



Burning Mouth Syndrome: Pathophysiology, Investigations and Management- A Review

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Abstract

Burning Mouth Syndrome (BMS), or idiopathic stomatodynia, is a chronic debilitating oral condition characterized by a burning sensation of the oral mucosa in an apparently normal person. Its etiology and pathogenesis remain unclear. However, psychophysical and neurophysiological studies highlight peripheral and central neuropathic sensory alterations rather than psychogenic factors. Dysgeusia and xerostomia are often associated with sensory and somatosensory disorders suggesting a multifactorial etiology. The available treatments are not very effective and focus on relieving symptoms and improving the quality of life. In order to improve treatment outcomes, a better understanding of the pathophysiology of this syndrome could provide a basis for the development of more effective management strategies. This article reviews current knowledge of the pathophysiology, diagnosis, and management of BMS.

Keywords: Neuropathic Pain; Stomatodynia; Glossodynia; Dysgeusia; Xerostomia; Review

Abbreviations

BMS: Burning Mouth Syndrome; IHS: International Headache Society; GRED: Gastroesophageal Reflux Disease; A1C: Glycosylated Hemoglobin; TRPV1: Transient Receptor Potential Vanilloid 1; P2X3: Purinergic Receptors Phenotypes P2X; PROP: 6-n-Propylthiouracil; VAS: Visual Analog Scale; OHIP: Oral Health Impact Profile; IgE: Immunoglobulin E; Quantitative Sensory Testing (QST); ALA: Alpha-Lipoic Acid

Introduction

Definition

The International Headache Society (IHS) defines Burning Mouth Syndrome (BMS), or primary stomatodynia, as spontaneous pain and burning sensation in an intact oral mucosa with no objective clinical sign and no identifiable dental or medical cause [1]. The pathology has been evolving for at least 4 to 6 months. The pain is continuous, moderate to severe, often variable during the day: weak in the morning, it often increases during the day but rarely disturbs patients' sleep. It is not exacerbated by food intake and often disappears during meals. The most commonly affected area is the tongue, but all areas of the oral cavity can be affected [1-5].

Epidemiology

The prevalence of primary BMS is low, but studies report very variable numbers because of methodological biases related to sample size, the definition of the condition more or less restrictive in studies, study design, and sampling selection bias [6]. The actual prevalence is around 0.5% [7,8] in the general population but

varies according to the groups considered. It increases in women, about 7 women to 1 man and with age [7,9]. The occurrence is rare before age 30 and the most exposed group is postmenopausal women with anti-depressive comorbidity. Prevalence rates of up to 25% are observed in specific groups such as postmenopausal women and psychiatric patients [10]. In Africa, few studies carried out mainly in South Africa [11,12] and Nigeria [13] have concerned the BMS. These studies were methodologically biased and did not distinguish between primary and secondary BMS. To our knowledge, no studies have been conducted on the BMS in French-speaking Africa.

Classification

BMS is classified as follows:

Based on etiology as:

Primary, where etiology is unknown

Secondary, where the etiology is known [6,14].

Based on symptoms as [6]:

- Type 1 BMS: Patients have no symptoms upon waking but symptoms progress throughout the day reaching its peak intensity by evening. Night-time symptoms are variable. It is linked to systemic disorders like nutritional deficiency and diabetes.
- Type 2 BMS: Patients have continuous symptoms throughout the day and are symptomatic at night resulting in sleepless nights. This type is associated with chronic anxiety due to altered sleep pattern and is related to use of antidepressant drugs, which cause xerostomia.

- Type 3 BMS: Patients have intermittent symptoms throughout the day with symptom free periods. Usually seen due to anxiety or allergic reactions especially to food allergens.

Etiologies

The etiologies of these nerve damage leading to stomatodynia are probably multiple. Neuropsychiatric, endocrine, immunological, nutritional, infectious and iatrogenic causes have been suggested [4] as the main factors associated with secondary BMS. These factors can disturb the oral environment and lead to sensory abnormalities (Table 1). The most common causes are oral mucosal ulcerations, fungal infections, lichen planus, adverse drug reactions, and hormonal [6] and vitamin deficiencies (Table 1). It was observed in a study of 123 patients initially diagnosed with primary BMS that 69% had subclinical thyroid abnormalities and could therefore be considered secondary BMS [15]. Some oral dysesthesia may also be associated with oral parafunctions (bruxism) [16], a general neurological problem [2], possibly related to toxic consumption such as alcohol or anxiety and psychological disorders, immunological causes [17] through exposure to dietary antigens [18-20], materials (resins, metals) used by the dentist [21]. Some autoimmune diseases such as Sjogren’s syndrome and systemic lupus erythematosus (Table 1) are also associated with oral burns mainly due to hyposialia [23].

Local factors	Systemic factors	Psychological factors
Xerostomia (decreased salivary flow)	Decreased levels of vitamins B1, B2, B12, folate, iron, zinc	Anxiety
Infections (Few microbes like <i>Candida</i> , <i>Enterobacter</i> , <i>Fusospirochetes</i> , <i>Helicobacter pylori</i> and <i>Klebsiella</i>)	Diabetes	Depression
Stomatitis under prosthesis	Thyroid hypofunction	Stress : psychosocial, post-traumatic
Chronic trauma	Menopause	
Inappropriate prostheses	Sjogren’s syndrome	Cancer phobia
Parafunctional habits (cheek sucking, tongue thrusting, bruxism, suction tics...)	Systemic lupus erythematosus	
Oral mucosal conditions (erythema/erosion of whatever cause, atrophic tongue, geographic tongue, lichen planus, pemphigoid, pemphigus)	Various peripheral or central neuropathies (Parkinson’s disease, acoustic neuroma, neuritis, neuralgia...)	
Gastritis, Gastroesophageal reflux disease (GRED)	Drug therapies: angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, antidepressants, hypoglycemic agents.	
Allergic stomatitis (allergic or immunological factors)		

Table 1: Different factors associated with oral pain sensations [4,6,7].

Research into these associated factors is fundamental to differential diagnosis between primary and secondary BMS.

Pathophysiology

The pathophysiology of stomatodynia is not exactly known. However, several types of injuries have been described.

Neuropathic and peripheral microcirculation disorders

Today, a consensus is established around a peripheral and/or central neuropathic origin. At present, BMS is considered a painful condition involving neuropathic mechanisms, as evidenced by the “burning” nature of pain. Patients diagnosed with primary BMS present the symptoms that are characteristic of trigeminal nerve disorders (alteration of pain perception and neuronal transmission, increased excitability of the vascular system).

Some authors have suggested that peripheral nerve damage may be responsible for stomatodynia [2,3,5,24]. A classification according to the origin of the pathology has been established: peripheral neuropathy of small caliber oral fibres (50 - 60% of cases), infra-clinical neuropathy of trigeminal major fibres (20 - 25% of cases) and central deficiency in descending dopamine inhibition (20 - 40% of cases).

At the peripheral level have been described in the affected mucous membranes:

- A lowering of the activation threshold of small diameter nerve fibres, responsible for the painful and thermal perception;
- A significant decrease in the density of epithelial nerve fibres, and morphological changes in epithelial and sub-epithelial nerve fibres, recalling the mechanisms of axonal degeneration and possibly responsible for painful sensations and dysgeusia [4,24,25];
- An increase in TRPV1 (transient receptor potential vanilloid 1) nociceptors and P2X3 receptors has also been described in the nerve fibres of mucous membranes affected by BMS. This increase has been linked to hypersensitivity and neuropathic pain [4,26].

Electro-neuro-myographic studies have shown that patients with BMS exhibited abnormalities of the masseterin and blink reflexes, reflecting abnormalities in the large diameter trigeminal nerve fibre network. Gremeau-Richard., *et al.* [27] reported that unilateral anaesthesia of the lingual nerve leads to a reduction or even a homolateral or bilateral disappearance of symptoms, and this only in a particular subgroup of patients, whose etiology of BMS has been linked to a peripheral cause. In this group, topical applications of clonazepam give the best results. In the other group, lingual nerve block does not improve or even worsen symptoms. In this group the etiology was linked to a central cause.

At the central level, some studies have reported disturbances of the sensory modulating pathways, including trigeminal nucleus and striatum [26]. The alterations observed in the dopamine inhibitor system are similar to those seen in the early stages of Parkinson’s disease [2]. Finally, the study of salivary and serum levels of neurokinin A showed a decrease in serum levels of neurokinin A, reflecting an ineffective dopamine system in patients with BMS [2].

Gustatory and salivary alterations

Taste to the anterior two third of the tongue is by the chorda tympani branch of facial nerve and somatosensory is supplied by lingual nerve branch of trigeminal nerve. Chorda tympani hypo-

function results in lingual nerve hyperfunction by disrupting the centrally-mediated equilibrium between the two [28]. Unilateral anesthesia of the chorda tympani nerve intensifies the perception of burning pain on the contralateral anterior portion of the tongue, suggesting the presence of central inhibitory interactions between taste and oral pain [28,29]. Damage to the chorda tympani or any alteration in the gustative papillae releases this inhibition, and may lead to an intensification of normal trigeminal sensations leading to spontaneous pain, altered sensations of touch, subjective sensations, of oral dryness and taste alterations (dysgeusia and phantom tastes) [28,29].

Individuals with high density of fungiform papillae present on the anterior aspect of the tongue are known as supertasters and are more at risk for developing BMS [29,30]. Supertasters are mainly females who are able to perceive the bitter taste of a substance called PROP (6-n-propylthiouracil) and also experience a more intense burning sensation in the oral cavity, especially when stimulated with chili peppers [29,30].

Xerostomia seen in BMS is more due to neuropathy than glandular dysfunction [30]. It is noted that salivary content shows differences but there is no change in salivary quantity or flow [30].

Psychological disorders

Many studies have found a significantly higher prevalence of depression, anxiety, irritability or somatization in patients with BMS [4,24,31]. A low brain dopamine level is also associated with psychiatric disorders such as major depression. Nevertheless, these psychological disorders, which have long been mentioned as a possible cause of stomatodynia, are probably the result of a chronic pathology whose management is difficult. Using reliable diagnostic criteria, there was no statistically significant association between BMS patients and patients with major depression [2,31].

Endocrine disorders

Menopause, whether surgical or physiological, is associated with higher prevalence of BMS. The mechanism is unclear but hormonal alterations may possibly affect the oral mucosa. Estrogen has documented effects on oral mucosa, and deprivation may lead to atrophic changes thereby altering stimulation of the nerve endings within the epithelium. Alternatively, atrophic epithelia may be more prone to inflammation [2,4]. Thyroid hormones are involved in maturation and specialization of taste buds and studies have shown that thyroid hypofunction may be responsible for hypogeusia, for bitter taste and for the release of inhibitions for sensitive trigeminal sensation [2,15].

Clinical features

Pain

The main complaint of stoma patients is pain which is generally bilateral and symmetrical and most often described as a prolonged burning sensation. However, the complaint can also be related to

symptoms similar to neuropathic pain, such as tingling, itching, numbness, discomfort, etc [23,32]. The intensity of sensation varies from simple to severe pain. It is on average 5 to 8 on a VAS scale of 10 and is often underestimated by the medical profession. Patients describe it as intense dental pain but of different quality [23,32]. Burns and other dysesthesias are mainly felt on the dorsal side of the tongue and especially at the tip (glossodynia). But they may also be of interest to the lower lip, palate, retro-incisal area, upper lip and more rarely, the jugal mucosa and floor of the mouth. Symptoms may fade or disappear over time or persist without remission for many years. Spontaneous remission was observed in 3% of patients 5 years after the onset of symptoms and a slight improvement in less than 30% of cases [33]. Traditionally, pain is described as daytime and does not interfere with sleep.

Oral pain may not be the only painful symptom, but many patients report other associated pain such as headaches, arthromyalgia [34] localized to the masticatory tract or neck; shoulders or suprahyoid muscles [35,36] and without evidence of a causal link being established, suggesting a general problem [37].

Dysgeusia

Persistent dysgeusias are found in 30-70% of patients with BMS [38,39]. The main ones are bitter or metallic tastes [39] but alterations in the intensity of sweet and acidic perceptions are also reported. Some foods worsen the symptoms, leading patients to avoid certain spicy and acidic foods (fruits), alcohol etc..

The tongue looks normal in most patients with BMS [38]. However, Ching, *et al.* reported that 27% of BMS patients had geographic and fissured tongue compared to 11.5% in controls [24].

Salivary Disorders

Subjective complaints of oral dryness (xerostomia) are frequent and concern about 46-67% of patients [7,9]. Changes in the quality of saliva (electrolytes and proteins) that can be acidic or thick have also been reported [7,9]. This sensation is not often associated with objective salivary dysfunction (hyposialia). It may be related to the adverse effects of psychotropic, anticholinergic, antihistamine and diuretic drugs taken as part of treatment [39].

The evidence of neuropathic alterations led to the suggestion that salivary disorders could result from autonomic nervous system dysfunction [40]. However, few studies have attempted to assess the function of the autonomic nervous system outside the salivary system.

Clinical forms

The clinical forms are varied both in the localization of symptoms which may concern only the tongue (glossodynia) or be felt in the other oral mucous membranes (stomatodynia) [25], in the cephalic (headache) or extracephalic (fibromyalgia, arthralgia) level [41], in the description of symptoms (pain, paresthesia), as-

sociated disorders (taste and salivary), as well as in the temporal course of pain [17,37] which can be continuous with a tendency to increase gradually during the day (type 1, approximately 35% of patients), constant of equal intensity (type 2 [55%]) or intermittent (type 3 [10%]), and possibly related to an allergic component [17]. Nevertheless, this classification only models the temporal decay imperfectly [32].

Quality of life

Studies using patient quality of life scales such as the Oral Health Impact Profile (OHIP) [42] have shown functional impairment of BMS patients [43], which also had high anxiety/depression scores, significant emotional distress, loss of ability to take initiative, or deterioration in social relationships. There is also an impairment in sleep quality compared to control subjects [44].

Table 2 summarizes the clinical description of primary BMS.

- Occurs most commonly, but not exclusively in females though occurs in men as well.
- Seen in perimenopausal or postmenopausal women.
- Unexplained, usually persistent burning sensation or pain of the oral soft tissues.
- The diagnostic criteria for BMS are that pain episodes must occur continuously for at least 4-6 months. They may last for 12 years or more with an average duration of 3.4 years.
- Commonly affects the tongue presenting as glossodynia (painful tongue) and glossopyrosis (burning tongue).
- Symptoms may vary from mild-to-severe but moderate pain is seen frequently.
- Symptoms may appear early in the morning or develop later in the day.
- Altered taste sensation such as bitter or metallic taste.
- Oral mucosa appears apparently normal without any visible changes.
- Xerostomia.
- Geographic and fissured tongue.
- Painful teeth, jaw and temporomandibular joint.
- Loss of a comfortable jaw position and uncontrollable jaw tightness.
- Headache, neck and shoulder pain.
- Increased parafunctional activity.
- Difficulty in speaking, nausea, gagging and dysphagia.
- Usually bilateral but can be unilateral as well.
- Multiple mood and emotional disturbances.

Table 2: Clinical description of primary BMS [6,23,36,43].

Investigations

Knowledge of the pathophysiology and clinical symptoms allowed for a diagnostic approach based on clinical and paraclinical investigations [5,6,15] (Table 3). If the interrogation is evocative, that the oral examination does not show any abnormalities, a certain number of examinations and tests, summarized in table 3, are to be conducted before referring to a primary BMS. Systematization

of the diagnostic approach avoids diagnostic errors. Additional tests for peripheral or central neuropathy [2] were also proposed to complete the clinical diagnostic protocol (Table 4).

Local examination	General examination
Measurement of salivary flow rate (hyposialia)	Blood tests: <ul style="list-style-type: none"> • Complete blood cell count, VS, CRP • Glucose level, glycosylated hemoglobin (A1C) • Nutritional factors (dosage vitamins B, zinc and folate) • Thyroid function (dosage free TSH, T3 and T4) • Immune function (Research of antinuclear anti-Ro(SSA) and anti-La(SSB) antibodies, Total serum IgE) Patch tests: To check allergy to certain foods, additives or even denture materials. Gastric reflux tests: To determine GERD
Oral cultures: For bacterial, viral and fungal	
Infections	
Inspection of mucous: erythema, erosion, ulcerations, trauma, contact reactions with removable prostheses	
Biopsy of tongue or oral mucosa.	
Search for parafunctional habits	
Scintigraphy of the major salivary glands	

Table 3: Clinical and paraclinical investigations to diagnose BMS [2,5,6,15].

Tests	Interest
Lingual electrogustometric	Test the response to a progressively increased thermal and gustatory stimulation compared to the sensations of paresthesia; differentiate between primary and secondary BMS; identify peripheral neuropathy
Quantitative Sensory Testing (QST)	
Evaluation of the blink reflex by stimulation of supraorbital, mental and lingual nerves	Confirms neuropathic primary BMS and distinguishes between peripheral and central origin
Evaluation of the density of epithelial nerve fibres, and morphological changes in epithelial and sub-epithelial nerve fibres by biopsy mucosal with BMS	Confirms neuropathic primary BMS and distinguishes central origin (no density disturbance) peripheral origin due to small diameter fibres (decreased epithelial density) and peripheral origin due to trigeminal fibre neuropathy (decreased sub-epithelial density)

Table 4: Complementary tests for peripheral or central neuropathies [2].

Treatment and management

The pathophysiological complexity of BMS and the prevalence of other associated painful or non-painful factors make treatment difficult. Numerous treatments have been proposed, targeting somatic and/or psychic effects according to the alleged etiology of the problem (antidepressants, analgesics, antiepileptics, antifungal, antibacterial, sialagogues, antihistamines, antihistamines, anxiolytics, antipsychotics, dietary supplements, vitamins and antioxidants, minerals and trace elements, capsaicin, hormones, etc). Several reviews of the literature [3,43] compiling several randomized clinical trials evaluating the different treat-

ments for BMS have shown that, despite the many treatments used, few treatments are truly effective in providing lasting relief of BMS pain, let alone its complete disappearance. There is currently no gold standard. The various treatments used are as follows.

Topical (local) and systemic therapies

Capsaicin is an alkaloid responsible for the burning sensation produced by chilli peppers. It is capable of desensitizing TRPV1 calcium channel nociceptors and C-fibres. Prolonged exposure to capsaicin results in a reduction of TRPV1 receptors in peripheral tissues, leading to long-term desensitization and symptom reduction. The systemic use of capsaicin is associated with severe gastric pain, but local use in mouthwash (250 mg/50 ml of water; 3 times/day) has shown some efficacy (76% of cases reporting improvement, with an average improvement of 3.2 on an VAS scale) without being able to solve the disease successfully and durably [46,47].

Oral lidocaine has also been used topically to relieve the burning sensation.

Anticonvulsant drugs are a drug class extensively tested in the treatment of BMS. Clonazepam (Rivotril®), considered for its central nervous system inhibitory action by specifically blocking the propagation of electrical impulses in damaged areas of the central nervous system. It was studied for topical application (tablet of 1 mg 3 times/day) or systemic application (0.25 to 0.75 g/day) and showed an improvement in both cases in about 70% of cases, with an average gain of 2.2 on an VSA scale [46,48-51]. In systemic use, side effects (heightening, drowsiness, increased dry mouth feeling, spasmophilia, euphoria) and the risk of addiction do not plead in favor of a favorable risk-benefit balance for the treatment of stomatodynia [48,49,51]. On the other hand, in topical application, the side effects are less or even zero, which makes it a treatment of choice for stomatodynia [46,48,50]. For a few months now in France, the prescription of clonazepam has been exclusively reserved for neurologists.

Gabapentin (Neurontin®) has also been used alone with reference to its action in the treatment of neuropathic pain [5], with daily doses starting at 300 mg/d and increasing from 300 mg/d every 2 days up to 2400 mg/d. The results are not significant [52].

Pregabalin (Lyrica®) performed better than gabapentin for the treatment of BMS [53]. However, side effects and addiction risks do not argue in favor of a favorable risk-benefit balance for the treatment of stomatodynia.

Antidepressants and antipsychotics have often been studied to treat BMS because of their effect on neuropathic pain. Trazodone (Oleptro®), Amisulpride (Solian®), Paroxetine (Deroxat®) and Amitriptyline (Laroxyl®) [54] were tested in turn, and did not show efficacy greater than placebo, with the exception of Amisulpride at 50 mg/day. This study has a high rate of abandonment and loss of sight (45%) [55].

Alpha-lipoic acid (ALA), a mitochondrial coenzyme as well as a natural hepatic protector is powerful antioxidant able to exert an activity of protection of nerve fibres by its regenerative neurological properties. It has been studied in numerous trials (prescribed systemically at daily doses of 600 - 800 mg/d). The results are heterogeneous: some authors report up to 80% improvement and 10% resolved, while others do not detect any statistically significant differences [56-60]. Combined with vitamin supplementation, ALA does not give better results. In combination with gabapentin, ALA gives better results than when used alone (70% improvement or resolution versus 55%).

Hormonal and behavioral therapies

Hormone replacement therapies have been proposed because stomatodynia often affect postmenopausal women, but these studies have many methodological biases and do not allow for a conclusion on the efficacy of such therapies [61].

Cognitive behavioral therapy has been proposed as an alternative to pharmaceutical treatments. A weekly one-hour session of 12 to 15 weeks per week results in statistically significant improvement over the 6 months following therapy compared to placebo. However, the study is small in size, with no description of the characteristics of the control and test groups, and the visual pain rating scale is not validated for the study of this type of pain. It should be noted that some studies report partial or total remission (with or without treatment) in about 50% of cases, with spontaneous complete remission in 3 to 20% of cases, within 5 to 7 years after onset of symptoms [62,63].

Conclusion

Despite significant advances in pathophysiology, primary BMS remains mysterious and further studies are needed to improve the management of this condition. There is significant diagnostic wandering for patients with BMS, emphasizing the importance of diagnostic criteria and methodology. New tests based on the identification of subclinical changes detectable by fine methods (QST, electrophysiology and immunohistochemistry) allow for the identification of different subgroups and differential treatment strategies. Time must be taken to find the treatment that will relieve the patient and often combine it with cognitive behavioral therapy.

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Conflict of Interest

The authors declare no potential conflict of interests.

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