# Effectiveness of Nonpharmacologic Treatments of Burning Mouth Syndrome: A Systematic Review

**Marco Cabras, DDS, MSc**
**Alessio Gambino, DDS, MSc, PhD**
**Roberto Broccoletti, DDS, MSc**
**Simona De Paola, DH**
Department of Surgical Sciences
Oral Medicine Section
CIR Dental School
University of Turin
Turin, Italy

**Savino Sciascia, MD, PhD**
Department of Clinical and Biological Sciences
Center of Research of Immunopathology and Rare Diseases
Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley
University of Turin
Turin, Italy

**Paolo G. Arduino, DDS, MSc, PhD**
Department of Surgical Sciences
Oral Medicine Section
CIR Dental School, University of Turin
Turin, Italy

**Correspondence to:**
Dr Marco Cabras
Department of Surgical Sciences; CIR Dental School
School of Medicine, University of Turin
Oral Medicine Unit, Via Nizza 230
I-10126 Turin, Italy
Fax: +39011618639
Email: cabrasmarco300@gmail.com

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**Aims:** To assess the efficacy of nonpharmacologic treatments for burning mouth syndrome (BMS). **Methods:** PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials were systematically searched. Reference lists from the latest systematic reviews (2015 to 2020) on BMS treatment in the PubMed, Scopus, Web of Science, and Cochrane Library databases were also scrutinized. Randomized controlled trials (RCTs) or clinical controlled trials (CCTs) in English were considered eligible. Trials on photobiomodulation were excluded to avoid redundancy with recent publications. Risk of bias was established through the Cochrane Risk of Bias tool for RCTs and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for CCTs. **Results:** This review included 27 RCTs and 6 open clinical trials (OCTs) describing 14 different nonpharmacologic interventions. Eleven trials experimented with 600 to 800 mg/day of alpha-lipoic acid for 30 to 120 days, with 7 placebo-controlled studies showing significant pain relief. Four trials tested topical and systemic capsaicin for 7 to 30 days, with 2 placebo-controlled studies revealing significant efficacy. Four of the 5 trials testing acupuncture offered favorable evidence of pain relief. Two trials reported significant pain relief after a 2- to 3-month regimen with tongue protectors and showed no difference after aloe vera addition. Short-term pain relief was reported in anecdotal placebo-controlled trials deploying tocopherol, catuama, ultramicronized palmitoylethanolamide, group psychotherapy, cognitive therapy, and repetitive transcranial magnetic stimulation of the prefrontal cortex. Most therapies were safe. **Conclusion:** Evidence was collected from highly biased, short-term, heterogenous studies mainly focused on BMS-related pain, with scarce data on quality of life, psychologic status, dysgeusia, and xerostomia. Long-term effectiveness of nonpharmacologic treatments should be further investigated, with a more rigorous, bias-proof study design. *J Oral Facial Pain Headache 2021;35:175–198. doi: 10.11607/ofph.2868*

**Keywords:** *alternative medicine, burning mouth syndrome, clinical trials, non-pharmacological, treatment*

With its first descriptions dating back to the 19th century—of "stomadodynia," "glossalgia," or "lingual neuralgia" as recurrent sensations of intraoral burning without any visible oral lesions[1]—what is today known as burning mouth syndrome (BMS) has fascinated clinicians and publishing authors ever since. Many classifications have been proposed over the last decades,[2,3] with the latest by the International Classification of Orofacial Pain in 2020[4] defining BMS as an idiopathic orofacial pain causing intraoral burning or dysesthetic sensation, recurring for more than 2 hours per day over more than 3 months, with no sign of oral disorder. If such a pattern is unique, BMS is defined as BMS with no somatosensory changes in order to distinguish it from an alternative subtype (BMS with somatosensory changes), where the aforementioned idiopathic orofacial pain/burning is accompanied by somatosensory changes (from hyperesthesia/hypoalgesia to hyperalgesia/allodynia) detectable through qualitative and/or quantitative somatosensory testing.[4]

The prevalence of BMS varies widely in the literature, from 0.01% to 40%,[5] although a more plausible range might be 1% to 3.7%,[5] with

a significant predilection for postmenopausal women of 60 years or older and a female to male ratio of 5–7:1.[6]

Despite the idiopathic nature of BMS, many studies have focused on its association with psychosocial disorders, especially depression and anxiety,[7,8] which are also elicited by endocrinologic and immunologic shifts of the postmenopausal period.[9] However, since the late 1980s, novel evidence has been accumulated on peripheral and/or central neuropathic events,[10–12] which redefined BMS as a multifactorial clinical entity triggered by psychosocial, endocrinologic, and neuropathic factors.[13]

Clinical features are typically variable, leading some authors to question the appropriateness of the "syndrome" aspect of BMS, suggesting that there may be instead a more appropriate term, such as "disorder."[14]

Burning is very often a nonexhaustive term, with other coexisting sensations described as "tingling," "itchy," "scalding," or "numb."[5,6] Furthermore, up to two-thirds of BMS patients also complain of xerostomia and dysgeusia, with the former being only recently associated with evidence of decreased unstimulated salivary flow,[15,16] and the latter being variously described as a stronger perception of bitter and sour flavors, a weaker perception of sweet flavor, a stronger or weaker perception of salty flavor, or a phantom taste sensation.[3–6]

Localization can be either circumscribed to the anterior two-thirds of the tongue, particularly the tip, or instead widespread to the lips, anterior palate, floor of the mouth, and, less frequently, the gums and pharynx.[3,5]

Diagnosis of BMS can be achieved only after a process of exclusion. Clinical oral examination confirming the absence of any oral mucosal lesion or intraoral disorder is the first step of a multi-step process that aims to progressively rule out any other local or systemic cause, such as underlying hematinic deficiencies, unidentified allergies to dental materials, latent psychiatric disorders, or somatosensory abnormalities.[5,6,13]

Several treatment protocols have been proposed for BMS with the aim of alleviating symptoms and improving the quality of life (QoL) of affected patients, and effects on the psychologic profile have been investigated—however, the overall evidence is poor, preventing the formulation of standardized guidelines, as pointed out in many recent systematic reviews.[17–19] In addition, as appropriately underlined in a recent critical review,[20] pharmacologic approaches should be cautiously evaluated, since BMS patients are often elderly individuals exposed to concurrent drug regimens and are thus more susceptible to severe drug adverse effects or even to a higher risk of drug addiction.

As, to the present authors' knowledge, none of the many systematic reviews published in the literature are focused on nonpharmacologic management alone, the aim of this systematic review was to assess the reliability and effectiveness of specific groups of alternative treatments for BMS.

## Materials and Methods

### PICO Question

The protocol for this systematic review, containing eligibility criteria, search strategy, and outcomes, was developed and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020205116). The PICO (patient, intervention, control, outcome) question, based on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) criteria,[21] was: In human patients affected by BMS, what is the effectiveness of nonpharmacologic treatments compared to other pharmacologic protocols, placebo, or no treatment in terms of reduction of oral pain, dysgeusia, and xerostomia?

Since two systematic reviews with meta-analyses on the effectiveness of low-level laser therapy/photobiomodulation (LLLT/PBM) were published in July 2020,[22,23] laser treatment was excluded from the scope of the present review in order to avoid redundancy of published data.

The PICO question was then formulated as follows:

- P: Adult patients affected by BMS
- I: Any kind of treatment not including administration of drugs or a drug-derived regimen (alpha-lipoic acid [ALA], vitamin supplementation, herbal treatments, acupuncture, homeopathy, tongue protectors, placebo, or others, with the exclusion of LLLT/PBM)
- C: Pharmacologic or nonpharmacologic treatment, placebo, or no treatment, with the exclusion of LLLT/PBM
- O: Effectiveness in terms of reduction of pain/burning, dysgeusia, and xerostomia (primary); effectiveness on psychologic well-being and/or quality of life (QoL; secondary)

### Search Strategy

A systematic search strategy for eligible studies was carried out in PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The latest electronic search was conducted on August 23, 2020. No restrictions were applied regarding year of publication, and no language restriction was applied for this first phase of study selection. The following 14 search strings were launched in each of the four electronic databases: burning mouth syndrome AND alpha lipoic

acid; burning mouth syndrome AND vitamins; burning mouth syndrome AND vitamin supplement; burning mouth syndrome AND herbal medicine; burning mouth syndrome AND herbs; burning mouth syndrome AND lycopene; burning mouth syndrome AND aloe vera; burning mouth syndrome AND capsaicin; burning mouth syndrome AND homeopathy; burning mouth syndrome AND placebo; burning mouth syndrome AND cognitive therapy; burning mouth syndrome AND psychotherapy; burning mouth syndrome AND transcranial stimulation; burning mouth syndrome AND acupuncture; and burning mouth syndrome AND tongue protector.

After the conclusion of this research, a second electronic search of systematic reviews was carried out. The search string "burning mouth syndrome AND treatment" was launched in PubMed, Scopus, Web of Science, and Cochrane library, with the following additional filters:

- Article type: systematic review
- Language: English
- Publication date: 5 years (from January 1, 2015, to August 18, 2020)
- Topic: BMS treatment (with the exclusion of reviews solely focused on LLLT/PBM)

The full texts of the reviews responding to these criteria were then acquired and read, and the reference lists were scrutinized in order to extrapolate additional trials on nonpharmacologic BMS treatments that may have eluded the first electronic search.

### Eligibility Criteria

The inclusion criteria were the following: randomized controlled trials (RCTs); controlled clinical trials (CCTs) or open clinical trials (OCTs); written in English; conducted in human adult (> 18 years of age) patients diagnosed with BMS; and testing the effectiveness of any nonpharmacologic treatment apart from LLLT/PBM against any kind of pharmacologic or nonpharmacologic treatment, placebo, or no treatment.

Exclusion criteria were the following: RCTs and CCTs focusing on LLLT/PBM as the main intervention/comparison against BMS; case reports, case series, observational, prospective, or retrospective studies sharing the same scope as the one demanded for RCTs and CCTs; articles published in languages other than English; articles focused on nonhuman patients; and nonrelevant articles addressing other aspects of BMS, such as etiopathogenesis, epidemiology, clinical features, and diagnosis.

### Study Selection

Two reviewers (M.C., P.G.A.) independently outlined the titles and abstracts of the publications generated by the search strategy. A first reading of titles and abstracts allowed the exclusion of irrelevant studies and studies in languages other than English. If an abstract was unable to provide enough information, the full text was retrieved. Disagreements were resolved through consultation with two other reviewers (R.B. and A.G.).

### Data Extraction and Quality Assessment

The following data were extracted from each study: first author/year; study design; main characteristics of the sample, such as number of patients, mean age, and male to female ratio; definition of BMS; type, dose and duration of nonpharmacologic intervention; type, dose, and duration of the comparison treatment; scores/outcomes used; and main clinical and/or statistical outcomes.

Risk of bias was evaluated using the Rob-2 (Cochrane Risk of Bias)[24] tool for RCTs and the ROBINS-I tool (Risk of Bias in Nonrandomized Studies of Interventions)[25] for OCTs.

## Results

### Study Selection

The results of the literature search are presented in a PRISMA flow diagram (Fig 1). After removal of 962 duplicates, 544 records remained. Title and abstract reading led to the exclusion of 489 records, of which 42 were not published in English. The remaining 55 articles were analyzed through full-text reading: of these, 22 were excluded based on study design (11 case reports, 6 case series, 4 retrospective studies, and 1 comparative study), and so 6 OCTs and 27 RCTs/CCTs were included in the qualitative synthesis.

The electronic search for systematic reviews on BMS treatments published in English, from January 1, 2015, to August 18, 2020, led to 129 records, of which 42 were duplicates and 76 were irrelevant (Fig 1). The full texts of the remaining 11 systematic reviews were retrieved and read, and reference lists were crosschecked with the results of the previous electronic search. No further trial, either CCT or RCT, was added to the qualitative synthesis, since the trials reported in the included systematic reviews were already integrated in the previous electronic search.

### Descriptive Synthesis

A total of 14 nonpharmacologic interventions for BMS were described in the 27 RCTs and 6 OCTs included.[26–61] They were collected in five groups: *(1)* natural antioxidants; *(2)* natural treatments; *(3)* acupuncture; *(4)* neuropsychologic approaches; and *(5)* physical barriers. Due to vast heterogeneity among the studies, no quantitative synthesis was performed. Instead, a narrative description is provided (Tables 1 to 5).

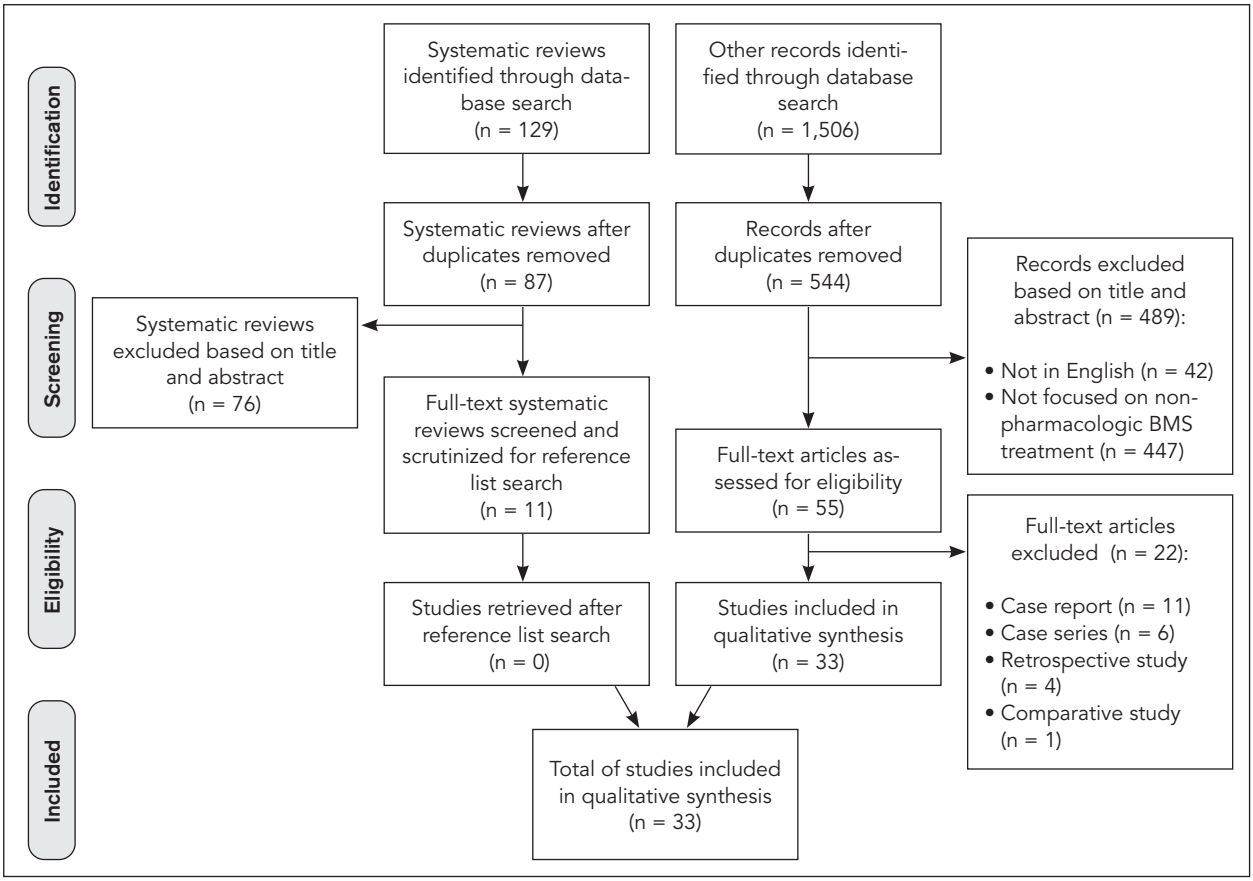


**Fig 1** PRISMA flowchart of study inclusion.

## Natural Antioxidants

***Alpha-lipoic acid.*** Alpha-lipoic acid (ALA), a natural antioxidant that increases the production of nerve growth factor, is the most commonly investigated natural agent for treatment of BMS. Eleven articles (10 RCTs and 1 OCT) were published between 2000 and 2018 describing it as a possible remedy for BMS (Table 1).[26–36] The total combined sample was 864 patients, of which 70.7% were women. The size of the samples varied widely, from 38[31] to 192[29] patients, with mean ages from 42[36] to 67[30] years.

The inclusion criteria for enrollment of BMS patients were overall aligned, with patients considered eligible in the absence of any local and/or systemic disease, oral lesions, and/or salivary laboratory abnormalities. The duration of BMS symptoms was often expressed as an additional eligibility criterion, although it varied from a minimum of 2 to 3 months[28,29,32] up to 4 to 6 months.[30–33,35]

ALA was administered mostly as a 600 mg/day regimen,[26–29,31,34–36] with only 3 studies scheduling an administration of 800 mg/day.[30,32,33] In 2 studies, ALA administration was enriched with lycopene and green tea extract.[32,35]

The duration of treatment was mostly 2 months,[27–30,32–35] with only 2 studies opting for a 30-day regimen[26,31] and 1 article extending treatment to 4 months.[36]

Ten of the 11 trials were placebo controlled and showed encouraging effectiveness of ALA when compared to placebo, with 7 studies revealing statistically significant improvement of symptoms.[26–29,33–35] Three studies experienced no significant differences.[30–32]

However, a variety of outcome measurements were adopted, ranging from symptomatology scales of unclear recording,[26,27] to "–/+" visual analog scale (VAS),[28] to either 0–3[29] or 0–4[34] numeric scales, to the standardized VAS.[30–33,35]

ALA was also tested against other treatments, showing higher effectiveness than bethanecol and lactoperoxidase in one trial[27] (as expected in a dis-

**Table 1 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Natural Antioxidants for BMS**

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/ no treatment protocol | Score/ outcome | Main results |
|---|---|---|---|---|---|---|---|
| *ALA* | | | | | | | |
| Femiano et al, 2000[26] | RCT | 42 patients (32 F, 10 M)<br>Mean age: 63 (43–78) y | No signs of oral lesions<br>Normal salivary secretion (> 15 mL/ 15 min unstimulated; > 1 mL/min after 5% citric acid stimulation)<br>Normal lab results | Group 1 (n = 21): ALA 600 mg/d for 20 d, followed by 200 mg/d for 10 d | Group 2 (n = 21): placebo (cellulose starch 100 mg/d for 30 d)<br>Then crossover with ALA treatment for 30 d | Evaluation after 30 d with a nonspecific scale (worsening; unchanged; slight improvement; decided improvement; resolution) | "Any improvement" in 76% of treatment group vs 14% of placebo group ($P < .0001$); 63% reported "any improvement" after crossover for placebo group |
| Femiano, 2002[27] | RCT | 80 patients (48 F, 32 M)<br>Mean age: 63 (30–74) y | No oral lesions<br>Normal salivary secretion<br>Normal lab tests<br>No clinical or laboratory evidence of organic disease | Group 3 (n = 20): ALA 600 mg/d for 2 mo | Group 1 (n = 20): betanechol 15 mg/d between meals for 2 mo<br>Group 2 (n = 20): lactoperoxidase (Biotene) 5–6 times/daily for 2 mo<br>Group 4 (n = 20): placebo (xylitol 3% in distilled water) | Unspecific scale (worsening; unchanged; slight improvement; decided improvement; resolution) assessed weekly | Significant improvements from ALA (90%) compared to bethanecol (10%), lactoperoxidase (0%), and placebo (0%) |
| Femiano and Scully, 2002[28] | RCT | 60 patients (42 F, 18 M)<br>Mean age: 45 (22–68) y | History of oral discomfort > 2 mo<br>No drug/medication history<br>No oral lesions<br>Normal lab tests (folate, B12, ferritin, glucose, thyroid hormone) | Group 1 (n = 30): ALA 600 mg/d for 2 mo | Group 2 (n = 30): placebo cellulose starch 300 mg/d for 2 mo | Unspecific scale (worsening; unchanged; slight improvement; decided improvement; resolution) at 2 mo and 12 mo | Significant ($P = .0001$) improvement in ALA (97%) vs placebo (40%) at 2 mo<br>Significant ($P < .0001$) deterioration in placebo (83%) vs ALA (17%) |

order where xerostomia and hyposalivation are usually indicated as associated features) and a similar effectiveness to capsaicin, a natural remedy similarly equipped against several neuropathic disorders.[28]

On the other hand, in the only non–placebo-controlled trial, ALA did not provide a significant decrease in VAS score when compared to pregabalin and clonazepam.[36] Interestingly, when combined with either gabapentin or cognitive behavioral therapy, ALA displayed an even greater symptom improvement than ALA alone.[29,34]

**Table 1 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Natural Antioxidants for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/ no treatment protocol | Score/ outcome | Main results |
|---|---|---|---|---|---|---|---|
| Femiano et al, 2004[29] | CCT | 192 patients (104 F, 88 M)<br><br>Mean age: 48 (24–67) y | History of oral discomfort: 2–48 mo (mean: 22 mo)<br><br>No history or examination suggestive of oral lesions<br><br>Normal lab test (CBC, B12, SGOT, SGPT, ANA, ENA, IgE, folate, glycemia)<br><br>No medical/ drug history<br><br>No abnormal sialometry | Group B (n = 48): 600 mg/d ALA for 2 mo | Group A (n = 48): CBT 1 h/wk for 2 mo<br><br>Group C: CBT+ALA 600 mg/d for 2 mo<br><br>Group D: placebo cellulose starch 300 mg/d for 2 mo | VATS: Negative changes: worsening Positive changes: 1 grade = slight improvement; 2 grade = decided improvement; 3 grade = resolution | Significant ($P$ < .0005) improvement in ALA (81%), CPT alone (40%), and ALA + CPT (90%) vs placebo (13%) |
| Carbone et al, 2009[30] | RCT | 66 patients (54 F, 12 M); 52 patients completed trial<br><br>Mean age of the 52 patients: 67.3 ± 11.9 y | Continuous, intraoral pain for > 4 mo with normal clinical examination<br><br>Normal lab test (CBC, iron, ferritine, folate, B12, glucose) | Group 1 (n = 22): ALA 800 mg/d for 8 wks<br><br>Group 2 (n = 22): ALA + vitamins 800 mg/d for 8 wks | Group 3: placebo (dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, silicon dioxide, vegetable magnesium stearate, shellac, and stearic acid), 1 pill for 8 wks | VAS and McGill Pain Questionnaire at beginning of therapy (T0), 2 wks (T1), 4 wks (T2), 8 wks (T3), 2 mo after end of treatment (T4) | No significant differences |
| Cavalcanti and da Silveira, 2009[31] | RCT | 38 patients (34 F, 4 M)<br><br>Mean age: 63.1 (36–78) y | Intraoral burning pain for > 6 mo<br><br>Normal appearance of oral mucosa<br><br>Normal salivary flow rate (≥ 0.1 mL/min)<br><br>Absence of *Candida* spp. through exfoliative cytology<br><br>Normal lab tests (CBC, glucose, iron, ferritin, B12, folate) | Group 1 (n = 19; 17 at end of trial): ALA 600 mg/d for 1 mo<br><br>Washout of 20 d, then placebo 300 mg/d for 1 mo | Group 2 (n = 19; 14 at end of trial): placebo (cellulose starch, 300 mg/d)<br><br>Washout of 20 d, then ALA 600 mg/d for 1 mo | Two scales at end of each cycle:<br><br>VAS scale: 5-point GPE scale: –1 = worse; 0 = no change; +1 = slight improvement; +2 = decided improvement; +3 = no burning anymore (resolution) | Nonsignificant ($P$ > .05) fluctuation of VAS and GPE |

**Table 1 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Natural Antioxidants for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/ no treatment protocol | Score/ outcome | Main results |
|---|---|---|---|---|---|---|---|
| López-Jornet et al, 2009[32] | RCT | 60 patients (45 F, 6 M); 39 patients completed trial<br><br>Mean age: 64.37 ± 11.61 y | Nonparoxysmal intraoral burning for > 6 mo<br><br>No clinical abnormalities<br><br>Lab test (CBC, glucose, iron, transferrin, B12, folate)<br><br>No candidiasis, lichenoid reactions, or other entities | Group 1 (n = 23): ALA 800 mg/d + lycopene (100 mg) + green tea extract (40% 50 mg) for 2 mo | Group 2 (n = 16): placebo (cellulose tablets of same appearance for 2 mo) | VAS scale before treatment, at 1 mo, and at 2 mo | No significant differences |
| Marino et al, 2010[33] | RCT | 56 patients (46 F, 10 M)<br><br>Mean age: 62 ± 9.8 y | Intraoral burning for > 4 mo<br><br>No evidence of local or systemic disorders<br><br>No medication related to oral burning or alteration of taste | Group 2 (n = 14): ALA 800 mg/d for 8 wks | Group 1 (n = 14): capsaicin (250 mg of red pepper in 50 mL water) for 8 wks<br><br>Group 3 (n = 14): lysozyme lactoperoxidase oral rinse (Biotene) 5 times/d for 8 wks<br><br>Group 4 (n = 14): placebo (0.05 g of boric acid dissolved in 100 mL of distilled water 3 times/d for mouthwash for 8 wks) | VAS scale at beginning and end of treatment | Significant effectiveness ($P < .01$) of each therapy compared to placebo; no significant difference among the 3 treatments |
| López-D'alessandro and Escovich, 2011[34] | RCT | 120 patients (94 F, 26 M)<br><br>Mean age: 57 ± 14.1 y | BMS for > 3 mo<br><br>No hematinic deficiencies<br><br>No previous history of psychotropics or antihypertensives<br><br>No psychiatric conditions | Group 1 (n = 20): ALA 600 mg/d for 2 mo | Group 2 (n = 20): GABA 300 mg/d<br><br>Group 3 (n = 20): ALA 600 mg/d + GABA 300 mg/d<br><br>Group 4 (n = 60): placebo: 100 mg starch and cellulose | Symptoms with 0–4 scale: 0 = no burning; 1 = burning in single area of tongue; 2 = burning in two oral areas; 3 = burning in three oral areas; 4 = burning spread throughout the mouth | Significant ($P < .001$) improvement of ALA and ALA+GABA compared to placebo; ALA+GABA 13.2 times better than placebo |

**Table 1 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Natural Antioxidants for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/ no treatment protocol | Score/ outcome | Main results |
|---|---|---|---|---|---|---|---|
| Palacios-Sánchez et al, 2015[35] | RCT | 60 patients (55 F, 5 M); 54 patients completed trial<br>Mean age: 62.13 (36–86) y | Intraoral burning for > 4 mo<br>Normal salivary rate<br>Normal lab test (CBC, ferritin, B12, folate) | Group 1 (n = 30): ALA 600 mg/d + lycopene (100 mg) + green tea extract (40% 50 mg) for 8 wks | Group 2 (n = 30): placebo pills for 8 wks | BDI at baseline<br>VAS scale at baseline, 1 mo, 2 mo | Significant ($P$ < .05) improvement in 64% of ALA group vs 27.6% of placebo group |
| Çınar et al, 2018[36] | RCT | 90 patients (48 F, 27 M); 75 enrolled<br>Mean age: 42–45 ± 2.75 y | No chronic systemic or oral diseases<br>No metallic implants<br>No BMS treatment in the last 6 mo | Group 3: ALA 600 mg/d for 4 mo | Group 1 (n = 30): CLO 2 mg/d for 4 mo<br>Group 2 (n = 30): PREG 150 mg/d | VAS before and at end of treatment | Significant ($P$ < .001) improvement in CLO and PREG groups<br>No effects in ALA group |
| *Tocopherol* | | | | | | | |
| Kang, 2018[37] | RCT | 60 BMS patients, 30 controls<br>Mean age and M/F ratio not reported | Not specified | Group 1 (n = 40 BMS patients): tocopherol, applied twice/d for 2 wks | Group 2 (n = 20 BMS patients): placebo, applied twice/d for 2 wks | Serum levels of uric acid and bilirubin as systemic oxidative stress markers, in both the 60 BMS patients and 30 controls<br>VAS and OHIP-14 scales at baseline and after 2 wks | Significantly higher levels of uric acid in BMS than controls<br>Significant improvement in VAS and OHIP-14 only in group 1<br>Significantly lower serum uric acid in responders than nonresponders in group 1<br>No statistical data available |

ALA = alpha-lipoic acid; ANA = antinuclear antibody; BDI = Beck Depression Inventory; CBC = complete blood cell count; CLO = clonazepam; CPT = cognitive psychotherapy; ENA = extractable antinuclear antigen; GABA = gabapentin; GPE = global perceived effect; IgE = immunoglobulin E; OHIP-14 = Oral Health Impact Profile-14; PREG = pregabalin; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VAS = visual analog scale; VATS = visual analog type scale.

Concerning evidence on QoL and/or psychologic assessment, 2 trials used anxiety/depression scales at baseline: One used both the Hospital Anxiety and Depression Scale (HADS) and the Hamilton Rating Scale for Depression (HAM-D),[34] and the other used the Beck Depression Inventory (BDI).[35] None of these papers repeated this data recollection during or after the end of protocol, thus preventing any insight on possible psychologic ramifications.[34,35]

ALA seemed to provide tolerable side effects, usually gastrointestinal complaints,[27,31,36] which reached enough severity to induce a dropout in only one patient. Thirty-two isolated reports of mild headache and myalgia were also registered.[31,36]

***Tocopherol.*** One prospective, single-blinded RCT investigated the effectiveness of tocopherol, a natural antioxidant, in 60 BMS patients (Table 1).[37] Systemic oxidative stress levels were evaluated through serum uric acid and bilirubin measurements in the BMS sample and in 30 sex- and age-matched controls. Pain was determined using a VAS scale, and QoL with the Oral Health Impact Profile-14 (OHIP-14) questionnaire. Forty BMS patients were assigned to treatment with tocopherol applications twice a day for 14 days, while 20

**Table 2 Main Characteristics of RCTs/CCTs Assessing the Effectiveness of Natural Treatments for BMS**

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| *Capsaicin* | | | | | | | |
| Petruzzi et al, 2004[39] | Triple-blinded CCT | 50 patients (36 M, 14 F)<br>Mean age: 55.6 ± 6 y (capsaicin), 57.4 ± 7 y (placebo) | Burning sensation of tongue/other oral mucosa with no clinical signs<br>Complete medical history and dental examination<br>No salivary abnormalities<br>Normal lab tests (CBC, iron/ferritin/transferrin, B12, folic acid)<br>No previous BMS treatment | Group 1 (n = 25): oral capsaicin 0.25% thrice/d for 1 mo | Placebo (unspecified) | 0–10 VAS scale at beginning and end of treatment | Statistically significant ($P < .001$) VAS decrease with capsaicin compared to placebo |
| Silvestre et al, 2012[40] | RCT | 30 patients (23 at end of trial; 19 F, 4 M)<br>Mean age: 72.65 ± 12.10 y | Discomfort for > 6 mo<br>No oral mucosal lesions<br>No BMS treatment for at least 1 mo before beginning of trial | Crossover approach:<br>Group 1 (n = 30): 30 s with 0.02% capsaicin rinse, thrice/d for 1 wk; 1 wk washout; 1 wk placebo | Group 1 (n = 30) | 0–10 VAS scale in morning and afternoon at beginning of trial, after 1st wk, and after 3 wks | Significant ($P < .05$) differences in VAS in the capsaicin group after 1st wk of treatment, both in morning and afternoon |

*continued next page*

underwent a placebo application with the same dose and duration. Despite the lack of clear statistical assessment, the authors claimed significantly higher serum uric acid levels in BMS samples when compared to controls. Furthermore, significant reductions of VAS and OHIP-14 scores were found only in the treatment group rather than in the placebo, with the latter revealing some intriguing preliminary findings in terms of a possible QoL improvement after the end of treatment. Interestingly, those who responded to tocopherol also carried significantly lower serum uric acid levels than nonresponders. No side effects were detailed.

## Natural Treatments

***Capsaicin.*** Capsaicin, a natural alkaloid contained in hot peppers, has proven successful against various chronic neuropathic disorders, including postherpetic neuralgia and diabetic neuropathy, due to its ability to provide "defunctionalization" of nociceptors.[38] These peculiar properties have interested researchers looking for alternative treatments targeting the neuropathic component of BMS.

Four trials, 2 RCTs and 2 OCTs, published between 2004 and 2017, were included (Table 2),[39–42] with a comprehensive sample of 201 patients with mean ages of 55 to 72 years. The female to male ratio varied widely: It was unspecified in one study,[41] amounted for an unusual minority of women in one article,[39] and, in another paper,[42] women were the only patients recruited.

Inclusion criteria for enrollment of BMS patients were assessed through an in-depth exclusion of clinical and laboratory abnormalities, with a history of BMS symptoms occurring for at least 6 months being required in two articles.[40,42]

Capsaicin was systemically administered for 1 month in the earliest clinical trial,[39] and was provided either as a 0.02% mouthrinse or as a 0.01% to 0.025% gel for 7 to 14 days in the later three studies.[40–42]

Two trials were placebo controlled,[39,40] of which one had a crossover design.[40] In both of these studies, which adopted the VAS scale to assess the intensity of BMS symptoms, a statistically significantly higher relief emerged in the capsaicin groups when compared to placebo ($P < .05$; $P = .000$, respectively). In the 2 non–placebo-controlled trials,[41,42] one tested a capsaicin-base rinse on neuropathic vs psychogenic BMS patients, proving more successful

**Table 2 Main Characteristics of RCTs/CCTs Assessing the Effectiveness of Natural Treatments for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| Azzi et al, 2017[41] | CCT | 99 patients (81 F, 18 M)<br>Mean age: 64.79 ± 9.96 y | Protocol of exclusion of local, systemic, hematochemical, microbiologic, and allergenic factors (according to Scala et al[3]) | Group 1 (collaborative patients with a predominantly neuropathic pattern): capsaicin-based mouthrinse 3 times/d for 12 mo | Group 2 (noncollaborative patients with a predominantly psychogenic pattern): capsaicin-based mouthrinse 3 times/d for 12 mo | Subjective improvement after 1, 3, 6, and 12 mo<br>0–10 VAS | Significantly ($P$ = .000) higher rate of success in group 1 (87%) vs group 2 (20%) |
| Jørgensen and Pedersen, 2017[42] | RCT | 22 patients (18 patients at end of trial; 22 F)<br>Mean age: 61 (34–70) y | Patients > 18 y<br>Burning for > 6 mo<br>No clinical lesions<br>No local/systemic disorders<br>No candidiasis | Crossover approach:<br>Group 1 (n = 22): 0.01% capsaicin oral gel, thrice/d for 14 d<br>14-d break, then switch to group 2 treatment | Group 2 (n = 22): 0.025% capsaicin oral gel, thrice/d for 14 d | 0–10 VAS | Both capsaicin gels significantly reduced pain compared to baseline ($P$ = .002)<br>No significant differences between the 2 groups |
| *Herbal compounds* | | | | | | | |
| Bessho et al, 1998[43] | RCT | 200 patients (153 F, 47 M)<br>Mean age: 61.3 (28–85) y | Glossodynia with no signs of tongue atrophy<br>No salivary abnormalities<br>No anemia, ferritin deficiency, folic acid deficiency, or vitamin B complex deficiency | Group 1 (n =100): Kampo medicine - saiboku-to containing extracts of 10 herbal ingredients: 7.5 g/d for 3 mo | Group 2 (n =100): oral diazepam 2 mg/d + 3 tablets of vitamin B complex for 3 mo | 0–10 scale for pain, burning sensation, discomfort<br>"Markedly effective" if all three disappeared; "effective" if pain improvement; "ineffective" if no pain improvement | Statistically significant ($P$ < .05) improvement in both groups at 3 mo<br>Significantly ($P$ < .01) better pain improvement at 3 mo in Kampo group compared to diazepam<br>No significant differences in burning sensation and discomfort |
| Sardella et al, 2008[44] | RCT | 43 patients (35 F, 4 M)<br>Mean age: 64.9 ± 4.7 y | Burning pain for > 6 mo<br>No local/systemic disorder causing burning sensation<br>No salivary abnormalities<br>Normal lab tests (CBC, glucose, iron/transferrin, B12, folate)<br>No candidiasis<br>No parafunctional activities | Group 1 (n = 21): hypericum perforatum extract 300-mg capsules (hypericin 0.31%, hyperforin 3.0%) thrice/d for 12 wks | Group 2 (n = 22): placebo (identical capsules thrice/d for 12 wks) | 0–10 VAS score at baseline, 28th d, 56th d, 84th d<br>Number of burning oral sites | No significant differences in VAS scores<br>Significantly ($P$ = .036) fewer burning oral sites in group 1 |

**Table 2 Main Characteristics of RCTs/CCTs Assessing the Effectiveness of Natural Treatments for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| Spanemberg et al, 2012[45] | RCT | 72 patients (60 patients at end of trial; 53 F, 7 M)<br><br>Mean age: 63.6 (41–79) y in group 1, 61.5 (46–73) y in group 2 | At least 40 y of age<br><br>Oral burning/pain for > 6 mo with clinically normal mucosa<br><br>No history of antidepressant, anxiolytic, or anticonvulsant intake<br><br>No radiotherapy<br><br>No salivary abnormalities (< 0.1 mL/min at rest)<br><br>Normal lab tests (CBC, glucose, iron, B12, folic acid) | Group 1 (n = 38): 310-mg capsules of catuama herbal compound (guarana 125 mg + catuaba 87.5 mg + ginger root 10 mg + potency wood 87.5 mg); 2 capsules/d for 8-wk evaluation | Group 2 (n = 34): placebo (identical magnesium silicate capsules), 2 capsules/d for 8 wks | 0–10 VNS at baseline, 4, 8, and 12 wks<br><br>0–5 FS at baseline, 4, 8, and 12 wks | Significantly ($P < .01$) greater FS reduction in catuama vs placebo at 4, 8, and 12 wks<br><br>Significantly greater VNS reduction in catuama vs placebo at 8 ($P = .03$) and 12 ($P < .001$) wks |
| Cano-Carillo et al, 2014[46] | RCT | 60 patients (48 F, 12 M; 50 patients at end of trial)<br><br>Mean age: 63.3 ± 12.9 y | Continuous oral burning/pain for > 6 mo<br><br>No clinical abnormalities<br><br>Normal lab tests (CBC, glucose, iron/transferrin, B12, folate)<br><br>No other local or systemic conditions | Group 1 (n = 30): extra virgin olive oil with lycopene 300 ppm, sprayed and swallowed, 1.5 m thrice/d for 12 wks | Group 2 (n = 30): placebo (identical water and dye spray agent) | At baseline and 12th wk: 0–10 VAS pain; 0-10 VAS burning<br><br>SF-36<br><br>OHIP-14<br><br>HADS | No significant differences |
| Silva et al, 2014[47] | RCT | 38 patients (35 F, 3 M)<br><br>Mean age: 66 ± 12.01 y in group 1; 58.42 ± 13.70 y in group 2 | In accordance with 1994 IASP guidelines[2] | Group 1 (n = 19): urea (10% topical medication) 3–4 times/d for 3 mo | Group 2 (n = 19): placebo (topical medication: 5% sodium carboxymethylcellulose + 0.15% methyl paraben + 10% glycerol in distilled water), 3–4 times/d for 3 mo | At baseline and 3 mo: EDOF-HC protocol; QST; gustative, olfactory, or sensory thresholds | No significant differences |

in the former than the latter,[41] while the other reported no significant differences in the effectiveness of 0.01% and 0.025% capsaicin gel tested through a crossover approach, with both formulations significantly reducing pain.[42]

Regarding available evidence on QoL and/or psychologic repercussions elicited by capsaicin, no data were found, with only one trial referring to a preliminary screening of the psychologic status of BMS patients through multi-dimensional scale

**Table 2 Main Characteristics of RCTs/CCTs Assessing the Effectiveness of Natural Treatments for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| Valenzuela et al, 2016[48] | RCT | 57 patients (50 F, 7 M)<br><br>Mean age: 65.8 ± 10.6 y in group 1; 67.2 ± 12.6 y in group 2 | In accordance with 2004 International Classification of Headache Disorders | Group 1 (n = 31): 2% *Chamaemelum nobile* (chamomile) gel, 2 times/d for 1 mo | Group 2 (n = 26): placebo gel (water, hydroxyethyl, sorbitol < 0.1%, E-202 [potassium sorbate] < 0.1%, E-223 [sodium metabisulfite] < 0.1%, food coloring < 0.1%), 2 times/d for 1 mo | At baseline, 15th d, and after 1 mo:<br><br>0–10 VAS; XI; OHIP-14 | No significant differences |
| Ottaviani et al, 2019[49] | RCT | 35 patients (29 F, 6 M; 29 patients at end of trial)<br><br>Age range: 35–80 y | In accordance with the 2016 International Classification of Headache Disorders criteria<br><br>Swab negative to yeast or bacterial infections<br><br>Normal lab tests (CBC, glucose, ferritin, TSH, fT3, fT4, folate, B12);<br><br>No concurrent xerostomia, dysgeusia, gastritis, and psychologic disorders<br><br>No smoking<br><br>Age: 35–80 y<br><br>Burning sensation > 4/10 according to NRS<br><br>No medications in previous 3 mo<br><br>No oral pathologies (including periodontal disease) | Group 1: um-PEA (Normast), 600 mg twice/d for 60 d | Group 2: identical placebo microgranules | Burning intensity: 0–10 NRS at baseline (T0), 30 d (T1), 60 d (T2), and 4 mo after end of treatment (T3) | Significantly ($P < .01$) higher improvement in um-PEA group at end of treatment (T2)<br><br>No significant differences at T0, T1, or T3 |

CBC = complete blood cell count; EDOF-HC = Orofacial Pain Clinic Questionnaire; FS = Faces Scale; fT3 = free triiodothyronine; fT4 = free thyroxine; HADS = Hospital Anxiety and Depression Scale; IASP = International Association for the Study of Pain; OHIP-14 = Oral Health Impact Profile-14; NRS = numeric rating scale; QST = quantitative sensory testing; SF-36 = Short-Form 36 Health Survey; TSH = thyroid-stimulating hormone; um-PEA = ultramicronized palmitoylethanolamide; VAS = visual analog scale; VNS = visual numeric scale; XI = Xerostomia Inventory.

questionnaires, with the aim of providing a rigorous distinction between neuropathic and psychogenic BMS patients.[41] However, such early evaluation was not followed by a thorough assessment or update of psychologic fluctuations during the 12-month protocol. From these studies, capsaicin seemed to be well tolerated, triggering either a transient burning or itching sensation when applied on the oral mucosa,[40,42] or, less frequently, gastrointestinal side effects, which were detailed in no more than 5% (11/201) of the whole sample.[39,42]

***Herbal compounds.*** There has been much attention on herbal treatments for BMS for decades due to the chronic nature of the disorder, which might discourage the use of prolonged pharmacologic regimens. From 1998 to 2019, 7 RCTs were published, each with a different treatment proposal.[43–49]

Of these, 6 were placebo-controlled trials, with many similarities in terms of BMS diagnostic criteria, sample size (35 to 60 patients, mostly middle-aged women), and choice of 0–10 visual scales for outcome assessment (VAS or VAS-like).[44–49]

Briefly, the most promising results when compared to placebo seem to be limited to the 2-month regimens of catuama, a Brazilian herbal compound with antinociceptive, antidepressant, and vasorelaxant properties,[45] and of ultramicronized palmitoylethanolamide (um-PEA), an N-acylethanolamine with neuroprotective and analgesic functions.[49]

On the other hand, 300-mg capsules of Hypericum perforatum,[44] 300-ppm lycopene-enriched virgin olive oil,[46] 10% topical urea,[47] and 2% chamomile gel[48] administered for 1 to 3 months did not show higher effectiveness in controlling BMS symptoms when compared to their placebo counterparts.

Finally, contrasting results emerged from the earliest and largest nonplacebo RCT, conducted in 200 patients with glossodynia[49]: Here, a 3-month protocol with 7.5 g/day of saiboku-to, a Japanese herbal compound of 10 herbal ingredients with antiallergic, analgesic, anxiolytic, and sialogogue-like properties, provided significant pain relief against diazepam when combined with a vitamin B complex. Conversely, no significant differences were registered concerning burning sensation or general discomfort.

Finally, a clear association between the absence of pain relief and subsequent lack of QoL and/or psychologic improvement was found throughout the trials that also explored these traits: no significant differences were found concerning the HADS, the Short-Form (SF-36), or the OHIP-14 between the lycopene-enriched olive oil treatment group and the placebo arm[46] ; similarly, the OHIP-14 revealed no significant amelioration in QoL between the treatment arm undergoing 1-month treatment with 2% chamomile gel and its placebo counterpart.[48] Finally, in the um-PEA trial, a subscale of the Sheffield Profile for Assessment and Referral to Care index was used to detect significant differences in psychologic status between the treatment arm and placebo. However, such in-depth analysis was limited to a baseline distinction.[49]

Of the 6 studies registering the occurrence of side effects,[43–46,48,49] Hypericum perforatum was the only compound responsible for a single dropout due to the occurrence of severe headache after the fourth week of treatment. No other side effect, either mild or severe, was otherwise described.

## Acupuncture

Acupuncture might provide relief for BMS symptoms due to its ability to improve altered microcirculation and to lead to the release of endogenous opioids.[50,53] Due to this intriguing possibility, 5 trials (3 OCTs and 2 RCTs) published between 2010 and 2017 tried to collect evidence on its effectiveness (Table 3).[50–54]

A relatively small sample of 89 BMS patients, predominantly women aged 62 to 65 years, enrolled with similar diagnostic pathways of exclusion and were able to complete acupuncture treatment without dropping out of the studies. A non–placebo-controlled approach was pursued, mainly comparing the effectiveness of acupuncture between BMS and healthy controls[50–52] or evaluating acupuncture against clonazepam[53] and vitamin C.[54] There was a variety of reported acupuncture points between patients due to the frequent need to pursue a tailored protocol often based on individual idiosyncracies.[51,52] Similarly, the duration and number of sessions changed widely: from 15 to 20 minutes[50] to 30 minutes,[51,53] and from 650 to 2,050 sessions, in a time span from 4 weeks[53] to 6 months.[50]

Some uniformity in outcome assessment emerged, with the VAS being applied in each trial together with other scores, such as the OHIP-14[52,54] and SF-36,[51,53] to acquire information on QoL. The SF-36 was unchanged after 4 weeks of acupuncture alone in one single-arm OCT,[51] while being significantly reduced in an RCT testing acupuncture against clonazepam.[53]

Conversely, the OHIP-14 appeared to be significantly lower after 4 weeks of treatment in one trial[52] and seemed to uphold such a significant reduction for 2 years after the end of treatment in another.[54] Psychologic repercussions were explored through the BDI in one trial in which acupuncture was tested against clonazepam, revealing a similarly significant reduction in each group after the end of both treatments.[53] Finally, both the State-Trait Anxiety Inventory and the HAM-D exhibited a significant reduction in a trial where acupuncture was compared to treatment with vitamin C.[54]

**Table 3 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Acupuncture for BMS**

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| Scardina et al, 2010[50] | CCT | 60 patients (40 F, 20 M)<br><br>Mean age of group 1: 65.4 (57–77) y<br><br>Mean age of group 2: 62 (52–70) y | Absence of oral lesions or candidiasis<br><br>No intake of anti-hypertensives<br><br>No signs of *Helicobacter pylori* infection<br><br>No allergy to dental materials, food, metals, etc<br><br>No signs of vitamin deficiency or Sjögren's antibodies | Group 1 (n = 30): acupuncture in accordance with (TCM) monthly for 6 mo: SI 1 unilateral; TE 1 unilateral; LI 4 unilateral; TE 21 bilateral; ST 5 bilateral; ST 6 bilateral; CV 24 | Group 2 (n = 30): Same TCM protocol as in treatment group applied to healthy controls | Microcirculation assessment through video-capillaroscopy: in the absence of acupuncture (t0); 1 minute after needle insertion (t1); 5 minutes after needle insertion, after stimulation (t2) | Significant ($P < .05$) restoration of microcirculation<br><br>Reduction of burning sensation up to 18 mo after end of treatment |
| Sardella et al, 2013[51] | Single-arm OCT | 14 patients (10 patients at end of trial; 9 F, 1 M)<br><br>Mean age: 65.2 (48–80) y | No signs of alteration after oral cavity inspection, salivary flow rate measurements, standard laboratory tests, isolation of *Candida* spp. | 20 sessions of acupuncture (TCM) for 8 wks (thrice/wk for 4 wks, twice/wk for 4 additional wks)<br><br>Choice of points tailored for each patient | None | Pain assessment through 0–10 VAS<br><br>Health-related quality of life through SF-36 | Slightly significant ($P < .009$) reduction of pain<br><br>No improvement of quality of life |
| Franco et al, 2017[52] | Single-arm OCT | 12 patients (8 patients at end of trial) | Burning/pain symptoms for > 4 mo persisting after conventional treatment<br><br>No oral lesions or local cause<br><br>No history of ACE inhibitors intake<br><br>Normal lab tests (CBC, glucose, glycated Hb, iron, ferritin, B12, folate, zinc, T3,T4, TSH) | 11 sessions (twice/wk for 6 wks) of acupuncture and auricolotherapy (TCM)<br><br>Acupuncture points<br><br>Anxious points: HT 3, HT 4, HT 7, and PC 6<br><br>Points with headache: GB 1, GB 20, GB 34, GB 40, GB 43, and LV 2<br><br>Throat discomfort: SJ 9<br><br>Stomach problems: ST 41, ST 44, and ST 45<br><br>Neck rigidity: LI 14 and LI 1 | None | Pain/burning through VAS<br><br>Salivary flow through unstimulated sialometry<br><br>Quality of life through OHIP-14 | Significant ($P = .005$) decrease of pain/burning after first session<br><br>7/11 sessions without statistically significant decrease of pain/burning<br><br>No significant change of average salivary flow<br><br>Significant ($P = .005$) improvement of quality of life maintained after 2 y |

**Table 3 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Acupuncture for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| Jurisic Kvesic et al, 2015[53] | RCT | 42 patients (38 F, 4 M)<br><br>Mean age: 66.7 ± 12.0 y | Continuous symptoms of burning for > 6 mo with clinically healthy appearance of oral mucosa | Group 1 (n = 20): acupuncture thrice/wk for 4 wks<br><br>Duration of session: 30 min<br><br>Points: ST 8, GB 2, TE 21, SI 19, SI 18, and LI 4 bilaterally; GV 20 in the midline | Group 2 (n = 22): CLO 0.5 mg/d for 2 wks, + 1 mg/d for 3–4 wks | At baseline and end of treatment:<br><br>0–10 VAS; BDI; LANSS pain scale; (SF-36); MoCA | Significant improvements in the scores of all outcome measures in both groups, except for MoCA<br><br>No significant differences between group 1 and group 2 |
| Zavoreo et al, 2017[54] | RCT | 42 patients (37 F, 5 M)<br><br>Mean age:<br>Group 1 M: 64.1 64.1 ± 8.2 y<br><br>Group 1 F: 61.2 ± 12.3 y<br><br>Group 2 M: 63 ± 7.6 y<br><br>Group 2 F: 65 ± 11.8 y | Burning symptoms with no oral lesions<br><br>Absence of local and/or systemic factors<br><br>Normal lab test (CBC, iron, B2, folate, glucose, thyroid hormones) | Group 1 (n = 21): Three sessions of acupuncture (TCM) per wk for 4 wks<br><br>Points: ST 8, GB 2, TE 21, SI 19, SI 18, LI 4, GV 20, bilaterally | Group 2 (n = 21): 1 g of vitamin C, 3 times/d for 4 wks | 0–10 VAS<br><br>OHIP-14<br><br>State-Trait Anxiety Inventory (STAI) questionnaire<br><br>HAM-D | Significant decrease of STAI, OHIP-14, HAM-D, and VAS scores in patients treated with acupuncture<br><br>No significant differences in patients treated with vitamin C |

ACE = angiotensin converting enzyme; BDI = Beck Depression Inventory; CBC = complete blood count; CLO = clonazepam; HAM-D = Hamilton Rating Scale for Depression; Hb = hemoglobin; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; MoCA = Montreal Cognitive Assessment; OHIP-14 = Oral Health Impact Profile; STAI = State-Trait Anxiety Inventory; T3 = triiodothyronine; T4 = thyroxine; TCM = traditional Chinese medicine; TSH = thyroid-stimulating hormone.

Unfortunately, proper assessment of microcirculation changes through videocapillaroscopy was provided in only one study, where a significant variation of the vascular pattern of the lower lip was detected.[50]

Bearing in mind the several limitations in methodology, acupuncture showed encouraging results, showing a statistically significant reduction of pain scores in four studies[50,52–54] and slightly significant relief in another.[51] Conversely, QoL appeared either unchanged in one trial[50] or significantly increased even 2 years after the end of treatment.[52]

Side effects consisted of two isolated reports of mild pain at the needle site and transient migraine.[51]

## Neuropsychologic Approaches

***Cognitive therapy, group psychotherapy, and transcranial stimulation.*** While it remains unclear whether the psychologic elements often found in BMS patients are promoters or associated factors of BMS,[13] the present reviews found only two placebo-controlled RCTs in the last three decades attempting to explore the effectiveness of cognitive therapy[55] and group psychotherapy[56] as adjuvant therapeutic methods for the treatment of BMS (Table 4).

Bearing in mind the anecdotal nature of these isolated reports conducted in relatively small (30 to 44) samples of patients for no more than 3 months, with no QoL assessment or psychologic evaluation available, promising results emerged, with a significant improvement of pain/burning symptoms registered either with the VAS[55] or with the short-form McGill Pain Questionnaire.[56]

Finally, driven by the most recent association between dysfunction of the central nervous system and the onset of BMS,[11,13] a placebo-controlled RCT provided favorable short-term evidence for repetitive

**Table 4 Main Characteristics of RCTs/OCTs Assessing Effectiveness of Neuropsychologic Approaches for BMS**

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| *Group psychotherapy* | | | | | | | |
| Miziara et al, 2009[55] | RCT | 44 patients (29 F, 15 M)<br><br>Mean age: 55 ± 6.7 y | No abnormalities after ORL assessment<br><br>Normal lab test (sodium, potassium, urea, creatinine, glucose, cholesterol, triglycerides, uric acid, estrogen/progesterone, thyroid status, rheumatoid factor, ANA, anti-Ro)<br><br>No abnormal salivary rates<br><br>No signs of *Candida*<br><br>No signs of disorders from upper digestive endoscopy | Group 1 (n = 44): 1 session of group psychotherapy/wk for 3 mo | Group 2 (n = 20): placebo pills = 1 capsule/d for 30 d | SFMPQ | Significant ($P$ = .04) improvement after psychotherapy compared to placebo |
| *Cognitive therapy* | | | | | | | |
| Bergdahl et al, 1995[56] | RCT | 30 patients (24 F, 6 M)<br><br>Mean age:<br><br>M: 46 (38–57) y<br><br>F: 56 (40–69) y | No abnormalities after complete anamnesis, medical and oral examinations, lab tests, and patch test | Group 1 (n =15): Therapy group: Phase 1 = motivational input + oral examination; Phase 2 = evaluation of BMS intensity; Phase 3 = cognitive therapy (CT) for 12–15 sessions; 1 h/wk; Phase 4 = evaluation of BMS intensity + oral examination at end of treatment; Phase 5 = evaluation of BMS intensity + oral examination 6 mo after end of treatment | Group 2 (n = 15): "attention/placebo group": Phases 1, 2, 4, and 5, as in group 1; Phase 3 = return visits 3 times for 12–15 wks for evaluation of BMS intensity + oral examination | 0–7 VAS at 12–15 wk | Significant ($P$ < .00001) reduction of symptom severity in group 1 |

**Table 4 Main Characteristics of RCTs/OCTs Assessing Effectiveness of Neuropsychologic Approaches for BMS *(continued)***

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/ other treatment/no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| *Transcranial stimulation* | | | | | | | |
| Umezaki et al, 2016[57] | RCT | 26 patients (24 F, 2 M)<br><br>Mean age: 63.9 ± 9.56 y | Daily bilateral burning for > 4–6 mo<br><br>No inflammatory/autoimmune disease<br><br>No concurrent psychiatric condition<br><br>No contraindications to treatment–history of seizures, brain surgery, intracranial hypertension, pacemaker, or other metallic implants<br><br>No medication changes in previous 4 wks | Group 1 (n = 14; 12 at end of trial): transcranial magnetic stimulation (10 daily sessions; 1 session/d for 5 d; no treatment for 2 d; 1 session/d for 5 d) | Group 2 (n = 10; 8 at end of trial): sham transcranial magnetic stimulation with same duration as in group 1 | 0–10 VAS, SFMPQ, BPI, PHQ-9, PGIC, CGI-I | Significant decrease of VAS in treatment group compared to sham group at 15 d ($P$ = .011) and 60 d ($P$ = .005)<br><br>No significant changes of the remaining scores |

ANA = antinuclear antibodies; ORL = otorhinolaryngologist; VAS = visual analog scale; SFMPQ = Short-Form McGill Pain Questionnaire; BPI = Brief Pain Inventory; PHQ-9 = Patient Health Questionnaire; PGIC = Patients' Global Impression of Change; CGI-I = Clinical Global Impression for global improvement.

transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex for BMS (Table 4).[57]

Such a technique, which has been previously adopted for drug-resistant depression[58] and peripheral neuropathies,[59] was applied to 14 BMS patients and led to a significant decrease in pain intensity assessed through a VAS scale when compared to the placebo arm, which was composed of 10 patients undergoing a sham rTMS where no actual brain stimulation was provided.

Concerning side effects, rTMS caused mild and transient headache, which also occurred in the placebo group.

## Physical Barriers

***Tongue protectors.*** Due to the potential influence of parafunctional behavior of the tongue in worsening BMS pain and burning, two RCTs were published by the same research group to explore the adjuvant role of a tongue protector, prepared as a polyethylene sheath and deployed for at least 45 minutes/day for 2 to 3 months (Table 5).[60,61]

Within a sample of 125 patients (113 women) assessed for burning/pain and depression/anxiety through a VAS, tongue protectors were able to provide significant relief either alone[60] or combined with topical application of aloe vera or placebo gel formulations.[61]

Conversely, no significant repercussions occurred in the general health profiles of these patients, with isolated significance of single domains of the OHIP-49.[60] Concerning psychologic evaluation, the HADS was deployed in both studies, but it was almost unchanged in the earliest paper[60] and was reported solely at baseline in the most recent one, with no comparison to the status of anxiety/depression at the end of treatment.[61]

**Table 5 Main Characteristics of RCTs/OCTs Assessing the Effectiveness of Physical Barriers (Tongue Protectors) for BMS**

| Study, y | Study design | Main features of sample | Definition of BMS | Nonpharmacologic protocol | Placebo/other treatment/ no treatment protocol | Score/outcome | Main results |
|---|---|---|---|---|---|---|---|
| López-Jornet et al, 2011[60] | RCT | 50 patients (46 F, 4 M)<br><br>Mean age: 61.18 (37–84) y | Symptoms > 3 mo<br><br>Normal lab test (vitamin B group, folic acid)<br><br>No lab signs of anemia<br><br>No previous treatment with antidepressants, anticonvulsants, psychotropic drugs, psychologic therapy | Group 1 (n = 25): Instructions not to rub tongue against teeth/ dentures (10 printed reminders given to each patient)<br><br>Tongue protector: polyethylene sheath (0.1 mm thick, 67 mm long, 66 mm wide) covering tongue from tip to posterior third, used at least 45 min/d for 2 mo | Group 2 (n = 25): Instructions not to rub tongue against teeth/dentures (10 printed reminders given to each patient) | At beginning and end of treatment: 0–10 VAS, HADS, OHIP-49, SF-36 | Significant ($P < .001$) reduction of VAS and OHIP-49 in group 1 vs group 2<br><br>No significant difference in HADS<br><br>Significant improvement of "physical role" ($P < .001$) and "emotional role" ($P < .05$) of SF-36 |
| López-Jornet et al, 2013[61] | RCT | 75 patients (67 F, 8 M; 71 patients at end of trial)<br><br>Mean age: 59 ± 11.3 y | Burning/pain for > 6 mo<br><br>No clinical abnormalities<br><br>Normal lab tests (CBC, glucose, iron/transferrin, B12, folate)<br><br>No thyroid disease<br><br>No previous treatment with antidepressants, anticonvulsants, psychotropic drugs, psychologic therapy<br><br>No previous topical (2 wks) or systemic (4 wks) treatment | Group 1 (n = 25): Tongue protector: polyethylene sheath (0.1 mm thick, 67 mm long, 66 mm wide) covering tongue from tip to the posterior third, used at least 45 min/d for 12 wks | Group 2 (n = 25; 22 at end of trial): tongue protector + placebo (0.5 mL gel to apply before tongue protector for 12 wks)<br><br>Group 3 (n = 25; 24 at end of trial): tongue protector + aloe vera (0.5 mL gel to apply before tongue protector for 12 wks) | At beginning and end of treatment:<br><br>0–10 VAS, HADS, OHIP-49 | VAS reduced in all three groups<br><br>No significant differences in VAS and OHIP-49 among groups<br><br>HADS differences between groups not specified (only baseline values available) |

HADS = Hospital Anxiety and Depression Scale; OHIP-49 = Oral Health Impact Profile-49; SF-36 = Short-Form 36; VAS = visual analog scale.

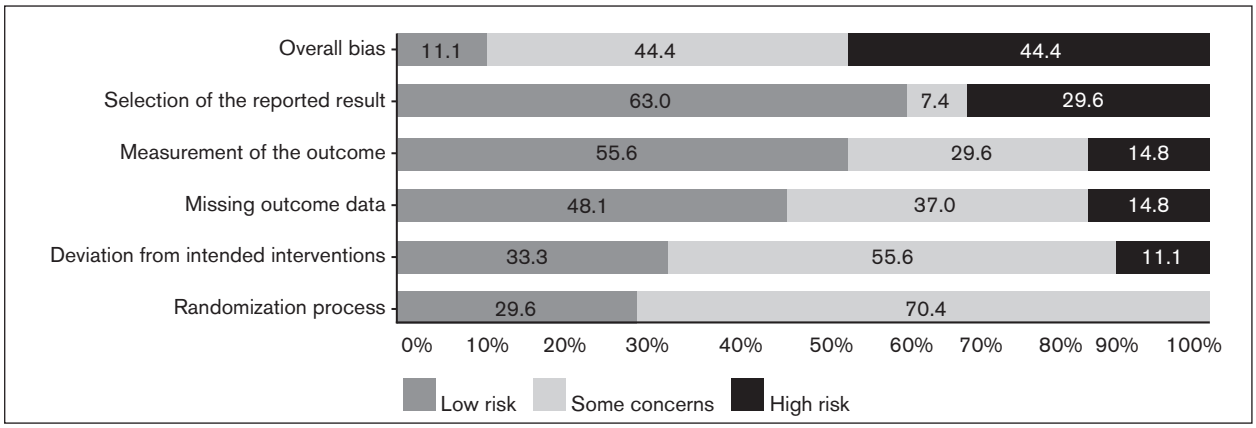


**Fig 2** Risk of bias graph across the 27 included RCTs/CCTs according to the Cochrane RoB-2.[24]

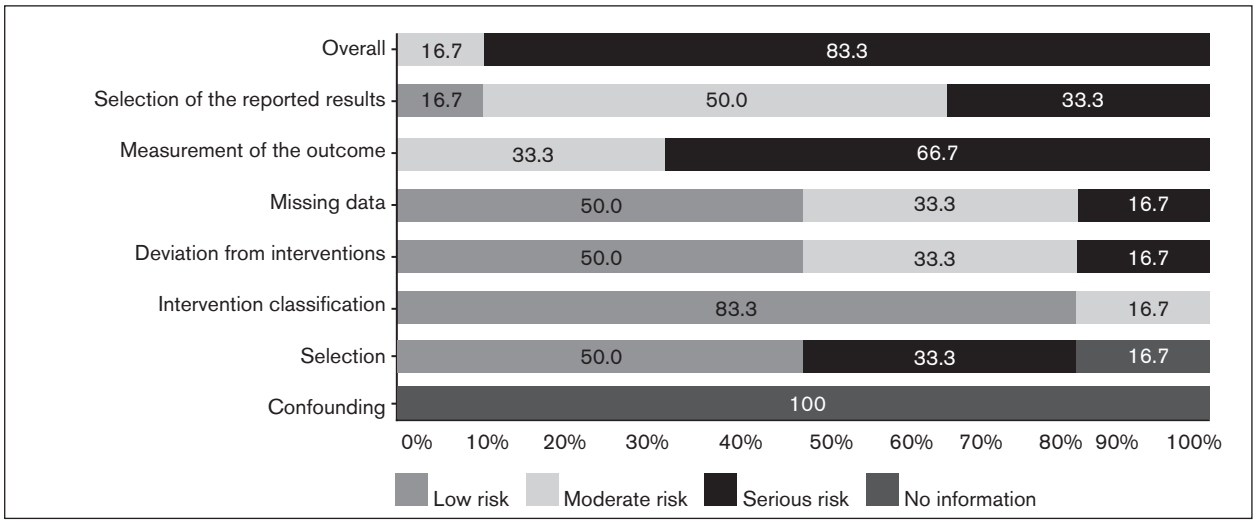


**Fig 3** Risk of bias across the 6 included OCTs according to the ROBINS-I tool.[25]

## Risk of Bias

***RCTs: RoB-2.*** Results of the methodologic quality assessment of the 27 included RCTs are shown in Fig 2 and in Appendix 1. A high risk of bias was detected in approximately one-third of the studies (29.6%, 8/27). Most of the studies failed to perform or report an appropriate randomization sequence or to provide allocation concealment throughout the entire duration of the trial (70.4%, 19/27). Furthermore, lack of blinding or lack of detail for the blinding techniques led to concerns regarding deviations from the intended interventions in more than half of the studies (55.6%, 15/27). Conversely, low-risk percentages were reported for selection of the reported results (63.7%, 17/27) and for measurement of the outcome (55.6%, 15/27). Only three trials achieved an overall low risk of bias,[44,49,57] with 12 trials carrying "some concerns."[30–33,36,42,43,45,48,53,54,61] The remaining 12 studies showed a high risk of bias.[26–28,34,35,37,40,46,47,55,56,60]

***OCTs: ROBINS-I tool.*** Results of the methodologic quality assessment of the 6 included OCTs are reported in Fig 3 and in Appendix 2. No explicit information was retrieved on methodologic efforts to reduce the role of confounding factors; however, it might be speculated that the necessity of excluding several local or systemic disorders to achieve a solid diagnosis of BMS before the beginning of treatment may shelter these specific subsets of open trials from the otherwise frequent risk of confounding bias.

Despite the intervention being clearly stated and based on information collected at the time of treatment, leading to a low bias in the domain of intervention classification (83.3%, 5/6), most studies displayed a high risk of bias in outcome measurement (83.3%, 5/6). Such a finding was a direct consequence of the subjective nature of outcome assessment and the awareness of type of intervention by nonblinded assessors. In conclusion, no OCT could be labeled with an overall low bias, with one OCT showing moderate risk[51] and the remaining 5 OCTs displaying a high risk of bias.[29,39,41,50,52]

## Discussion

Natural antioxidants, natural treatments, acupuncture, neuropsychologic approaches, and physical barriers have been tested as nonpharmacologic treatments of BMS in 14 different formulations.

ALA was by far the most commonly tested medication. With 7 studies (63.6%) reporting positive results, ALA showed encouraging properties in providing pain relief, at least within a brief time span (less than 3 months) while displaying no differential profile than placebo in the only two studies where such a comparison was protracted to 4 months.[30,33]

Furthermore, with the three earliest studies being published in rapid succession by the same group of authors,[26–28] there might have been some overlapping of data from patients enrolled in these studies. In addition, the unblinded designs of two of these trials,[26,27] combined with the use of subjective outcome assessment scales, might contribute to downsizing the overall validity of these early findings.

No clear evidence on QoL has been reported in any of the 11 papers, with only two studies reporting baseline scores from anxiety/depression scales,[34,35] which in both cases were deployed solely to assess the initial psychologic status of their patients. With neither of these trials demanding subsequent completion of these questionnaires after the end of treatment, no evidence could be gathered concerning the implications on the psychologic well-being ensuing from pain relief, especially when the relief was significantly higher in the ALA group than the placebo arm, as was experienced in both studies.[34,35]

Finally, no clear conclusions could be extrapolated from the anecdotal and limited data provided on tocopherol.[37]

Regarding natural treatments, capsaicin was the second most frequently tested substance. As with ALA, its promising efficacy was verified as short term (1-month pain relief), with no data on QoL or psychologic implications. Only one trial focused on the latter,[40] in which psychologic multidimensional scale questionnaires were required for a baseline distinction of patients as carriers of either a neuropathic or a psychogenic BMS pattern. However, no further psychologic investigation was carried out throughout the 12 months of protocol with capsaicin mouthrinse in any of the two groups, thus preventing any speculation on this intriguing association, especially in the peculiar subset of psychogenic BMS patients.

Of the herbal compounds (Kampo medicine, Hypericum perforatum, catuama, lycopene, urea, chamomile, and um-PEA), catuama[45] and um-PEA[49] were the only two showing promising results in a placebo-controlled setting, despite being tested for an application period of only 1 to 2 months, with um-PEA failing to maintain its efficacy 4 months after the period of application.[49] No additional data were provided on QoL, nor on psychologic well-being: in the um-PEA trial, a generic baseline assessment of psychologic status was provided, showing no significant difference of psychologic status between the treatment and placebo arms. Once again, no further information or statistical comparison was drawn between before and after treatment.[49]

Similarly, very limited evidence can be deduced from the studies on acupuncture, which rely so far on favorable evidence of immediate pain relief. Conflicting outcomes have emerged with regard to QoL: on one hand, the SF-36 showed antithetic results,[51,53] whereas the OHIP-14 appeared more consistent in highlighting improvement of QoL both in the short term[52] and in the long term.[54] Scattered findings on psychologic well-being were detailed as well, with no placebo-controlled setting and different scores used each time: BDI was lowered significantly in a trial where acupuncture was tested against clonazepam, with the former showing a very similar trend of decline compared to the latter,[53] whereas the State-Trait Anxiety Inventory and HAM-D were significantly decreased in the acupuncture arm when compared to a debatable comparison group of BMS patients exposed to a vitamin C regimen for 1 month.[54]

Overall, such findings should be considered with caution, as they originate from small-sized, nonrandomized, non–placebo-controlled trials carrying a moderate to high risk of bias.

Concerning neuropsychologic approaches, apart from the promising evidence of pain relief from rTMS (flawed by the very small size sample enrolled) and inevitable concerns on the accessibility of such a novel technique in everyday clinical practice, the most unexpected findings were those of just two trials focused on psychologic management.[55,56] With psychosocial components being assumed as paramount in the pathogenesis of BMS since its earliest reports,[1,13] such results raise a strong suspicion of an underlying publication bias. In addition, both of the trials available were conducted in a small number of patients (< 50) and were surprisingly focused on pain intensity alone—with an uneven timing for pain assessment between the treatment and placebo in one paper[55]—and no evaluation of the psychologic aftereffects.

Concerning physical barriers, two trials[60,61] focused on pain intensity. QoL and psychologic well-being were assessed with a relatively homogenous methodology. However, despite the positive effects in terms of pain relief provided by tongue protectors, either alone[60] or combined with topical applications,[61] opposing evidence occurred for the QoL implications, with the OHIP-49 displaying antithetic

results between the two studies—significant in the earliest,[60] not significant in the latest[61]—and very limited information on psychologic well-being, with the HADS staying unaltered in the earliest paper[60] and lacking a clear statistical comparison between baseline and end of treatment in the later one.[61] Besides, both protocols shared a very limited duration (no more than 3 months) and an overall moderate/high risk of bias.

In any case, the present review carries its own limitations: first, the absence of a quantitative synthesis due to the vast methodologic flaws and heterogeneity of the included studies; second, the exclusion of non-English literature, which might have led to some type of reporting bias, especially on phytotherapy or acupuncture, particularly from Chinese authors.

Bearing in mind these concerns, conclusions from the vast majority of trials assessing the effectiveness of nonpharmacologic treatments must be interpreted cautiously. Apart from ALA, capsaicin, and acupuncture, the alternative treatments were described in single studies. With almost no data provided beyond 3 months, the variety of burning/pain intensity scores, the scarce information on QoL, and the only occasional evidence on associated BMS symptoms, none of the nonpharmacologic approaches appears to deliver unequivocal, solid results for the treatment of BMS.

However, since similar limitations are attributed to the pharmacologic approaches for BMS,[17,18,62] the potential effectiveness of some of the alternative/complementary medicine protocols should be further explored, especially as they have a very low, if not absent, spectrum of side effects, unlike drugs.[13,62]

Future double-blinded, properly randomized, placebo-controlled trials contemplating at least 12 months of follow-up in a larger sample of patients are thus warranted. Further suggestions would be to design methods of inquiry through a multidisciplinary effort, where oral physicians, neurologists, and psychiatrists/psychologists discuss which standardized outcome assessment scales/surveys would be most appropriate and how their subsequent interpretations should ensue.

## Conclusions

Many nonpharmacologic treatments are available for BMS, but none seem to be adequate from an evidence-based medicine standpoint, given the heterogeneity, bias assessment, and short-term evaluations found in the present review. Administration of ALA and capsaicin showed the most encouraging outcomes, as they were tested in more than one study. The roles of behavioral and cognitive therapy need to be further explored. Studies with a more rigorous methodology and larger samples are necessary to collect a higher quality of evidence and to offer valid options for alternative, long-term regimens.

## Highlights/Key Findings

- This is the first systematic review to provide a comprehensive analysis of the effectiveness of nonpharmacologic treatments for BMS.
- Through a narrative approach and a thorough analysis of risk of bias, this sytematic review highlights the incomplete, short-term, and heterogenous evidence of nonpharmacologic protocols to date.
- This review warrants the need for a more rigorous methodology of future trials eager to explore the effectiveness of nonpharmacologic approaches for BMS, ideally driven by a multidisciplinary team, with the aim of providing a standardized, evidence-based assessment of psychologic fluctuation of BMS patients throughout the entire duration of the protocols rather than at baseline alone.
- This review also highlights the necessity for future research on nonpharmacologic protocols to expand their scope to a long-term, comprehensive evaluation, since almost no long-term assessment has been provided thus far.

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## References

1. Périer JM, Boucher Y. History of burning mouth syndrome (1800–1950): A review. Oral Dis 2019;25:425–438.
2. Merskey H, Bogduk N. Classification of Chronic Pain, ed 2. Seattle: International Association for the Study of Pain, 1994.
3. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino A. Update on burning mouth syndrome: Overview and patient management. Crit Rev Oral Biol Med 2003;14:275–291.
4. International Classification of Orofacial Pain, 1st edition (ICOP). Cephalalgia 2020;40:129–221.
5. Jääskeläinen SK, Woda A. Burning mouth syndrome. Cephalalgia 2017;37:627–647.
6. Bender SD. Burning mouth syndrome. Dent Clin North Am 2018;62:585–596.

7. van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:664–668.
8. Kim MJ, Kim J, Kho HS. Comparison between burning mouth syndrome patients with and without psychological problems. Int J Oral Maxillofac Surg 2018;47:879–887.
9. Koike K, Shinozaki T, Hara K, et al. Immune and endocrine function in patients with burning mouth syndrome. Clin J Pain 2014;30:168–173.
10. Lauria G, Majorana A, Borgna M, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332–337.
11. Hagelberg N, Forssell H, Rinne JO, et al. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. Pain 2003;101:149–154.
12. Koszewicz M, Mendak M, Konopka T, Koziorowska-Gawron E, Budrewicz S. The characteristics of autonomic nervous system disorders in burning mouth syndrome and Parkinson disease. J Orofac Pain 2012;26:315–320.
13. Imamura Y, Shinozaki T, Okada-Ogawa A, et al. An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives. J Oral Rehabil 2019;46:574–587.
14. Miller CS, Farag AM, Chmieliauskaite M, et al. Is burning mouth a syndrome or a disorder? A commentary. Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:361–363.
15. Poon R, Su N, Ching V, Darling M, Grushka M. Reduction in unstimulated salivary flow rate in burning mouth syndrome. Br Dent J 2014;217:E14.
16. Spadari F, Venesia P, Azzi L, et al. Low basal salivary flow and burning mouth syndrome: New evidence in this enigmatic pathology. J Oral Pathol Med 2015;44:229–233.
17. Kisely S, Forbes M, Sawyer E, Black E, Lalloo R. A systematic review of randomized trials for the treatment of burning mouth syndrome. J Psychosom Res 2016;86:39–46.
18. Zakrzewska J, Buchanan JAG. Burning mouth syndrome. BMJ Clin Evid 2016;2016:1301.
19. de Souza IF, Mármora BC, Rados PV, Visioli F. Treatment modalities for burning mouth syndrome: A systematic review. Clin Oral Investig 2018;22:1893–1905.
20. Tu TTH, Takenoshita M, Matsuoka H, et al. Current management strategies for the pain of elderly patients with burning mouth syndrome: A critical review. Biopsychosoc Med 2019;13:1.
21. Moher, D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097.
22. Zhang W, Hu L, Zhao W, Yan Z. Effectiveness of photobiomodulation in the treatment of primary burning mouth syndrome—A systematic review and meta-analysis. Lasers Med Sci 2021;36:239–248.
23. de Pedro M, López-Pintor RM, de la Hoz-Aizpurua JL Casañas E, Hernández G. Efficacy of low-level laser therapy for the therapeutic management of neuropathic orofacial pain: A systematic review. J Oral Facial Pain Headache 2020;34:13–30.
24. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
25. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
26. Femiano F, Gombos F, Scully C, Busciolano M, De Luca P. Burning mouth syndrome (BMS): Controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. Oral Dis 2000;6:274–277.
27. Femiano F. Burning mouth syndrome (BMS): An open trial of comparative efficacy of alpha-lipoic acid (thioctic acid) with other therapies. Minerva Stomatol 2002;51:405–409.
28. Femiano F, Scully C. Burning mouth syndrome (BMS): Double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. J Oral Pathol Med 2002;31:267–269.
29. Femiano F, Gombos F, Scully C. Burning mouth syndrome: Open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. Med Oral 2004;9:8–13.
30. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: A double-blind, randomized, placebo-controlled study. Eur J Pain 2009;13:492–496.
31. Cavalcanti DR, da Silveira FR. Alpha lipoic acid in burning mouth syndrome—A randomized double-blind placebo-controlled trial. J Oral Pathol Med 2009;38:254–261.
32. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: A randomized, placebo-treatment study. J Oral Rehabil 2009;36:52–57.
33. Marino R, Torretta S, Capaccio P, Pignataro L, Spadari F. Different therapeutic strategies for burning mouth syndrome: Preliminary data. J Oral Pathol Med 2010;39:611–616.
34. López-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of burning mouth syndrome: A randomized, double-blind, placebo controlled trial. Med Oral Patol Oral Cir Bucal 2011;16:e635–e640.
35. Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, Llamas-Martínez M, Esparza-Gómez G. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Med Oral Patol Oral Cir Bucal 2015;20:e435–e440.
36. Çinar LS, Kartal D, Pergel T, Borlu M. Effectiveness and safety of clonazepam, pregabalin, and alpha lipoic acid for the treatment of burning mouth syndrome. Erciyes Med J 2018;40:35–38.
37. Kang JH. Influences of systemic oxidative stress levels on therapeutic efficiency of tocopherol in treatment of burning mouth syndrome: Preliminary study. J Oral Pathol Med 2019;48:s20.
38. Anand P, Bley K. Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth 2011;107:490–502.
39. Petruzzi M, Lauritano D, De Benedittis M, Baldoni M, Serpico R. Systemic capsaicin for burning mouth syndrome: Short-term results of a pilot study. J Oral Pathol Med 2004;33:111–114.
40. Silvestre FJ, Silvestre-Rangil J, Tamarit-Santafé C, Bautista D. Application of a capsaicin rinse in the treatment of burning mouth syndrome. Med Oral Patol Oral Cir Bucal 2012;17:e1–e4.
41. Azzi L, Croveri F, Pasina L, et al. A "burning" therapy for burning mouth syndrome: Preliminary results with the administration of topical capsaicin. J Biol Regul Homeost Agents 2017;31(suppl 2):s89–s95.
42. Jørgensen MR, Pedersen AM. Analgesic effect of topical oral capsaicin gel in burning mouth syndrome. Acta Odontol Scand 2017;75:130–136.
43. Bessho K, Okubo Y, Hori S, Murakami K, Iizuka T. Effectiveness of kampo medicine (sai-boku-to) in treatment of patients with glossodynia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:682–686.
44. Sardella A, Lodi G, Demarosi F, Tarozzi M, Canegallo L, Carrassi A. Hypericum perforatum extract in burning mouth syndrome: A randomized placebo-controlled study. J Oral Pathol Med 2008;37:395–401.

45. Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. Effect of an herbal compound for treatment of burning mouth syndrome: Randomized, controlled, double-blind clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:373–377.
46. Cano-Carrillo P, Pons-Fuster A, López-Jornet P. Efficacy of lycopene-enriched virgin olive oil for treating burning mouth syndrome: A double-blind randomised. J Oral Rehabil 2014;41:296–305.
47. Silva LA, Siqueira JT, Teixeira MJ, Siqueira SR. The role of xerostomia in burning mouth syndrome: A case-control study. Arq Neuropsiquiatr 2014;72:91–98.
48. Valenzuela S, Pons-Fuster A, López-Jornet P. Effect of a 2% topical chamomile application for treating burning mouth syndrome: A controlled clinical trial. J Oral Pathol Med 2016;45:528–533.
49. Ottaviani G, Rupel K, Gobbo M, et al. Efficacy of ultramicronized palmitoylethanolamide in burning mouth syndrome-affected patients: A preliminary randomized double-blind controlled trial. Clin Oral Investig 2019;23:2743–2750.
50. Scardina GA, Ruggieri A, Provenzano F, Messina P. Burning mouth syndrome: Is acupuncture a therapeutic possibility? Br Dent J 2010;209:E2.
51. Sardella A, Lodi G, Tarozzi M, Varoni E, Franchini R, Carrassi A. Acupuncture and burning mouth syndrome: A pilot study. Pain Pract 2013;13:627–632.
52. Franco FR, Castro LA, Borsatto MC, Silveira EA, Ribeiro-Rotta RF. Combined acupuncture and auriculotherapy in burning mouth syndrome treatment: A preliminary single-arm clinical trial. J Altern Complement Med 2017;23:126–134.
53. Jurisic Kvesic A, Zavoreo I, Basic Kes V, et al. The effectiveness of acupuncture versus clonazepam in patients with burning mouth syndrome. Acupunct Med 2015;33:289–292.
54. Zavoreo I, Basic-Kes V, Sikora M, Boras VV, Gabric D, Rogulj AA. Efficacy of acupuncture and vitamin C in burning mouth syndrome—A pilot study. Acta Stomatologica Croatica 2017;51:81–82.
55. Miziara ID, Filho BC, Oliveira R, Rodrigues dos Santos RM. Group psychotherapy: An additional approach to burning mouth syndrome. J Psychosom Res 2009;67:443–448.
56. Bergdahl J, Anneroth G, Perris H. Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: A controlled study. J Oral Pathol Med 1995;24:213–215.
57. Umezaki Y, Badran BW, DeVries WH, Moss J, Gonzales T, George MS. The efficacy of daily prefrontal repetitive transcranial magnetic stimulation (rTMS) for burning mouth syndrome (BMS): A randomized controlled single-blind study. Brain Stimul 2016;9:234–242.
58. Baeken C, Brem AK, Arns M, et al. Repetitive transcranial magnetic stimulation treatment for depressive disorders: Current knowledge and future directions. Curr Opin Psychiatry 2019;32:409–415.
59. Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G, Zis P. Non-pharmacological management of painful peripheral neuropathies: A systematic review. Adv Ther 2020;37:4096–4106.
60. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P. A prospective, randomized study on the efficacy of tongue protector in patients with burning mouth syndrome. Oral Dis 2011;17:277–282.
61. López-Jornet P, Camacho-Alonso F, Molino-Pagan D. Prospective, randomized, double-blind, clinical evaluation of Aloe vera Barbadensis, applied in combination with a tongue protector to treat burning mouth syndrome. J Oral Pathol Med 2013;42:295–301.
62. McMillan R, Forssell H, Buchanan JA, Glenny AM, Weldon JC, Zakrzewska JM. Interventions for treating burning mouth syndrome. Cochrane Database Syst Rev 2016;11:CD002779.


*Appendix 1: See next page.*

**Appendix 2 Risk of Bias Summary of the 6 OCTs According to the ROBINS-I Tool[25]**

| Study | Intervention | Confounding | Selection | Intervention classification | Deviation from intervention | Missing data | Measurement of outcome | Selection of the reported results | Overall |
|---|---|---|---|---|---|---|---|---|---|
| Femiano et al, 2004[29] | Alpha-lipoic acid | No information | Serious risk | Low risk | Serious risk | Low risk | Serious risk | Serious risk | Serious risk |
| Petruzzi et al, 2004[39] | Capsaicin | No information | Low risk | Low risk | Low risk | Low risk | Moderate risk | Serious risk | Serious risk |
| Azzi et al, 2017[41] | Capsaicin | No information | No information | Moderate risk | Moderate risk | Serious risk | Serious risk | Moderate risk | Serious risk |
| Scardina et al, 2010[50] | Acupuncture | No information | Low risk | Low risk | Low risk | Moderate risk | Serious risk | Moderate risk | Serious risk |
| Sardella et al, 2013[51] | Acupuncture | No information | Low risk | Low risk | Low risk | Low risk | Moderate risk | Moderate risk | Moderate risk |
| Franco et al, 2017[52] | Acupuncture | No information | Serious risk | Low risk | Moderate risk | Moderate risk | Serious risk | Low risk | Serious risk |

**Appendix 1 Risk of Bias Summary of the 27 RCTs According to the RoB-2[24]**

| Study | Type of intervention | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|---|
| Femiano et al, 2000[26] | ALA | Some concerns | Some concerns | Low risk | High risk | Low risk | High risk |
| Femiano et al, $2002_a$[27] | ALA | Some concerns | Some concerns | Low risk | High risk | High risk | High risk |
| Femiano and Scully, $2002_b$[28] | ALA | Some concerns | Some concerns | Low risk | Some concerns | High risk | High risk |
| Carbone et al, 2009[30] | ALA | Some concerns | Low risk | Some concerns | Low risk | Some concerns | Some concerns |
| Cavalcanti and da Silveira, 2009[31] | ALA | Low risk | Low risk | Some concerns | Low risk | Low risk | Some concerns |
| López-Jornet et al, 2009[32] | ALA | Low risk | Some concerns | Some concerns | Low risk | Low risk | Some concerns |
| Marino et al, 2010[33] | ALA | Some concerns | Some concerns | Low risk | Some concerns | Low risk | Some concerns |
| López-D'alessandro and Escovich, 2011[34] | ALA | Some concerns | Low risk | Some concerns | Some concerns | High risk | High risk |
| Palacios-Sánchez et al, 2015[35] | ALA | Some concerns | Some concerns | High risk | Low risk | High risk | High risk |
| Çinar et al, 2018[36] | ALA | Some concerns | Some concerns | Low risk | Low risk | Low risk | Some concerns |
| Kang, 2019[37] | Tocopherol | Some concerns | Some concerns | High risk | Some concerns | High risk | High risk |
| Bessho et al, 1998[43] | Sai-boku-to | Some concerns | Some concerns | Low risk | Some concerns | Low risk | Some concerns |
| Sardella et al, 2008[44] | Hypericum perforatum | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Spanemberg et al, 2012[45] | Catuama | Low risk | Some concerns | Some concerns | Low risk | Low risk | Some concerns |
| Cano-Carillo et al, 2014[46] | Lycopene | Low risk | Low risk | Some concerns | Some concerns | High risk | High risk |
| Silva et al, 2014[47] | Urea | Some concerns | Some concerns | High risk | Low risk | High risk | High risk |
| Valenzuela et al, 2016[48] | Chamomile | Low risk | Some concerns | Some concerns | Low risk | Low risk | Some concerns |
| Ottaviani et al, 2019[49] | Um-PEA | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Silvestre et al, 2012[40] | Capsaicin | Some concerns | Some concerns | High risk | Some concerns | High risk | High risk |
| Jørgensen and Pedersen, 2017[42] | Capsaicin | Some concerns | Low risk | Low risk | Low risk | Low risk | Some concerns |
| Jurisic Kvesic et al, 2015[53] | Acupuncture | Some concerns | Some concerns | Low risk | Low risk | Low risk | Some concerns |
| Zavoreo et al, 2017[54] | Acupuncture | Some concerns | Some concerns | Low risk | Low risk | Low risk | Some concerns |
| Bergdhal et al, 1995[56] | Cognitive therapy | Some concerns | High risk | Some concerns | Some concerns | Low risk | High risk |
| Miziara et al, 2009[55] | Group psychotherapy | Some concerns | High risk | Some concerns | High risk | Low risk | High risk |
| Umezaki et al, 2016[57] | Repetitive transcranial magnetic stimulation | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| López-Jornet et al, 2011[60] | Tongue protectors | Some concerns | High risk | Low risk | High risk | Low risk | High risk |
| López-Jornet et al, 2013[61] | Tongue protectors | Some concerns | Low risk | Some concerns | Low risk | Some concerns | Some concerns |

ALA = alpha-lipoic acid; um-PEA = ultramicronized palmitoylethanolamide.