Review

Place of placebo therapy in the treatment of burning mouth syndrome: A systematic review

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Abstract

Burning mouth syndrome (BMS) is defined as an idiopathic orofacial pain with intraoral burning or dysesthesia. This systematic review aimed to analyze the scientific literature with regard to the effectiveness of placebo therapy in patients with BMS. A literature search was conducted through the PubMed-indexed journals within MEDLINE®, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Trip databases from their inception to May 31, 2022. The search terms were defined by combining (medical subject headings (MeSH) terms OR keywords) "burning mouth syndrome" AND (MeSH terms OR keywords) "placebo". Methodological quality assessments were performed utilizing the Joanna Briggs Institute (JBI) Critical Appraisal tool to attribute scores from 1 to 11 to the selected studies. The literature search, study selection and data extraction were carried out by 2 authors. Disagreements between the authors were resolved by the 3rd author, if necessary. A total of 44 articles met the inclusion criteria. After assessing full-text articles for eligibility, 20 articles were excluded. Consequently, 24 articles were retained. A total of 21 studies included in this systematic review had a low score of bias. In 13 studies, a positive response to placebo was noted. Among them, 7 showed a placebo response indistinguishable from active treatment. These changes were more pronounced in patients receiving placebo therapy compared to active treatment in 1 study. Placebo therapy may occasionally be beneficial and ethically acceptable for patients with BMS. To get stronger evidence for the use of a placebo, future studies with standardized methodology and outcomes are required.

Keywords: pain, trigeminal, stomatodynia, placebo effect

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Introduction

According to the International Classification of Orofacial Pain, burning mouth syndrome (BMS) is defined as "an idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 h for over more than 3 months. It has no identifiable causative lesions, and it is manifested with and without somatosensory changes".[1] It has a prevalence of 0.1–3.9% and appears to be more frequent in females, especially in post-menopausal women between the age of 50 and 70 years.[2] Burning mouth syndrome is accompanied by normal clinical or laboratory findings.[3] Burning pain may affect multiple sites within the oral cavity, but most commonly affects the tongue.[4] Investigators have proven that this syndrome "may exist coincidentally with other oral conditions".[5] The use of the term "syndrome" is explained by the co-occurrence of BMS with other subjective symptoms.[6] Stomatodynia is the main indicator of this condition. It can be accompanied by other sensory disorders, such as xerostomia and complaints of altered taste with or without the presence of salivary hypofunction.[7] There is also no clear consensus on the exact etiopathogenesis of this syndrome. However, it is often considered idiopathic. Additionally, no definitive remedy is available and most of the treatment methods produce unsatisfactory results.[3] Given the complex etiopathogenesis of BMS, numerous therapeutic regimens have been proposed.[3] Treatment regimens should be adapted to each individual and a multidisciplinary approach is recommended.[8] In recent years, a number of therapeutic options have been developed by exploiting stem cells, opening up an important therapeutic possibility for this syndrome.[9,10] Treatments can consist of pharmacological agents (topical or systemic medications), cognitive behavioral therapy, and complementary or alternative medicinal therapies to soothe the patient's pain.[11] However, no therapeutic modality is considered the gold standard, and these treatments are not considered to be reliable and effective.[3] A placebo has thus been suggested as a solution for BMS.

A placebo is an "inert substance", usually a carbohydrate tablet or something that closely mimics the active treatment.[12] The term "placebo" has Latin origins. Etymologically, it means "I shall please".[13] It was first introduced into the medical field during the 18th century as a medicine responding to a patient's expectations without providing any real concrete outcomes.[13] Placebos have the potential to alleviate many medical conditions. The healing result of non-specific therapy increases a patient's belief in the placebo effect.[13]

Several systematic reviews have assessed the efficacy of various treatments for BMS,[11,14–23] but to the best of the authors' knowledge, only 1 study reviewed the placebo effect in the management of this syndrome.[24]

This study aimed to perform a systematic analysis of the literature regarding the effectiveness of placebo therapy in patients with BMS, evaluating short- and long-term outcomes.

Material and methods

Study design

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure transparency and comprehensiveness.[25] The search protocol was specified in advance and registered with International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42021231242).

Focused PICOS question

The criteria for including studies in this systematic review were determined according to the Participant–Intervention–Comparison–Outcome–Study (PICOS) design scheme (Table 1). Numerical scores were used to standardize the format of the questionnaires, such as mono-dimensional pain scores including a numeric rating scale (NRS), visual analog scale (VAS), face scale, present pain intensity (PPI), or multi-dimensional scores involving the McGill Pain Questionnaire (MPQ).

Search strategy

An electronic search was performed using 4 databases: the National Library of Medicine (MEDLINE®, PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Trip. The search terms used were a combination of (medical subject headings (MeSH) terms OR keywords) "burning mouth syndrome" AND (MeSH terms OR keywords) "placebo". No language or time restrictions were applied. The last electronic search was performed on May 31, 2022. It was enriched by hand searches and citation screenings. All reference lists

Table 1. Study inclusion criteria according to the PICOS design scheme

Criterion	Description
Types of studies (S)	randomized controlled trials, clinical controlled trials, blinded and controlled trials, clinical trials on non-pharmacological treatment dealing with the placebo effect in BMC
Participant characteristics (P)	patients of both sexes with BMC diagnosis
Intervention (I)	treatment with placebo
Comparison (C)	studies assessing current pharmacological treatment of BMC
Outcome (O)	immediate, short-term, long-term
Oral Pain	localization, surface, intensity

BMC – burning mouth syndrome.

of the selected full-text articles and related reviews were scanned for additional studies.

Screening and selection

Three reviewers (DC, RBK and MK) independently screened the titles and abstracts obtained during the 1st search. If a publication did not meet the inclusion criteria, it was excluded after agreement between all reviewers. Any disagreement between the 3 reviewers was resolved after a discussion. Full texts of the eligible articles were examined by the reviewers. When necessary, the original authors were contacted to obtain additional information.

Data extraction

Data extraction was independently conducted by 2 reviewers (DC and MK). Data extraction forms were subsequently compared between the researchers and a final form was obtained. The authors of eligible articles were contacted via e-mail for clarification in cases of doubt or missing data. In crossover studies, the 2 periods (before and after the crossover) were used.

Data recording

The design, sample size, intervention type, and control of each study were analyzed and summarized according to the Consolidated Standards of Reporting Trials (CONSORT) protocol:
– methods: study design, location/setting, recruitment period, and follow-up time;
– participants: inclusion and exclusion criteria, demographics and number of participants;
– intervention: details regarding the type of BMS treatments and types of placebo;
– outcome: pain.

Risk of bias in the included studies

Two reviewers (DC and MK) independently performed a quality assessment using the Joanna Briggs Institute (JBI) Critical Appraisal tool, specifically the checklist for randomized controlled trials (RCTs).[26] The checklist is a 13-item appraisal consisting of the following areas: (1) randomization component, (2) allocation concealment, (3) treatment group similarity at baseline, (4) blinding of participants, (5) blinding of personnel, (6) blinding of outcome assessors, (7) groups treated identically other than the intervention of interest, (8) follow-up, (9) intention to treat, (10) similar outcome measurements, (11) reliable method of outcome measurements, (12) statistical analysis, and (13) trial design. These items were scored as either "yes", "no", "unclear", or "not applicable". Two reviewers (DC and MK) independently evaluated the included studies with discrepancies handled through discussion. If discrepancies could not be resolved through discussion, the third reviewer (RBK) was involved to reach a consensus.

Three levels of bias were determined[26]:
– high risk of bias: "yes" scores below 49%;
– moderate risk of bias: "yes" scores between 50% and 69%;
– low risk of bias: "yes" scores higher than 70%.

Results

Search results

The search process yielded 89 articles, of which 12 were duplicates. Among the 77 remaining papers, 33 were excluded after a review of the title and abstract. After assessing 44 full-text articles for eligibility, 20 were excluded for other reasons.[27–46] Consequently, 24 articles were included in the review.[47–70] The search results are presented in Fig. 1.

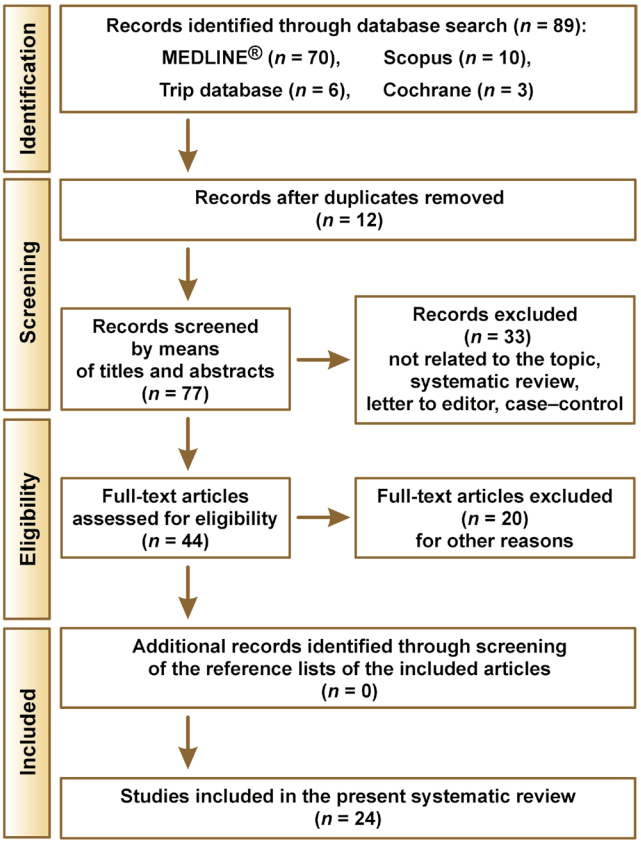

Fig. 1. Study selection flowchart

Study selection and characteristics

The retained studies were assessed for methodological quality (Table 2). A total of 21 studies included in this systematic review had a low score of bias.[47–59,62–69] Three studies had a moderate score of bias.[60,61,70] The final bias scores ranged from 53.8% to 100%.

Table 2. Quality scoring of the retained articles according to the Joanna Briggs Institute (JBI) Critical Appraisal checklist

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	Score	Risk of bias
De Pedro et al.[52] 2020	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Scardina et al.[66] 2020	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	12	low
Škrinjar et al.[64] 2020	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Zoric et al.[70] 2018	U	U	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	8	moderate
Varoni et al.[55] 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13	low
Valenzuela and Lopez-Jornet[53] 2017	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Sugaya et al.[65] 2016	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Valenzuela et al.[49] 2016	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Palacios-Sánchez et al.[51] 2015	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	11	low
Cano-Carrillo et al.[67] 2014	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Heckmann et al.[68] 2006	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	11	low
Spanemberg et al.[54] 2012	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Rodríguez de Rivera Campillo et al.[69] 2010	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Cavalcanti and da Silveira[59] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	11	low
Carbone et al.[48] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Miziara et al.[58] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
López-Jornet et al. [50] 2009	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Sardella et al.[56] 2008	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Petruzzi et al.[47] 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13	low
Gremeau-Richard et al.[62] 2004	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Femiano et al.[60] 2004	N	U	U	N	N	N	Y	Y	Y	Y	Y	Y	Y	7	moderate
Femiano and Scully[61] 2002	Y	U	U	N	N	N	Y	Y	Y	Y	Y	Y	Y	8	moderate
Sardella et al.[57] 1999	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	12	low
Tammiala-Salonen and Forssell[63] 1999	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	11	low

N – no; U – unclear; Y – yes.

Table 3 details the main characteristics and methodology points of the retained studies. The studies were published between 1999[57,63] and 2020.[52,64,66] They were conducted in Spain,[49,50,52,53,67,69] Croatia,[64] Serbia,[70] Italy,[48,55–57,60,61] Brazil,[54,58,59,65] Germany,[68] France,[62] and Finland.[63] Three studies failed to report where they were carried out.[47,51,66] The number of treated participants varied from 20[55,68] to 192,[60] with a wide range of ages, varying from 22[61] to 89[68] years. All BMS participants were appropriately defined as having chronic pain for more than 3, 4 or 6 months with normal oral mucosa.

Table 3. Main characteristics of the studies evaluating the placebo effect in burning mouth syndrome (BMS)

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
De Pedro et al.[52] 2020	Madrid, Spain	single-blind RCT	TG: 10, 2/8, 60.30 ±15.19[a] CG: 10, 2/8, 67.60 ±10.68[a]	2019	age >18 years diagnosis of BMS	hyposalivation or Sjögren's syndrome previous head and neck radiotherapy pregnant women patients with uncontrolled systemic diseases patients suffering from burning mouth symptoms secondary to local factors	laser treatment	silent/off laser therapy	5 weeks (4 months)	VAS MPQ
Scardina et al. [66] 2020	NR	double-blind RCT	40, 0/40, 62.06 ±3.1[a]	NR	diagnosis of BMS patients who had healthy mucosa	candidiasis, lichen planus, glossitis, periodontitis systemic pathologies smokers previous appearance of mycosis hypertension patients with daily pharmacological treatments	laser treatment	silent/off laser therapy	4 weeks (60 days)	VAS NRS
Škrinjar et al.[64] 2020	Zagreb, Croatia	double-blind RCT	TG: 12, 1/11, 61 (47–70)[b] CG: 11, 2/9, 62 (50–69)[b]	NR	burning >3 months normal appearance of the oral mucosa	diabetes serum iron and vitamin B deficiency previous head and neck radiotherapy patients with autoimmune diseases patients taking antidepressants, anxiolytics, anticonvulsants, and hormonal therapy	laser treatment	silent/off laser therapy	10 days (NR)	VAS
Zoric et al.[70] 2018	Belgrade, Serbia	RCT, crossover	TG: 50, 13/37, 67.4 ±8.8[a] CG: 50, 11/39, 62.2 ±13.8[a]	2014–2016	burning sensation in the oral cavity absence of any visible oral lesions symptoms duration ≥3 months	previous therapy with antidepressants previous treatment for BMS pregnant/breastfeeding women diagnosed neurodegenerative disorders previously diagnosed depression presence of local infection, allergic stomatitis xerostomia subjects with alterations in blood cell count, iron vitamin B12 and folic acid levels trigeminal neuropathic or atypical facial pain autoimmune diseases cancer, radiotherapy	fluoxetine	cellulose	6 months (NR)	VAS
Varoni et al.[55] 2018	Milan, Italy	triple-blind RCT, crossover	20, 4/16, 64.4 ±11.6[a]	2013–2015	age ≥18 years burning or stinging chronic oral pain pain ≥4 months normal oral mucosa	hyposalivation therapy with melatonin therapy with anticoagulants working at night pregnant/lactating women	active melatonin compresses	NR	8 weeks (NR)	VAS
Valenzuela and Lopez-Jornet[53] 2017	Murcia, Spain	RCT	44, 3/41, 65.5 ±10.6[a], 33–88[c]	NR	diagnosis of BMS patients with continuous burning/pain on a daily or almost daily basis during all/part of the day >6 months no local/systemic factors that could produce the same symptoms	history of head and neck malignancy radiation diabetes mellitus chronic thyroid disease Sjögren's syndrome fibromyalgia and rheumatoid arthritis anemia analgesic and/or anti-inflammatory medications pregnancy unwillingness to give consent to participate	laser treatment	silent/off laser therapy	4 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Sugaya et al.[65] 2016	São Paulo, Brazil	double-blind RCT	23, 2/21, 59.7 (29–83)[b] TG: 13, 0/13, 57.3 (29–83)[b] CG: 10, 2/8, 62.7 (53–81)[b]	NR	patients meeting the diagnostic criteria for BMS	clinical alterations in the oral mucosa hyposalivation diabetes hypovitaminosis B anemia previous laser radiation previous malignant/benign head and neck neoplasia pregnant and breastfeeding women	laser treatment	silent/off laser therapy	2 weeks (90 days)	VAS
Valenzuela et al.[49] 2016	Murcia, Spain	double-blind RCT, crossover	TG: 31, 3/28, 65.8 ±10.6[a] CG: 26, 4/22, 67.2 ±12.6[a]	NR	diagnosis of BMS in accordance with the International Classification of Headache Disorders	oral lesion endocrine, immunological, nutritional, or infectious disorders patients with history of head and neck malignancy radiation therapy to the head and neck area poorly managed diabetes mellitus chronic thyroid disease Sjögren's syndrome	2% *Chamaemelum nobile* + water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, chamomile aroma	water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, chamomile aroma	4 weeks (NR)	VAS
Palacios-Sánchez et al.[51] 2015	NR	double-blind RCT	60, 5/55, 62.13 (36–86)[b]	NR	diagnosis of BMS age >18 years history of continuous oral burning pain >4 months	burning sensation related to local alterations alteration and uncontrolled systemic diseases patients treated with cisplatin, cyclophosphamide, gentamicin, and amikacin patients undergoing any type of BMS treatment	ALA	cellulose	2 months (NR)	VAS
Cano-Carrillo et al.[67] 2014	Murcia, Spain	double-blind RCT	60, 12/48, 63.3 ±12.9[a] TG: 30, 9/21, 61.7 ±11.6[a] CG: 30, 3/27, 64.9 ±14.1[a]	2011–2013	clinical history of continuous symptoms of oral burning/pain >6 months normal blood test findings non-smokers	patients with pain attributable to other conditions history of hypersensitivity or allergy to the materials used in the study known neurological disorders patients previously treated with antidepressants, anticonvulsants and psychotropic drugs previous psychological therapies no treatment for BMS in the last 2 weeks in the case of topical treatments or in the last 4 weeks in the case of systemic therapies	lycopene + virgin olive oil	water and dye	12 weeks (NR)	VAS
Heckmann et al.[68] 2006	Erlangen, Germany	double-blind RCT	TG: 10, 5/5, 67.5 (49–89)[b] CG: 10, 2/8, 65.4 (49–78)[b]	NR	idiopathic cases	general diseases human immunodeficiency virus infection vitamin B12 deficiency asthma narrow angle glaucoma sleep apnea syndrome general reduction of health condition Candida infection of the oral mucosa allergy toward dental materials or dentures or drugs used in this study severe diseases of the central nervous system psychiatric diseases radiation therapy pregnant/lactating women alcoholism	clonazepam	lactose monohydrate	9 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Spanemberg et al.[54] 2012	São Lucas (Brazil)	double-blind RCT	TG: 30, 3/27, 63.6 ±9.61[a], 41–79[c] CG: 30, 4/26, 61.5 ±6.76[a], 46–73[c]	NR	age ≥40 years burning or pain in the oral mucosa ≥6 months clinically normal mucosa	individuals who were taking antidepressant, anxiolytic or anticonvulsant drugs previous chemo- and/or radiotherapy hyposalivation alterations in hemogram, serum levels of glucose, iron, folic acid, and vitamin B12	*Paullinia cupana* + *Trichilia catigua* + *Zingiber officinale* + *Ptychopetalum olacoides*	magnesium silicate	8 weeks (4 weeks)	VAS face scale
Rodríguez de Rivera Campillo et al.[69] 2010	Barcelona (Spain)	double-blind RCT	66, 2/64, 64.9 (48–85)[b]	2005–2006	oral burning no apparent oral lesions no treatment of the patients in the last month	oral mucosa disorders patients who did not attend the follow-up visits	clonazepam	lactose	6 months (NR)	VAS
Cavalcanti and da Silveira[59] 2009	São Paulo (Brazil)	double-blind RCT, crossover	31, 4/27, 63.1(36–78)[b]	2005–2007	history of oral burning pain ≥6 months absence of oral findings	local and/or systemic causes for oral burning	ALA	cellulose	30 days (NR)	VAS
Carbone et al.[48] 2009	Turin (Italy)	double-blind RCT	52, 9/43, 67.3 ±11.9[a]	2004–2006	previous untreated BMS presence of an isolated complaint of chronic pain in the oral mucosa with a normal clinical examination pain >4 months, continuous throughout all/part of the day, with no paroxysms and not following a nerve trajectory	diabetes that was not under effective pharmacological control patients with known abnormal neurological disorders individuals who were taking antidepressant, anticonvulsant or psychotropic drugs/ psychological therapy signs of parafunctional habits hypersensitivity to ALA hypersensitivity related to dental material contact	ALA + vitamins ALA	dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, silicon dioxide, vegetable magnesium stearate, shellac/ stearic acid	8 weeks (2 months)	VAS MPQ
Miziara et al.[58] 2009	São Paulo (Brazil)	double-blind RCT	44, 15/29, 55 ±6.7[a]	2002–2007	patients with BMS no other symptoms of systemic disease patients who accepted to undergo a psychotherapy group session	patients with a doubtful diagnosis patients followed up for less than 3 months patients who did not agree with the treatment protocol	psychotherapy sessions	NR	3 months for psychotherapy (NR) 1 month for the placebo (NR)	MPQ PPI
López-Jornet et al.[50] 2009	Murcia (Spain)	double-blind RCT	60, 6/54, 64.4 ±11.6[a]	2004–2007	continuous oral burning or pain, daily or almost daily, during all/part of the day >6 months, independent of the nervous pathway and without paroxysms normal blood analysis	patients with pain attributable to other entities patients with problems with dentures, biochemical anomalies and a previous history of hypersensitivity or allergy to ALA pregnant/lactating women patients taking medication which interfered with the study medication	ALA	cellulose	8 weeks (NR)	VAS

Author, year	Location	Study design	Patients (*n*, M/F, age [years])	Period	Inclusion criteria	Exclusion criteria	Treatment	Placebo	Duration (follow-up)	Pain scale
Sardella et al.[56] 2008	Milan (Italy)	double-blind RCT	TG: 19, 1/18, 65.9 ±4.2[a] CG: 20, 3/17, 63.9 ±4.9[a]	2014–2016	history of oral burning pain ≥6 months	local/systemic condition causing an oral burning antidepressant, sedative, anticonvulsant, cardiovascular, hypoglycemic, immunosuppressant, anticoagulant drugs, diltiazem, tamoxifen, bronchodilator treatment	*Hypericum perforatum* extract	NR	12 weeks (NR)	VAS
Petruzzi et al.[47] 2004	NR (NR)	triple-blind RCT	50, 14/36 TG: 55.6 ±6[a] CG: 57.4 ±7[a]	NR	diagnosis of BMS patients never been treated for BMS	NR	capsaicin	NR	30 days (NR)	VAS
Gremeau-Richard et al.[62] 2004	Paris, Lyon, Bordeaux, Saint-Étienne, Clermont-Ferrand (France)	double-blind RCT	48, 4/44, 65 ±2.1[a]	NR	presence of an isolated complaint of chronic pain in the oral mucosa with a normal clinical examination continuous pain ≥4 months without paroxysms and not following a nerve trajectory	diabetes anemia patients with abnormal neurological conditions patients treated on a daily basis with antidepressant, anticonvulsant, or other psychotropic drugs/psychological therapy	clonazepam	NR	2 weeks (6 months)	NS
Femiano et al.[60] 2004	NR (Italy)	RCT	192, 88/104, 48 (24–67)[b]	1999	BMS diagnosis corrected whole blood folate and blood sugar assays	patients with a positive medical or drug history abnormal sialometry evidence of mucosal disease biochemical or hematological abnormalities	ALA + psychotherapy	cellulose	2 months (6 months)	VAS
Femiano and Scully[61] 2002	NR (Italy)	single-blind RCT	60, 18/42, 45 (22–68)[b]	NR	continuous burning discomfort ≥2 months no relevant drug or medical history	NR	ALA	cellulose	2 months (1 year)	VAS
Sardella et al.[57] 1999	Milan (Italy)	double-blind RCT	30, 4/26, 69 (54–85)[b]	1996–1998	diagnosis of "idiopathic" or "essential" BMS clinically normal oral mucosa absence of local or systemic diseases	nutritional and hematological deficiencies diabetes mellitus *Candida* infection, oral lichen planus, geographic tongue xerostomia denture design faults, parafunctional habits allergy to dental materials	benzydamine hydrochloride	HCl	4 weeks (NR)	VAS
Tammiala-Salonen and Forssell[63] 1999	Turku (Finland)	double-blind RCT	37, 0/37, 58.6 (39–71)[b]	1992–1996	daily or almost daily burning pain ≥6 months with moderate to severe intensity	NR	trazodone	NR	8 weeks (NR)	VAS MPQ

M – male; ; F – female; RCT – randomized controlled trial; TG – treatment group; CG – control group; ALA – alpha lipoic acid; HCl – hydrogen chloride; VAS – visual analog scale; MPQ – McGill Pain Questionnaire; NRS – numeric rating scale; PPI – present pain intensity; NS – numerical scale; [a] mean ± standard deviation (*M* ±*SD*); [b] median (minimum–maximum) (*Me* (min–max)); [c] min–max; NR – not reported.

Randomization was applied in 22 studies (Table 2).[47–59,61–69] All 24 studies were controlled clinical trials, involving 2 triple-blind studies (participant, caretaker and assessor),[47,55] 17 double-blind studies,[48–51,54,56–59,62–69] and 2 single-blind studies (participants).[52,61] Four of the clinical trials had a crossover design (Table 3).[49,55,59,70] All studies reported data on items 7 (i.e., groups treated identically other than the intervention of interest), 8 (i.e., follow-up), 9 (i.e., intention to treat), 10 (i.e., similar outcome measurements), 12 (i.e., statistical analysis), and 13 (i.e., trial design; Table 2). Twenty-two studies with a treatment duration between 10 days and 3 months were categorized as short-term assessments.[47–68] The remaining 2 studies performed long-term assessments of 6 months.[69,70] At the end of the intervention, follow-up was reported in 8 studies,[48,52,54,60–62,65,66] ranging between 1 month and 1 year (Table 3).

Visual analog scale was the primary assessment tool for measuring pain intensity. It was used in 22 studies.[47–57,59–61,63–70] Supplementary assessment tools, such as MPQ,[48,52,58,63] NRS,[66] PPI,[58] numerical scales,[62] and face scales[54] were also used to evaluate pain (Table 3). Secondary outcome assessments were performed to assess the quality of health, anxiety, depression, and quality of sleep using patient-reported questionnaires, including the 36-item short form survey,[52] oral health on quality of life,[49,52,53,67] Crown-Crisp Experimental Index,[58] Hamilton Depression Rating Scale,[70] Hamilton Anxiety Rating Scale,[53,55,56,67,70] Beck Depression Inventory,[51,63,68,70] psychometric Symptom Checklist-90-R,[52] Medical Outcomes Study Sleep Scale,[55] Epworth Sleepiness Scale,[55] xerostomia severity test,[49,53] salivary flow-rate,[68] taste test,[68] and smell test.[68] Quantitative assessments of pain intensity were performed in 17 studies.[48–50,52–56,59,62–64,66–70] Functional improvement was quantitatively assessed in 7 studies (Table 4).[47,51,57,58,60,61,65]

Placebo effects in burning mouth syndrome

Although the placebo was administered in the same way as the active treatment in all of the studies, its composition was noted in only 13 (54.2%) studies.[48–51,54,57,59–61,67–70] The most commonly used placebo was cellulose.[50,51,59–61,70] The placebo pill in one study contained cellulose as the primary ingredient and dicalcium phosphate, microcrystalline cellulose, hydroxypropyl methylcellulose, silicon dioxide, vegetable magnesium stearate, and shellac/stearic acid as secondary ingredients.[48] Other placebo formulations included ingredients such as water and dye,[67] lactose monohydrate,[68] magnesium silicate,[54] lactose,[69]

Table 4. Comparison of pain before and after placebo treatment

Author, year	Data	Baseline	End of the treatment	End of the follow-up	Treatment vs. placebo	Key findings
De Pedro et al.[52] 2020	VAS[a]	TG: 6.8 CG: 7.1	TG: 3.4* CG: 7.6	TG: 3.9† CG: 7.6	VAS for pain decreased significantly in the TG vs. the CG at the end of treatment and after 4-month follow-up	no placebo effect
Scardina et al.[66] 2020	NRS[a]	TG: 7 CG: 7	TG: 3* CG: 5*	TG: 3† CG: 7	clear improvement was seen on the NRS of the linear type in the 2 groups after 2 months, patients in CG showed a recurrence of burning sensation	placebo effect
Škrinjar et al.[64] 2020	VAS[b]	TG: 5.5 (4–9) CG: 5 (0–8)	TG: 4 (3–7) * CG: 3 (1.5–6.5)*	NR	VAS scores were significantly lower in both groups	placebo effect
Zoric et al.[70] 2018	VAS[c]	TG: 7.5 ±1.7 CG: 7.2 ±1.7	TG: 3.5 ±2.5* CG: 3.9 ±2.8*	NR	good efficacy of the medication in treating BMS compared to placebo	possible placebo effect
Varoni et al.[55] 2018	ΔVAS[c]	TG: 0.6 ±0.5	CG: 1.2 ±0.4	NR	melatonin and placebo have comparable efficacy in reducing pain caused by BMS lack of difference can be attributed to the effect of placebo on BMS patients	possible placebo effect
Valenzuela and Lopez-Jornet[53] 2017	VAS[c]	TG: 7.56 ±1.5 TG': 8.38 ±1.7 CG: 7.83 ±1.3	TG: 6.38 ±1.6* TG': 7.06 ±1.8* CG: 7.65 ±1.2	NR	VAS scores obtained from the 2 groups treated with laser were significantly lower than scores for placebo group	no placebo effect
Sugaya et al.[65] 2016	*n*	TG: 6 of the 13 patients reported complete remission of symptoms in all sites affected by the burning sensation at the last control checkpoint. CG: 4 of the 10 patients reported total remission of symptoms in all affected sites at the end of the control period.			laser protocol used to treat this group of BMS patients produced benefits similar to those of the placebo group	possible placebo effect
Valenzuela et al.[49] 2016	VAS[c]	TG: 7.4 ±1.5 CG: 6.9 ±1.8	TG: 6.7 ±1.4 CG: 6.2 ±1.9	NR	no significant differences were found between the groups	no placebo effect
Palacios-Sánchez et al.[51] 2015	%	TG: improvement 64%, worsened 0%, no change 36% CG: improvement 27.5%, worsened 17.2%, no change 55.2%		NR	$p < 0.05$	no placebo effect

Author, year	Data	Baseline	End of the treatment	End of the follow-up	Treatment vs. placebo	Key findings
Cano-Carrillo et al.[67] 2014	VAS[b]	TG (pain): 9 (5–10) CG (pain): 9 (6–10) TG (burning): 5 (1–10) CG (burning): 5 (2–10)	TG (pain): 6 (3–10) * CG (pain): 6 (2–10) * TG (burning): 4 (1–8)* CG (burning): 4 (1–8) *	NR	no significant differences were found between the groups	placebo effect
Heckmann et al.[68] 2006	VAS[c]	TG: 7.4 ±2.4 CG: 6.0 ±2.2	TG: 3.9 ±2.9* CG: 4.6 ±2.4*	TG: 4.5 ±2.4† CG: 4.5 ±1.8†	changes were much more pronounced in patients receiving clonazepam compared to placebo	possible placebo effect
Spanemberg et al.[54] 2012	VAS[c]	TG: 6.87 ±2.16 CG: 7.17 ±2.0	TG: 3.33 ±2.56* CG: 5.47 ±2.76*	TG: 3.33 ±2.49† CG: 5.73 ±2.71†	improvement in TG was significantly greater than that of CG after 4 and 8 weeks of herbal compound use reduction in symptoms was still evident after 12 weeks	possible placebo effect
Rodríguez de Rivera Campillo et al.[69] 2010	VAS[c]	TG: 7.7 ±1.5 CG: 7.6 ±1.6	TG: 3.0 ±1.3* CG: 4.4 ±1.0*	NR	clonazepam showed a significant improvement compared to placebo	possible placebo effect
Cavalcanti and da Silveira[59] 2009	VAS[d]	TG: 64.2 TG (after placebo): 47.8 CG: 53.4 CG (after placebo): 78.9	TG: 44.2* TG (after placebo): 41.8 CG: 38.4* CG (after placebo): 52.0*	NR	reduction on symptoms after oral administration of ALA did not have statistical significance compared to the results obtained after oral administration of placebo	placebo effect
Carbone et al.[48] 2009	VAS[c]	TG: 6.89 ±2.42 TG′: 6.50 ±2.59 CG: 6.65 ±2.41	TG: 5.94 ±2.73* TG′: 4.71 ±3.10* CG: 5.05 ±3.39*	TG: 5.11 ±3.98† TG′: 4.50 ±3.39† CG: 5.40 ±3.05†	no significant difference between the TG and CG	placebo effect
Miziara et al.[58] 2009	*n* (%)	TG: improvement 17 (70.8%), no change 7 (29.2%) CG: improvement 8 (40.0%), no change 12 (60.0%)		NR	difference in the results between the 2 groups	no placebo effect
López-Jornet et al.[50] 2009	VAS[c]	TG: 6.3 ±2.8 CG: 6.6 ±2.5	TG: 4.0 ±2.7 CG: 2.8 ±2.5	NR	no significant differences between the 2 groups	no placebo effect
Sardella et al.[56] 2008	VAS[b]	TG: 6.8 (3–10) CG: 7.45 (2–10)	TG: 4.5 (0–10) CG: 6.2 (0–10)	NR	no statistically significant differences were observed in the VAS scores between active treatment and placebo	no placebo effect
Petruzzi et al.[47] 2004	VAS (%)	TG: 8–10 (60%), 4–7 (32%), 0–3 (8%) CG: 8–10 (52%), 4–7 (28%), 0–3 (20%)	TG: 8–10 (4%), 4–7 (12%), 0–3 (84%)* CG: 8–10 (52%), 4–7 (24%), 0–3 (24%)	NR	differences between TG and CG were not mentioned	no placebo effect
Gremeau-Richard et al.[62] 2004	VAS[c]	TG: 6 ±0.3 CG: 6.2 ±0.4	TG: 3.5 ±0.7* CG: 5.5 ±0.4	NR	differences between active treatment and placebo were significant	no placebo effect
Femiano et al.[60] 2004	*n* (%)	TG: worsening 7 (15%), unchanged 22 (46%), improvement 19 (40%) TG′: worsening 2 (4%), unchanged 7 (15%), improvement 39 (81%) TG″: worsening 1 (2%), unchanged 4 (8%), improvement 43 (90%) CG: worsening 18 (37%), unchanged 24 (50%), improvement 6 (13%)		NR	differences between TG and CG were significant	no placebo effect
Femiano and Scully[61] 2002	*n* (%)	TG: worsening 0 (0%), unchanged 1 (3%), improvement 29 (97%) CG: worsening 6 (20%), unchanged 12 (40%), improvement 12 (40%)		NR	statistically significant symptomatic improvement with alpha-lipoic acid (97%) used over 2 months compared to placebo (40%)	possible placebo effect
Sardella et al.[57] 1999	*n* (%)	TG: worsening 0 (0%), unchanged 9 (90%), improvement 1 (10%) CG: worsening 0 (0%), unchanged 8 (80%), improvement 2 (20%)		NR	oral rinses seemed to be no more effective than a placebo solution in the symptomatic relief of essential BMS	no placebo effect
Tammiala-Salonen and Forssell[63] 1999	VAS[a] MPQ[a]	TG: 59.2 CG: 46.6 TG: 8.2 CG: 7.5	TG: 46.6* CG: 34.3* TG: NR CG: NR	NR	VAS: no significant differences between the groups in terms of treatment effects	placebo effect

[a] *M*; [b] *Me* (min–max); [c] *M* ±*SD*; [d] *Me*; NR – not reported; * $p < 0.05$ (end of the treatment vs. baseline); † $p < 0.05$ (end of the follow-up vs. baseline).

and hydrogen chloride (HCl).[57] Valenzuela et al.[49] applied water, hydroxyethyl, sorbitol, potassium sorbate, sodium metabisulfite, food coloring, and chamomile aroma as a gel. Three studies confirmed that the placebo matched the treatment arm with respect to shape, taste, smell, and color.[47,69,70] In 8 other trials, the authors mentioned that the placebo was identical-looking to the treatment.[48,49,51,54,59,61,62,67] Silent/off laser therapy in contact with the mucosa was applied as a treatment in 5 studies (Table 3).[52,53,64–66]

In 13 studies, a positive response to the placebo was noted.[48,54,55,59,61,63–70] Moreover, in 7 of these studies,[48,59,63–67] the placebo response was statistically indistinguishable from the active treatment (Table 4). These changes were more pronounced in patients receiving a placebo compared to alpha lipoic acid (ALA) when the treatment was administered after the placebo during a crossover trial.[59] Carbone et al.[48] found that pain significantly decreased in the placebo group at the end of 4 months of follow-ups compared to the treatment group. However, in one study, patients treated with silent/off laser therapy had a recurrence of the burning sensation.[66]

Discussion

Our systematic review included 24 RCTs investigating the placebo effect in BMS. Randomized controlled trials are widely considered the most rigorous method for evaluating treatment efficacy or preventive interventions.[71] In fact, 87.5% of the included studies had a low risk of bias. It is known that systematic reviews can be affected by bias at the level of individual studies.[72] For this reason, an assessment of the validity of these studies was a crucial step when conducting this systematic review.[73] If bias is ignored, the true effect of the intervention may be overestimated or underestimated.[72] The main result in 7 of the studies was that treatment with a placebo produces a response that may be as large as the response to active drugs.[48,59,63–67] In 6 RCTs, the placebo arm showed a positive response but was less pronounced than in patients receiving active treatment.[54,55,61,68–70]

Burning mouth syndrome is one of the most difficult conditions facing oral health care professionals due to its variation in clinical manifestations.[3] Disagreements arise with regard to whether this condition should be considered a disease, disorder or syndrome. However, no sufficient data is available to justify any modification in taxonomy.[7] Burning mouth syndrome has a negative impact on a patient's life since it is always accompanied by pain.[5] Pain levels were the principal outcome in the patients of the included studies. They were evaluated using many assessment tools. Visual analog scale, which is a unidimensional measurement for pain intensity was most commonly used, especially in diverse adult populations.[74] McGill Pain Questionnaire was used in a few studies not only to describe the pain intensity but also the sensory, affective and evaluative aspects of pain. It is a multi-dimensional questionnaire designed to measure pain and its qualities in adults with chronic pain.[74]

There is no consensus on how to treat BMS.[3] Consequently, treatment modalities based on a patient's symptomatology often lead to unsatisfactory results. A recent systematic review[11] concluded that the effectiveness of both pharmacological and non-pharmacological treatments remains low. The latter should be tried first to manage BMS due to their low side effect profiles. It is important to mention that the key to treatment success depends on the following number of issues that must be solved: correct diagnosis, confirmation of diagnosis, patient's acceptance, patient's understanding of the likely clinical course, patient's participation in the elaboration of a treatment strategy, compliance, positive feedback during treatment, and ongoing interest of the clinicians.[75] Building trust and reassurance with patients is essential in the management of BMS.[3] Moreover, affected individuals should have a realistic understanding of the probability of being cured. The impact on a patient's attitude often results in long-term beneficial effects. The practitioner should meticulously investigate the patient's family, medical, dental, and personal history. He should also carefully interpret the data obtained from various physical and laboratory tests. In cases of underlying local, systemic or psychological factors, treating or eliminating these factors is crucial in the therapeutic process.[3]

A placebo can be of great use in reducing the burning and associated symptoms in patients with BMS. Placebo analgesia "is recognized as a positive response to the administration of a substance known to be inert and to have no analgesic action".[76] However, it is strongly thought to be a potent painkiller by the patient.[76] Current clinical pharmacologic research relies on the superiority of treatment over placebo.[76] It has been confirmed that the overall response to treatment is the result of the specific effect of the treatment and the effect of the context in which the treatment is given. Placebo interventions are designed to stimulate a therapeutic context, affecting the patient's brain, body and behavior.[77] This systematic review revealed that a placebo may be effective in reducing pain caused by BMS.[48,59,63–67] In addition, these studies reported a short-term assessment of the placebo effect. The reduction in symptoms was still evident 2 months after the end of the intervention.[48] Many mechanisms are involved in producing the placebo effect, such as expectations, conditioning, learning, motivation, memory, somatic focus, reward, anxiety reduction, and meaning.[77] Recent advances in placebo research and neuroimaging have shown that the placebo effect is a real neurobiological phenomenon. Placebo analgesia is regulated, at least in part, by endogenous opioid mechanisms and results in the active inhibition of nociceptive activity.[78] Nevertheless, no placebo effect was observed in 11 studies, and an improvement in the test group

was significantly greater than that in the placebo group in 6 RCTs.[54,55,61,68–70] Thus, it is not inherent that patients with BMS will feel better in response to the treatment with a placebo, particularly in the case of subjective outcomes, such as pain. Greene et al.[76] suggested that a third "no treatment" waitlist control group should be included in future RCTs. It would allow differentiation between the natural course of symptoms and a genuine placebo effect. However, whenever treatment is withheld, ethical questions arise. The use of placebo controls in RCTs is ethically acceptable in 4 conditions: "(i) when there is no proven effective treatment for the condition under study; (ii) when withholding treatment poses negligible risks to participants; (iii) when there are compelling methodological reasons for using placebo, and withholding treatment does not pose a risk of serious harm to participants; and more controversially, (iv) when there are compelling methodological reasons for using placebo, and the research is intended to develop interventions that can be implemented in the population from which trial participants are taken, and the trial does not require participants to forgo treatment they would otherwise receive".[71] The methodological reasons are important to ensure the ethical use of placebo controls in these last 2 controversial conditions.[71] In addition, a no-treatment waitlist control group in which patients eventually receive active drugs raises ethical questions similar to those connected with the use of placebo arms in RCTs. In both cases, an institutional review board would need to weigh the potential benefit of the scientific knowledge to be gained against the potential harm that could be derived from withholding active treatment. In case of disorders such as BMS, for which there is no standard of care, the inclusion of a no-treatment waitlist control group may be ethically acceptable.[24] Nevertheless, close attention should be paid to ensure that basic ethical principles are respected when placebo therapy is prescribed.[79]

Limitations

The present systematic review has some limitations. The first limitation concerns the sample size which differs between included studies. The second limitation is related to the duration of therapy. Patients were followed up for a short period of time, whereas the pain occurring in BMS is chronic. Future studies should last more than 3 months. The third limitation concerns the definition of clinically significant outcome. Although VAS was used in almost all the studies, this tool was applied in different ways. The 4th limitation is related to the placebo control which varied depending on the treatment used (laser therapy, for example). The 5th limitation concerns the definition of BMS, which is still lacking.[3] It is worth noting that there is an urgent need to give an exact and universally accepted definition of this syndrome. Despite these limitations, the magnitude of the placebo response in BMS appears to be quite robust.[24] Future RCTs investigating BMS would benefit from larger sample sizes, adequate follow-up periods and the use of a standard placebo. With respect to reporting data, we suggest that in future studies all available data should be reported, particularly VAS data, so that comparisons will be simpler.

Conclusions

Placebo therapy can sometimes be beneficial and ethically acceptable. The placebo effect found in this systematic review represents a significant challenge for future RCTs evaluating therapies for BMS. To obtain stronger evidence for placebo use, such trials should follow a standard protocol. An adequately long follow-up period must be established to discern if the treatment is more effective than a placebo.

Highlights

- Key finding: Placebo may be effective in reducing pain caused by BMS.
- Clinical implication: Placebo can be used as a treatment for BMS in some cases, especially since there is no gold standard treatment for this syndrome.

Ethics approval and consent to participate

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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