

# Therapeutic Options in Idiopathic Burning Mouth Syndrome: Literature Review

Ivan Miziara<sup>1</sup> Azis Chagury<sup>1</sup> Camila Vargas<sup>1</sup> Ludmila Freitas<sup>1</sup> Ali Mahmoud<sup>1</sup>

<sup>1</sup>Department of Otolaryngology, Universidade de São Paulo, São Paulo, Brazil

**Address for correspondence** Azis Chagury, Department of Otolaryngology, Universidade de São Paulo, Avenida Dr. Eneas de Carvalho Aguiar, 155, São Paulo 05403-000, Brazil (e-mail: azischagury@gmail.com).

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## Abstract

**Introduction** Burning mouth syndrome (BMS) is characterized by a burning sensation in the tongue, palate, lips, or gums of no well-defined etiology. The diagnosis and treatment for primary BMS are controversial. No specific laboratory tests or diagnostic criteria are well established, and the diagnosis is made by excluding all other possible disorders.

**Objective** To review the literature on the main treatment options in idiopathic BMS and compare the best results of the main studies in 15 years.

**Data Synthesis** We conducted a literature review on PubMed/MEDLINE, SciELO, and Cochrane-BIREME of work in the past 15 years, and only selected studies comparing different therapeutic options in idiopathic BMS, with preference for randomized and double-blind controlled studies.

**Final Comments** Topical clonazepam showed good short-term results for the relief of pain, although this was not presented as a definitive cure. Similarly,  $\alpha$ -lipoic acid showed good results, but there are few randomized controlled studies that showed the long-term results and complete remission of symptoms. On the other hand, cognitive therapy is reported as a good and lasting therapeutic option with the advantage of not having side effects, and it can be combined with pharmacologic therapy.

## Keywords

- ▶ treatment
- ▶ stomatodynia
- ▶ burning mouth syndrome

## Introduction

Burning mouth syndrome (BMS), or glossalgia, stomatodynia, and glossopyrosis, is characterized by a burning sensation with pain or itching, which may occur in the local tongue, palate, lips, and gums, with no etiology defined.<sup>1,2</sup> Scala et al proposed that the BMS be classified into two clinical types<sup>3</sup>: primary or essential/idiopathic BMS, for which local or systemic causes cannot be identified, and secondary BMS, which is due to organic causes, such as oral infections, autoimmune diseases of the oral mucosa (lichen planus), nutritional/vitamin deficiencies, allergies, irritation caused by reflux, candidiasis, diabetes mellitus, or administration of certain drugs.<sup>4,5</sup>

The epidemiology of BMS is still poorly described in the literature, with prevalence rates ranging from 15 to 0.7% of the general population.<sup>6</sup> Symptoms are described more often in women aged around 40 to 60 years of age, near menopause,

coexisting in strong association with psychological disorders such as anxiety and depression.<sup>7</sup>

The pathophysiology of BMS is not yet fully established. Several studies have shown significant differences in thermal nociception and the limits of patients with BMS compared with controls,<sup>8,9</sup> demonstrating that there may be neuropathic changes involved. However, it is not known if the dysfunction is peripheral or central.

The diagnosis and treatment for primary BMS are controversial. There are no specific, well-established laboratory tests or diagnostic criteria, and the diagnosis is made by exclusion of all other possible disorders.

## Review

We conducted a literature review on the main treatment options in idiopathic BMS and compared the best results of

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the major studies in the previous 15 years. A literature review was performed on PubMed/MEDLINE, SciELO, and Cochrane-BIREME, using the terms “treatment and burning mouth syndrome” or “glossodynia and treatment.”

Approximately 295 studies were described in the past 15 years, but only studies comparing different therapeutic options in idiopathic BMS, with preference for randomized controlled trials (RCTs), were selected. Studies with nonsignificant and/or nonstandard sample methodology were excluded. All studies included patients with idiopathic BMS along with continuous pain, and patients with organic causes were excluded. Thus, no abnormalities were found on physical or laboratory examination. The method of pain assessment in most studies was the visual analog score (VAS) with scores of 0 to 10, where 0 is no pain and 10 is unbearable pain.

### **Hypericum perforatum**

Hipericin is an herbal medicine used to relieve the symptoms of mild to moderate depression and associated symptoms such as anxiety, generalized muscle tension, and pain. In the literature, we found only the article by Sardella et al,<sup>10</sup> which was a randomized, double-blind, placebo-controlled study conducted at a single center and studied 43 patients with BMS, dividing them into two groups. The first used *Hypericum perforatum* extract (hyperforin 0.31% and 3.0%, 900 mg/d) and the second used placebo (control group) three times a day for 12 weeks. After 3 months of treatment, no significant improvement in symptoms were noted, and the main side effect was headache.

### **Tongue Protector**

The parafunctional habit can contribute to pain in the oral cavity. Few articles were found in the treatment of BMS using the tongue protector. The single RCT found, by López-Jornet et al, divided 50 patients into two groups. Group A ( $n = 25$ ) used only techniques of self-control and group B ( $n = 25$ ) used self-control plus tongue protector (transparent polyethylene cover single size, used for 15 minutes, three times daily) for 2 months.<sup>11</sup> The second group had better results with a statistically significant difference. However, the study had a small number of patients with little follow-up.

### **Capsaicin**

Capsaicin, a component of peppermint, can bind TRPV1 (Transient Receptor Potential Vanilloid 1), a potent calcium receptor. When inactive, neuronal responses are linked to heat, thus prolonged exposure to capsaicin can deplete the TRPV1 in peripheral tissues, contributing to the long-term desensitization of peripheral nociceptors and consequently a reduction in the sense of ardor.<sup>12</sup>

Petruzzi et al analyzed 50 patients with BMS; 25 used systemic capsaicin (0.25%) and 25 received a placebo for 30 days.<sup>12</sup> Symptoms improved in 80% of patients using capsaicin; however, epigastric pain has been reported as a major side effect.

On the other hand, Marino and colleagues compared topical capsaicin (250 mg/50 mL),  $\alpha$ -lipoic acid (ALA) 800 mg/d, lactoperoxidase lysozyme, and placebo in the 56 patients divided equally between groups; symptoms improved

in 76, 57, 57, and 79%, respectively.<sup>13</sup> The study showed great results with no reported side effects, but the rate of placebo was close to the tested drugs.

More recent studies with topical 0.02% capsaicin also showed slight improvement, but with few significant results.<sup>14</sup>

### **Clonazepam**

Clonazepam is a benzodiazepine that has an inhibitory effect on the central nervous system and is widely used as an anxiolytic agent.

Gremeau-Richard et al studied 48 patients with BMS, divided into topical clonazepam (3 mg/d;  $n = 24$ ) and placebo ( $n = 24$ ), treated for 2 weeks. Results showed 72% improvement, with main side effects of xerostomia, sleepiness, and increased burning.<sup>15</sup>

Another study by Rodríguez de Rivera Campillo et al evaluated 33 patients who received clonazepam 0.5 mg/d, used for 3 minutes in the mouth without swallowing, and 33 placebo tablets used in the same way, with follow-up of 1 month and 6 months.<sup>16</sup> Approximately 69% of those using clonazepam showed improvement of symptoms, and only 12% of controls had a positive response. However, regarding the cure of symptoms, the result was not significant in either group.

Amos et al conducted a study with the combination of topical (0.5 mg tablets three times per day) and systemic (ingested the pills after a few minutes) clonazepam in 36 patients.<sup>17</sup> After 6 months of treatment, 80% achieved significant improvement in pain and 33% had complete resolution of symptoms. However, there is need for further randomized studies to better assess the effects of this association.

In a more recent case-control study, Heckmann et al evaluated 20 patients with BMS for 9 weeks and separated into two groups.<sup>18</sup> The clonazepam group ( $n = 10$ ) took 0.5 mg/d and the other group took only placebo. There were no significant physiologic changes or improvement in the gustatory tests and salivary flow over time in both groups. However, pain was significantly reduced in the test group, and the study concluded that at low doses, the drug was more effective in younger individuals who with shorter time of illness.

With respect to potential predictors of the outcome of therapy with clonazepam, Ko et al evaluated 100 patients with BMS and suggested that the drug had a greater effect in patients with major salivary flow, patients who were more symptomatic, and patients who were not using psychotropic drugs.<sup>19</sup>

Despite the possible side effects that may occur at low doses, clonazepam has shown promising results for relief of symptoms.

### **Cognitive Therapy**

Cognitive therapy, or psychotherapy, is emerging increasingly in the literature. Bergdahl et al showed improved symptoms with only cognitive therapy, with a significant difference from placebo.<sup>20</sup> Subsequently, Femiano and colleagues studied therapy alone (2 h/wk for 2 months), ALA (600 mg/d for 2 months), the combination of both (ALA and therapy), and placebo (control).<sup>21</sup> The most important result was seen in the group using ALA + cognitive therapy, with complete resolution in 53% and some improvement in 90%.

A more recent study by Komiyama et al studied 24 women with BMS who consulted with a dentist (20-minute lecture) and a neurologist (cognitive and behavioral therapy).<sup>22</sup> The lecture was repeated after 6 months, and most patients showed improved graduation anxiety and, consequently, pain.

### Acupuncture

Acupuncture is an ancient healing technique used for centuries in the treatment and prevention of diseases in China. Furthermore, it has been increasingly used in Western countries as an alternative method for treating pain.<sup>23</sup>

A systematic review examined Chinese articles that compared the treatment of BMS through acupuncture, and we selected nine relevant studies.<sup>24</sup> In seven trials acupuncture showed a significant improvement in symptoms compared with the control. However, all studies have only been published in local magazines and had questionable methodologies.

### *Aloe vera* (*Aloe barbadensis*)

Topical application of a combined *Aloe vera* (AV) can eliminate parafunctions that can protect the oral mucosa from repeated trauma and alleviate the symptoms of the BMS. In one study, López-Jornet used topical application of AV three times per day along with a tongue protector.<sup>25</sup> The double-blind, randomized, case-control study lasted 12 weeks. Patients were divided into three groups: group I used a tongue protector alone, group II used AV and a tongue protector, group III used a tongue protector and placebo. Patients were homogeneous in terms of anxiety, and an improvement in VAS score was noted in all groups, but no significant difference was evident between groups in the category anxiety and quality of life, requiring more multicentric studies with treatment for longer periods.

### Catuama

Catuama, an herbal product made in Brazil for over 20 years, is known for its revitalizing effects, with diminishment of physical and mental fatigue. Catuama is a mixture of four medicinal plants: *Paullinia cupana* (guarana), *Trichilia catigua* (Catuaba), *Zingiber officinale* (ginger), and *Ptychopetalum olacoides* (Muirá Pauma). The combination of these four components showed antinociceptive, antidepressant, and vasorelaxing properties with involvement of the dopaminergic and serotonergic systems.

Spanemberg et al did a randomized, double-blind controlled study of 72 patients with BMS.<sup>26</sup> The patients were divided into test group ( $n = 38$ ) and controls ( $n = 34$ ), and patients were instructed to take two capsules per day for 8 weeks. Following treatment, symptoms were reduced by 52.4% in the test group (VAS) and 24.2% in the control group, and these results remained stable until the end of the 12 weeks. One patient complained of drowsiness and weight gain and another, insomnia.

### $\alpha$ -Lipoic Acid

ALA is an antioxidant able to scavenge free radicals, exerting activity in nerve repair. Femiano and Scully studied its effect

in patients with BMS, who obtained better results than patients who received placebo.<sup>27,28</sup> Likewise, López-D'alexandro and Escovich also showed superior results with the combination of ALA (600 mg/d) and  $\gamma$ -aminobutyric acid (300 mg/d), an anticonvulsant agent used for the treatment of peripheral neuropathy, with up to 70% improvement in symptoms associated with it.<sup>29</sup>

However, Cavalcanti and da Silveira used ALA 600 mg/d in 19 patients with BMS, and 89.9% of them achieved symptom improvement, but there was no significant difference between groups.<sup>30</sup>

In parallel, Carbone et al compared 18 patients who had been treated with ALA (800 mg/d), 14 patients treated with ALA (400 mg/d) and vitamins (twice a day), and 20 patients treated with placebo; no significant improvement was evident between groups.<sup>31</sup> In a randomized clinical trial, López-Jornet et al compared ALA (400 mg/d) and placebo and found no significant difference between groups.<sup>32</sup>

### Paroxetine

Yamazaki et al performed a dose-dependent pilot study on the effect of paroxetine in the treatment of 52 patients with BMS.<sup>33</sup> By 12 weeks, patients received paroxetine 10 to 30 mg/d (dose adjusted to every 15 days according to symptoms, and 10 mg each time) and domperidone to avoid side effects of nausea in the first 2 weeks. About 80% had improvement in pain after 12 weeks of treatment, with few reported side effects. Thus, the author proposes to start with 10 mg/d and increase by 10 mg every 2 weeks, reaching a maximum up to 30 mg/d if the dose is insufficient. However, in this study there was no comparison with placebo.

## Discussion

The treatment of patients with idiopathic BMS offers a wide variety of therapeutic options, from tongue protectors to drugs with restricted use. This broad diversity requires more studies to assess which treatment should be the gold standard for this common malady affecting the quality of life of people around the world.

In the literature, the use of *H. perforatum* was found in only one RCT, which did not show superiority to placebo. Likewise, we found only one RCT using a tongue protector for patients with BMS; however, López-Jornet et al used a limited number of patients and with little follow-up, proving no statistically benefit.<sup>11</sup>

Capsaicin showed significant improvement of burning symptoms, but is not in systemic use in Brazil, and although collateral effects may limit its use, the topical presentation can be used as an alternative form of relief in the short term. This short-term symptom relief was also shown in studies involving clonazepam,<sup>17,18</sup> which, despite possible collateral effects that may arise in high doses, can be part of the therapeutic strategy in these patients, mainly for short-term pain relief.

Another nonpharmacologic treatment that has proven effective is cognitive therapy; in the studies of Femiano et al<sup>21</sup> and Komiyama et al,<sup>22</sup> the results were promising

and with the advantage of not having side effects that may often be associated with drug therapy.

The studies involving acupuncture, AV, Catuama, and paroxetine had statistically unsatisfactory results, requiring further RCTs for better evaluation.

Finally, ALA treatment had the most published studies. Femiano and colleagues,<sup>27,28</sup> who initially began researching this treatment, found significant clinical improvement in their groups, but this result was not successfully replicated in the following studies,<sup>30,31</sup> demonstrating the need for more randomized controlled studies that show long-term results and a complete remission of symptoms.

## Conclusion

Although there are various forms of pharmacologic treatment for idiopathic BMS, there are no well-defined data and studies to formulate a consensus on this syndrome. It is necessary that in the future there is a systematic improvement in the diagnosis of these patients, including which patients will respond best to various lines of treatment available according to possible predictors of treatment response.

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