**Jordan Journal of Dentistry,** Volume **3**, No. **1**, **2026**
DOI: https://doi.org/10.14525/JJD.v3i1.09

**Jordan Journal of Dentistry**

https://jjd.just.edu.jo

# Treatment Options for Burning Mouth Syndrome: A Narrative Review

**A.F.M. Shakilur Rahman[1], Shaheen Ahamed[1]**

1 Department of Oral and Maxillofacial Surgery, Rajshahi Medical College, Dental Unit, Rajshahi, Bangladesh.

**ARTICLE INFO**

**Article History:**
Received: 2/10/2025
Accepted: 16/10/2025

**Correspondence:**
A.F.M. Shakilur Rahman,
Department of Oral and Maxillofacial Surgery,
Rajshahi Medical College,
Dental Unit, Rajshahi,
Bangladesh.
raselblackpearl@gmail.com

**ABSTRACT**

Burning mouth syndrome is a persistent, idiopathic pain syndrome that is associated with burning pains in the mouth with no observable clinical abnormalities. Burning mouth syndrome is multi-factorial and heterogeneous, mostly affecting middle-aged and elderly women, which makes its diagnostics and treatment particularly difficult. The evidence-based narrative review synthesizes results from randomized controlled trials that were published between 2020 and 2025 from comprehensive searches of PubMed (MEDLINE), Embase, and DOAJ databases. Thirteen randomized controlled trials of pharmacological, non-pharmacological, and integrative therapies were chosen with the help of strict inclusion criteria. Antidepressants, especially vortioxetine, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors, were proven to be very effective, especially on patients who experience psychological co-morbidities. Non-pharmacological treatments, such as low-level laser therapy, photobiomodulation, oral cryotherapy, and low-level laser therapy in combination with the other two intervention types, demonstrated positive effects on pain and oral health-related quality of life. Melatonin and standardized herbal regimens were also other therapeutic options that had safety profiles. According to general trends, most interventions are well accepted, and placebo responses are still prevalent, particularly in device-based studies. Limitations of the studies are small sample sizes, variability of intervention protocols, brief follow-up time, and the inability to generalize the results of single-center studies. These results suggest the use of a personalized, multi-modal treatment approach to burning mouth syndrome and the necessity of conducting larger, multi-center studies with standard outcomes to maximize patient care.

**Keywords:** Antidepressants, Burning mouth syndrome (BMS), Low-level laser therapy, Non-pharmacological interventions, Pharmacological therapies, Randomized controlled trials, quality of life.

## 1. Introduction

Burning Mouth Syndrome (BMS) is an intraoral pain disorder that is chronic, idiopathic, and burning or dysesthetic, presenting with perennial pain in the tongue, lips, palate, or diffuse oral mucosa, usually without any overt clinical abnormalities or local or systemic identifiable causes (1-3). More symptoms, including xerostomia and taste disorders, are frequently present as part of the clinical picture, making the diagnosis and treatment even more complicated (4,5). BMS can typically be divided into primary (idiopathic) and secondary; in the latter case, it is combined with other factors, such as nutritional deficiencies, hormonal imbalances, or medication side effects (1,2).

Epidemiological research has estimated BMS as a disease between 1.7 and 7.9 percent, and a higher incidence was found in clinical facilities and post-menopausal women (1,4,6). Middle-aged and older adults have a higher risk of acquiring the disorder, and its distribution is strongly female-oriented, which may

be due to hormonal changes during menopause (4-6). As the BMS symptoms are long-lasting and frequently refractory, they can cause serious disabilities in everyday life, including the inability to eat, talk, or sleep, and psychological distress, such as anxiety and depression (1,4,5). The quality-of-life measurement (oral health-related and general health-related) always shows that the quality of life of BMS remains poorer than that of healthy controls (2,4,7).

The pathogenesis of BMS is not clearly understood, and all potential mechanisms are involved, such as neuropathic, hormonal, psychological, and inflammatory (1,3,5). This etiological heterogeneity makes the diagnosis more complicated and the treatment responses unequivocal. Regardless of the progress in the literature, BMS remains a therapeutic problem, and there is no universally effective treatment regime that has been identified yet (1-3). Tricyclic anti-depressants (TCAs), anticonvulsants, topical clonazepam, and capsaicin all have been found to have different levels of effectiveness as pharmacological interventions (1,3,8). Non-pharmacological interventions, including cognitive behavioral therapy (CBT), low-level laser therapy (LLLT), acupuncture, and lifestyle modifications, have yielded variable, but generally favorable, outcomes in managing BMS symptoms (1,9).

There are some studies conducted on alternative and complementary therapies, including alpha-lipoic acid supplementation, herbal medicines, and nutritional interventions, but the data about the effectiveness of these approaches is very limited and even conflicting (3,8). The systematic reviews and meta-analyses highlight the importance of the bigger, well-designed trials to be able to inform clinical practice better and set standardized treatment protocols (1,3,9).

Since BMS has a considerable load on individuals with this condition and the current issues remain inadequate in its management, the purpose of this narrative review is to summarize existing evidence on treatment administration, critically assessing both pharmacological and non-pharmacological approaches to be able to advise clinicians on how to maximize patient care and enhance the quality of life.

## 2. Materials and Methods

### 2.1 Search Strategy

A comprehensive literature search was undertaken to identify randomized controlled trials (RCTs) evaluating therapeutic interventions for Burning Mouth Syndrome (BMS). Three electronic databases-PubMed (MEDLINE), Embase, and the Directory of Open Access Journals (DOAJ)-were systematically searched using a combination of Medical Subject Headings (MeSH) and free-text terms with Boolean operators: (Burning Mouth Syndrome OR BMS) AND (Treatment OR Therapy OR Management) AND (Randomized Controlled Trial OR RCT).

The search was restricted to English-language publications between January 1, 2020 and June 30, 2025. Only RCTs investigating any therapeutic intervention for BMS were included. Exclusion criteria comprised observational studies, case reports, animal studies, non-interventional articles, and papers lacking full-text availability. Reference lists of eligible studies and relevant systematic reviews were also screened manually to identify additional studies.

Titles and abstracts were reviewed by two independent reviewers who assessed them on relevancy, and then the full-text content was filtered against inclusion and exclusion criteria. The primary limitations of this search included language restriction, exclusion of grey literature, and the focus solely on RCTs, which may have led to partial omission of relevant evidence from alternative study designs.

### 2.2 Study Selection

The database search initially identified 56 unique RCTs (28 from PubMed, 27 from Embase, and one from DOAJ). After screening and elimination of 14 duplicate records shared by both PubMed and Embase, all the remaining articles were further evaluated according to preset inclusion/exclusion criteria. After full-text screening, 13 RCTs (10-22) met the inclusion criteria and were included in this review. These trials represent the most recent and methodologically robust evidence available on the management of BMS. They form the foundation for the synthesis and critical appraisal presented herein.

## 3. Results

The selected RCTs were published between 2020 and 2025 and assessed pharmacological and non-pharmacological interventions for BMS. Studies differed in design, sample size, intervention duration, measured outcomes and comparison groups, but together provided data for critical evaluation of

treatment efficacy, safety and quality of life outcomes. Table 1.
Main study characteristics and results are summarized in

**Table 1:** Summarization and comparison of the treatment options for BMS based on the selected studies

| Study/ Author(s) (Number) | Study Design/ type | Sample Size & Gender (F/M) | Treatment Modality | Intervention Details | Treatment Duration | Outcome Measures | Findings | Adverse Effects | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Adamo et al. (10) | Open-label RCT, 5 arms | 150 patients (30/group) | Vortioxetine, Paroxetine, Sertraline, Escitalopram, Duloxetine | Vortioxetine (15 mg/d), Paroxetine (20 mg/d), Sertraline (50 mg/d), Escitalopram (10 mg/d), Duloxetine (60 mg/d) | 12 months | VAS, T-PRI, HAM-A, HAM-D, CGI | All effective; vortioxetine fastest, most sustained, highest remission (83.3%) | Mostly mild GI or sleep-related; vortioxetine had lowest AE rate | Vortioxetine recommended as first-/second-line; open-label |
| Garcia Martinez et al. (11) | RCT, single-blind, 4 arms | 89 patients (74F/4M) | LLLT + Clonazepam (26), Placebo (20), LLLT (22), Clonazepam (21) | Group 1: LLLT+Clonazepam; Group 2: Laser Sham (Helbo® 3D probe, 30 s/spot); Group 3: LLLT (Helbo® laser: 6 J/cm², 30 s/spot, weekly×4); Group 4: Clonazepam (0.25 mg **oral dissolve, nightly**) | 4 weeks | VAS, OHIP-14, salivary biomarkers | LLLT+Clonazepam and LLLT alone reduced VAS and inflammatory markers | Not detailed; no serious AEs | LLLT effective; needs standardized protocol |
| Nosratzehi et al. (12) | Double-blind RCT (15/ group) | 30 patients (22 F/8M) | Melatonin vs. Placebo | Melatonin (3 mg capsule 4 times/day) vs. placebo | 5 months | VAS, Pittsburgh Sleep Quality Index | Melatonin reduced burning pain (VAS), no sleep quality change | No significant AEs | Melatonin may help pain, not sleep; small sample |
| Zborowski & Konopka (13) | RCT, 2 arms | 57 patients (34F/23M) | Clonazepam (28) vs. Tongue Protector (29) | Clonazepam (0.5/2 mg tablet suck until dissolved, 2-3 times/day); tongue protector (0.1 mm polyethene, 60×67 mm, 3times/day, 15 min) | 4 weeks | VAS, BDI, AIS, WHOQOL | Clonazepam superior in VAS reduction, recovery; both improved QOL | Minor; 2 dropouts (clonazepam) | Psychological factors strongly linked to symptoms |
| Castillo-Felipe et al. (14) | Double-blind RCT, 3 arms | 64 patients (57 F/7M) | Melatonin (23 pts) vs. Clonazepam (16 patents) vs. Placebo (25 patients) | Melatonin (1 mg/d), Clonazepam (0.5 mg solution for rinsing, 1.5 minutes, 2 times/day ), Placebo | 8 weeks | VAS, OHIP-14, HADS, salivary markers | Both melatonin and clonazepam effective vs. placebo | Mild GI effects (melatonin/placebo); none in clonazepam) | Melatonin safe alternative; both help with pain and QOL |
| Li et al. (15) | RCT, 3 arms | 45 patients | Laser + Medication vs. Medication vs. Laser | Group A: Laser+Medication; Group B: Methylcobalamin (0.5mg, 3 times/day), xylitol chlorhexidine lozenge (3 times/day), 2% sodium bicarbonate rinsing solution (3 times/day); Group C: Laser (1064 nm, 0.5 W, 10 s/point, weekly×4) | 1 month | NRS (pain) | All improved; combination therapy most effective | Not detailed | Small sample, short duration |
| Gao et al. (16) | Open-label RCT, 2 arms | 78 patients (39/group) | Danzhixiaoyao + Methylcobalamin vs. Methylcobalamin | Trial: Danzhi Xiaoyao (2.8g tablet 2times/day) + Methylcobalamin; Control: Methylcobalamin (0.5 mg 3 times/day) only | 6 weeks | VAS, BDI, BAI, OHIP-14, TCM score | Combo superior in pain, depression, QOL; no anxiety difference | None reported | Chinese herbal combo effective; no recurrence at 2 weeks |
| Lu et al. (17) | Multi-center RCT, 4 arms | 128 patients (32/group) (118F/10/ M) | PBM + OCT vs. PBM vs. OCT vs. Drug Therapy | PBM (1 time/ week)+OCT (3 times/day), PBM, OCT (20 mm intraoral ice-ball movement), Drug Therapy (3 times/day) (mecobalamin 0.5mg tablet + sodium bicarbonate 2% oral solution for gargling) | 7 weeks | VAS, OHIP-14, GAD-7, PHQ-9, PSQI | PBM+OCT best for pain/anxiety; all groups improved | 4% minor events; no severe AEs | PBM+OCT most effective; safe, large multi-center study |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Skrinjar et al. (18) | RCT, double-blind | 23 patients (LLLT/12, Placebo/11) (3M/ 20F) | LLLT vs. placebo | LLLT: Ga-Al-As diode, 685 nm, 2 J/cm², 30 mW, 10 sessions (once daily, 10 days, excluding weekends); Placebo: inactive probe with audio signal | 10 days (excluding weekends) | VAS (burning symptoms), salivary cortisol | Both groups showed significant reduction in VAS and salivary cortisol after treatment; no significant difference between groups | None reported | First study to measure salivary cortisol before/after LLLT in BMS; possible placebo effect; small sample size |
| de Pedro et al. (19) | RCT, single-blind, parallel trial | 20 patients (8F/2M per group) | PBM (LLLT) vs. placebo | LLLT: Diode laser, 810 nm, 0.6 W, 12 J/cm², 10 sessions (twice/week, 5 weeks); Placebo: device off | 5 weeks (10 sessions) | VAS (pain), McGill, OHIP-14, SF-36, Epworth, SCL 90-R | LLLT group: significant pain reduction (VAS), improvement in some QoL and psychological measures; effect maintained at 4 months. Placebo: minimal change. | None reported | Longer follow-up (4 months) than most studies; small sample size; not double-blind |
| Lončar-Brzak et al. (20) | RCT, open-label | 62 patients (13 informative, 17 B vitamins, 17 probiotics, 15 LLLT) (47F/15 M) | Verbal/written information, B vitamin injections, oral probiotics, LLLT | LLLT: Ga-Al-As diode, 685 nm, 2 J/cm², 30 mW, 10 sessions; B vitamins: Neurobion (B1, B6, B12) i.m. every other day x9; Probiotics: L. reuteri lozenge daily x1 month | LLLT: 10 days; B vitamins: 3 weeks; Probiotics: 1 month | OHIP-14 (QoL), VAS (symptoms) | LLLT and probiotics significantly improved QoL (OHIP-14); all groups improved VAS; probiotics had largest effect size for QoL | None reported (mild transient discomfort at injection site for B vitamins) | No placebo group; short follow-up (1 month); all treatments improved symptoms |
| Assiri (21) | RCT | 80 patients (40/group) (62 F/18 M) | Tricyclic antidepressants (TCAs) vs. anticonvulsants | TCAs (e.g., amitriptyline/ nortriptyline) *vs.* anticonvulsants (gabapentin/pregabalin), oral, dose adjusted for tolerability | 6 months (assessed at 3 and 6 months) | VAS (pain), OHIP (QoL), HADS (psychological distress) | Both groups: significant pain, QoL, and psychological improvement; TCAs: 70% pain reduction, anticonvulsants: 65%; no significant difference | Not detailed | No significant difference between TCAs and anticonvulsants; short-term follow-up |
| Palmer et al. (22) | RCT, double-blind, sham-controlled pilot study | 22 patients (11/group) (approx. 77% F) | CES + TENS vs. sham stimulation | CES: 100 µA, 0.5 Hz, 60 min/day x28 days to auricular lobules; TENS: 3 min tongue stimulation; Sham: identical device, no current | 4 weeks | NRS (pain), OHIP-14, PSQI (sleep), PHQ, HADS, PDI | Both groups: significant pain reduction, improved sleep and somatic symptoms; no difference between active and sham | None reported | Small sample, short duration, possible strong placebo effect, no long-term follow-up |

AE, Adverse Effects; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CES, Cranial Electrotherapy Stimulation; **CGI**, Clinical Global Impression scale; HADS: Hospital Anxiety and Depression Scale; **HAM-A**, Hamilton Anxiety Rating Scale; **HAM-D**, Hamilton Depression Rating Scale**;** LLLT, Low-level Laser Therapy; NRS: Numeric Rating Scale (pain); OCT: Oral Cryotherapy; OHIP-14: Oral Health Impact Profile (quality of life); PBM: Photobiomodulation; PDI, Pain Disability Index; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL, Quality of Life; RCT, Randomized Controlled Trial; TCM: Traditional Chinese Medicine; **T-PRI**, Total Pain Rating Index (McGill Pain Questionnaire)**;** TENS, Transcutaneous Electrical Nerve Stimulation; VAS: Visual Analogue Scale (pain).

### 3.1 Efficacy Across Interventions

Interventions for BMS across all studies demonstrate efficacy in the alleviation of symptoms and evidence demonstrates that both pharmacological and non-pharmacological modalities both alleviate symptoms, although the magnitude and consistency of the benefits occur by modality. Pharmacological treatments, such as anti-depressants (vortioxetine, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine re-uptake inhibitors [SNRIs], tricyclic anti-depressants [TCAs]), anti-convulsant drugs (gabapentin, pregabalin) and topical clonazepam, have shown a significant decrease in pain and psychological distress (10,13,21). For patients carrying high comorbidity in the psychiatric sphere, it is important to note that vortioxetine and SSRIs/SNRIs have been shown to result in higher remission rates which expect transmission of focus on a tailored psychotherapy possibility depending upon

psychiatric profiles. Low-level laser therapy (LLLT), photobiomodulation (PBM), and oral cryotherapy (OCT) have demonstrated effectiveness in reducing the intensity of pain and improving oral health-related quality of life, and among them, PBM combined with OCT has been shown to have the greatest improvement in larger multicentre studies (17). Melatonin has shown promise of another alternative with similar characteristics to clonazepam for pain relief, but with a better safety and adverse effect profile (14). Chinese herbal medicines combined with methylcobalamin, especially integrative therapies, have shown greater improvements in both symptoms and psychological outcome than those of control therapies (16). Meanwhile, adjuvant treatments, such as probiotics, B vitamins, and various types of electrotherapies, have resulted in more small effects, mainly improving quality of life, but these effects are contingent and oftentimes less than those seen in other studies (17,20). This heterogeneity highlights the need for a personalized multi-modal approach to the management of BMS.

### 3.2 Safety and Tolerability

Most interventions were generally well tolerated, and there were some reports of serious or lasting adverse effects. Pharmacological treatments were found to be associated with mild gastrointestinal or sleep related side effects (10,14). The non-pharmacological therapies, especially LLLT, PBM and OCT, showed excellent safety profiles (11,17,19).

### 3.3 General Trends

Most studies showed that there are improvements in pain and quality of life outcomes with some type of intervention. However, there were a high number of placebo responses, especially in device-and laser-based studies, highlighting the need for stringent blinding and control conditions. Any findings would be limited in generalizability and any comparisons across modalities depending on the heterogeneity of the sample sizes, as well as the variety of intervention protocols.

Many pharmacological, non-pharmacological and integrative interventions have been found to be effective for BMS, with good safety profiles in general. Treatment effects were most pronounced for patients treated with newer anti-depressants, PBM (particularly when combined), melatonin and some herbal remedies. Results of multi-modal care suggested that no single modality proved universally superior, further supporting a personalized multi-modal approach to care.

## 4. Discussion

BMS is a therapeutic challenge; it is complex, multifactorial in etiology, variable in symptoms and has few universally effective interventions. Some developments have taken place over the last years in the design of clinical trials (use of multi-arm RCTs and the use of patient-reported outcome measures), but heterogeneity of studies and small sample sizes remain important barriers to definitive recommendations.

### 4.1 Comparison of Pharmacological Therapies

#### 4.1.1 Anti-depressants

Several high-quality randomized controlled trials have shown the effectiveness of anti-depressants (including vortioxetine, SSRIs and SNRIs) at reducing pain and influencing comorbid psychological symptoms in BMS. For example, Adamo et al conducted a five-arm RCT of vortioxetine compared with paroxetine, sertraline, escitalopram and duloxetine all for 12 months, and showed significant decreases in three pain scales, three anxiety scales, and three depression scales in all arms (10). Group-I focus was especially on vortioxetine, which demonstrated the highest percentage of remission (up to 83.3%), the quickest onset of action and the most favorable adverse effect profile (mainly mild gastrointestinal or sleep-related adverse effects), confirming its role as a preferential choice as first- or second-line therapy in well-selected patients (10). It was also determined that maximal and sustained effects were localized only in the treatment duration; minimal benefits were present with only 1 or 2 incidents of treatment while maximal and globally lasting effects were observed at a minimum about 6 or 12 months of continuous treatment.

This is also supported by recent network meta-analyses and primary trials, which found a comparable level of effects for SSRIs and SNRIs for BMS mainly with significant psychological comorbidities (23). However, consideration of tolerability profiles and potential for drug interaction, particularly in older and medically complex patients, deserves individual consideration.

#### 4.1.2 Tricyclic Anti-depressants (TCAs) and Anti-convulsants

The utility of more ancient agents, such as

amitriptyline and nortriptyline (TCAs) and anti-convulsants (gabapentin, pregabalin) have also been appraised. Assiri published an RCT to directly compare the effects of TCAs *vs*. anticonvulsants over 6 months and found that both drug classes provided significant reductions in pain (mean reductions 65%-70%), oral health-related quality of life (OHIP) and psychological distress (HADS), but there were no significant differences between groups (21). These findings are consistent with those from Cochrane reviews and other trials, which suggest that they are effective in both classes, but have limited side-effect spectra (e.g. sedation, dizziness, anti-cholinergic side effects for TCAs; somnolence, weight gain for anticonvulsants) (24).

#### 4.1.3 Clonazepam

Clonazepam (oral or topical) has been the most thoroughly studied agent to date with several RCTs showing it to be effective for short- and long-term symptom reduction. Zborowski and Konopka (13) noted that clonazepam was superior to the tongue protector in VAS pain reduction and in achieving higher rates of complete resolution of the symptoms. Importantly, benefits were also seen for related areas of depression, insomnia and quality of life. However, doubts over benzodiazepine dependence, cognitive impact and regulatory constraints are likely to limit its long-term application while dropout in response to mild adverse effects is occasionally reported. This is in agreement with systematic reviews, where there is evidence to support the use of clonazepam (predominantly in topical/oromucosal regimens) as a reasonable choice in patients where other treatments have failed or are not tolerated (1, 25).

### 4.2 Non-pharmacological and Combination Interventions

#### 4.2.1 Low-level Laser Therapy (LLLT) and Photobiomodulation (PBM)

A considerable amount of randomly-controlled treatment trials (RCTs) have been addressed in the latter years in the field of evaluation of LLLT and PBM either as monotherapy or as part of combination protocols. The synthesis of evidence from these and other studies (11,17,19) and several meta-analyses, tends to support a positive response in the effects of LLLT/PBM on pain intensity (changes and higher median differences, up to 2-4 points) and enhancement in quality of life and biomarker profile (lowered pro-inflammatory cytokines, decreased salivary cortisol) compared to placebo or standard drug therapy. The greatest benefits were reported when PBM was combined with adjunctive treatments (e.g. OCT), as in the multi-center RCT (17) in which PBM + OCT showed the highest response levels and improvements in both pain and anxiety compared to these interventions alone or in combination with standard drug therapy.

Despite these results, there is still a great heterogeneity in the parameters used in laser treatment (wavelength, energy density, duration, treatment schedule) and a percentage of studies show significant placebo effects. Some double blind RCTs (18) did not report these notable improvements in both active and sham groups, underscoring the need for careful blinding and placebo controls. Importantly, no severe adverse effects have been reported in PBM/LLLT trials, confirming their safety.

#### 4.2.2 Melatonin

Melatonin has been increasingly studied for its pleiotropic analgesic, mood regulatory and sleep stabilizing effects. These RCTs (12,14) show that melatonin is as efficacious as clonazepam in terms of reduction of the burning pain and improvement of oral health-related quality of life with a better safety profile (mainly mild GI effects, no major neuropsychiatric adverse effects). However, the evidence for the use of melatonin to improve quality of sleep was not much more compelling than placebo - contrary to its theoretical mechanism of action. Overall, melatonin presents a strong case for being regarded as a reasonable adjunct (or alternative), particularly in patients with a history of polypharmacy and/or those who are contraindicated to usual therapies (12,14).

#### 4.2.3 Herbal and Integrative Medicine

There is a reported article for traditional medicine and integrative modalities. Gao et al. reported that Danzhi Xiaoyao tablets (a Chinese herbal formula) plus methylcobalamin were significantly better than methylcobalamin alone in terms of pain reduction, improvement of depression and oral health quality, without any adverse effects or relapses (16). This data is consistent with the findings of meta-analyses on herbal interventions, but should be treated with caution,

because of differences in quality, lack of international standardization and shorter follow-up periods. Larger, multi-center, long term RCTs are required to confirm these promising approaches worldwide.

**4.3 Other Interventions**

Topical agents (e.g. capsaicin, oral cavity probiotics), CBT, cranial electrotherapy stimulation (CES), and devices (tongue protectors)) have been investigated. The numbers needed to treat for capsaicin and probiotics are still high, and while reports of quality-of-life improvements are sometimes made (20), effect sizes are generally lower than with pharmacologic/laser therapies. CES and transcutaneous electric nerve stimulation (TENS), evaluated in a pilot RCT (22) showed significant symptom reduction in both the active and the sham groups, again underscoring a pronounced placebo effect and the need for larger trials with a rigorous methodological approach. Of note, there have been no significant adverse events reported in the combined device-based interventions.

**4.4 Critical Appraisal of Study Quality**

On critical analysis of the quality of the included studies, one can notice that the methodological rigor of recent RCTs exploring the subject of burning mouth syndrome has an important improvement. These advances are defined by greater multi-center enrollment, systematic randomization of studies, use of active comparator arms, and validated outcome measures which include Visual Analog Scale (VAS), Oral Health Impact Profile-14 (OHIP-14) and Hospital Anxiety and Depression Scale (HADS). In addition, overall adverse event documentation has been included in these trials, indicating the increased concern to safety reporting (10-12).

Although these are the strengths, the constraints remain severe and curtail the strength and overall generalizability of the existing evidence. The major issue is associated with statistical power: most RCTs are underpowered with a number of participants across arms less than 100, which prevents the representativeness of sub-groups, including males and patients with severe psychological co-morbidities. Furthermore, even in high quality and well-designed double-blind and sham-controlled trials, there is a high placebo effect which makes it difficult to attribute the overall benefits to be realized only to active interventions (13,14,22).

Heterogeneity of diagnostic criteria, type of intervention, and length of follow-up (between four weeks and up to 12 months) further impact meta-analytic synthesis and indirect comparisons, which increases a lack of interpretability. Few studies have gone past six to twelve months and thus long-term issues pertaining to intervention durability, relapse rates, and safety profiles are not resolved (15,17). Additionally, single-centre studies are predominant, and in particular, those studies, focusing on herbal and traditional medicine regimens, limit the global applicability of the findings to various healthcare settings (16,18).

Taken together, all these methodological issues highlight the urgency of bigger, multicenter, and internationally standardized clinical trials with sufficient statistical power, uniform diagnostic criteria, stringent outcome measures, and extended follow-up to obtain strong evidence on clinical management of BMS (19,21).

**4.5 Integration and Recommendations**

A synthesis of current RCTs suggests using a stepwise, patient-focused approach as the foundational strategy in management of BMS. The application of SSRIs, SNRI, newer anti-depressants, like vortioxetine (10), topical or oromucosal clonazepam (11,13), have all been supported by evidence as first-line treatments, depending on the psychological co-morbidities of a patient, and personal preferences. There are also benefits of adjunctive or alternative interventions, such as LLLT and PBM (11,17) combined or where pharmacological interventions are inadvisable or rejected, as well as melatonin (12,14) and standardized herbal formulations (16), that show additional pain-reducing and quality of life benefits.

In the case of refractory or complicated cases, TCAs, anti-convulsants, or multi-disciplinary interventions that include cognitive behavioral therapy, cranial electrotherapy stimulation, and other integrative medical methods are also an option to maximize the effect (22). According to cumulative research, there is urgency to conduct strong, multi-center, and double-blind clinical trials that utilize standard outcome and adverse effect reporting to improve the evidence-based and clinical practice. Although many modalities are effective, patient education and therapeutic expectation management are still paramount, as the placebo effects are important and frequent across interventions (10,22).

## 5. Conclusions

Burning Mouth Syndrome (BMS) is a chronic and multi-factorial disorder of pain with no universal cure. Recent high-quality RCTs show that pharmacological as well as non-pharmacological therapies can provide meaningful relief of symptoms. Among pharmacological options, the newer anti-depressants (e.g. vortioxetine), as well as tricyclics, SSRIs, SNRIs, and anticonvulsants, have moderate-to-high efficacy in reducing pain, improving oral health-related quality of life, and managing psychological co-morbidities and good tolerability in suitable patients. Non-pharmacological treatments, like LLLT, PBM (with OCT), and clonazepam, have significant pain and quality-of-life benefits without many side effects. Integrative approaches are promising, but require further validation. Overall, individualized, evidence-based, and standardized multi-center research is essential to optimize the management of BMS in the long term.

## Conflict of Interests

Regarding the publishing of this review, the authors affirm that there are no conflicting interests. There are no personal or financial ties that could have impacted the work.

## Funding Information

There were no outside funding sources for this study.

## References

1. Tan HL, Smith JG, Hoffmann J, Renton T. A systematic review of treatment for patients with burning mouth syndrome. Cephalalgia. 2022;42:128-161.
2. Lopez-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sanchez-Siles M, Gomez-Garcia F. Burning mouth syndrome: An update. Med Oral Patol Oral Cir Bucal. 2010:e562-e568.
3. Christy J, Noorani S, Sy F, Al-Eryani K, Enciso R. Efficacy of alpha-lipoic acid in patients with burning mouth syndrome compared to that of placebo or other interventions: A systematic review with meta-analyses. J Dent Anesth Pain Med. 2022;22:323.
4. Meneguette AF, Moraes PD, Guimarães AS, Rodrigues L, Cruz MM. Pain perception and quality of life in burning mouth syndrome. Br J Pain. 2020;3:153-157.
5. Rinaldi F, Gerardi D, Burdo P, Angiolani F, Durate Mendes G, et al. Burning mouth syndrome: Review of etiopathogenetic factors and update on clinical management strategies. Oral Implantol. 2025;17:35-43.
6. Ghalwash D, Abou-Bakr A, Ammar A, Hamdy A, El-Gawish A. Prevalence profile of burning mouth syndrome in a sample of Egyptian population: A cross-sectional clinical based study. Explor Med. 2024;5:615-625.
7. Pereira JV, Normando AG, Rodrigues-Fernandes CI, Rivera C, Santos-Silva AR, et al. The impact on quality of life in patients with burning mouth syndrome: A systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131:186-194.
8. de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, de Oliveira Soares AC, Pinto LP, et al. Randomized trials for the treatment of burning mouth syndrome: An evidence-based review of the literature. J Oral Pathol Med. 2012;41:281-287.
9. Cabras M, Gambino A, Broccoletti R, De Paola S, Sciascia S, et al. Effectiveness of non-pharmacologic treatments of burning mouth syndrome: A systematic review. J Oral Fac Pain Headache. 2021;35:175-198.
10. Adamo D, Pecoraro G, Coppola N, Calabria E, Aria M, et al. Vortioxetine *versus* other anti-depressants in the treatment of burning mouth syndrome: An open-label randomized trial. Oral Dis. 2021;27:1022-1041.
11. Garcia Martinez A, Lopez-Jornet P, Pardo Marin L, Pons-Fuster E, Tvarijonaviciute A. Burning mouth syndrome treated with low-level laser and clonazepam: A randomized, single-blind clinical trial. Biomedicines. 2024;12:1048.
12. Nosratzehi T, Payandeh A, Arbab K. Evaluation of the effect of melatonin in patients with burning mouth syndrome: A double-blind, placebo-controlled randomized clinical trial. Braz J Pharm Sci. 2023;59:e21748.
13. Zborowski J, Konopka T. Comparison of clonazepam and tongue protector in the treatment of burning mouth syndrome. Int J Environ Res Public Health. 2022;19:8999.
14. Castillo-Felipe C, Tvarijonaviciute A, Lopez-Arjona M, Pardo-Marin L, Pons-Fuster E, et al. Response to treatment with melatonin and clonazepam *versus*

placebo in patients with burning mouth syndrome. J Clin Med. 2022;11:2516.

15. Li X, Li Q, Li J, Wang X, Zou H, et al. The improvement of pain symptoms in patients with burning mouth syndrome through combined laser and medication therapy. Technol Health Care. 2024;32:501-509.
16. Gao Y, Yang J, Sun H, Zhou H. Efficacy of Danzhixiaoyao tablets combined with methylcobalamin tablets in the treatment of burning mouth syndrome: An open-label, randomized controlled trial. BMC Oral Health. 2024;24:603.
17. Lu C, Zhou X, Yang C, Jiang X, Li X, et al. Efficacy and safety of photobiomodulation combined with oral cryotherapy on oral mucosa pain in patients with burning mouth syndrome: A multi-institutional, randomized, controlled trial. BMC Med. 2025;23:196.
18. Škrinjar I, Lončar Brzak B, Vidranski V, Vučićević Boras V, Andabak Rogulj A, et al. Salivary cortisol levels and burning symptoms in patients with burning mouth syndrome before and after low level laser therapy: A double blind controlled randomized clinical trial. Acta Stomatologica Croatica: Int J Oral Sci Dental Med. 2020;54:44-50.
19. de Pedro M, López-Pintor RM, Casañas E, Hernández G. Effects of photobiomodulation with low-level laser therapy in burning mouth syndrome: A randomized clinical trial. Oral Dis. 2020;26:1764-1776.
20. Lončar-Brzak B, Škrinjar I, Brailo V, Vidović-Juras D, Šumilin L, et al. Burning mouth syndrome (BMS): Treatment with verbal and written information, B vitamins, probiotics, and low-level laser therapy: A randomized clinical trial. Dent J. 2022;10:44.
21. Assiri KI. Evaluating the efficacy of two pharmaceutical therapies for burning mouth syndrome. J Pharm Bioallied Sci. 2024; 16:S2670-S2672.
22. Palmer A, Hamann T, Liese J, Müller B, Kropp P, et al. Efficacy of cranial electrotherapy stimulation in patients with burning mouth syndrome: A randomized, controlled, double-blind pilot study. Front Neurol. 2024;15:1343093.