



## BURNING MOUTH DISEASE, MODERN TREATMENT AND CLINICAL MANAGEMENT: A NARRATIVE REVIEW

<b>Luciani F</b>	DDS, PhD, Catholic University "Our Lady of Good Counsel" - Tirana
<b>Papa E*</b>	University of Roma "Tor Vergata" – Department of Biomedicine and Prevention, U.O. Oral-Maxillofacial Surgery, Post Graduate Course in "Oral Surgery". Director and Chief: Prof. Leonardo Calabrese *Corresponding Author
<b>Leggeri A</b>	Freelands Dentist in Tivoli (Rome - Italy)
<b>Calabrese C</b>	MD, DDS, Department Odontostomatology ASL RM/2 – Rome, Italy
<b>Condo' R</b>	University of Roma "Tor Vergata" – Department of Clinical Science and Translational Medicine, School of Dentistry, Rome, Italy
<b>Calabrese L</b>	University of Roma "Tor Vergata" – Department of Biomedicine and Prevention, U.O. Oral-Maxillofacial Surgery, Post Graduate Course in "Oral Surgery". Director and Chief: Prof. Leonardo Calabrese

**ABSTRACT** **PURPOSE:** The purpose of this review was to investigate the current and modern therapy approach of BMD (burning mouth disease) also referred as BMS (burning mouth syndrome), in order to have a better comprehension for the best and most successful way of treatment and management for this pathology. **MATERIALS & METHODS:** A literature research was carried out mainly using online sources, Pubmed database, and paper sources (specialized books). articles published over the last years have been firstly examined. Systematic reviews, narrative reviews, mini reviews and meta-analysis were primarily selected. If a subject matter appeared to have few or no such sources, articles based on case reports were also considered. **RESULTS:** Finally, 20 sources have been considered eligible for the purpose of the review, 19 scientific articles and 1 specialized book were selected. **CONCLUSIONS:** Clonazepam, capsaicin and Vortioxetine are currently the most widely used and known drugs even if further studies are needed especially in the case of Vortioxetine and selective serotonin reuptake inhibitors.

**KEYWORDS :** Burning Mouth Disease, BMD, Burning Mouth Syndrome, BMS, burning mouth treatments, burning mouth management.

### INTRODUCTION

#### Terminology

As many authors point out when they introduce this pathology, different names, definitions and classifications have alternated over time. The most used terms in recent years to identify this condition are: BMD (burning mouth disease) or BMS (burning mouth syndrome). Since this pathology is often related to the tongue, glossopyrosis, glossodynia and glossalgia, have been used in the past. when the oral mucosa is involved, the term stomatodynia is usually used.

Burning mouth disease (BMD) is a rare but serious, chronic disease. Patients suffering from BMD may consult not only their dentist or family doctor but also various medical specialists, such as the otolaryngologist, the oral and maxillofacial surgeon, the dermatologist and the neurologist. First-line healthcare providers often do not recognize the symptoms associated with it. As a result, BMD patients may undergo unnecessary diagnostic tests and treatments for their complaints, varying from drug prescriptions, extractions of teeth to psychiatric treatment. [1]

#### Definition

For the medical definition of this pathology, we will just report the two most recent ones: the International Headache Society (2020) and the international classification of disease of the WHO (2018) have recently contributed to a modern and updated definition of BMD.

The Headache Classification Committee of the International Headache Society stated: "an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without evident causative lesions on clinical examination and investigation". The pain of Burning Mouth Syndrome is usually bilateral, but on rare occasions it is unilateral. Its intensity fluctuates. The most common site is the tip of the tongue. Subjective xerostomia, dysesthesia and altered taste are present in two-thirds of cases reported. There is a high preponderance in menopausal women. Some studies show psychosocial comorbidities similar to those of other persistent pain conditions. [2]

The 11th revision of the international classification of disease (WHO) describes it as a chronic burning mouth pain is chronic orofacial pain

with an intraoral burning or dysaesthetic sensation that recurs for more than two hours per day on 50 % of the days over more than three months, without evident causative lesions on clinical investigation and examination. It is characterised by significant emotional distress (anxiety, anger/frustration or depressed mood) or interference with orofacial functions such as eating, yawning, speaking etc. Chronic burning mouth pain is multifactorial: biological, psychological and social factors contribute to the pain condition. The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms. [3]

#### Classification

Regarding the classification, even in this case we do not find unanimous agreement in the literature. In 2003 Scala et al. suggested a classification based on the purpose of simplifying therapy management. They divided the BMS in two clinical forms: "Primary BMS", or essential/idiopathic BMS for which organic local/systemic causes cannot be identified; and "Secondary BMS", resulting from local/systemic pathological conditions and thus potentially sensitive to etiology-directed therapy.

According to their criteria, "idiopathic" BMS as well as the "secondary" form may represent two distinctive subgroups of the same "pathological entity". [4]

Other well-known classifications proposed in literature, still valid to this day, are based on the course of the symptoms (Lamb AB. et al. 1988 and Lamey et al. 1996) [5] [6];

#### MATERIALS AND METHODS

Initially, 50 articles published over the last years were firstly examined. Systematic reviews, narrative reviews, mini reviews and meta-analysis were primarily selected. If a subject matter appeared to have few or no such sources, articles based on case reports were also considered. The sources have been selected to be as recent and impactful as possible.

#### RESULTS

Finally, 16 sources were considered eligible for the purpose of the

review. The results of this literature search show that although BMS is a condition about which much has been written in the literature and although many of the characterizing aspects of this syndrome are known, fundamental aspects such as the etiology still remain unknown. However, it is possible to see from our small bibliographic search how there are effective methods to counter the syndrome, in particular conventional therapy (capsaicin, clonazepam and serotonin reuptake inhibitors) and non-pharmacological ones (low laser therapy).

## DISCUSSION

### Management

The aetiology of BMD is unknown therefore, eradicating the triggering cause is a major problem from many points of view. Since the main aspect of the disease is the induction of painful / burning symptoms in the oral cavity, the primary aim of clinicians should be to alleviate the symptoms and possibly seek a triggering cause. Over time, numerous strategies have been proposed to try to reduce the symptoms of BMD although there are still unclear aspects such as the incidence of the psychological component.

Since symptoms develop in the oral cavity and they are frequently associated with the tongue, the dentist is often the first specialist that patients turn to. However, BMD presents a diagnostic challenge for clinicians and as such, patients experience a significant delay from onset of symptoms to definitive diagnosis. Moreover, BMS is a diagnosis of exclusion with no discernable clinical features, and because there are seemingly unrelated comorbidities that frequently occur concurrently, BMS is very challenging to diagnose for a dentist who is not familiar with its classical presentation. [7]

Furthermore, it is necessary to specify that many local and systemic conditions can in fact induce a burning sensation or dysesthesia of the mouth. However, this set of conditions should not be confused with BMD. It is not the purpose of this paper to deepen the aforementioned conditions which we will report schematically. [1]

### Local causes

Mucosal lesions  
Atrophy of the lingual mucosa  
Cancer and precancer of the oral mucosa  
Candidiasis  
Coated or hairy tongue  
Fissured tongue  
Fungiform papillae involvement  
Papillitis  
Geographic tongue  
Herpes Simplex virus and varicella zoster virus infection  
Lichen planus and lichenoid lesions  
Lymphoid hyperplasia  
Median rhomboid glossitis  
Stomatitis  
Dentures  
Dental faults  
Sensitivity to acrylic resin in dentures  
Allergy to dental materials  
Dental treatment  
Galvanism  
Oral parafunctional habits  
Smoking and the use of alcohol  
*Systemic causes*

Achlorhydria and gastritis  
Allergy  
Iron-deficiency anaemia  
Pernicious anaemia caused by lack of vitamin B  
Zinc deficiency  
Sjogren's Syndrome  
Celiac disease  
Helicobacter pylori infection  
Diabetes mellitus  
Gonadal Hormones disorder  
Hypothalamus-pituitary-adrenal Axis  
Hypothyroidism and Hashimoto thyroiditis  
Oropharyngeal reflux  
Vascular disturbance  
Mast cell activation disorder  
Oxidative stress

According to the authors of this paper, the classification by Scala et al. (2003) developed with the practical aim of having a strategy based on the type of BMD, it is extremely useful for the management of the pathology since it includes any patient who has the symptoms described above. The first essential step is to carry out a thorough medical history of the patient and his family in order to collect as much data as possible and to be able to have a clear vision of the possible triggering cause. Later if it is possible to find a cause that triggered the symptoms (secondary BMD), it will be necessary to try to treat the patient in order to remove that cause. If this is not possible (primary or idiopathic BMD) we will proceed with treatments related to pain control. [4]

Modern pathology management strategies are essentially divided into pharmacological and non-pharmacological treatments. Below, we report what turned out to be the most effective pharmacological and non-pharmacological treatment for BMS.

### Pharmacological treatment

#### Serotonin Modulator: Vortioxetine

VO exhibits these properties through the modulation of the systems of neurotransmission of serotonin, norepinephrine, dopamine, acetylcholine, histamine, glutamate, and gamma-aminobutyric acid in relevant brain areas. The mechanisms of VO are not fully understood, but it is known that VO is a new class of multimodal serotonergic agent with two different types of pharmacological target: serotonin receptors and transporters.

VO inhibits the serotonin transporter (SERT) and modulates 5-hydroxytryptamine (5-HT) receptors. It is a full agonist with a highly selective affinity for 5-HT<sub>1A</sub>, a partial agonist of the 5-HT<sub>1B</sub> receptors, and an antagonist of the 5-HT<sub>1D</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>7</sub> receptors. [8]

In a study of 30 BMD patients the efficacy of VO has been evaluated. BMD patients were treated with topical clonazepam and a flexible dose of VO (10 mg, 15 mg, or 20 mg). VO proved to be efficacious and well tolerated in the treatment of BMD in first-line therapy on account of its better receptor pharmacological profile and in second-line treatment for patients who have only partially responded or have reported adverse effects to previous treatments. Adamo et al. concluded that despite the limitations of the study, these findings are relevant and suggest a new possibility of a safe treatment for BMS and other chronic pain conditions with a psychiatric comorbidity, where previous therapy has caused side effects or produced inadequate results. [9]

#### Anxiolytic Drugs: Clonazepam

Clonazepam is a benzodiazepine that is currently used to treat neuropathic pain and nonetheless the only drug that has demonstrated benefits in relieving BMS pain. Both the topical and the systemic administration of clonazepam have proven to be effective in inducing symptom relief in patients with BMS. [10]

Moon-Jong et al. stated that since the effect of the topical and systemic administration of clonazepam on BMS were first reported, many studies have consistently reported that clonazepam is effective for managing oral symptoms in BMS and has better efficacy and fewer side effects than other benzodiazepines. Nowadays, clonazepam therapy is the most widely accepted treatment option for BMS based on this evidence. The majority of patients with BMS were prescribed clonazepam in their study, were significantly decreased after clonazepam therapy. [11]

In a recent study, some authors [12] evaluate and compare the effectiveness of two concentrations of topical clonazepam solution in improving symptoms of burning mouth syndrome (BMS). A retrospective chart review was conducted of patients diagnosed with BMS and managed with topical clonazepam solution between 2008 and 2015. A 0.5-mg/mL solution was prescribed until 2012, when this was changed to a 0.1 mg/mL solution. Patients were instructed to swish with 5 mL for 5 minutes and spit two to four times daily. The efficacies of the two concentrations were compared using patient-reported outcome measures at the first follow-up, including the reported percentage of improvement in burning symptoms and the change in burning severity from baseline ranked on an 11-point numeric rating scale (NRS). Response to treatment was compared between the two concentrations using Wilcoxon rank sum test. The use of either outcome measure revealed that the response to treatment with the 0.5-

mg/mL solution was superior to that of the 0.1 mg/mL solution ( $P < .01$ ). Conclusion: These findings suggest that a 0.5-mg/mL topical clonazepam solution is effective in the management of BMS.

#### • Capsaicin

Topical capsaicin has been used as a treatment alternative for controlling neuropathic pain. This substance induces desensitization to thermal, chemical and mechanical stimuli. It has also been used for the treatment of the discomfort caused by BMS, with positive results. [12]

Jorgensen et al. investigated the effectiveness of topical capsaicin oral gel 0.01% and 0.025% in 22 patients with BMS. Of the patients, 18 completed the trial and showed good compliance to the given instructions; four dropped out due to minor adverse side effects.

A pooled effect of the two concentrations of the gels proved effective in the patients with BMS as treatment led to a statistically significant reduction of the oral burning pain scored on VAS, and the null hypothesis could therefore be rejected.

No patients obtained complete pain relief. Some patients obtained pain relief in continuation of using the gels but experienced the pain returning in the 14-day break and some experienced continued pain relief. They concluded that within the limitations and shortcomings of their study, topical capsaicin might be a useful short-term alternative to treat BMS, but further clinically controlled studies are necessary for further definition of its usefulness in the management of BMS. [13]

#### • Herbal Compounds: Alpha-Lipoic Acid

Alpha lipoic acid (ALA) is a potent antioxidant that is produced naturally in the body. It can also be found in some natural foods, such as potatoes, tomatoes and spinach. To date, ALA's main contribution is to slow down cutaneous ageing. [14] The main use for supplemental ALA is to treat diabetic neuropathy. Doses range from 200 to 800 mg/day. Reported side effects of ALA are low blood sugar levels, headache, hunger, weakness, sweating, skin rash, confusion, irritability, dizziness and fast heart rate. Although there is limited evidence of a positive effect of lipoic acid supplements on any disease, ALA has been used in the management of BMD patients. [14]

López-D'alessandro et al. demonstrates that the use of Alpha Lipoic Acid and Gabapentin used both individually and jointly, were beneficial for reducing the burning in patients with BMS. The most favourable results were obtained with the administration of both drugs. To establish specific therapies in the treatment of BMS, further study of the pathophysiological mechanisms involved in its pathogenesis would be required, as well as determine the neurological changes involved in this disease, focusing on this entity within the Central Sensitization Syndromes. [15]

#### Non-pharmacological treatment

##### • Low Level Laser Therapy

The low intensity laser therapy (or biomodulation) is an alternative for the treatment of symptoms of BMS. The low intensity laser (LLL) is the application of light with a low power laser or LED that promotes tissue regeneration, reduces inflammation and relieves pain. There is no thermal effects and analgesia in LLL is usually gradual, cumulative and requires multiple sessions, besides not having side effects.

Matos et al. in a recent systematic review in order to answer the following question: "Is low-level laser therapy effective in reducing the symptoms of Burning Mouth Syndrome (BMS)?" concluded that even though low laser intensity is still considered a new alternative in need of greater understanding of its mechanism of action through high-quality studies with larger sample sizes and longer periods of follow-up and there are controversies about the real effectiveness of this therapy, could be suggested that laser therapy might be effective in treating an alternative BMS. The sample consisted of women with an average age of 60.89 years, a period that corresponds to post-menopause. Since BMS is still a clinical condition under investigation and an understanding of its pathophysiology is essential for planning treatments that really work, without confounding effects. Other randomized trials should consider protocols well established laser therapy. [16]

#### CONCLUSIONS

BMS is a very special condition that negatively affects the lives of patients. Due to its characteristic aspects, it is very complex to

establish effective management strategies. Certainly, communication with the patient is of fundamental importance. In the event that a general doctor or dentist should come across this condition and does not have the necessary knowledge to treat it, the patient must be referred to a specialist center. The patient will tend to trust that doctor more because of his honesty. Once the pathology has been framed, it is necessary to carry out a diagnosis by exclusion in order to eliminate any condition that may have triggered the burning and or pain associated with the oral cavity. The authors of this text suggest, as many illustrious authors have previously stated in the literature, that excluding any possible cause for identifying a primary burning mouth is essential before proceeding with therapy.

As demonstrated by our short review, there are different pharmacological and non-pharmacological strategies to counteract the symptoms of BMS which in some cases are relegated until they disappear. We have chosen not to treat the psychological component as an alternative method to pharmacology because it usually presupposes a patient's medical history not responsive to any form of drug treatment. Clonazepam, capsaicin and Vortioxetine are currently the most widely used and known drugs even if further studies are needed especially in the case of Vortioxetine and selective serotonin reuptake inhibitors.

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