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REVIEW

Treatment modalities for burning mouth syndrome: a systematic review

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Abstract

Objectives In the burning mouth syndrome (BMS), patients experience a burning sensation in the oral cavity with no associated injury or clinical manifestation. The etiology of this condition is still poorly understood, and therefore, treatment is challenging. The aim of this study is to perform a systematic review of treatment possibilities described in the literature for BMS.

Materials and methods PubMed, Embase, and SciELO databases were searched for randomized clinical trials published between 1996 and 2016.

Results Following application of inclusion and exclusion criteria, 29 papers were analyzed and divided into five subcategories according to the type of treatment described: antidepressants, alpha-lipoic acid, phytotherapeutic agents, analgesic and anti-inflammatory agents, and non-pharmacological therapies. In each category, the results found were compared with regard to the methodology employed, sample size, assessment method, presence or absence of adverse effects, and treatment outcomes.

Conclusions The analysis revealed that the use of antidepressants and alpha-lipoic acid has been showing promising results; however, more studies are necessary before we can have a first-line treatment strategy for patients with BMS.

Clinical relevance To review systematically the literature about Burning Mouth Syndrome treatment may aid the clinicians to choose the treatment modality to improve patients symptoms based on the best evidence.

Keywords Burning mouth syndrome · Stomatodynia · Treatment modalities · Systematic review

Introduction

The burning mouth syndrome (BMS) is characterized by the presence of chronic orofacial pain despite the absence of any visible lesion in the patient's oral mucosa [1]. The condition occurs more frequently in post-menopausal women and is relatively common, with an incidence estimated at 5:100,000 people; no predilection for a specific ethnicity or socioeconomic class has been identified [2]. The actual cause of BMS remains to be clarified, but several local, systemic, and psychological factors have been investigated as potentially related to the condition [1, 3, 4]. The term syndrome is used because BMS co-occurs with other subjective symptoms, such as xerostomia and dysgeusia [3].

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BMS manifests as pain of unknown origin and a burning sensation affecting oral soft tissues, most commonly the tongue, but also lips, palate, gums, and buccal mucosa, and less frequently the floor of the mouth and oropharynx [3, 5]. For the diagnosis of BMS, the oral mucosa must be intact, with all clinical aspects within normality standards [3]. Differential diagnosis should rule out chronic orofacial pains and painful oral diseases that cause injuries to the mucosa, such as thrush, Sjögren's syndrome, xerostomia and hyposalivation, among others, and also systemic conditions such as hormonal alterations, vitamin deficiencies, use of medications, and diabetes [6, 7] (Fig. 1).

Given the difficulties faced by practitioners in understanding the etiology of this syndrome, adequate treatment becomes challenging and several therapeutic options can be found in the literature. Therefore, the objective of this study was to conduct a systematic review of therapeutic possibilities for BMS, the question behind the review being "what is the best treatment for BMS?"

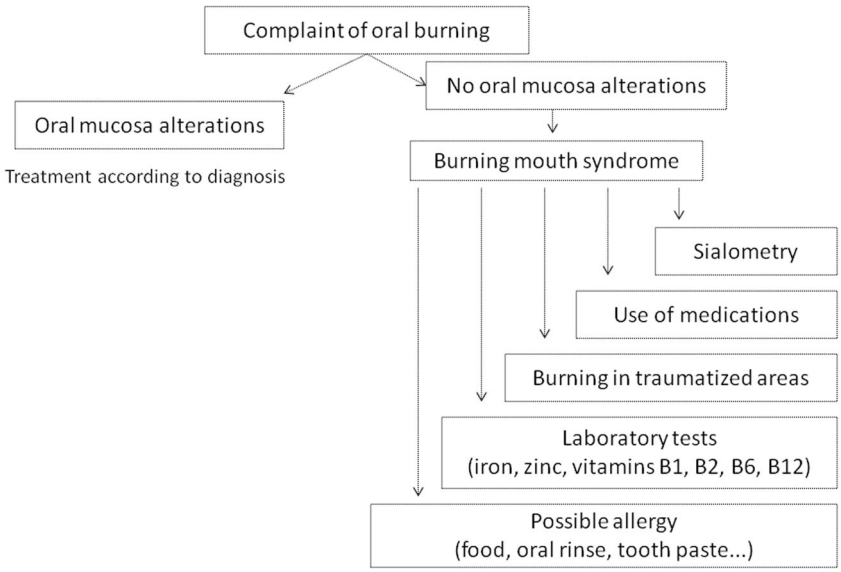

Fig. 1 Flowchart illustrating differential diagnoses for burning mouth syndrome

Materials and methods

Databases and search strategy

This study was conducted in accordance with the PRISMA checklist [8]. The PubMed, Embase, and SciELO databases were searched using the following keywords combined: "(burning mouth syndrome [MeSH Terms] OR burning mouth syndrome [Supplementary Concept] OR burning mouth syndrome [All Fields] OR stomatodynia [Supplementary Concept] OR stomatodynia [All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])". Randomized clinical trials reporting the effects of different treatments for BMS were selected. The search focused on papers published between 1996 and 2016, and was performed on November 27, 2016. This systematic review was registered at the PROSPERO International Prospective Register of Systematic Reviews with protocol no. CRD42017054237.

Inclusion and exclusion criteria

After searching the three databases using the selected keywords, a total of 233 papers were retrieved. Only randomized clinical trials were selected. After reviewing title and abstracts, 157 were found to be duplicates and 5 were excluded because they were published in languages other than English. The complete article review resulted in 19 papers excluded because they were not randomized clinical trials (case reports, letters to the editor, clinical observations with no control group, and literature reviews), and 23 were excluded because they focused on other conditions and not BMS. As a result, our final review comprised 29 papers (Fig. 2).

Analysis of results

Data from selected papers were entered into tables for subsequent analysis, divided into five subcategories according to the type of treatment assessed.

Analysis of biases

Following data analysis, papers were assessed with regard to possible biases. We evaluated patient randomization, whether both patients and research staff were blinded to group allocation, and the statistical tests employed. In case of doubts, an email would be sent to the corresponding author asking for more information.

Results

Following literature search and selection, a total of 29 papers were included in the analysis. These papers were divided into five subcategories, as described below.

Antidepressants

This category included papers in which BMS symptoms were treated with topical or oral antidepressants (Table 1). We found six papers: two using systemic clonazepam compared to placebo [9] and acupuncture [10], two using topical clonazepam comparing its effectiveness with placebo [11, 12], one using trazodone compared to placebo [13], and one using paroxetine compared to sertraline hydrochloride and amisulpride [14]. Treatment time for all substances ranged from 4 to 9 weeks. The most common adverse effects were drowsiness and dizziness, reported in four of six papers. With

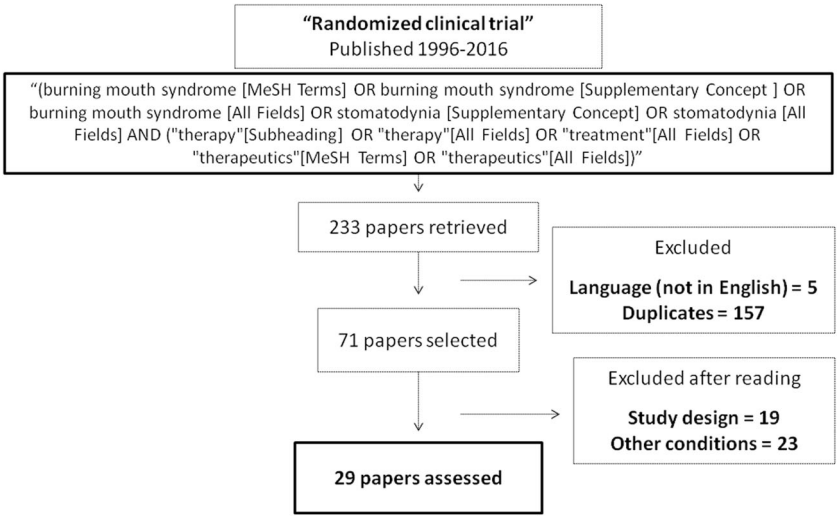

Fig. 2 Flowchart illustrating database searching process

regard to treatment, clonazepam topical presented improvement in the two articles studied [11, 12]. Already in its systemic use, it only showed improvement in one of the papers [9]. Trazodone was not effective in improving BMS symptoms [13], whereas paroxetine, sertraline hydrochloride, and amisulpride equally improved symptoms at similar levels—the latter three, however, were not compared to placebo [14].

Alpha-lipoic acid (ALA)

Alpha-lipoic acid (ALA) is a compound produced at small amounts in the human body. It is essential to the functioning of different oxidative enzymes involved in metabolism. Currently, it is believed that ALA, or its reduced form, dihydrolipoic acid (DHLA), has several biochemical functions, acting as a biological antioxidant, chelating agent for metals, reducer of oxidized forms of other antioxidants, such as vitamins C and E and glutathione (GSH), and modulator of the signaling transduction of several pathways, e.g., insulin and nuclear factor kappa B [15, 16].

We found seven papers that assessed the effectiveness of ALA in the treatment of BMS (Table 2). In all seven papers, ALA was administered systemically at concentrations ranging from 400 to 800 mg, divided into two or three daily administrations, and most studies lasted for 2 months [4, 15–20]. With regard to side effects, only two studies reported patients with gastrointestinal discomfort [18, 19]. Five studies assessed patients after the end of the treatment protocol: four of them after 2 months [4, 18–20] and one after 1 year [15]. All studies were placebo-controlled, and three of them compared and/or associated the use of ALA with other substances. Of the seven studies, only one did not find a significant reduction in burning after treatment [19]. The other six reported improved symptoms, even though ALA was superior to placebo in only four [4, 15, 16, 19].

Phytotherapeutic agents

Another group of therapies used in the treatment of BMS are natural substances, including a wide variety of agents (Table 3). We found seven papers in this category [21–27], with drugs being administered either topically or systemically. Each of the seven studies analyzed a different substance. Minimal side effects were reported: one patient with drowsiness and weight gain [25]; and another with insomnia and two patients with burning after the use of capsaicin 0.02% oral rinse [26]. All seven substances caused symptom improvement.

In the two papers testing the effectiveness of Catuama [28], and capsaicin 0.02% oral rinse [26], significant improvement was observed when compared to placebo. The other five papers, testing the use of 2% chamomile gel [21], urea 10% [23], a spray containing lycopene-enriched virgin olive oil (300 ppm) [22], the use of a tongue protector associated with 0.5 mL of *Aloe Vera* 70% [24], and *Hypericum perforatum* extract 300 mg [27], reported effectiveness in symptom reduction, however, without statistical difference when compared with the placebo/control groups.

Analgesic and anti-inflammatory agents

Another category of medications investigated for the treatment of BMS included analgesic and anti-inflammatory drugs (Table 4). Four papers tested topical anesthesia with 5 mg bupivacaine lozenges [29], topical anesthesia with lidocaine [30], oral administration of Lafutidine 10 mg associated with gargling with azulene 4% [31], and Benzydamine hydrochloride 0.15% oral rinse [32].

Adverse effects were described in the papers testing bupivacaine (burning sensation in eight patients treated with bupivacaine and in five receiving placebo) [29] and Lafutidine (two patients reported minimal effects) [31]. No

Table 1 Treatment of burning mouth syndrome: antidepressants

Author, year	Methodological characteristics	Treatment	Assessment method	Side effects	Main findings
(Kvesic et al., 2015)	Randomized clinical trial	Group 1 = systemic clonazepam 0.5 mg $n = 22$ (2 first weeks 1×/day, 2 last week's 2×/day) Group 2 = acupuncture $n = 20$ (1×/week for 4 weeks)	VAS (before treatment and after 4 weeks)	Five patients in the clonazepam group reported side effects (drowsiness, dizziness, and nausea). None of the patients in the acupuncture group reported side effects	Improvement observed with both treatments. No significant differences between the groups
(Heckmann et al., 2012)	Randomized clinical trial	Group 1 = systemic clonazepam 0.5 mg/day ($n = 10$) Group 2 = placebo (lactose) ($n = 10$) for 9 weeks	VAS (before, at 5 and 7 weeks)	No side effects reported	Clonazepam was statistically superior to placebo
(Campillo et al., 2010)	Double-blind randomized clinical trial	Group 1 = topical clonazepam (0.5 mg) $n = 33$ Group 2 = placebo (lactose) $n = 33$ up to 4×/day (patient's decision)	VAS (at 1 week to assess adverse effects, at 1 month and 6 months)	Five patients in the experimental group reported drowsiness	After 1 month, the clonazepam group showed statistically significant improvement
(Gremeau-Richard et al., 2004)	Double-blind, placebo-controlled, multicenter randomized clinical trial	Group 1 = topical clonazepam (1 mg) $n = 24$ Group 2 = placebo $n = 24$ 3×/day	Numeric scale from 0 to 10 (0, first day and at 14 days)	Side effects reported in both groups, e.g., drowsiness, burning, and reflux	Clonazepam was statistically superior to placebo
(Maina et al., 2002)	Double-blind, prospective, randomized trial	Group 1 = amisulpride (50 mg/day) $n = 27$ Group 2 = paroxetine (20 mg/day) $n = 26$ Group 3 = sertraline (50 mg/day) $n = 23$	VAS (0, 2, 4, 6 and 8 weeks)	Nausea and insomnia were the most common side effects	All treatments caused significant reduction of symptoms
(Tammiala-Salonen and Forssell, 1999)	Double-blind, placebo-controlled, longitudinal randomized clinical trial	Group 1 = trazodone (100 mg for 4 days and then 200 mg for 8 weeks) $n = 18$ Group 2 = Placebo $n = 19$	VAS (baseline, 2, 4, 8 weeks)	Dizziness (11) and drowsiness (9) were the most common side effects in the 18 patients in the experimental group	There was no improvement in any group

VAS visual analog scale

Table 2 Treatment of burning mouth syndrome: alpha-lipoic acid

Author, year	Methodological characteristics	Treatment	Assessment method	Side effects	Main findings
(Palacios-Sánchez et al., 2015)	Double-blind, placebo-controlled randomized trial	Group 1 = ALA 600 mg/day (3 × 200 mg every 8 h) ($n = 25$) Group 2 = placebo ($n = 29$) for 2 months	VAS (baseline and after 1 month of treatment)	No side effects reported	ALA was statistically superior to placebo
(López-D'alessandro and Escovich, 2011)	Double-blind, placebo-controlled randomized trial	Group 1 = ALA 600 mg/day ($n = 20$) Group 2 = GABA 300 mg/day ($n = 20$) Group 3 = combined ALA+GABA Group 4, 5, 6 = cellulose starch placebo 100 mg/day ($n = 20$ in each group) for 2 months	Scale from 0 to 4: 0 = no burning, 1 = burning in a single area of the tongue, 2 = burning in two distinct areas (tongue and gums, tongue and lips, or tongue and palate), 3 = three areas, and 4 = burning all over the mouth	The groups reported very mild effects	Groups 1, 2, and 3 were statistically superior to placebo (groups 4, 5, and 6)
(Marino et al., 2010)	Blind, placebo-controlled randomized trial	Group 1 = capsaicin, 250 mg in 50 ml of water ($n = 14$) Group 2 = 400 mg of ALA 2×/day ($n = 14$) Group 3 = lysozyme lactoperoxidase oral rinse 5×/week ($n = 14$) Group 4 = control, 0.05 g of boric acid dissolved in 100 ml of distilled water, oral rinsing 3×/day ($n = 14$), for 8 weeks	VAS (baseline, after 8 weeks of treatment and after 2 months)	No side effects reported	Groups 1, 2, and 3 were statistically superior to placebo group (4) at 8 weeks. After 2 months, only group 1 (capsaicin) showed significant results
(Cavalcanti and da Silveira, 2009)	Double-blind, placebo-controlled, single-center cross-over randomized trial	Two cycles of treatment with ALA 200 mg 3×/day for 30 days, then 20 days of rinsing, then 30 days with 100 mg of starch placebo, or the opposite ($n = 17$ or 14)	VAS (t1, t2, and t3, in addition to follow-up at 60 days)	ALA—headache $n = 4$; abdominal pain $n = 6$ Placebo—headache $n = 0$, abdominal pain $n = 2$	Both groups showed improvement, but without differences between the groups
(López-Jornet et al., 2009)	Double-blind, placebo-controlled randomized trial	Group 1 = 800 mg/day ($n = 23$) Group 2 = placebo ($n = 16$) = for 8 weeks	VAS (0, 1 month, 2 months)	1 patient in ALA group—abdominal discomfort	There was no improvement in any group
(Carbone et al., 2009)	Double-blind, placebo-controlled randomized trial	Group 1 = ALA 400 mg + Vit ($n = 18$) Group 2 = ALA 400 mg ($n = 14$) Group 3 = placebo 2×/day ($n = 20$) for 8 weeks of treatment + 2 months of follow-up	VAS (T0 = baseline, T1 = 2 weeks, T2 = 4 weeks, T3 = 4 weeks, T4 = end, follow-up of 2 months)	No side effects reported	Both groups showed improvement, but without differences between the groups
(Femiano and Scully, 2002)	Double-blind, placebo-controlled randomized trial	Group 1 = ALA 600 mg/day (3 × 200 mg every 8 h); Group 2 = placebo (cellulose 100 mg/day 3×/day) for 2 months	VAS (after 15 days and 1 year)	No side effects reported	ALA was statistically superior to placebo

ALA alpha-lipoic acid, *VAS* visual analog scale

Table 3 Treatment of burning mouth syndrome: phytotherapeutic agents

Author, year	Methodological characteristics	Treatment	Assessment method	Side effects	Main findings
(Valenzuela et al., 2016)	Prospective double-blind, placebo-controlled, single-center randomized trial	Group 1 = applications of 2% chamomile gel ($n = 31$) Group 2 = placebo ($n = 26$) 2×/day for 1 month	VAS (baseline, 15 and 30 days)	No side effects reported	Both groups showed improvement, however, without differences between the groups
(Cano-Carrillo et al., 2014)	Double-blind, placebo-controlled randomized trial	Group 1 = spray containing lycopene-enriched virgin olive oil 300 ppm ($n = 30$) Group 2 = placebo ($n = 30$) 3×/day	VAS (0 and after 12 weeks)	No side effects reported	Symptoms significantly reduced in the groups. No significant differences found between the groups
(da Silva et al., 2014)	Double-blind, placebo-controlled randomized trial	Group 1 = Anti-xerostomic topical medication (urea 10%) ($n = 19$) Group 2 = Placebo (n = 19), applied 3-4×/day for 3 months	Assessed before and after treatment: EDOF-HC protocol, xerostomia questionnaire, quantitative sensory testing	No side effects reported	All groups showed improvement, but without differences between the groups
(López-Jornet et al., 2013)	Double-blind, placebo-controlled randomized trial	Group 1 = tongue protector alone, 3×/day ($n = 25$); Group 2 = protector + .5 mL of *Aloe vera* 70% ($n = 25$) Group 3 = tongue protector + placebo ($n = 25$)	VAS (0 and after 12 weeks)	No side effects reported	All groups showed improvement, but without differences between the groups
(Spanemberg et al., 2012)	Double-blind, placebo-controlled randomized clinical trial	Group 1 = herbal drug Catuama (310 mg) $n = 30$ Group 2 = placebo (lactose) $n = 30$ 2×/day for 8 weeks	VAS (4, 8, and 12 weeks)	Drowsiness and weight gain (1), insomnia (1)	Herbal drug Catuama was statistically superior to placebo
(Silvestre et al., 2012)	Prospective double-blind, placebo-controlled randomized trial	Group 1 = oral rinse with 0.02% of capsaicin ($n = 23$) Group 2 = placebo ($n = 23$) (administered 3×/day for 30 s at volumes of 15 ml)	VAS = in the morning, before starting treatment; in the afternoon on the first day of treatment; and at the end of week	Burning sensation after using the substance (2)	Capsaicin was statistically superior to placebo
(Sardella et al., 2008)	Double-blind, placebo-controlled randomized trial	Group 1 = *Hypericum perforatum* extract 300 mg 3×/day for 12 weeks ($n = 19$) Group 2 = placebo ($n = 20$)	VAS (0, 4, 8, and 12 weeks), number and location of burning areas	Headache (1)	Both groups showed improvement, but without differences between the groups

VAS visual analog scale

Table 4 Treatment of burning mouth syndrome: analgesic and anti-inflammatory agents

Author, year	Methodological characteristics	Treatment	Assessment method	Side effects	Main findings
(Treldal et al., 2016)	Double-blind, placebo-controlled crossover randomized trial	Group 1 = Bupivacaine lozenges 5 mg Group 2 = Placebo 3×/day for 2 weeks (n = 15)	VAS daily during treatment	Burning sensation (eight with bupivacaine and five with placebo)	Bupivacaine lozenges showed a statistically significant reduction of symptoms compared to placebo
(Grémeau-Richard et al., 2010)	Double-blind, placebo-controlled randomized trial	Group 1 = topical anesthesia with lidocaine n = 20 Group 2 = placebo n = 20	VAS at baseline, 1 week and 3 weeks	No side effects reported	There was no significant improvement
(Toida et al., 2009)	Randomized clinical trial	Group 1 = oral Lafutidine 10 mg 2×/day + gargling with azulene 4% at concentrations of 2–4 ml in 60 ml of water (n = 34) 4×/day Group 2 = control = H2RA + gargling (n = 30), both for 12 weeks	VAS (1, 2, 4, 8, and 12 weeks)	Minimal symptoms in two patients from the study group	Lafutidine 10 mg was statistically superior to placebo
(Sardella et al., 1999)	Double-blind, placebo-controlled randomized trial	Group 1 = benzydamine hydrochloride 0.15% oral rinse 3×/day for 4 weeks, 15 ml for 1 min (n = 10) Group 2 = placebo (n = 10); Group 3 = no treatment (n = 10)	VAS at the beginning and end of study	No side effects reported	There was no significant improvement

VAS visual analog scale

side effects were reported for lidocaine [30]. Of the effects reported, none resulted in treatment abandonment. In this subcategory, 5 mg bupivacaine lozenges and Lafutidine 10 mg were statistically superior to placebo in symptom improvement [29, 31]. Conversely, topical anesthesia with lidocaine and oral rinsing with Benzydamine hydrochloride 0.15% did not show significant results with regard to BMS symptom improvement [30, 32].

Non-pharmacological therapies

The remainder of the papers that tested treatments for BMS used strategies categorized as non-pharmacological, i.e., that did not fit any of the preceding subcategories. A total of seven papers were included in this group (Table 5), being two already present in other categories [10, 24]. In these papers, five different therapies were identified, namely laser techniques [25, 33], repetitive transcranial magnetic stimulation (rTMS) [34], acupuncture [10], use of tongue protectors [24, 35], and psychotherapy [36]. Of these seven papers, only the one using rTMS reported side effects: 12 patients complained of headache at the beginning of the study. In the other studies, no side effects were reported.

With regard to treatment results, three papers observed statistically significant improvement with the strategy tested when compared to placebo, namely the ones using rTMS [34], laser techniques (infrared and red) [25], and tongue protector [35]. Acupuncture [10], use of tongue protector associated or not with *Aloe Vera* 70% [24], and use of infrared laser [33] showed symptom improvement, however, without statistically significant differences in relation to the control groups. No symptom improvement was found with psychotherapy [36].

Analysis of biases

In the study quality analysis, all studies mentioned randomization: Nine informed that patients were randomly allocated but did not inform how this was accomplished; the other 20 specified the method employed (computer software, web sites, or list of numbers). Also, most studies reported patient blinding, offering similar formulations (similar appearance and administration) to both the experimental group and that taking the placebo. However, we also found studies in which patient blinding was not a concern, especially when therapies involved personal interventions or combined treatments. Conversely, with regard to examiner blinding, most studies did not report or specify how this was achieved, and only 12 papers detailed the process (Table 6). Due to the great heterogeneity of the studies included, it was not possible to conduct a meta-analysis.

Table 5 Treatment of burning mouth syndrome: non-pharmacological treatment

Author, year	Methodological characteristics	Treatment	Assessment method	Side effects	Main findings
(Umezaki et al., 2016)	Blind, placebo-controlled randomized trial	Group 1 = Repetitive transcranial magnetic stimulation ($n = 12$) Group 2 = Placebo ($n = 8$), daily for 14 days	VAS during 14 days of treatment and after 15, 30, 60 days	Twelve patients reported headache at the beginning of the study	There was significant pain reduction after 1 week of treatment in the study group, but not in the control group
(Sugaya et al., 2016)	Double-blind, placebo-controlled randomized trial	Group 1 = infrared laser 2×/week for 2 weeks ($n = 13$) Group 2 = control ($n = 10$)	VAS before and 15 min after each irradiation, and at control times: 7, 14, 30, 60, and 90 days after the last irradiation	No side effects reported	Both groups showed improvement, but without differences between the groups
(Spanemberg et al., 2015)	Placebo-controlled randomized clinical trial	Group 1 = infrared laser 1×/week for 10 weeks ($n = 20$) Group 2 = infrared laser 3×/week for 3 weeks ($n = 20$) Group 3 = red laser 3×/week for 3 weeks ($n = 19$) Group 4 = placebo 3×/week for 3 weeks ($n = 19$)	VAS at each session and after 8 weeks of treatment	No side effects reported	All therapies showed significant reduction of symptoms compared to placebo
(Kvesic et al., 2015)	Randomized clinical trial	Group 1 = clonazepam (0.5 mg) $n = 22$ (2 first weeks 1×/day, 2 last week's 2×/day) Group 2 = acupuncture $n = 20$ (1×/week for 4 weeks)	VAS (before treatment and after 4 weeks)	Five patients in the clonazepam group reported side effects (drowsiness, dizziness, and nausea). None of the patients in the acupuncture group reported side effects	Improvement observed with both treatments. No significant differences between the groups
(López-Jornet et al., 2013)	Double-blind, placebo-controlled randomized trial	Group 1 = tongue protector alone, 3×/day ($n = 25$) Group 2 = protector + 0.5 mL of aloe vera 70% ($n = 25$) Group 3 = tongue protector + placebo ($n = 25$)	VAS (0 and after 12 weeks)	No side effects reported	All groups showed improvement, but without differences between the groups
(López-Jornet et al., 2011)	Prospective randomized clinical trial	Group 1 + tongue protector + information $n = 25$ Group 2 = information only $n = 25$	VAS - Beginning of treatment and after 2 months	No side effects reported.	Use of tongue protector was statistically superior to placebo.
(Miziara et al., 2009)	Placebo-controlled randomized clinical trial	Group 1 = placebo $n = 20$ Group 2 = group psychotherapy $n = 24$ (1×/week for 3 months)	Short McGill pain questionnaire	No side effects reported	There was no significant improvement

VAS visual analog scale

Table 6 Analysis of biases

	Author, year	Selection (randomization)	Blinding (treatment/patients)	Blinding (assessment/ research examiner)	Statistical tests
Antidepressants	Kvesic et al., 2015	Yes (coin)	No	No	Student's *t* test and Pearson correlation test
	Heckmann et al., 2012	Yes (software)	Yes (same presentation as placebo)	No	Descriptive statistics (mean and standard deviation)
	Campillo et al., 2010	Yes (number table)	Yes (same presentation as placebo)	Yes	Chi-square test
	Gremeau-Richard et al., 2004	Yes (only mentions randomization)	Yes (same presentation as placebo)	Yes	Bilateral Mann-Whitney test
	Maina et al., 2002	Yes (only mentions randomization)	No (patients knew they were in different groups due to the different medication dose)	No	ANOVA
	Tammiala-Salonen and Forssell, 1999	Yes (blocks)	Yes (same presentation as placebo)	Yes	Fisher
Alpha-lipoic acid	Palacios-Sánchez et al., 2015	Yes (list divided into two groups)	Yes (same presentation as placebo)	Yes	Contingency tables and Pearson chi-square test
	López-D'alessandro and Escovich, 2011	Yes (does not inform how)	Yes (same presentation as placebo)	Yes	Chi-square test and odds ratio
	Marino et al., 2010	Yes (computer-generated random number tables)	No (different doses between t he groups)	No	Wilcoxon
	Cavalcanti and da Silveira, 2009	Yes (software)	Yes (same presentation as placebo)	Yes	Paired *t* test and *t* test
	López-Jornet et al., 2009	Yes (randomization table)	Yes (same presentation as placebo)	Yes	Student's *t* test
	Carbone et al., 2009	Yes (software)	Yes (same presentation as placebo)	Yes	Kruskal-Wallis test
	Femiano and Scully, 2002	Yes (does not inform how)	Yes (same presentation as placebo)	No	Does not inform what tests were used
Phytotherapeutic agents	Valenzuela et al., 2016	Yes (randomization web site)	Yes (same presentation as placebo)	Yes	Student's *t* test
	Cano-Carrillo et al., 2014	Yes (randomization web site)	Yes (same presentation as placebo)	Yes	Shapiro-Wilk test
	da Silva et al., 2014	Yes (does not inform how)	Yes (same presentation as placebo)	Yes	Pearson chi-square or Mann-Whitney *U* test
	López-Jornet et al., 2013	Yes (random numbers in Excel by a third party)	No (different treatments between the groups)	Yes	Pearson chi-square test or Kruskal-Wallis test
	Spanemberg et al., 2012	Yes (does not inform how)	Yes (same presentation as placebo)	Yes	Bonferroni test
	Silvestre et al., 2012	Yes (does not inform how)	Yes (same presentation as placebo)	Yes	Wilcoxon test
	Sardella et al., 2008	Yes (randomization web site)	Yes (same presentation as placebo)	Yes	Mann-Whitney *U* test
Analgesic and anti-inflammatory agents	Treldal et al., 2016	Yes (software)	Yes	Yes	Paired *t* test
	Grémeau-Richard et al., 2010	Yes (does not inform how)	No	Yes	Paired *t* test, chi-square analysis or Fisher exact test
	Toida et al., 2009	Yes (does not inform how)	Yes	No	Pearson chi-square test and Fisher exact test

Table 6 (continued)

	Author, year	Selection (randomization)	Blinding (treatment/patients)	Blinding (assessment/ research examiner)	Statistical tests
Non-pharmacological treatment	Sardella et al., 1999	Yes (number list)	No	Yes	Kruskal-Wallis
	Sugaya et al., 2016	Yes (software)	Yes	Yes	Fisher exact test
	Umezaki et al., 2016	Yes (randomization web site)	Yes	No	ANOVA
	Spanemberg et al., 2015	Yes (does not inform how)	Yes	No	ANOVA
	López-Jornet et al., 2011	Yes (randomization web site)	No	No	Student's *t* test
	Míziara et al., 2009	Yes (does not inform how)	No	No	Chi-square test

Discussion

BMS remains poorly understood with regard to both its etiology and treatment. It is described as the presence of chronic orofacial pain in the absence of any detectable injury in the patient's oral mucosa [1]. Several factors have been suggested as possible causes of BMS, including local, systemic, and psychological characteristics [1, 3]; even risk factors have been researched to try to understand patients with BSM [37]. Because a well-defined etiology is lacking, a number of diverse treatments have been proposed in the literature to deal with this condition. However, such therapies do not always take into consideration the possible causes of burning in the oral cavity. Moreover, a totally effective protocol for the treatment of BMS is not currently available.

In the present review, we divided therapies into five categories. In the antidepressant category, we found reports on the use of both systemic clonazepam [9, 10] and topical clonazepam [11, 12]. Clonazepam is a benzodiazepine and an agonist for gamma-aminobutyric acid (GABA) receptors; this receptor is widely distributed in the central nervous system and also along the peripheral tissues, and this medication, acting in this receptor, can present good results in the treatment of this syndrome [11]. Used systemically, clonazepam causes inhibition of the central nervous system as a result of its anticonvulsive action, leading to sedation, muscle relaxation, and tranquilization [38]. Used topically, clonazepam has been shown to reduce BMS symptoms without the adverse effects associated with systemic use [11, 12]. Therefore, topical use of clonazepam seems to be a promising alternative for the treatment of BMS. More studies, with larger samples and longer follow-up times, are required to confirm these preliminary findings.

Drugs such as amisulpride (50 mg/day), paroxetine (20 mg/day), and sertraline hydrochloride (50 mg/day) have also been reported to improve symptoms in BMS—paroxetine and sertraline hydrochloride are selective serotonin reuptake inhibitors [14]. This category not only presented positive results but also showed the highest number of adverse effects, including dizziness, insomnia, nausea, and drowsiness [10–14]. The occurrence of side effects should be taken into consideration when prescribing these drugs, especially because of their systemic administration, which may bring other problems to the patient.

As previously mentioned, ALA is produced in the human body at small amounts; its presence is essential to the functioning of different oxidative enzymes involved in metabolism [15, 16]. ALA works as a coenzyme, producing energy (adenosine triphosphate (ATP)) and improving glucose metabolism. Moreover, ALA seems to stimulate the production of nerve growth factor (NGF) and has been used in the treatment of diabetic neuropathy [39]. Another mechanism of action of ALA reported in the literature is the increase in cellular levels

of glutathione, which when low can cause oxidative stress, inflammation, and damage to the nerves, leading to peripheral neuropathy; thus, ALA is beneficial in this supplementation [40, 41]. ALA was tested in seven of the papers included in the present review, and all of them, except one [19], found positive results. Cavalcanti and da Silveira, and Carbone et al. compared ALA with placebo and found improvement, however, without differences between the groups, suggesting that psychological aspects of patients with BMS should be taken into consideration. The other papers tested ALA vs. placebo but included other experimental groups, using, e.g., GABA [17] and capsaicin [42], all with positive results. In the study by [18], treatment was maintained for 1 month only (compared to 2 months in all other papers). However, differences in treatment duration do not seem to have an influence on treatment outcomes, as the only study that did not find positive effects of ALA in the treatment of BMS [19] used the standard 2-month protocol [42]. Considering that ALA presented results superior to placebo in only four of the seven studies, its efficacy is still controversial. More studies, with longer follow-up, could shed more light on its efficacy.

The use of phytotherapeutic agents for medical purposes is a millennium-old practice. Phytotherapy or herbal medicine, derived from popular knowledge, has been increasingly investigated to confirm the beneficial effects of the substances employed. In our literature review, seven papers were found in this segment, testing different protocols; all seven reported positive results, with symptom improvement. Again, it should be taken into consideration that five papers described symptom improvement [21–24, 27], but one of them also observed improvement in the placebo group. Once again, these results reinforce the importance of looking into psychological characteristics of patients with BMS. Treatments with the herbal drug Catuama 310 mg [28] and capsaicin 0.02% oral rinse [26] yielded positive results in improving BMS symptoms when compared to placebo, suggesting that these potential therapies should be studied in more detail. One last aspect that favors the potential use of phytotherapy in BMS is the virtual absence of side effects.

In our review, laser therapy emerged as a non-pharmacological treatment option. Low-intensity laser radiation is used due to its capacity to modulate metabolic, biochemical, and photophysical processes that transform laser light into energy that is useful to cells. The energy provokes mitochondrial reactions and increases in ATP production, intracellular calcium levels, and number of mitoses. The analgesic, anti-inflammatory, and tissue repair properties of low-intensity laser radiation are consensual. In BMS, laser therapy seems to have a positive effect only if used more frequently, i.e., three times weekly for 3 weeks [25, 33]—studies with shorter treatment durations failed to find results superior to placebo. The analgesic action of laser therapy is related to the inhibition of pain mediators and the increase of the cell membrane potential, reducing the speed of conduction of the nerve impulse [43, 44], and this may be the explanation for the results found for this treatment.

Several treatment modalities were found in the literature for BMS, but very few were tested in more than one randomized clinical trial with a control group; this scarcity of clinical trials prevents the comparison of results. Therapies involving psychotherapy [36], topical anesthesia with lidocaine [30], and benzydamine hydrochloride 0.15% oral rinse [32] failed to obtain significant results. This scenario underscores the need to investigate the effectiveness of a multidisciplinary treatment approach to patients with BMS. Some of the therapies described in the papers showed positive results, e.g., the use of 5 mg bupivacaine lozenges three times daily for 2 weeks [29] and rTMS daily for 14 days [34]. Both therapies were associated with statistically significant symptom reductions compared to placebo; however, some patients reported side effects such as burning sensation after the use of lozenges and headache after rTMS sessions. Therefore, even though these therapies were associated with symptom improvement, the occurrence of side effects urges them to be better evaluated before being indicated.

An important point to be considered is the improvement of the symptoms reported by the patients under placebo treatment. In our review, seven articles fit into this situation [11, 13, 18, 19, 25, 31, 33], where placebo treatment showed improvement of symptoms even though it was not statistically significant, thus showing that psychological factors may be related to BMS pathogenesis. The articles reported the exclusion of patients with other alterations (systemic or psychological), which leads us to suggest that to be under a clinical follow-up already is beneficial for BMS patients. However, we can not only focus on psychological treatment, since in the study where the efficacy of psychotherapy was evaluated solely [36], no promising results were found either. Therefore, we can suggest that combined therapies be used, taking into account the symptoms and psychological aspects of the patients.

In summary, assessment of the papers included in the present review revealed that, in addition to the difficulties involved in diagnosing BMS, major difficulties are also present in treatment decision-making. Initially, more research is warranted to improve our understanding of the etiology of this syndrome, up to possible genetic polymorphisms have been studied to try to understand the mechanisms of the BMS, without success [45]. In the papers here reviewed, patients with disorders other than true BMS were excluded. Another important point is the assessment of treatment duration and follow-up time: The syndrome has continuous, long-lasting symptoms, and treatment should be long enough and last for at least 2 months, as most papers propose. Finally, more studies, with larger samples, are necessary to further assess existing therapies, testing each of the protocols in randomized clinical trials with control groups and adequate blinding.

Final remarks

Several treatment modalities are available for BMS, but none is totally satisfactory from the point of view of evidence-based research, given the heterogeneity of the studies and therapies employed. The use of Clonazepan and ALA was the only tested in more than two studies and showed promising results, but more studies, with larger samples, are necessary before we can have a first-line treatment strategy for patients with BMS. Also, it is important to point out that in some studies, both the therapies assessed and placebo showed similar results. This underscores the need to look into psychological and/or psychiatric characteristics of the patients, possibly requiring a multidisciplinary approach to the treatment of BMS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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