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Burning Mouth Syndrome: A Contemporary Approach to Diagnosis and Treatment

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Abstract

Background: Burning mouth syndrome (BMS) is a chronic pain disorder with a complex etiopathogenesis. Its diagnosis is based on the exclusion of local and systemic causes of burning sensations affecting the oral mucosa. Despite advances in current knowledge, the diagnosis and treatment of BMS remain significant clinical challenges.

Objective: To present the current state of knowledge regarding the etiopathogenesis, diagnosis, and contemporary treatment strategies for burning mouth syndrome.

Materials and Methods: A narrative literature review was conducted, including 24 full-text publications published between 2015 and 2025 and identified through searches of the PubMed/MEDLINE, Scopus, and Web of Science databases. The analysis included clinical trials, randomized controlled trials, observational studies, and selected review articles addressing the diagnosis and treatment of BMS.

Results: Current evidence indicates that BMS is a multifactorial disorder in which neuropathic mechanisms play a predominant role. Comprehensive differential diagnosis and the exclusion of secondary causes of oral burning symptoms remain fundamental to the diagnostic process. Available therapeutic strategies, including pharmacological and non-pharmacological interventions such as photobiomodulation and neuromodulation, may reduce symptom severity in some patients. However, the quality of the available evidence is limited by substantial heterogeneity among studies.

Conclusions: Effective management of BMS requires an individualized therapeutic approach and multidisciplinary collaboration. Further well-designed clinical studies employing standardized diagnostic criteria, treatment protocols, and outcome measures are needed to develop reliable evidence-based recommendations for the management of BMS.

Keywords: burning mouth syndrome, BMS, orofacial pain, small fiber neuropathy, differential diagnosis, neuropathic pain treatment, xerostomia, taste disorders

Introduction

Burning mouth syndrome (BMS) is a chronic oral pain disorder whose principal manifestation is a burning, scalding, or dysesthetic sensation affecting the oral mucosa in the absence of clinically evident lesions that could adequately explain the patient's symptoms. According to contemporary classifications of orofacial pain, BMS is diagnosed when symptoms occur daily for more than 2 hours per day and persist for longer than 3 months, with no visible pathological changes in the oral mucosa and after local and systemic causes of oral burning have been excluded (Headache Classification Committee of the International Headache Society 2018; International Classification of Orofacial Pain 2020). Therefore, BMS should not be regarded solely as a disorder of the oral mucosa, but rather as a complex chronic orofacial pain syndrome in which altered somatosensory processing, neuropathic mechanisms, systemic factors, and psychological components may all play a role (Tan and Renton 2020; Adamo and Spagnuolo 2023).

From a clinical perspective, BMS remains a diagnosis of exclusion. Before the diagnosis can be established, it is necessary to determine whether the symptoms may be attributable to other local or systemic conditions. Disorders that may cause oral burning include oral candidiasis, oral lichen planus, xerostomia, contact hypersensitivity to dental materials or ingredients in oral hygiene products, periodontal disease, deficiencies of iron, folic acid, and B-group vitamins, diabetes mellitus, thyroid disorders, Sjögren syndrome, gastroesophageal reflux disease, and adverse drug reactions (Freilich et al. 2020; Adamo and Spagnuolo 2023). Earlier literature frequently distinguished between primary and secondary BMS. However, it is now increasingly emphasized that the diagnosis of BMS should be reserved primarily for cases in which no identifiable local or systemic cause can be established, whereas oral burning symptoms attributable to other diseases should be classified according to their underlying etiology (International Classification of Orofacial Pain 2020).

The most commonly reported symptom of BMS is a burning sensation of the tongue, particularly its anterior portion and tip. However, symptoms may also affect the lips, palate, buccal mucosa, gingiva, or the entire oral cavity. The pain may be continuous, recurrent, or progressively intensify throughout the day. In many patients, symptoms are less pronounced in the morning and increase during the afternoon and evening; in some individuals, the discomfort temporarily subsides while eating or drinking (Adamo and Spagnuolo 2023). In addition to burning, patients frequently report subjective oral dryness, taste disturbances, a metallic or bitter taste, tingling, numbness, a sensation of mucosal roughness, hypersensitivity to spicy or

acidic foods, and generalized oral discomfort (Tan and Renton 2020; de Lima-Souza et al. 2024). An important characteristic of BMS is the discrepancy between the severity of the symptoms reported by the patient and the normal or nearly normal clinical appearance of the oral mucosa. This discrepancy frequently complicates the diagnostic process and may delay the establishment of an appropriate diagnosis (Freilich et al. 2020).

The etiopathogenesis of BMS has not yet been fully elucidated. Current concepts indicate that the syndrome is likely multifactorial and may involve abnormalities in both peripheral and central pain processing. Increasing importance is attributed to neuropathic mechanisms, including damage to or dysfunction of the small nerve fibers responsible for transmitting pain and thermal sensations within the oral mucosa (Kouri et al. 2024). Trigeminal nerve dysfunction, abnormalities in gustatory perception, altered central nervous system pain processing, and a possible contribution of hormonal changes, particularly among perimenopausal and postmenopausal women, have also been described (Tan and Renton 2020; Adamo and Spagnuolo 2023). The complex nature of BMS suggests that neuropathic mechanisms may predominate in some patients, whereas systemic factors may be more prominent in others, and psychosomatic factors or chronic stress may play an important role in a further subgroup.

The epidemiology of BMS is difficult to assess conclusively because reported estimates depend on the diagnostic criteria applied, the population studied, and the methods used to distinguish BMS itself from secondary oral burning symptoms. The global prevalence of BMS in the general population has been estimated at approximately 1.7%, whereas prevalence rates among patients attending clinical centers may be several times higher (Wu et al. 2022). Data on the actual incidence of BMS, defined as the number of new cases occurring within a specified period, are more limited than prevalence data. Consequently, epidemiological studies more commonly report the frequency or prevalence of BMS rather than precise annual incidence rates. The disorder occurs predominantly in middle-aged and older adults, most commonly between the fifth and seventh decades of life, with perimenopausal and postmenopausal women constituting a particularly prominent risk group (Wu et al. 2022; de Lima-Souza et al. 2024). Nevertheless, BMS may also occur in men and younger individuals and should therefore not be regarded exclusively as a disorder affecting postmenopausal women.

The clinical significance of BMS arises not only from the presence of chronic pain but also from its substantial effect on patients' daily functioning. Symptoms may interfere with eating, drinking, speaking, concentration, sleep, and psychological well-being. The chronic nature of the symptoms, the absence of visible oral lesions, and inconclusive findings on routine investigations may contribute to patient frustration, a sense of being misunderstood, and repeated attempts to seek assistance from multiple healthcare professionals. BMS is associated with reduced health-related and oral-health-related quality of life (Pereira et al. 2021). Some patients also experience coexisting anxiety and depressive symptoms, sleep disturbances, and increased emotional distress, although these associations do not necessarily imply a straightforward causal relationship (Galli et al. 2017; de Lima-Souza et al. 2024).

BMS represents a considerable challenge in dentistry, oral medicine, neurology, and pain management because its manifestations lie at the intersection of mucosal, neuropathic, somatosensory, and psychological disorders. The absence of specific clinical or laboratory biomarkers means that the diagnostic process requires a comprehensive medical history, careful examination of the oral mucosa, review of current medications, assessment of comorbid conditions, appropriate laboratory investigations, and, in selected cases, specialist consultations. At the same time, the heterogeneous clinical presentation and likely multifactorial etiology make it difficult to develop a uniform treatment algorithm. Consequently, the investigation of novel diagnostic and therapeutic approaches to BMS is important both for improving recognition of the condition and for developing more personalized management strategies for patients experiencing chronic oral burning.

Methodology

This article is a narrative review based on an analysis of the current literature concerning the etiopathogenesis, diagnosis, and treatment of burning mouth syndrome (BMS). The aim of the review was to summarize the current state of knowledge and discuss contemporary diagnostic and therapeutic approaches used in patients with BMS.

The analysis included publications issued between 2015 and 2025. A literature search was conducted in the PubMed/MEDLINE, Scopus, and Web of Science electronic databases using combinations of keywords and the Boolean operators AND and OR. The following search terms were used: *burning mouth syndrome, BMS, diagnosis, treatment, management, clonazepam, photobiomodulation, low-level laser therapy, neuromodulation, capsaicin, pregabalin, and antidepressants*.

The review included full-text English-language publications comprising clinical studies, randomized controlled trials, observational studies, and selected review articles addressing the diagnosis and treatment of burning mouth syndrome. Case reports, letters to the editor, conference abstracts, animal studies, and publications for which the full text was unavailable were excluded.

Following the screening of titles, abstracts, and full-text articles, 24 publications meeting the predefined eligibility criteria were included in the review. Duplicate publications identified in more than one database were included only once. The analysis considered the characteristics of the study populations, the diagnostic criteria applied, treatment modalities, assessed outcomes, and the effectiveness of individual therapeutic interventions.

The selected publications were subjected to a qualitative comparative analysis. The extracted data were organized according to the principal topics of etiopathogenesis, diagnosis, and treatment of burning mouth syndrome, with particular emphasis on pharmacotherapy, photobiomodulation, and other contemporary therapeutic modalities. Owing to the narrative nature of the review, neither a meta-analysis nor a quantitative synthesis of the findings was performed.

Results

1. Photobiomodulation

Photobiomodulation (PBM), most commonly administered as low-level laser therapy (LLLT), has been investigated as a therapeutic modality for burning mouth syndrome (BMS). The available evidence indicates a favorable safety profile and potential efficacy in reducing symptom severity. However, study findings remain heterogeneous, primarily because of differences in laser parameters, treatment protocols, sample sizes, and outcome-assessment methods.

The most frequently evaluated endpoint in studies of PBM for BMS is a reduction in burning pain intensity. Several randomized controlled trials have demonstrated a significant reduction in symptoms following LLLT, with the effects persisting during follow-up (Spanemberg et al. 2015; Spanemberg et al. 2019). De Pedro et al. (2020) observed progressive improvement over the course of 10 PBM sessions, with the therapeutic effect maintained in most patients at four months and with beneficial effects on both the sensory and emotional components of pain. Comparisons between LLLT and pharmacological treatment have also suggested that the analgesic effect of laser therapy may be sustained. In the study by Arduino et al. (2016), LLLT provided a longer-lasting improvement than topical clonazepam.

Conversely, several studies failed to demonstrate the superiority of active PBM over placebo. Sikora et al. (2018), Škrinjar et al. (2020), and Sugaya et al. (2016) observed symptom improvement in both active laser and sham-treatment groups, with no significant between-group differences. These discrepancies may be attributable to methodological heterogeneity and the substantial placebo response characteristic of BMS, in which symptom perception may also be influenced by psychological and behavioral factors.

In addition to pain reduction, studies have evaluated the effects of PBM on quality of life and psychosocial functioning. Some investigations demonstrated improvements in Oral Health Impact Profile-14 (OHIP-14) scores following LLLT compared with placebo, suggesting a potential beneficial effect on patients' daily functioning (Spanemberg et al. 2015; Spanemberg et al. 2019). De Pedro et al. (2020) also reported favorable effects on selected psychological outcomes and sleep quality. However, other studies did not identify significant laser-specific improvements in anxiety, depression, or quality-of-life parameters (Arduino et al. 2016; Sugaya et al. 2016; Sikora et al. 2018).

The potential biological mechanisms of PBM include modulation of inflammatory processes, sensory nerve function, and the physiological stress response. LLLT has been shown to reduce the levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin 6 (IL-6), although these biochemical changes have not consistently correlated with clinical improvement (Barbosa et al. 2018). Studies employing quantitative sensory testing have suggested that laser therapy may partially improve small-fiber nerve dysfunction. Nevertheless, the relationship between sensory changes and symptom reduction remains inconclusive (Spanemberg et al. 2015; Spanemberg et al. 2019). Similarly, reductions in cortisol levels observed after treatment were not specific to PBM, as they also occurred in placebo groups (Škrinjar et al. 2020).

Studies conducted to date indicate a highly favorable safety profile for PBM. No treatment-related adverse events, oral mucosal abnormalities, or systemic complications have been reported (Arduino et al. 2016; Škrinjar et al. 2020; Spanemberg et al. 2019). A retrospective analysis involving 94 patients demonstrated the possibility of achieving a rapid reduction in pain following a single LLLT session. However, the study was limited by the absence of a control group and its short follow-up period (Mu et al. 2024).

Despite promising findings, the interpretation of PBM efficacy is limited by substantial variation in treatment protocols, including laser parameters, energy doses, the number of sessions, and the anatomical sites irradiated. The most consistent evidence currently supports the potential efficacy of PBM in reducing burning pain and improving oral-health-related

quality of life. Nevertheless, study findings remain partly contradictory, and the precise role of PBM in the long-term management of BMS cannot be established without further well-designed randomized clinical trials employing standardized treatment protocols and outcome measures.

2. Neuromodulation

The available evidence regarding cerebral neuromodulation in BMS is limited. It comprises one randomized controlled trial evaluating repetitive transcranial magnetic stimulation (rTMS), one double-blind pilot randomized controlled trial of cranial electrotherapy stimulation (CES), and one case report assessing transcranial direct current stimulation (tDCS) combined with cognitive rehabilitation and therapeutic exercise (Umezaki et al. 2016; Sánchez-Cuesta et al. 2021; Palmer et al. 2024).

Analgesic efficacy was the primary endpoint in all studies, although the findings were inconsistent. Umezaki et al. (2016) demonstrated a clinically meaningful reduction in pain intensity following high-frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC). Pain intensity decreased by approximately two thirds relative to baseline, and the effect persisted for up to two months. At least a 50% reduction in pain was achieved in 75% of participants. By contrast, Palmer et al. (2024) found no significant difference between active and sham CES, despite improvement in both groups, suggesting a substantial placebo effect. Sánchez-Cuesta et al. (2021) reported a 47% reduction in pain intensity following a multimodal rehabilitation program incorporating tDCS. However, the analgesic effect gradually diminished during follow-up, and pain returned to baseline levels within 45 days.

Findings relating to functional and psychosocial outcomes were more consistent than those concerning analgesic efficacy. Improvements in functional capacity and oral-health-related quality of life were reported in both the rTMS study and the tDCS case report (Umezaki et al. 2016; Sánchez-Cuesta et al. 2021). The tDCS-based intervention was additionally associated with improved cognitive function and sleep quality and reduced pain catastrophizing. CES produced only moderate improvements in sleep quality and the severity of somatic symptoms, which did not exceed those observed with sham stimulation (Palmer et al. 2024). Notably, neither rTMS nor CES resulted in significant improvements in anxiety or depressive symptoms, suggesting that their potential analgesic effects may occur independently of measurable changes in mood (Umezaki et al. 2016; Palmer et al. 2024).

The proposed mechanisms of action varied among the studies. The favorable outcomes observed following rTMS of the DLPFC support the hypothesis that cortical stimulation modulates the activity of central pain-processing networks (Umezaki et al. 2016). In the tDCS

case report, however, the clinical improvement was not accompanied by corresponding changes in quantitative sensory testing (QST) or conditioned pain modulation (CPM). This finding challenges the hypothesis that the observed improvement was directly attributable to modification of central pain processing (Sánchez-Cuesta et al. 2021). The absence of superiority of active over sham stimulation in the CES trial further emphasizes the uncertainty surrounding the specific neuromodulatory mechanisms responsible for the observed therapeutic effects (Palmer et al. 2024).

Substantial methodological heterogeneity limits direct comparisons between the studies. The interventions involved different neuromodulation techniques—rTMS, tDCS, and CES—and employed different stimulation parameters, treatment durations, and study designs, ranging from a single-patient case report to randomized sham-controlled trials. Furthermore, in the tDCS study, neuromodulation was combined with cognitive rehabilitation and therapeutic exercise, precluding the unequivocal attribution of the observed benefits to tDCS alone.

Collectively, the available evidence indicates that prefrontal neuromodulation is feasible and generally well tolerated, with the strongest preliminary evidence of efficacy relating to rTMS. Nevertheless, the current evidence base remains limited because of small sample sizes, short follow-up periods, and inconsistent findings across different neuromodulation techniques. These limitations underscore the need for adequately designed and sufficiently powered randomized controlled trials.

3. Pharmacotherapy

The rationale for pharmacological treatment is partly based on determining whether the pain is predominantly peripheral, involving nerve dysfunction or injury at the level of the oral mucosa, or central, resulting from abnormalities within the central nervous system. Clonazepam is among the most extensively investigated medications for BMS. Its topical administration may be effective in patients with a predominantly peripheral form of BMS because it acts directly on gamma-aminobutyric acid (GABA) receptors located on nerve fibers within the oral mucosa. Its systemic effects are primarily associated with a generalized anxiolytic action; consequently, systemic treatment may be more beneficial in patients with clinically apparent anxiety or depressive symptoms.

Some patients with a central BMS phenotype may exhibit reduced dopaminergic activity in the nigrostriatal pathway, resembling abnormalities observed in Parkinson's disease. This pathway is considered to participate in the descending inhibition of pain signals. Dopaminergic agents may therefore restore the capacity to inhibit chronic neuropathic pain by stimulating endogenous dopamine activity.

Although BMS was historically attributed to psychogenic causes, the analgesic effects of antidepressants should be distinguished from their antidepressant effects. These medications may be effective in the treatment of neuropathic pain, and some may additionally influence dopaminergic mechanisms. Topical capsaicin has also been recommended in patients with a predominantly peripheral BMS phenotype. Immunohistochemical studies of oral mucosal specimens obtained from patients with BMS have demonstrated increased expression of nerve growth factor (NGF) and transient receptor potential vanilloid 1 (TRPV1) ion channels in peripheral nerve fibers. As a potent TRPV1 agonist, capsaicin acts directly on these structures, providing a potential explanation for its efficacy in modulating peripheral pain hypersensitivity (Jääskeläinen and Woda 2017).

A. Clonazepam

In a retrospective study evaluating the effects of a six-week course of clonazepam, Shin et al. (2023) included 41 patients with BMS, comprising 37 women and four men, with a mean age of 66.5 ± 7.92 years. Reported comorbidities included hypertension and diabetes mellitus, and some patients had previously received psychological treatment. Initial pain intensity was classified as high, corresponding to a visual analogue scale (VAS) score of 6–10, in 65.8% of patients. The mean baseline VAS score for the entire cohort was 6.56 ± 1.92 .

The burning sensation affected the tongue, palate, and buccal mucosa, and most patients reported pain involving more than two anatomical sites. Pain was accompanied by other sensory disturbances, including dysgeusia and subjective oral dryness. Psychological assessment indicated that most patients experienced low mood, including depressive and anxiety symptoms.

After six weeks, the overall response rate to sublingual clonazepam was 78% ($n = 32$), and the mean VAS score decreased from 6.56 to 5.34 in the overall cohort. When treatment efficacy was analyzed according to the affected oral region, the highest response rate was observed for symptoms involving the tongue (78%), followed by the lips (44.4%) and palate (41.6%).

An important finding was the relationship between treatment response and combinations of accompanying symptoms. No significant improvement was observed in patients reporting burning alone or burning accompanied by oral dryness. By contrast, patients presenting with both burning and taste disturbances ($n = 17$) experienced a significant reduction in pain, with the mean VAS score decreasing from 6.41 to 4.58 ($p = 0.02$) (Shin et al. 2023).

Another study evaluated the topical efficacy of clonazepam in 30 patients, including 27 women and three men. Participants were instructed to use half a tablet, corresponding to 0.5 mg, three times daily after meals. The mean baseline pain intensity was 7.4 on the VAS (Zborowski and

Konopka, *Comparison of Clonazepam and Tongue Protector in the Treatment of Burning Mouth Syndrome*).

After three weeks, the mean VAS score among all 30 patients had decreased to 5.0. After six weeks, 24 patients remained in the study, and their mean pain score was 4.6; complete resolution of burning symptoms was reported in three patients. After 12 weeks, 20 patients completed treatment, and their mean VAS score had decreased to 3.1. Thus, 20 of the initial 30 participants completed the full three-month study.

Among the 20 participants who completed treatment, therapy was classified as highly effective in 13 patients, defined as a reduction of at least four VAS points. Five of these patients experienced complete symptom resolution. Treatment was partially effective in four patients, with a reduction of two to three VAS points, and ineffective in three patients. The authors noted that the nonresponders experienced burning of the lips, where limited physical contact with saliva containing dissolved clonazepam may have contributed to the lack of efficacy.

B. Vortioxetine or an SSRI/SNRI With Pregabalin Augmentation

Adamo et al. (2025), in the prospective clinical trial *Vortioxetine versus SSRI/SNRI with Pregabalin Augmentation in Treatment-Resistant Burning Mouth Syndrome*, evaluated a cohort of 203 patients with BMS who had not improved following 12 weeks of antidepressant monotherapy. Patients were assigned to two groups. Group A received vortioxetine (VO) in combination with pregabalin (PGB), whereas Group B received a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) in combination with PGB.

A high prevalence of comorbid conditions was observed in the study population, with hypertension being the most common. All patients reported oral burning as the predominant symptom. The most frequent associated symptoms were xerostomia, dysgeusia, and globus pharyngeus, whereas subjective halitosis occurred exclusively in Group B.

After 52 weeks of treatment, most patients in both groups achieved a complete clinical response, defined as a reduction in the VAS score to 1. The overall between-group difference was not statistically significant ($p = 0.761$). However, patients in Group A experienced a more rapid reduction in VAS scores at the first follow-up assessment at 12 weeks.

Anxiety and depressive symptoms decreased in both groups. Early and marked improvement was particularly evident in Group A between baseline and the first follow-up assessment ($p = 0.005$). At the end of week 52, patients receiving vortioxetine with pregabalin achieved slightly more favorable Clinical Global Impression–Improvement (CGI-I) scores ($p = 0.046$).

Logistic regression analysis suggested that treatment outcomes in BMS may be associated not only with pharmacotherapy but also with patient-related and lifestyle factors. Smoking (odds ratio [OR] = 2.79), physical activity (OR = 4.51), the use of angiotensin II receptor blockers (OR = 2.79), and the use of paroxetine (OR = 5.24) were reported as independent predictors of a positive treatment response.

C. Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) has been investigated as a potential treatment for BMS, primarily because of its antioxidant and neuroprotective properties. Although several studies have demonstrated reductions in burning symptom severity following ALA administration, the overall evidence regarding its efficacy remains inconclusive. Some studies have reported clinically meaningful improvement, particularly when ALA was combined with gabapentin. However, placebo-controlled studies have generally failed to demonstrate a significant advantage of ALA over placebo (López-Jornet et al. 2009; Cavalcanti and da Silveira 2009). Differences in reported outcomes may be attributable to methodological variation, including differences in treatment protocols, dosages, treatment duration, and the selection of control groups. Studies employing combination therapy or less rigorous comparator conditions suggested a greater therapeutic effect. By contrast, studies using appropriate placebo controls indicated that the specific effect of ALA may be limited because of the substantial placebo response and the variable natural course of BMS symptoms (López-Jornet et al. 2009; Cavalcanti and da Silveira 2009).

Data regarding the long-term efficacy of ALA remain insufficient. Although short-term symptom improvement has been observed, the available studies provide limited information on the persistence of therapeutic effects after treatment discontinuation. The findings of Cavalcanti and da Silveira suggest that improvement may be transient, indicating that ALA may act primarily as a symptomatic treatment rather than as a disease-modifying intervention (Cavalcanti and da Silveira 2009).

Comparative studies suggest that ALA may provide clinical benefits but may not be the most effective available therapeutic option. Compared with LLLT, ALA reduced symptom severity, although greater improvement was observed in patients treated with laser therapy, particularly infrared photobiomodulation (Barbosa et al. 2018). ALA administration was also associated with an increase in unstimulated salivary flow, whereas no significant changes in salivary TNF- α concentrations were identified (Barbosa et al. 2018).

ALA appears to be a safe and well-tolerated therapeutic option for BMS, with adverse effects occurring infrequently and generally being mild (López-Jornet et al. 2009; Cavalcanti and da

Silveira 2009). Nevertheless, the current evidence is limited by methodological heterogeneity, small sample sizes, inconsistent efficacy findings, and insufficiently long follow-up periods. Further randomized controlled trials employing standardized treatment protocols and extended follow-up are required to determine the precise role of ALA in the management of BMS.

D. Melatonin

Scientific evidence regarding the use of melatonin in BMS remains limited, with only three randomized clinical trials published to date. Collectively, their findings suggest that melatonin is a safe intervention with potential analgesic effects and possible benefits for neuropsychological functioning. However, its efficacy remains uncertain because of methodological differences among the studies and their small sample sizes.

The primary endpoint in all three studies was a reduction in burning pain intensity, although the results were inconsistent. In a triple-blind randomized crossover trial involving 20 patients receiving melatonin at a dose of 12 mg/day, Varoni et al. (2018) found that melatonin did not produce a greater reduction in pain than placebo. Improvement occurred in both treatment arms, indicating a substantial placebo effect.

By contrast, Castillo-Felipe et al. (2022) and Nosratzahi et al. (2023) reported statistically significant reductions in burning intensity following melatonin administration. Castillo-Felipe et al. observed a significant reduction in VAS scores relative to baseline with a melatonin dose of 1 mg/day. Nosratzahi et al. demonstrated lower burning symptom severity at the end of treatment in the melatonin group than in the placebo group, despite using the same dose of 12 mg/day as Varoni et al.

The discrepancies among these studies may be attributable to differences in study design, sample size, melatonin dosage, treatment duration, and outcome-assessment methods. They may also reflect the substantial placebo response commonly observed in patients with chronic pain disorders such as BMS.

A second recurrent area of investigation concerned psychological outcomes and sleep quality. Despite the well-established role of melatonin in regulating circadian rhythms, improvements in sleep quality were modest and inconclusive. Varoni et al. (2018) found no significant improvement in overall sleep quality, although participants slept slightly longer. Similarly, Nosratzahi et al. (2023) identified no significant differences in sleep quality between the melatonin and placebo groups.

Varoni et al. nevertheless reported a small but statistically significant reduction in anxiety severity. This finding suggests that the potential benefits of melatonin may extend beyond

analgesia and include improved psychological well-being, although the clinical relevance of this effect was considered limited.

The available evidence also indicates that melatonin is well tolerated. In all three trials, adverse events were mild and occurred at frequencies comparable to those observed with placebo, supporting the favorable safety profile of this intervention. Castillo-Felipe et al. (2022) additionally reported improvements in oral-health-related quality of life and evaluated changes in salivary biomarkers associated with oxidative stress and neuroinflammation. However, no definitive biological mechanism explaining the observed therapeutic response was identified. Overall, the available evidence does not permit definitive conclusions regarding the efficacy of melatonin in BMS. Although two more recent randomized trials demonstrated reductions in pain severity, the methodologically most rigorous crossover trial failed to confirm the superiority of melatonin over placebo. Melatonin may therefore represent a promising adjunctive treatment because of its highly favorable safety profile and potential antioxidant and neuroprotective mechanisms. Nevertheless, larger, appropriately designed, and adequately powered randomized controlled trials using standardized treatment protocols are required before its routine use in clinical practice can be recommended.

E. Cannabinoids and Palmitoylethanolamide

Recent interest in novel neuromodulatory therapies for BMS has focused on cannabinoids and palmitoylethanolamide (PEA), reflecting the increasing recognition of BMS as a neuropathic pain disorder. Although the available scientific evidence remains limited, three published studies suggest that these agents may provide clinically meaningful symptom improvement (Chirchiglia et al. 2019; Ottaviani et al. 2019; Gambino et al. 2021).

The most consistent finding across these studies was a reduction in pain intensity. In the only available randomized controlled trial, ultramicronized PEA administered at a dose of 600 mg twice daily produced a significantly greater reduction in burning intensity than placebo after 60 days of treatment. The benefits were maintained during a four-month follow-up period (Ottaviani et al. 2019).

Similarly, Gambino et al. (2021) demonstrated a significant improvement in pain symptoms after four weeks of treatment with *Cannabis sativa* oil. Outcomes were assessed using several validated instruments, including the Visual Analogue Scale, McGill Pain Questionnaire, Present Pain Intensity scale, and Oral Health Impact Profile. A case report evaluating ultramicronized PEA as adjunctive therapy also documented a gradual reduction in pain severity and the frequency of pain episodes in a patient with treatment-resistant BMS who was concurrently receiving gabapentin (Chirchiglia et al. 2019).

A second recurring finding was the possibility of benefits extending beyond pain reduction alone. Gambino et al. (2021) observed improvements in neuropathic pain characteristics and reductions in anxiety and depressive symptoms, suggesting that cannabinoids may affect both the sensory and psychological dimensions of BMS. By contrast, studies of PEA focused primarily on pain intensity, with limited assessment of psychosocial outcomes and quality of life (Ottaviani et al. 2019; Chirchiglia et al. 2019). This difference limits direct comparisons of their broader therapeutic effects.

All three studies reported favorable tolerability. Neither the cannabinoid pilot study nor the randomized PEA trial identified serious treatment-related adverse events or treatment discontinuations attributable to adverse effects. Similarly, no safety concerns were reported in the PEA case report (Chirchiglia et al. 2019; Ottaviani et al. 2019; Gambino et al. 2021). These findings suggest that both treatments have favorable short-term safety profiles, although their long-term safety remains uncertain.

Despite the promising findings, the evidence base has substantial methodological limitations. Only one placebo-controlled randomized trial has been published to date (Ottaviani et al. 2019). The cannabinoid study employed an open-label, single-arm design and was therefore susceptible to placebo effects and observer bias (Gambino et al. 2021), whereas the remaining evidence was derived from a single case report (Chirchiglia et al. 2019).

Furthermore, considerable heterogeneity in study design, interventions, treatment duration, and assessed endpoints precludes reliable comparisons between cannabinoids and PEA and limits the comprehensive synthesis of the available evidence. The current findings should therefore be regarded as preliminary. Appropriately designed and adequately powered randomized controlled trials are required before either therapy can be recommended for the routine management of BMS.

Table 1: Summary of the principal therapeutic interventions and clinical outcomes reported in studies of burning mouth syndrome

<i>Intervention</i>	<i>Evidence reviewed</i>	<i>Main findings</i>	<i>Safety and principal limitations</i>
<i>Photobiomodulation / low-level laser therapy</i>	Randomized controlled and observational studies	Several studies reported reductions in burning pain and improvements in oral-health-related quality	Generally well tolerated, with no major treatment-related adverse events reported.

		of life, with benefits sometimes persisting during follow-up. Other trials found no significant difference between active treatment and sham therapy.	Interpretation is limited by heterogeneous laser parameters, treatment schedules, sample sizes, and outcome measures.
<i>Neuromodulation</i>	One rTMS randomized trial, one pilot CES randomized trial, and one tDCS case report	rTMS produced clinically meaningful and sustained pain reduction in one study. CES was not superior to sham stimulation, while multimodal treatment incorporating tDCS produced temporary improvement. Functional capacity, sleep, and quality of life improved in some studies.	Generally feasible and well tolerated. Evidence is limited by small samples, short follow-up, different stimulation techniques, and the use of combined interventions.
<i>Topical or sublingual clonazepam</i>	Retrospective and clinical comparative studies	A six-week retrospective study reported a 78% treatment response, although the mean reduction in pain was modest. Another study demonstrated a progressive reduction in mean VAS scores	May be more effective when the affected area has direct contact with the dissolved medication. The reviewed studies were limited by retrospective or non-placebo-controlled

***Vortioxetine or
SSRI/SNRI with
pregabalin
augmentation***

	over 12 weeks, with complete symptom resolution in some patients.	designs and participant attrition.
Prospective clinical trial involving treatment-resistant BMS	Most patients in both treatment groups achieved a complete clinical response after 52 weeks. Vortioxetine with pregabalin was associated with faster early pain reduction and slightly better global clinical improvement, but the final difference in pain response was not statistically significant.	Treatment response may be influenced by comorbidities, lifestyle, and concomitant medications. The source does not provide a detailed comparative adverse-event analysis.

Alpha-lipoic acid

Placebo-controlled and comparative studies	Some studies reported symptom improvement, particularly when ALA was combined with gabapentin. However, placebo-controlled trials generally failed to demonstrate clear superiority over placebo, and laser therapy appeared more effective in one comparative study.	Usually safe and well tolerated. Evidence is limited by small samples, heterogeneous protocols, inconsistent outcomes, and insufficient long-term follow-up.
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<i>Melatonin</i>	Three randomized clinical trials	Two studies reported reductions in burning pain, whereas a methodologically rigorous crossover trial found no superiority over placebo. Effects on sleep and psychological outcomes were modest and inconsistent.	Favorable safety profile, with mild adverse events comparable to placebo. Evidence remains insufficient for routine clinical recommendation.
<i>Cannabinoids and palmitoylethanolamide</i>	One placebo-controlled PEA trial, one open-label cannabinoid study, and one case report	PEA significantly reduced burning intensity compared with placebo, with benefits maintained during follow-up. Cannabis oil was associated with improvements in pain, neuropathic symptoms, quality of life, anxiety, and depressive symptoms.	Short-term tolerability was favorable, but long-term safety remains uncertain. Evidence is preliminary because of small samples, open-label designs, and substantial methodological heterogeneity.

Discussion

Burning mouth syndrome (BMS) remains one of the most complex conditions encountered in contemporary oral medicine. Despite advances in research into its pathogenesis, no single diagnostic biomarker or universally accepted therapeutic protocol is currently available. Consequently, diagnosis and treatment continue to rely primarily on a detailed clinical history, the exclusion of secondary causes, and an individualized management strategy. Recent publications indicate that the contemporary understanding of BMS is progressively moving away from considering it an exclusively idiopathic disorder and toward a multidimensional

biopsychosocial model that incorporates the coexistence of neuropathic, psychological, and systemic mechanisms.

One of the most important advances in the understanding of BMS is the growing body of evidence supporting the neuropathic basis of primary BMS. The systematic review by Kouri et al. identified multiple findings indicative of small-fiber nerve damage in both the oral mucosa and the peripheral nervous system. These included reduced nerve-fiber density, altered expression of receptors involved in nociceptive signal transmission, and abnormalities in nerve conduction. These findings strengthen the hypothesis that BMS should be classified as a neuropathic pain disorder in a substantial proportion of patients. This interpretation supports the use of medications that modulate neural transmission rather than conventional analgesics.

Nevertheless, neuropathy alone does not explain all cases of BMS. Adamo and Spagnuolo emphasized that BMS is a multifactorial disorder in which peripheral mechanisms may coexist with central sensitization, chronic stress, and psychological factors. The high prevalence of comorbid anxiety, depressive symptoms, and chronic stress indicates that a comprehensive psychological assessment should constitute an integral component of the diagnostic process. This approach is also supported by Tomova et al., who emphasized that failure to consider psychosomatic factors may contribute to poor therapeutic outcomes despite appropriately conducted dental treatment.

The distinction between primary and secondary forms of oral burning remains an important component of contemporary diagnostic assessment. The review by Gholizadeh et al. confirmed that deficiencies of iron, vitamin B12, folic acid, zinc, and other micronutrients may contribute to secondary oral burning symptoms. These findings highlight the need to perform basic laboratory investigations in all patients before a diagnosis of idiopathic BMS is established. Correction of an identified deficiency may result in complete symptom resolution, distinguishing secondary oral burning from primary BMS, which generally requires symptomatic treatment.

The greatest controversy continues to concern treatment. Current systematic reviews indicate that no available therapeutic modality has demonstrated unequivocal superiority over the others. The umbrella review by Almeida et al., which synthesized the findings of multiple systematic reviews, identified only moderate efficacy for some interventions, with the overall

quality of evidence generally rated as low or moderate. The strongest evidence continues to support topical clonazepam, which remains one of the best-documented pharmacological treatments for primary BMS.

Some antidepressants with analgesic properties have also demonstrated efficacy. Of particular interest are the findings of the randomized study by Adamo et al., in which vortioxetine showed efficacy comparable or superior to that of conventional antidepressants while exhibiting a more favorable adverse-effect profile. These findings suggest that modulation of serotonergic neurotransmission may represent an important component of treatment, particularly in patients with a predominant central pain mechanism.

Alpha-lipoic acid has also attracted considerable interest. The meta-analysis by Christy et al. demonstrated that this agent may provide symptom improvement in some patients, although the magnitude of the effect was moderate and did not consistently exceed that observed with placebo. Similar conclusions were reported by Homeida, who suggested that alpha-lipoic acid may be considered as a component of combination therapy but should not be regarded as a first-line treatment.

Non-pharmacological interventions are receiving increasing attention. The systematic review by Khemiss et al. suggested that low-level laser therapy may reduce pain intensity and improve patients' quality of life. However, the quality of the available evidence remains limited because of small sample sizes and substantial variation in irradiation parameters and treatment protocols.

Another emerging area of research is the use of *Cannabis sativa* preparations. The study by Adamo et al. indicated that cannabis oil may have potential efficacy in reducing BMS symptoms, possibly through modulation of the endocannabinoid system and nociceptive transmission. Nevertheless, the currently available evidence remains preliminary and requires confirmation in larger and methodologically rigorous clinical studies.

An analysis of the contemporary literature also emphasizes the need for a multidisciplinary model of care for patients with BMS. Given its complex etiopathogenesis, optimal management should involve collaboration among dentists or oral medicine specialists, neurologists, pain medicine physicians, psychiatrists or clinical psychologists, and, when clinically indicated, endocrinologists or dietitians. Such an approach increases the likelihood of identifying

reversible secondary causes while also facilitating more effective management of chronic neuropathic pain.

In summary, current evidence indicates that BMS should be regarded as a multifactorial disorder with a predominantly neuropathic basis and substantial contributions from psychological and systemic factors. The diagnostic process should focus on excluding secondary causes of oral burning and conducting a comprehensive patient assessment. Treatment should be individualized and will frequently require a combination of pharmacotherapy, non-pharmacological interventions, and psychological support.

Conclusions

The analysis of the available literature indicates that the treatment of burning mouth syndrome remains a considerable clinical challenge. The currently available therapeutic modalities may reduce symptom severity in some patients; however, study findings remain inconclusive because of differences in study design, evaluated interventions, sample sizes, and follow-up duration.

The present state of knowledge does not support the identification of any single therapeutic modality as unequivocally the most effective. Management should therefore be individualized according to the patient's clinical presentation, predominant pathophysiological mechanisms, comorbidities, and specific therapeutic needs.

Further well-designed randomized clinical trials employing standardized diagnostic criteria, treatment protocols, and outcome measures are required. Such studies are essential for the development of reliable, evidence-based recommendations for the diagnosis and treatment of burning mouth syndrome.

Disclosure

Author Contributions:

Conceptualization: JG

Methodology: WP

Formal analysis: JG

Investigation: KB, KO

Data curation: KG, JK

Writing – original draft preparation: AJ, WP, KK, KG, GC

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