Family Medicine & Primary Care Review 2022; 24(1): 78–82, https://doi.org/10.5114/fmpcr.2022.113018

REVIEWS

ISSN 1734-3402, eISSN 2449-8580

Burning Mouth Syndrome Treatment. A challenge to Evidence-Based Medicine

GUILHERME ROOK DE LIMA[A–F], SARA FAUSTINO[A–F]
ORCID ID: 0000-0002-7631-1011 ORCID ID: 0000-0002-1938-0678

USF Conde Saúde, Administração Regional de Saúde Lisboa e Vale do Tejo, Lisbon, Portugal

A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary Burning Mouth Syndrome (BMS) is defined as a burning sensation or numbness in the oral mucosa, which occurs more than 2 hours per day for more than 3 months, in the absence of clinical changes. The prevalence varies between 0.1 and 7%. Of unknown aetiology, it is more frequent in individuals with anxiety, personality disorders and depression, affecting quality of life (QoL).
The objective of this article is to review the effectiveness of existing therapies versus a placebo regarding symptomatic relief and changes in QoL.
Research was carried out during December 2020 utilising PubMed and The Cochrane Library databases, with the MeSH terms "burning mouth syndrome treatment". This research was limited to randomised clinical trials including a placebo group, published after a systematic review by Cochrane in 2016, in English. To classify levels of evidence and the strength of recommendations, we used the "Strength of Recommendation Taxonomy of the American Academy of Family Physicians".
In studies with a low level of evidence, there seems to be symptomatic improvement with laser radiation, palmitoylethanolamide tablets and serotonin reuptake inhibitors. Oral melatonin and topical chamomile therapy are no better than a placebo.
This is a difficult condition to treat, in which there is limited evidence. Fluoxetine seems to play a role in the long-term symptomatic improvement of these patients, and low-level laser therapy is an alternative therapy to consider. As it is a condition of unknown aetiology, and it is difficult to find adequate treatment with consistent results.
Key words: burning mouth syndrome treatment.

Rook de Lima G, Faustino S. Burning Mouth Syndrome Treatment. A challenge to Evidence-Based Medicine. *Fam Med Prim Care Rev* 2022; 24(1): 78–82, doi: https://doi.org/10.5114/fmpcr.2022.113018.

Background

The International Headache Society defines Burning Mouth Syndrome (BMS) as an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions [1]. This sensation is mainly located bilaterally, in the anterior two-thirds of the tongue (71–78%), followed by the dorsum and lateral borders of the tongue (72%) or even in the hard palate and lips. It often occurs simultaneously in various sites [2].

It is a debilitating condition for the patients and is known for its persistent moderate to severe intensity of burning pain, with a pain score of 8/10, and therefore significantly reducing patients' quality of life (QoL) [3].

This burning mouth sensation can be associated with xerostomia or dysgeusia, even with a normal salivary flow, and the association of these symptoms with local or systemic factors is called Secondary Oral Burning**.** Failure to rule out this differential diagnosis will result in inappropriate management strategies.

In BMS, symptoms may decrease when eating or chewing; they are typically bilateral in presentation and may be present at multiple oral sites. Secondary oral burning related to mucosal changes may be located in areas of mucosal lesions and typically increases when eating, particularly with spicy or acidic foods. Secondary oral burning associated with systemic conditions may be bilateral [4].

Its prevalence varies between 0.1 and 7% in the general population, increasing with age in both genders, and can rise to 12–18% in postmenopausal women. It is more frequent in individuals with anxiety, personality disorders and depression [5].

The aetiology of this syndrome is unknown, although recent findings suggest BMS is associated with a neuropathic mechanism affecting peripheral or central levels of the nervous system [6]. It can be attributed to various factors, either local or systemic. Regarding local factors, it can be caused by parafunctional habits, badly fitting prostheses, oral infections, allergic reactions or even xerostomia. On the other hand, numerous systemic factors can contribute to this complex syndrome. First, endocrine disorders like hypothyroidism, diabetes and menopause, followed by deficiencies in certain items like vitamin B complex, iron or zinc, anaemia, gastroesophageal reflux and Sjögren's syndrome have been pointed to as possible causes for BMS [5].

The existence of an imbalance in the antioxidant status and a reduced anti-inflammatory response has been reported, suggesting the influence of these factors on the pathogenesis.

Since the etiopathogenesis is not completely clear, the approach to this syndrome is challenging. Treatment is usually personalised and aimed at symptomatic relief.

In 2016, McMillan et al. produced a review published in *Cochrane* that reported the effects of some experimental therapies. They found evidence of short-term relief of symptoms with directed energy waves, topical clonazepam, thin plastic tongue covers and gabapentin. Regarding long-term relief of symptoms, psychological therapy, a chili pepper mouth rinse and clonazepam showed the best results [6].

In many cases, medical therapy, when effective, will help to decrease the severity of the burning symptoms; however, complete resolution is less frequent. Setting the patients' expectations regarding the effects of treatment is a central component of the therapeutic process [7].

Even though it is not one of the most common clinical problems addressed by family doctors in their practice, it represents a significative burden to a patient's life. Since no optimal treatment has been presented so far, and the previous Cochrane BMS treatment review was more than five years ago, there is an urgent need to identify which treatment shows the best results in light of current knowledge.

Thus, the objective of this article is to review the effectiveness of existing therapies versus a placebo in terms of symptomatic relief and quality of life, excluding articles on the same topic carried out by *Cochrane* in 2016 prior to the review.

Material and methods

The research was carried out between 2 and 6 December 2020 utilising *PubMed* and *The Cochrane Library* databases, with the MeSH terms "burning mouth syndrome treatment".

It was restricted to the English language and narrowed down to articles published after the 2016 *Cochrane* review on the same subject.

Subsequently, studies were excluded based on an assessment of relevance of title and abstract. The remaining studies were evaluated in their entirety, and those that met the following criteria were included: placebo randomised controlled trial (RCT); change in pain/burning sensation as a primary outcome.

Of 86 total studies identified during the initial database search, 8 remained for final review after eliminating those that did not fit our inclusion criteria.

For the attribution of level of evidence and strength of recommendations, we used the Strength of Recommendation Taxonomy of the American Academy of Family Physicians.

Results

Electromagnetic radiation

Three randomised controlled trials (RCTs) studied the effect of lasers with different characteristics versus a placebo in patients with BMS: 815nm GaAlAs laser (Valenzuela 2017) [8], 830nm GaAlAs laser (Sikora 2018) [9], K Laser Cube 3 660–970 nm (Bardellini 2019) [10], each of which had different intervention protocols. These studies, which mostly assessed symptomatic relief and effect on the quality of life, produced evidence of intermediate quality. It should also be noted that the side effects reported after this intervention were scarce or non-existent.

Symptomatic relief

In the RCT performed by Valenzuela et al. in 2017 [8] with 44 participants, values recorded on the Visual Analog Scale (VAS) were significantly lower in the intervention groups (Groups I and II) than those recorded in the placebo group. In this study, laser application was performed according to two different protocols (differing in the applied dose), and no significant differences were found between these two groups after 2 weeks of treatment. The outcomes were also assessed at two moments (2 and 4 weeks) of the study, and no substantial symptomatic improvement was revealed from the first to the second assessment (percentages of improvement in VAS: Group I – 15.7%; Group II – 15.6%, and placebo group – 7.3%).

In the work carried out in 2018 by Sikora et al. [9], also with 44 participants, the results presented were different from those mentioned above. Also using VAS for pain assessment, and a slightly different intervention protocol, this randomised clinical trial found a symptomatic improvement in the intervention group, as well as in the placebo group, both with statistical significance.

In 2019, Bardellini et al. [10], in a study including 85 participants and using a laser different from those previous mentioned, obtained encouraging results, since the intervention group showed statistically significant symptomatic improvement. It is critical to note that this improvement was maintained after 1 month of follow-up.

Quality of life

Oral health-related quality of life was assessed according to the OHIP-14 scale in the three studies mentioned.

Based on the research carried out by Valenzuela et al. [8], QoL improved after 2 weeks in both intervention groups; however, it did not show significant differences in the 4-week assessment.

In turn, Sikora et al. [9] recorded different results, as they did not obtain significant differences in the OHIP-14 scale after laser treatment.

In the recent RCT by Bardellini et al. [10], there was an improvement in the QoL index, which was evident from the seventh out of the ten laser sessions performed, which was maintained after 1 month of follow-up.

Xerostomia and anxiety/depression

Of the studies mentioned above, only the one carried out by Valenzuela et al. [8] assessed these two outcomes, using the Xerostomia Index and the Hamilton Rating Scale for Anxiety/Depression (HAM-A/HAM-D, respectively). From this assessment, it should be noted that there was no change after the laser treatment.

Melatonin

Varoni et al., in 2018 [5], performed a cross-over, randomised, triple-blind study, in which 20 patients took 12 mg of melatonin (MLT) or a placebo for 8 weeks.

They used a different pain evaluation scale (five-point categorical scale), as well as VAS, and no therapeutic advantage of melatonin was found, since it had similar efficacy when compared to the placebo. However, this result must take into account that there was incomplete therapy compliance, as suggest by MLT serum concentrations.

Furthermore, changes in sleep quality and anxiety were also assessed using the MOS (Medical Outcomes Survey) Sleep Scale and HAM-A – no clinically relevant changes were found.

Palmitoyethanolamide (PEA)

Known as PEA, it is composed of an endogenous fatty acid and ethanolamine and is often used for its alleged anti-inflammatory and analgesic properties. In 2018, Ottaviani et al. [11] carried out a controlled, double-blind trial with 35 patients, where they assessed the effect of this substance in reducing BMS symptoms (60 mg twice a day for 60 days). In this study, only patients with a BMS intensity greater than 4 (Numeric Rating Scale – NRS) were included.

When compared to the placebo, PEA reduced BMS-related complaints. After the end of therapy, the improvement was maintained, although it was not statistically significant. It is important to mention that the scale used to assess pain in this study was not VAS but NRS.

Bupivacaine (local anaesthetic)

Treldal et al. [12] assessed the effect of bupivacaine tablets in reducing pain, dry mouth and taste disorders in a crossover, double-blind, randomised study with 18 patients diagnosed with BMS. Bupivacaine or placebo lozenges were administered twice a day for two weeks over two different periods. Regarding pain, there was a statistically significant decrease during treatment with bupivacaine; however, it had no effect on xerostomia in most of the participants. One of the subjects even revealed a general worsening of xerostomia after the experimental treatment. Regarding taste alteration, it also led to a statistically significant aggravation. Despite having a positive effect on pain,

Table 1. Results. Summary

Intervention	Study	Participants	Burning pain	Other outcomes	Notes	LE	SR
Electromagnetic radiation	Valenzuela et al. 2016	44	Significantly improved	• QoL improved only 2 weeks after • Xerostomia and depression unchanged		2	B
	Sikora et al. 2018	44	Significantly improved	QoL unchanged	Pain also improved in placebo group	2	B
	Bardelini et al. 2019	85	Significantly improved	QoL improved		2	B
Melatonin	Varoni 2018	20	No changes	Sleep quality and anxiety unchanged		2	B
PEA	Ottaviani et al. 2019	35	Significantly improved	Not assessed	Effect persists over time	2	B
Bupivacaine	Treldal et al. 2016	18	Significantly improved	• Xerostomia unchanged • Taste alteration worsened		2	B
Chamomile	Valenzuela et al. 2016	57	Significantly improved	Xerostomia and QoL improved	Pain, xerostomia and QoL also improved in placebo group	2	B
Fluoxetine	Zoric 2018	100	Significantly improved	Depression and anxiety improved		2	B

LE – Level of Evidence; SR – Strength of Recommendation.

this lozenge caused some side effects (although tolerable), such as a stinging sensation or discomfort when swallowing.

Chamomile

In 2016, Valenzuela et al. [13] carried out a randomised, double-blind study to assess the efficacy chamomile gel in treating BMS pain and xerostomia, as well as in improving the quality of life of these patients. This study conducted based on its anti-inflammatory and analgesic properties, which are given by the flavonoids and volatile oil making up part of its composition.

After randomising 62 patients, both groups (the placebo group and the group that was administered 2% chamomile gel twice a day) experienced improvement (with statistical significance) in all outcomes (pain, xerostomia and QoL).

Beyond this, the aforementioned study revealed a different result – the time factor showed a moderate but relevant effect, leading to a pain improvement through time.

Fluoxetine

Zoric et al. [14] assessed the efficacy of fluoxetine on pain and psychological symptoms associated with BMS in a crossover study with 100 patients, most of whom (70–80%) fit the criteria for depression according to the scales used (HAM-D and BDI), and almost half fit the criteria for anxiety syndrome (HAM-A scale). For 6 months, half of the participants took 20 mg/day of fluoxetine, and in the absence of results, they could go up to a maximum dose of 40 mg/day after 3 months. At the end of this 6-month period, there was a statistically significant improvement in pain (assessed with VAS) and anxiety (assessed with HAM-A). The depressive symptoms of these patients were also significantly reduced, as reported by the improvement in the HAM-D scale.

Among all the studies presented, it should be mentioned that after using the Strength of Recommendation Taxonomy of the American Academy of Family Physicians, they were rated with a Level 2 evidence and a B-level recommendation.

Discussion

As mentioned above, in 2016, *Cochrane* presented a review of therapeutic interventions in BMS, using studies from 1995 to 2015. Since 2016, the studies produced correspond to only four of these categories (antidepressants, food supplements, electromagnetic radiation and topical treatments); there is no new data in the categories of cholinergic medications, benzodiazepines, anticonvulsants, physical barriers and psychotherapy.

Regarding this cited review, evidence was found of short-term relief for directed energy waves, clonazepam, thin plastic tongue covers and gabapentin. In the long-term, psychological therapy, chili pepper mouth rinse and clonazepam have shown the best evidence of relief of symptom [3].

From the data above, we can conclude the following in relation to the reviewed categories in this article:

Antidepressants

The association between BMS, depression and anxiety is frequent; however, evidence for the effectiveness of antidepressants on BMS symptoms is weak/insufficient. In the study by Zoric et al. [14], fluoxetine reduced the intensity of depressive symptoms and pain, with an efficacy in relation to pain similar to the placebo. There is no sufficient evidence to treat symptoms using this pharmacological class. In the case of overlapping depressive symptoms, as in the case of this study, the improvement of depressive complaints seems obvious, given this drug's characteristics. Its use is justified in the presence of underlying depressive symptoms or even in the presence of anxiety.

Fluoxetine is not the only antidepressant used in BMS treatment, since the data presented in the study produced by Maina et al. suggested that Amisulpride and SSRIs may be effective treatments for BMS. It was also mentioned that they were well tolerated in the short-term treatment of this syndrome [15].

Dietary supplements

ALA (alpha-lipoid acid) [16–18], lycopene [19], green tea extract [18] or hyperium [20] were investigated regarding BMS

symptoms relieving potential and no positive effect in outcomes like burning pain and QoL was found, making them useless for treating this syndrome.

However, the dietary supplement ultramicronised PEA, a pleiotropic lipid mediator with established anti-inflammatory and anti-hyperalgesic activity, assessed by Ottaviani et al. [11] in 2019, revealed a significant decrease of burning sensation, making this a viable therapy. Beyond this, Ottaviani's et al. work produced an interesting result – the persistence of PEA effect after its suspension – suggesting that it behaves as a disease modifying drug.

Topical medications

Topical medications, like urea, lactoperoxidase rinse or benzydamine hydrochloride oral rinse, as reported by Alvarenga da Silva et al., Femiano et al. and Sardella et al. [20–22], revealed insufficient or contradictory evidence regarding the benefit over a placebo. On the other hand, substances like topical capsaicin showed long-term relief of patients' complaints [23].

In the present review, both topical chamomile and bupivacaine significantly improved BMS pain, although in the first case, the placebo group also showed that all the outcomes had improved. This made the study by Valenzuela et al. [13] less reliable. In the bupivacaine study by Treldal et al. [12], taste alteration become worse, which makes this treatment less tolerable.

Electromagnetic radiation

Electromagnetic radiation therapy acts by inhibiting the secretion of inflammatory mediators, like prostaglandin E2 and interleukin 1α. The only study included in the *Cochrane* review that compared this radiation (infrared and red laser) with a placebo was done by Spanemberg et al. [24] and produced very low-quality evidence when comparing electromagnetic radiation (infrared laser, red laser) with a placebo. This study demonstrated a short-term benefit in both symptom relief and QoL [10].

Regarding this type of treatment, from the aforementioned studies, it was possible to conclude that, in general, they led to symptomatic relief and improvement in quality of life; nevertheless, these results are not very reproducible or consistent, since they were obtained by different protocols, and the laser types are not comparable to each other. However, this is a non-invasive, fast and safe therapy, without the adverse effects of medication [8].

Conclusions

Overall, we can conclude that the studies following the Cochrane systematic review in 2016 are few and present a low level of evidence. Most of them, except for Melatonin, produced improvement in the relief of BMS pain, but the majority failed to successfully complete their secondary outcome (such as reducing anxiety, depression, taste alteration or xerostomia).

In patients with depressive symptoms, SSRI's, such as fluoxetine, showed satisfactory results in all outcomes, making it an important treatment possibility to be taken into account [14].

Regarding dietary supplements, PEA showed a statistically significant improvement in symptoms, but this study failed to assess QoL alteration, which makes it less reliable.

Electromagnetic radiation resulted in a decrease in BMS pain [8–10], although an improvement in QoL did not occur [9], or it only occurred for a short period of time [8].

On the other hand, since melatonin [5] and chamomile [13] demonstrated to be no better than a placebo, they might be considered a viable option.

Hence, it is clear that more and better studies are required in order to find a treatment with good tolerance and significantly higher levels of efficacy on the various outcomes.

Source of funding: This work was funded from the authors' own resources.
Conflicts of interest: The authors declare no conflicts of interest.

References

1. International Headache Society Classification Committee. The International Classification of Headache disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
2. Freilich JE, Kuter-Shorrer M, Treister NS, et al. Burning mouth syndrome: a diagnostic challeng. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2020; 129: 120–124.
3. Tan HL, Renton T. Burning mouth syndrome: an update. *Cephalalgia Reports* 2020; 3, doi: 10.1177/2515816320970143.
4. Minor JS, Epstein JB. Burning mouth syndrome and secondary oral burning. *Otolaryngol Clin North Am* 2011; 44(1): 205–219.
5. Varoni EM, Lo Faro AF, Lodi G, et al. Melatonin Treatment in Patients with Burning Mouth Syndrome: A Triple-Blind, Placebo-Controlled, Crossover Randomized Clinical Trial. *J Oral Facial Pain Headache* 2018; 32(2): 178–188.
6. McMillan R, Forssell H, Buchanan JA, et al. Interventions for treating burning mouth syndrome. *Cochrane Database Syst Rev* 2016; 11(11): CD002779.
7. Moghadam-Kia S, Fazel N. A diagnostic and therapeutic approach to primary burning mouth syndrome. *Clin Dermatol* 2017; 35(5): 453–460.
8. Valenzuela S, Lopez-Jornet P. Effects of low-level laser therapy on burning mouth syndrome. *J Oral Rehabil* 2017; 44: 125–132.
9. Sikora M, Včev A, Siber S, et al. The Efficacy of Low-Level Laser Therapy in Burning Mouth Syndrome – A Pilot Study. *Acta Clin Croat* 2018; 57(2): 312–315.
10. Bardellini E, Amadori F, Conti G, et al. Efficacy of the photobiomodulation therapy in the treatment of the burning mouth syndrome. *Med Oral Patol Oral Cir Bucal* 2019; 24(6): e787–e791.
11. Ottaviani G, Rupel K, Gobbo M, et al. Efficacy of ultramicronized palmitoylethanolamide in burning mouth syndrome-affected patients: a preliminary randomized double-blind controlled trial. *Clin Oral Investig* 2019; 23(6): 2743–2750.
12. Treldal C, Jacobsen CB, Mogensen S, et al. Effect of a local anesthetic lozenge in relief of symptoms in burning mouth syndrome. *Oral Dis* 2016; 22(2): 123–131.
13. Valenzuela S, Pons-Fuster A, López-Jornet P. Effect of a 2% topical chamomile application for treating burning mouth syndrome: a controlled clinical trial. *J Oral Pathol Med* 2016; 45(7): 528–533.
14. Zoric B, Jankovic L, Kuzmanovic Pficer J, et al. The efficacy of fluoxetine in BMS-A cross-over study. *Gerodontology* 2018; 35(2): 123–128.
15. Maina G, Vitalucci A, Gandolfo S, et al. Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: a single-blind study. *J Clin Psychiatry* 2002; 63(1): 38–43.
16. Carbone M, Pentenero M, Carrozzo M, et al. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. *Eur J Pain* 2009; 13(5): 492–496.
17. Cavalcanti DR, da Silveira FR. Alpha lipoic acid in burning mouth syndrome – a randomized double-blind placebo-controlled trial. *J Oral Pathol Med* 2009; 38(3): 254–261.

18. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. *J Oral Rehabil* 2009; 36(1): 52–57.
19. Cano-Carrillo P, Pons-Fuster A, López-Jornet P. Efficacy of lycopene-enriched virgin olive oil for treating burning mouth syndrome: a double-blind randomised. *J Oral Rehabil* 2014; 41(4): 296–305.
20. Sardella A, Lodi G, Demarosi F, et al. Hypericum perforatum extract in burning mouth syndrome: a randomized placebo-controlled study. *J Oral Pathol Med* 2008; 37(7): 395–401.
21. Alvarenga da Silva L, Siqueira JT, Teixeira MJ, et al. The role of xerostomia in burning mouth syndrome: a casecontrol study. *Arquivos de Neuro-psiquiatria* 2014; 72(2): 91–98.
22. Femiano F, Gombos F, Scully C, et al. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis* 2000; 6(5): 274–277.
23. Marino R, Torretta S, Capaccio P, et al. Different therapeutic strategies for burning mouth syndrome: preliminary data. *J Oral Pathol Med* 2010; 39(8): 611–616.
24. Spanemberg JC, López López J, de Figueiredo MA, et al. Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: a randomized, controlled trial. *J Biomed Opt* 2015; 20(9): 098001.

Tables: 1
Figures: 0
References: 24

Received: 03.10.2021
Reviewed: 10.11.2021
Accepted: 23.11.2021

Address for correspondence:
Guilherme Rook de Lima, MD
USF Conde Saude – ARSLVT
Rua Latino Coelho 1668-1675
2975-326 Quinta do Conde
Portugal
Tel.: +351 911914021
E-mail: guilhermerookelima@gmail.com