a significant reduction in VAS scores for patients treated with clonazepam. De Souza et al. [28] and Liu

et al. [14] reported mixed results with systemic clonazepam and significantly superior results with topical clonazepam compared to that with placebo. Additional studies are required to confirm the efficacy of clonazepam.

3) ALA vs pregabalin/gabapentin

The use of pregabalin for BMS has shown inconclusive results. Çinar et al. (2018) [25] reported significant improvements in pain intensity with pregabalin compared to that with ALA (P < 0.001). López-D'alessandro and Escovich [26] used topical gabapentin for BMS treatment and reported that patients receiving ALA plus gabapentin had an 83.3% increased chance of improvement compared to those receiving ALA alone, although this result was not statistically significant (P = 0.127). Reyad et al. [30] evaluated one case report using systemic pregabalin or gabapentin alone for the treatment of BMS and reported positive results for pregabalin, but not for gabapentin. Reyad et al. [30] also included a case series with mixed results that failed to confirm the efficacy of gabapentin. Further studies are required to evaluate pregabalin or gabapentin alone or in combination with ALA as a treatment modality for BMS.

4) ALA vs. Biotène/laser/capsaicin

Compared with ALA for the treatment of BMS, Biotène® (P = 0.645), laser (P = 0.416), and capsaicin (P = 0.224) showed no significant differences in pain intensity changes from baseline. Reyad et al. [30] reported positive effects of topical capsaicin and low-level laser therapy compared to that of placebo. Additional studies are needed owing to the limited availability of data.

2. Overall completeness and quality of the evidence

The search was conducted on four electronic databases (EMBASE, MEDLINE through PubMed, Web of Science, and Cochrane library) for articles published in the English language up to February 3, 2021. Three reviewers (S.N., J.C., and F.S.) independently assessed the risk of bias according to the guidelines of the

Cochrane Reviewers' Handbook. Only RCTs comparing ALA with placebo or other active interventions were included in this review [5,10–12,20,24–27]. The risk of bias in the included articles was unclear or high. In addition to the lack of overlap in confidence intervals, the quality of the evidence was low.

3. Applicability of the evidence

The results of this study are applicable to people between 22 and 86 years of age of both sexes who suffer from BMS anywhere from 2 months to 6 months [5,10–12,20,24–27]. The RCTs were conducted in Brazil [20, 24], Italy [5,10,27], Spain [11,12], Argentina [26], and Turkey [25], and all were performed in medical or dental university institutions.

4. Heterogeneity of the review

Heterogeneity was present in terms of the study design, as we included randomized clinical trials [20,25], double-blind, randomized placebo-controlled studies [5,11,12,26], one randomized placebo-controlled double-blind crossover study [24], one double-blind controlled study [10], and one single-blind randomized, prospective study [27]. The studies also had different treatment durations, ranging from 1 month [11,20], 2 months [10–12,24,26], to 4 months [5,25,27]. Placebo was used as a control in only six of the included studies [5,10–12, 24,27]. Other comparison groups were laser [20], ALA in combination with vitamins [5], pregabalin [25], clonazepam [25], gabapentin [26], gabapentin in combination with ALA [26], capsaicin [27], and Biotène[®] [27].

The dosage of ALA administered varied, with one study administering 400 mg [5], six studies utilizing a treatment dose of 600 mg [10,12,20,24–26], and two studies using an 800 mg dose [11,27]. Reporting of trial outcomes also varied among studies, with the most common being a change in VAS pain intensity (0–10 or 0–100) [5,11,12,20,24,25,27]. Other measurements of outcomes included unstimulated salivary flow rate, determination of TNF-alpha levels, global perceived effect, and changes in BMS symptomatology. How this heterogeneity might have affected the results of this systematic review remains unclear.

5. Implications for research and clinical practice

Areas that would be beneficial to evaluate in future research:

- Combination therapies such as topical ALA and topical clonazepam and gabapentin [26].
- Double-blind placebo-controlled randomized trials for the study of ALA with balanced sexes per group, large sample size, minimizing bias through computer-based randomization, and allocation concealment, ensuring that all patients are controlled for similar symptoms, medications, and underlying conditions.
- Further studies should include standardized outcomes (such as pain using the VAS scale 0–10), quality of life (such as improvement in daily activities and perception of improvement in symptoms), and unstimulated and stimulated salivary flow rates (to rule out symptomatic xerostomia).
- Studies with similar doses (ALA dosage of 600 mg or less owing to the high dropout rate and gastric side effects for doses higher than 600 mg).

The utilization of ALA in clinical practice may be beneficial as an adjunct to other therapies for BMS, such as gabapentin, clonazepam, or capsaicin. Further evaluation of this is warranted, as well as any allergies to sulfur.

6. Conclusions

Several therapies have been proposed for the treatment of BMS, but with a low grade of evidence. ALA is a naturally occurring agent that contains sulfur, is processed by humans, and prevents glutamate toxicity, which causes peripheral neuropathy. Our systematic review showed no significant improvement in pain intensity on the VAS and a significant improvement in symptoms in patients with BMS using ALA with a low grade of evidence. Due to small sample sizes, a limited number of studies, different doses of ALA, duration of the studies, and the presence

of heterogeneity, further studies with a larger sample size are required to assess its efficacy.

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