International Journal of Dentistry Research

Review Article

IJDR 2016; 1(1): 14-23
December

www.dentistryscience.com

Burning Mouth Syndrome – Latest update

Olga Susana Tomattis Piñeyro de Serrano[1], Maria Cristina Munerato[2]*

1 *Dental Surgeon, Post graduate student of the Specialization Course in Pain Treatment and Palliative Medicine, Federal Universityof Rio Grande do Sul, Brazil*

2 *Associate Professor, Departmentof Odontologia Conservadora, Federal Universityof Rio Grande do Sul, Brazil*

Abstract

Introduction: Burning mouth syndrome (BMS) is characterized by a recurrent daily burning sensation with no evidence lesions in the oral mucosa. It is accompanied by subjective dry mouth and dysgeusia. The tongue is the most commonly affected site, but the condition also affects other sites in the mouth. Its etiopathogeny is multifactorial and its diagnosis is made by exclusion. **Objective:** This article reviews the literature about the epidemiology, etiopathogeny, and diagnosis of BMS in the past 15 years. Articles were selected from PubMed/MEDLINE, and included clinical assays, case reports, and reviews. We found 509 articles, and only 136 were chosen. The key words were: burning mouth syndrome (BMS), review, etiopathogeny, diagnosis. **Conclusions:** BMS remains an important diagnostic challenge, though the disease is considered a neuropathy characterized by damage to trigeminal peripheral nervous fibers, which triggers central sensitization. In addition to BMS and secondary BMS, it seems relevant to include complicated BMS, in which symptoms persist despite the elimination of local and systemic causes. BMS should be investigated by a transdisciplinary team that will take into account all aspects active in the mental and physical dimensions of the condition, in the most detailed way. Therefore, QST, imaging investigations, various evaluation scales of mental health and of the impact of BMS on quality of life as well as the investigation of sleep disorders and changes in circadian rhythm could be useful tools in the development of treatment strategies based on findings and observing the characteristics of each BMS patient in light of specifics of diagnosis.

Keywords: Burning mouth syndrome, Epidemiology, Etiopathogeny, Diagnosis.

INTRODUCTION

The International Headache Society acknowledged burning mouth syndrome (BMS) in 2004. The condition has been defined as a recurring burning sensation or dysesthesia lasting over two hours for more than three months on a daily basis with no clinical evidence of oral mucosa lesions and that is not caused by any other condition or disease. BMS is accompanied by xerostomia and dysgeusia, and the tongue apex is the most commonly affected site[1].

The specialized literature mentions other names of BMS, like stomatodynia, stomatopyrosis, glossodynia, glossopyrosis, burning tongue, and oral dysesthesia. Two variants of BMS have been described, the primary form, which is idiopathic and is defined according to the criteria above, and the secondary form, which is observed when a local or systemic causal agent is present[2-10].

BMS epidemiology

Besides the fact that studies on BMS have been carried out in various geographic locations, differences in inclusion and exclusion criteria may explain why epidemiological data on the disease are so dissimilar, making it difficult to establish reliable prevalence figures. Ample research shows that prevalence of BMS varies considerably, between 0.7% and 15%, depending on the population investigated[5,7-9,11-14]. For example, one study found age-adjusted prevalence rates of 18.8 and 3.7 cases in women and men, respectively in 100,000 people[15], while another investigation discovered that BMS occurs in 1 in every 1,000 subjects, mainly in women over 50 years old[16]. Also, the evaluation of 3,243 medical records found that 0.99% of patients could have BMS[17]. Women are the most affected group, usually at a 7 to 1 ratio against men, 90% of whom are in the perimenopausal stage. Typically, BMS manifests three years before and as late as 12 years after the onset of menopause[2,4,7-9,11,13,18-22].

Though BMS manifests spontaneously, one third of cases have been attributed to a dental procedure, recent disease, or use of some medication. The burning sensation is felt in the morning, worsening

***Corresponding author:**
Dr. Maria Cristina Munerato
Associate Professor, Departmentof Odontologia Conservadora, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos 2492, Porto Alegre, RS, CEP 90035-003, Brazil

progressively during the day and subsiding at night[3,11]. Risk factors include standing gastrointestinal or urogenital conditions[12,17], mild neuropathy in small autonomic and sensory fibers, side effects of medical drugs, and former smoking habit[12].

Though BMS manifests in various sites in the oral mucosa, the tongue is the organ most commonly affected, followed by the palate and lips. In some cases the burning sensation is felt diffusely across the oral mucosa[2,3,5,8,9,11,12]. BMS is rare in people under 30 years of age, and it has not been diagnosed in children and adolescents[5,8,9].

Since BMS affects quality of life, concomitant psychiatric conditions often imply the consequent use of psychotropic drugs. Yet, the association between use of hypotensive medication and BMS is but a hypothesis, since the disease usually manifests at the same age as the first signs of hypertension are observed[20].Also, the condition has been reported in two thirds of BMS patients wearing removable prostheses (which in cases was worn inappropriately). Besides prostheses, other factors linked with the onset of symptoms include tooth extraction, emotional conditions, systemic diseases, and menopausal changes. BMS manifested without association with prior condition in only 22.58% of patients[21].

Signs and symptoms of BMS in men and young women are different from those reported by menopausal women. Men exhibit lower incidence of gustatory changes and higher prevalence of comorbidities and abnormalities in blood tests, compared with young women. Unstimulated saliva flow rates were significantly higher in men and young women, who presented higher anxiety scores and greater prevalence of subclinical hypothyroidism. This lent strength to the hypothesis that BMS in pre-menopausal women has its own physiopathological mechanism. The symptom triad burning sensation-xerostomia-dysgeusia has been shown to be more common in women[23].

BMS etiopathology

A previous study indicated that BMS is a multifactorial condition that involves the interaction between the biological and the psychological systems[14,24,25].

Gustatory changes

Taste is closely associated with olfactory stimuli, and any imbalance in this relationship affects quality of life and nutrition habits. It has been shown that taste loss and phantogeusia are common complaints in elderly populations[26].

Taste is transmitted to the central nervous system (CNS) by taste buds,which are innervated by the facial and glossopharyngeal nerves. Sensory branches of the trigeminal nerve also contribute, innervating taste buds. It is thus that the afferent branches of these nerves overlap, exactly on the tongue region, where the burning sensation is most often reported(Fig. 1). Therefore, it has been alleged that taste could be affected by BMS, in conjunction with the activation of the chronic trigeminal neuralgia pathway[11,12,14,24,27-31].

BMS may be caused by the hyperactivity of somatosensory fibers of the trigeminal nerve, followed by the loss of central inhibition due to the damage to the sensory of the chorda tympani nerve or of the glossopharyngeal nerve. Research has suggested a correlation between BMS and the number of fungiform taste buds in individuals considered to have increased taste sensitivity that, in turn, are predominantly women[5,9,11,31,32],who often use medicinal drugs that influence taste. Also, it has been hypothesized that taste changes could be responsible for pain and oral burning sensation, especially in more sensitive individuals[33].

A standardized protocol of quantitative sensory tests (QST) revealed that individuals over 60 years old had higher sensory thresholds, and that women were more taste-sensitive than men[34]. Capsaicin has been shown to mitigate pain, showing that both pain and gustatory thresholds were significantly low in BMS patients[35].

The electrogustatory test revealed that response varied significantly among patients with BMS symptoms for over 41 months, though the number of fungiform taste buds did not vary[36]. However, another study found a comparatively high density of fungiform taste buds in BMS patients[37].

Changes in taste such as peripheral and/or central neuropathy have been given more attention, being associated with the etiopathogeny of BMS, since A-δ fibers mediate not only taste, but also the first sensation of pain after a cold stimulus. It has been argued that future research on BMS should include clinical trials that look into pain, taste dysfunction, and xerostomia as well as psychological evaluations to assess the effect of the disease on quality of life[30].

In addition, a study that compared one group of BMS patients and one group with dysgeusia revealed marked changes in central grey matter. In BMS patients, most changes were observed in pain regions, while most changes in dysgeusia individuals were observed in the emotion, motor anticipation, and somesthesia area. The authors concluded that different cerebral mechanisms cause BMS and dysgeusia, ruling out the hypothesis that these conditions have similar etiology.[38]

Saliva changes

Qualitative and quantitative changes in saliva influence the health of the oral cavity and may play an important role both in the onset and in the continuation of the burning sensation.The lubricating function of saliva is affected by such changes and therefore the patient's perception of the oral mucosa may vary. Viscous saliva induces xerostomia, when lingual receptors are continually exposed to stimuli. Further studies on xerostomia may elucidate its actual role in the etiopathogeny of BMS[39]. The attempt to treat xerostomia with urea 10% topically failed to improve saliva flow and taste, olfactory, and somesthetic thresholds[40]. Unstimulated saliva flow rates were shown to drop significantly only in BMS patients[41-43], though scintillography of salivary glands did not evince any functional loss in either healthy or hyposalivation patients[41].

The anatomical site of taste buds, nearby the salivary gland ducts, also affects taste. So, it may be said that BMS is associated to the activation of peripheral taste mechanisms so that BMS as well as xerostomia of unknown causes and changes in taste perception might be seen as expressions of the same oral neuropathy, in what is interpreted as a peripheral neurological dysfunction[29].

Other studies have investigated additional saliva parameters, like viscosity, Secretory immunoglobulin A (SIgA) levels, α-amylase activity, and serum antioxidant potential. This indicates that immune activity may be low in BMS patients, sIgA/min levels were low. Also, the high α-amylase levels and the low serum buffer capacity observed in BMS patients may signal that anxiety and stress due to burning sensation[38]. Interestingly, levels of trace elements and minerals did not vary significantly between BMS patients and healthy subjects[44].The peptide opiorphin (QRFSR peptide) is secreted by submandibullary salivary glands, with analgesic action. BMS patients had low saliva and high blood levels of opiorphin, which may reflect systemic deregulation in BMS[45].

Using saliva biomarkers in BMS patients, one study demonstrated a mild negative correlation between levels of cortisol I and interleukin-6 (IL-6) and the predisposition to face new challenges, in what could be attributed to stress[46]. In addition, statistically high salivary levels of IL-2

and Il-6 that could be associated with the severity of BMS suggest that these markers indicate the existence of an inflammatory and immunologic mechanism behind its etiology[47].

BMS as a peripheral and/or central neuropathy

Including routes at various levels, the neuropathic mechanisms of BMS may be divided into three possible subclasses, namely small peripheral oral fiber neuropathy (with 50% to 60% of cases), subclinical trigeminal neuropathy (20% to 25% of cases), and central pain syndrome involving dopaminergic neuron hypofunction in the basal ganglion (20% to 40% of cases)[9,12,14,25,32,48].Also, QST and blink reflex (BR) afforded to evaluate the neurological mechanisms behind BMS. The QST showed that 76% of patients presented one or more anomalous sensory triggers, indicating dysfunction of fine nervous fibers. Changes in BR results in 19% of patients signal a peripheral disease, with subclinical alterations in the trigeminal system[49].

Anesthetic block of the lingual nerve using lidocaine was yet another way to discover whether BMS has one peripheral neuropathic component. Mitigation of symptoms after lidocaine-mediated block led to the diagnosis of BMS by peripheral neuropathy; yet, continuation of symptoms afforded to conclude that BMS was due to central neuropathy. It was argued that these results indicated the existence of a peripheral or central mechanism (or a combination thereof) active in BMS physiopathology, and that topic use of clonazepam and evaluations using anxiety and stress scales could help identify the major mechanism behind BMS[50]. In addition, the origin of the neuropathy involved, whether central or peripheral, interfered with the choice of medicinal drugs for the treatment of BMS[51].

Image-based functional evaluation of brain is a source of additional information to understand the neural mechanisms behind the etiopathology of BMS.The sensory changes suggest that both the CNS and the peripheral nervous system are involved in the manifestation of BMS[9,28,52].The correlation between BR and BMS was similar to that observed between BR and Parkinson's disease, which is considered one of the causes of secondary BMS[9,28]. BMS patients exhibited higher thresholds for savory, sweet, sour, and olfaction stimuli, lending strength to the idea that central sensitization is involved in the physiopathology of the disease[53].

Functional magnetic resonance imaging (fMRI) revealed that, although lasting pain in BMS does not affect anxiety and stress levels directly, long-term vulnerability and plasticity of affective and motivational circuits are influenced[54].

The literature also mentions disruption in the autonomic innervation and in blood flow in the oral region, besides changed levels of neuroactive steroids in skin and oral mucosa as a consequence of chronic stress and anxiety[9]. The evaluation of the immune endocrine function revealed that adrenalin levels in plasma are lower and that anxiety is greater in BMS patients, which was interpreted as a deregulation of the hypothalamic–pituitary–adrenal axis and the consequent reduction in the adrenomedullary response to stress[55]. Lower CD4:CD8 ratios were also observed in this group, due to the drop in CD8 counts. Also, a relationship between oxidative stress and BMS was observed in post-menopausal women[56].

Another theory about the etiopathogeny of BMS presupposes that some patients may suffer from some malfunction in mastocyte activation,which could be responsible for the perineural inflammatory status of the oral mucosa, causing peripheral neuropathy[57]. Another hypothesis to explain pain and a neurogenic inflammatory process was magnesium deficiency. One study reported that patients with burning sensation restricted to the tongue had lower magnesium levels, when compared with patients complaining of BMS also on other oral sites and healthy individuals. The authors additionally concluded that such deficiency was the likely mechanism behind BMS confined to the tongue[58].

Histological changes in the oral mucosa

The overexpression of cytokeratin 16 in the stratum spinosum of the mucosa is characteristic of quite differentiated epithelia under pathological conditions[59], which may be linked with neurodegenerative changes previously described as significant loss of subpapillary and epithelial nervous fibers in the tongues' anterior two thirds[60]. Epithelial atrophy has also been described in a study that concluded that it could lead to greater exposure of nervous terminations and the consequent symptoms described for this syndrome[61].Low density of intraepithelial nervous fibers was observed on area and length basis in samples of the tongue dorsum mucosa[62].

Secondary BMS

Stomatological and clinical evaluations are useful tools to identify lesions or conditions that may play a role in the genesis of BMS. The possible organic etiologies are grouped under three categories, namely local, systemic, and psychiatric.

Local causes

Oral lesions caused by trauma

This class includes lesions caused by accidental bite, physical and chemical burns, chronic use of mouthwash and tongue scrapers, and parafunctional habits such as teeth grinding and biting of lips and buccal mucosa[3,5,7,8,11-14,63-67].

Patients complaining of burning sensation in a very specific site such as the tip or the edges of the tongue require investigation of a local factor, since this would be the site of transient lingual papillitis[68].

Allergies

Factors such as incomplete polymerization of acrylic used to manufacture a prosthesis, food additives and dyes, and the aldehyde present in cinnamon are some of the possible causes of secondary BMS associated with allergy[3,5,8,11-13,64-67].

Diseases of the oral mucosa

Conditions that induce atrophy, erosion, or ulceration of the oral mucosa may be characterized by burning sensation. Among these conditions, geographic or fissured tongue, candidiasis, and oral lichen planus stand out[3,8,11-13,14,64-67].

Geographic tongue is often observed in patients with BMS, and may be considered a risk factor for the emergence of the syndrome[69]. Candidiasis has also been mentioned to cause BMS[14,70,71].A relationship between feeding and burning mouth has been observed. Studies have shown that if the burning sensation worsens after eating, candidiasis has to be suspected, since BMS signs improve after consumption of food[63,64]. However, one study did not find any association between candidiasis and BMS[23].

The erosive, ulcerous, or blister manifestations of oral lichen planus are symptomatic and should be ruled out during the investigation of BMS[13,14,65]. BMS has also been reported in association with infection with the varicella zoster vírus, with total or partial remission of symptoms after antiviral therapy[78].

Temporomandibular disorders

One study showed that two thirds of BMS patients also had a temporomandibular disorder (TMD). It was inferred that several

patients did not find it important to report TMD, since BMS was more relevant to them at the moment the study was being conducted. The high number of patients with TMD and concomitant BMS could be attributed to an overworked masticatory function, since anxiety and insomnia were often mentioned during appointments. Wear sites indicate parafunctional habits, and were observed in 72.7% of patients. The stress associated with BMS may explain this finding, since this is the main cause of TMD. Dopaminergic system disorders, which could affect the regulation of the nociceptive system, lead to the complete loss of inhibition of the trigeminal system, triggering sensory and motor hyperfunction, causing hyperactivity of masticatory muscles and DTM[72].

Systemic diseases with oral manifestations

Esophageal reflux, autoimmune conditions, hypertension, diabetes, thyroid dysfunctions, Sjögren's syndrome, Parkinson's disease (PD), deficiency in B complex vitamins, in iron, and in zinc were listed as maladies whose symptoms include BMS[2,3,5,7,8,11-13,14,18,25, 64-67,79].

The evaluation of the thyroidal function and of vitamin B12, iron, and hemoglobin levels should be included in the investigation of the origins of BMS[17,25,64]. The success rate of 44.4% in treatments based on supplementation with B complex vitamins, folic acid, iron, and zinc underscores the relevance of serum levels of homocysteine as a predictor of subclinical megaloblastic anemia[75]. A case report that described BMS in an elderly male with vitamin B12 deficiency and who responded to the treatment with injections as supplementation strategy for three months demonstrated the importance of differential diagnosis[76].

It has been hypothesized that zinc deficiency is associated with the loss or to changes in taste[24], which is one of the complaints most often linked with BMS. A clinical trial about the effect of zinc supplementation in BMS patients[77] failed to follow the required methodological accuracy level to confirm that it could be used as a therapeutic alternative[80].

The lack of a correlation between laryngopharyngeal reflux and BMS has led to the conclusion that the prescription of omeprazole should be revised due to this drug's side effects and the modest benefits in using it to treat the condition[81].

Electroneuromyographic findings in BMS patients were similar to those observed in Parkinson's disease. Both the sympathetic and parasympathetic autonomic nervous systems are significantly damaged. However, if the functional balance is preserved, resulting in mild dysautonomia, it might be suggested that the pathogenesis of both BMS and PD share some aspects in common[82]. A case report describing Parkinson's disease in a woman with symptoms compatible with BMS during treatment of the former condition afforded to conclude that BMS may have originated from the drop in endogenous dopamine levels associated with the deregulation of dopamine receptors at central level, whose symptoms disappear when cardidopa and levodopa were replaced by pramipexole[83].However, the study carried out by Bonenfant *et al*.(2016) revealed that the prevalence of BMS is low in PD patients[79].

Menopause

In light of the significant prevalence of BMS in pre-menopausal and post-menopausal women, hormonal changes coincide with complaints of xerostomia and dysgeusia[2,3,5,6,8,11,12,14,66,84-88].

Since the oral mucosa is equipped with estrogen receptors, variations in hormone levels affect the structure directly. But the mucosa is affected by age, increasing xerostomia and reducing periodontal health[14,21,85,87-89]. A recent study revealed that the low level of dehydroepiandrosterone (DHEA) in these patients may contribute to the etiopathogeny of BMS[90].

Although hormone replacement is effective to mitigate the classical symptoms of menopause, this is not observed in BMS patients. The prescription of hormone replacement to treat BMS is challenged in the specialized literature[19,22,85,87-89].

Chronic use of medical drugs

The list of medical drugs with adverse effects on the oral cavity is long. Xerostomia, dysgeusia, and burning sensation stand as the main side effects triggered by chronic use of medical drugs. So, all medications used by a BMS patient have to be considered in the investigation of possible causes of the disease[2,3,12,13,65,66].

One specific class of drugs induces burning sensation in the oral cavity: angiotensin-converting-enzyme inhibitors (ACEIs). These medical drugs are prescribed to treat arterial hypertension[3,5,11,12,14,65,91,92].Only one study did not find any significant difference for the consumption of IECA between healthy individuals and BMS patients[73].

It has been observed that 95% of medical drugs used by a group of BMS patients induced xerostomia, among which the most commonly prescribed were psychotropic, analgesic, anti-inflammatory, hypotensive, diuretic drugs as well as more specific medicines to treat cardiovascular and digestive disorders. These patients also presented statistically significant incidence of anxiety and/or depression in comparison with the control group, besides other comorbidities[93]. Other investigations listed hypertension, gastroesophageal reflux, hypercholesterolemia, autoimmune diseases, thyroid diseases, and anemia as the most frequent comorbidities. The medical drugs used to treat these diseases may have potentially triggered BMS in these patients[94,95].

Topiramate has also been considered responsible for xerostomia and oral burning sensation in a case report[96].

Increasing doses of fluoxetine to treat depression have also had oral burning sensation as adverse effect, though without concomitant xerostomia and dysgeusia[87].

Psychogenic causes

Life events and family environments are known risk factors for BMS, especially maternal depression and recent loss[98]. BMS patients have higher anxiety and depression scores. Also, it is widely accepted that pain is a somatic aspect of depression and anxiety worsens somatization[99-113].

Psychological conditions may play an important role in the modulation of pain perception. Such conditions may increase or reduce nervous transmission, changing perception, lowering the pain threshold, and inducing the nervous system to perceive regular stimuli as painful. Therefore, it is reasonable to associate these psychological disorders with BMS, since they share some characteristics in common. However, research has also revealed that these conditions are a consequence, not a cause, of BMS[2,6,8,11,12,14,86].

It has been shown that sleep deprivation lower pain thresholds, in addition to causing mood swings, sleepiness, and fatigue. Research has claimed that any advancement in BMS etiology and treatment should consider the correct management of the disease[114-118]. Table 1 lists studies that looked into the correlation between psychological and sleep disorders and BMS.

Another important aspect is the resistance of BMS patients to accepting the fact that the primary cause of the disease is an underlying psychological condition. Explaining that BMS is bilateral and

Table 1: Studies that investigated the relationship between BMS and psychological and sleep disorders

Author	Type of study	Psychological disorders	Sleep disorders
Takenoshita et al. (2010) (99)	Longitudinal, retrospective, non-controlled study - 162 patients	BMS: mood swings and affective disorders. OA: somatoform disorders associated with stress and neurosis.	NA
Chainani-Wu, Madden, Silverman (2011) (114)	Case control study - 28 BMS/27 controls	NA	BMS with high level of sleep disorders that may be a risk factor for the disease.
Schiavone et al. (2012)(101)	Transversal, prospective, controlled clinical study - 53 BMS/51 controls	BMSis influenced by depression that in turn is affected by anxiety BMScould be a somatic aspect of depression.	NA
Malik et al. (2012) (109)	Prevalence study - 56 BMS/44 controls	MostBMSpatients had mild to moderate depression.	NA
Prakash, Ahuja, Rathod (2012) (118)	Case report - 05 patients	NA	Four patients with restless leg syndrome and one patient with a family member with BMS.
De Souza et al. (2012)(102)	Transversal, controlled study - 30 BMS/31 controls	BMS with generalized anxiety disorder associated with depression and social phobia besides cancerphobia and hypochondria.	NA
Komiyama et al. (2012)(100)	Longitudinal, non-controlled study 282 BMS/83 trigeminal nerve neuropathy	Much lower odds ratio for the worsening of pain in BMS patients. Odds ratio for somatization found to be 3.8 times as high forBMS.	NA
Komiyama et al.(2013)(137)	Case control study - 24 BMS/24 controls	BMS with higher anxiety scores.	NA
Adamo et al. (2013) (115)	Case control - 50 BMS/50 controls	BMS with depression and anxiety that could be important risk factors for sleep disorders.	BMS group with the prevalence of worst sleep quality (80% of patients).
Lee et al.(2014) (116)	Analytical, longitudinal, retrospective cohort study	NA	Sleep disorders may be a risk factor for BMS.
Kontoangelos et al. (2014) (108)	Case report - 01 patient	Intense depression with suicidal intentions.	NA
López-Jornet et al., 2015 (117)	Descriptive, transversal, observational study 70 BMS/70 controls	BMS with intense anxiety and depression.	Poor sleep quality in 67.1% of BMS patients.
Bhatia, Bhatia, Bhatia (2015) (103)	Case report - 01 patient	Psychogenic lingual paresthesia and patient with depression.	NA
De Souza et al. (2015) (110)	Controlled, transversal study - 30BMS/30 controls	BMS with high rates of depression (present and past) and generalized anxiety disorders. Poor scores of the personality trait 'open to new experiences.	NA
Marino et al. (2015) (104)	Case control study - 58 BMS/58 controls	BMS with high incidence ofalexithymia (79%). Alexithymia may interfere in the relationship between health professional and the patient playing a significant role in somatization.	NA
Liu et al. (2015) (105)	Case control study - 29 BMS/10 controls	BMS with depression rate of31% and high scores in anxiety and depression scales accompanied by low blood flow into the left temporal and parietal lobes.	NA
Tokura et al. (2015) (107)	Case control study - 65 BMS/116 controls	BMS with low scores for search for novelty in the TCI. Influence of depression on the score of damage avoidance score (high) andon the self-directing trend score (low) .	NA
dasNevesAraújo Lima et al. (2016) (90)	Cross sectional study - 64 BMS/99 SOB	Significant difference between the two groups, symptoms of depression more prevalent in BMS.	NA
Davies et al. (2016) (111)	Cross sectional study - 30BMS/11 other oral conditions	Specific BMF symptoms are associated differentially with generalized anxiety and depression.	NA

NA, not assessed; BMS, burning mouth syndrome; SOB, secondary oral burning; TCI, Temperament and Character Inventory

does not run along the anatomical route of the peripheral sensory nerve may help patients accept the existence of a condition that transcends the physical dimension into the mental element of a disease. Nevertheless, BMS should not be seen as a mere somatic symptom of a psychological disorder[63,119.]

The investigation about somatic comorbidities showed that several BMS patients had at least one extraoral symptom that could not be explained. The most common sites affected were the gastrointestinal and neurological systems, apart from the eyes, nose, and throat in addition to pain in other regions. It has been alleged that these unexplained symptoms are associated with CNS disorders and, in some cases, with psychological conditions. Also, physical symptoms are considered manifestations of such abnormalities[106]. However, the study conducted by Moisset et al (2016) concluded that there is no evidence of high comorbidity rates of the chronic pain spectrum and somatosensory sensitivity associated with BMS[120].

Chronobiology

Chronobiological evaluation has shown that BMS patients do not feel any symptom of the disease upon waking up, and that discomfort emerges and becomes worse within a 24-hour period, depending on anxiety levels[121]. All circadian rhythms are directed by the biological clock located in the hypothalamus, and interfere with the salivary flow, the oral epithelium, and inflammatory response, even in the IL-6 route[122]. BMS patients have low serum IL-6 levels, which play a neuroprotective role in the trigeminal nociceptive pathway through the underlying mechanisms thereof remain to be ellucidated[117]. The table 1 presents the articles about psychologic disorders and chronobiology in patients with BMS.

Differential diagnosis

Orofacial pain poses a significant challenge in diagnosis. Obtaining a detailed record from patients and conducting the appropriate medical examination are essential steps when formulating a diagnostic hypothesis and in the effort to establish the best treatment strategy for each case. BMS is considered one of the orofacial pain syndromes of neuropathic origin, though the way it should be managed remains shrouded in controversy, pointing to the importance of identifying local factors, evaluating the impact of BMS in quality of life, and identifying associated systemic and psychiatric comorbidities[14,66,124-128]. Questionnaire 4 for neuropathic pain (DN4 scores) is a useful tool in the investigation of BMS[113].

However, patients presenting oral lesion may also present underlying BMS. If symptoms persist after successful treatment of the disease, the patient may be considered to have a complicated manifestation of BMS. This differentiation between BMS and the secondary and complicated manifestations of the disease should be used in the decision-making process about the best treatment strategy[129].

In light of the complexity of the diagnosis of BMS, one protocol was developed especially to conduct this investigation process (Fig.2). Since it is necessary to rule out local and systemic factors that cause this symptom, the protocol highlights the importance of a transdisciplinary approach involving health professionals of relevant areas. Therefore, oral health should be analyzed searching for the scenarios listed above that could explain complaints at the same time that an investigation about systemic diseases is carried out, considering the possible adverse effects of medical drugs being used by the patient suspected of BMS[130].

Also, ideally the collection of data on BMS should include the in-depth pain record, detailed physical examination, the collection of information regarding the patient's psychological and psychosocial health status, and the evaluation of saliva flow and of gustative sensitivity. Other important measures to be considered include the clinical assessments of patients, a neurological analysis using imaging resources, an investigation of oral infections based on biological cultures, in addition to tests to detect allergies, exams looking into gastric reflux, and the evaluation of nutritional, hormonal, and autoimmune conditions[131].

As observed in most studies on BMS, late diagnosis influences responses to treatment. So, the elderly is the patient and the longer BMS remains untreated, the worse will be the prognosis[95,132].

Interestingly, QST may help understand the neuronal mechanisms involved in various kinds of chronic pain. These tests evaluate the function of a variety of nervous fibers and detect both sensory gains and losses, and are being adapted to investigate the intraoral somatosensory function[32,62,133]. The changes associated with BMS that have thus far been described include the reduction of thermal sensitivity and low scores for tonic painful stimuli in the oral cavity, as well as lower thresholds of pain caused by heat on the tip of the tongue, anomalies in the BR, and qualitative alterations of saliva[5].

The strategy to diagnose BMS include electrogustometry, bilateral thermal QST of the lingual mucosa, BR and masseteric reflex, biopsy of the lingual mucosa to investigate the density of subepithelial and epithelial nervous fibbers, electroneuromyography (ENMG), and fMRI of brain[134].

So far ENMG, neurophysiological tests, and evaluations of the autonomic nervous system indicate that neuropathy of small sensory and autonomic fibers accompanied by central disorders as the main factor behind the symptoms that characterize BMS[135].

Another sensory study protocol included the evaluation of taste, olfactory, thermal, tact, and vibration thresholds, as well as an effort to assess sensitivity to mechanical pain both superficial and deep.These investigations covered the three branches of the trigeminal nerve of both sides of the face. The protocol afforded to observe high prevalence of sensory changes both in BMS patients and in those complaining of neuropathic pain (as in BMS) and somatic pain (TMD and fibromyalgia)[136]. The figure 2 shows a fluxogram with the strategy to reach the BMS diagnosis.

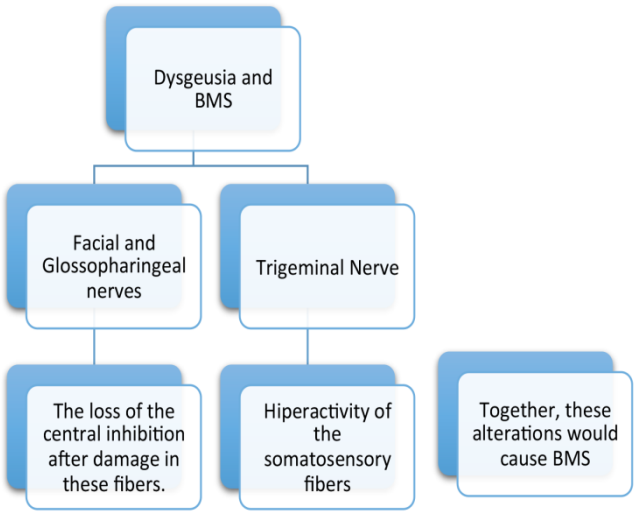

Figure 1: Diagram of dysgeusia and BMS correlations

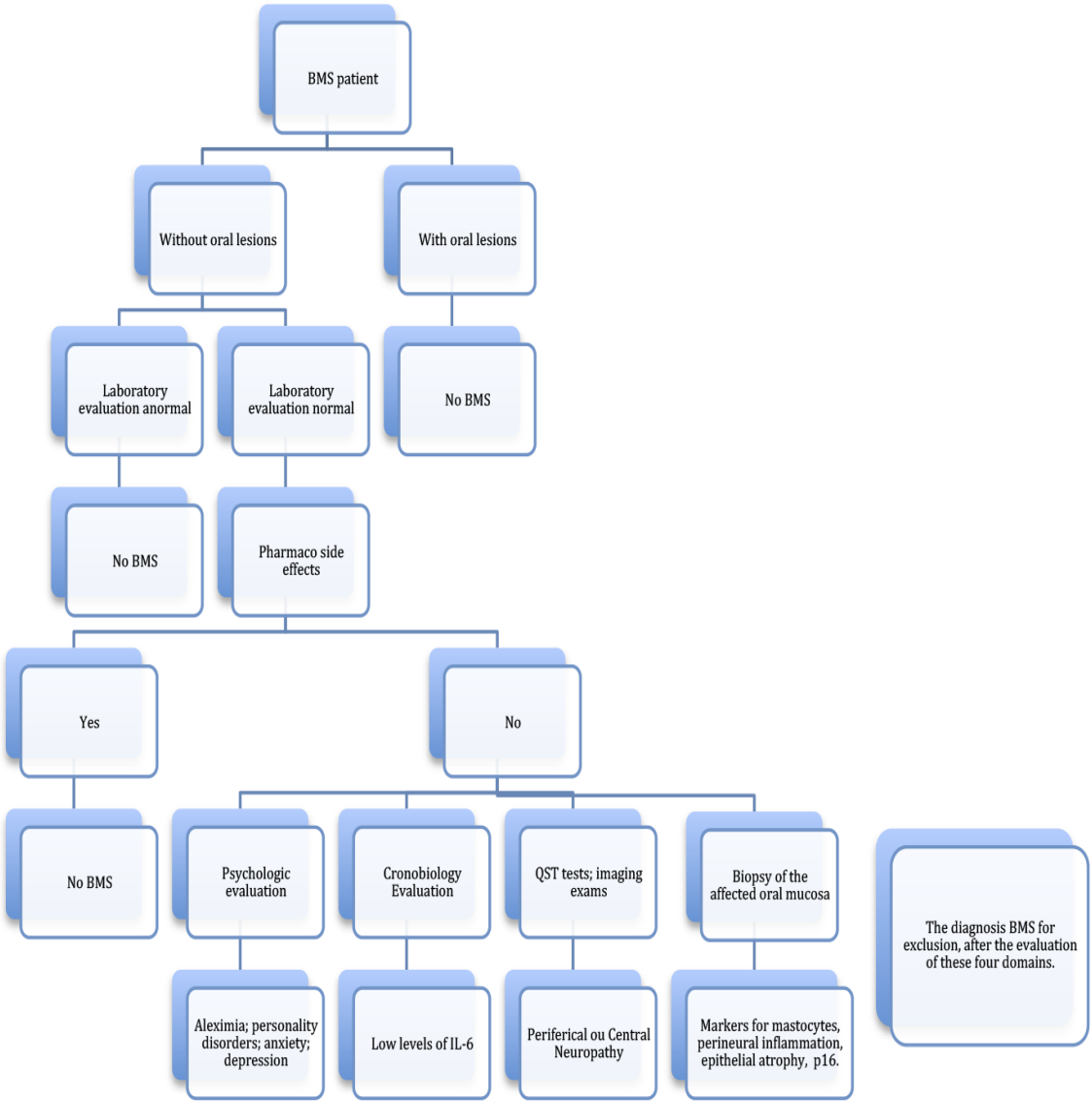

Figure 2: Diagram of differential diagnostic of BMS patients

CONCLUSION

BMS remains an important diagnostic challenge, though the disease is considered a neuropathy characterized by damage to trigeminal peripheral nervous fibers, which triggers central sensitization.

In addition to BMS and secondary BMS, it seems relevant to include complicated BMS, in which symptoms persist despite the elimination of local and systemic causes.

Of the possible causes of BMS, high IL-2 and IL-6 levels in saliva should also be considered, besides psychological factors like alexithymia and personality disorders (marked avoidance to danger and low self-esteem).

BMS should be investigated by a transdisciplinary team that will take into account all aspects active in the mental and physical dimensions of the condition, in the most detailed way.

Despite the absence of lesions on the affected oral mucosa, biopsy may be useful to investigate neurodegenerative and epithelial changes, disorders affecting mastocytes, the interleukins detected, and other factors using a panel of specific markers based on what is known about the etiopathogeny of BMS.

Therefore, QST, imaging investigations, various evaluation scales of mental health and of the impact of BMS on quality of life as well as the investigation of sleep disorders and changes in circadian rhythm could be useful tools in the development of treatment strategies based on findings and observing the characteristics of each BMS patient in light of specifics of diagnosis.

Conflict of interest: None.

Financial support and sponsorship: Nil.

REFERENCES

1. InternationalClassificationofHeadaches. 3th. Ed. 2014. p.139. Available from: www.ihs-headache.org/.../2086_ichd-3-beta-versao-pt-portuguese.pdf. Accessed 20th August 2015.
2. Del Valle AE, Aguirre-Urizar JM, Martinez-Conde R, EchebarriaGoikouria MA, SagastaPujana O. Síndrome de boca ardienteenel país Vasco: estúdio preliminar de 30 casos. Med Oral 2003;8:84-90.
3. Cerchiari DP, de Moricz RD, Sanjar MA, Rapoport PB, Moretti G, Guerra MM. Síndrome da bocaardente: etiologia.Braz J Otorhinolaryngol 2006; 72(3):419-423.
4. Buchanan JE, Zakrzewska J. Burning mouth syndrome. BMJ ClinEvid 2010; pii:1301.
5. López-Jornet P, Camacho Alonso F, Andujar–Mateus P, Sánchez-Siles M,

Gómez-García F. Burning mouth syndrome: update. Med Oral Pathol Oral Cir Bucal. 2010;15(4):e562-568.
6. Minguez-Sanz MP, Salort-Llorca C, Silvestre-Donat FJ. Etiology of burning mouth syndrome: a review and update. Med Oral Patol Oral Cir Bucal 2011;16(2):e144-148.
7. Gurvits GE, Tan A. Burning mouth syndrome. World J Gastroenterol 2013; 19(5):665-672.
8. Balasubramaniam R, Klasser GD. Orofacial pain syndromes. Med Clin N Am 2014;98:1385-1405.
9. Aravindhan R, Vidyalakshmi S, Kumar MS, Satheesh C, Balasubramanium AM, Prasad VS. Burning mouth syndrome: a review on its diagnostic and therapeutic approach. J Pharm BioalliedSci2014;S21-5. Doi: 10.4103/0975-7406.137255.
10. Miziara I, Chagury A, Vargas C, Freitas LE, Mahmoud A. Therapeutic options in idiopathic burning mouth syndrome: literature review. Int Arch Otorhinolaryngol 2015;19(1):86-89.Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. Am Fam Physician 2002;65(4):615-620.
11. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. Am Fam Physician 2002;65(4):615-620.
12. Thoppay JR, de Rossi SS, Ciarrocca KN. Burning mouth syndrome. Dent Clin North Am 2013;57(3):497-512. Doi: 10.1016/j.cden.2013.04.010.
13. Coculescu EC, Tovaru S, Coculescu BI. Epidemiological and etiological aspects of burning mouth syndrome. J Med Life 2014;7(3):305-309.
14. Klasser GD, Grushka M, Su N. Burning mouth syndrome. Oral MaxilofoacialSurgClin N Am. 2016; 28:381-396. Doi: 10.1016/j.coms.2016.03.005.
15. Kohorst JJ, Bruce AJ, Torgerson RR, Schenck LA, Davis MD. A population-based study of the incidence of burning mouth syndrome. Mayo Clin Proc 2014;89(11):1545-1552.
16. Kohorst JJ, Bruce AJ, Torgerson RR, Schenck LA, Davis MD. The prevalence of burning mouth syndrome: a population-based study. Br J Dermatol 2015; 172(6):1654-6. Doi: 10.1111/bjd.13613.
17. Netto FOG, Diniz IMA, Grossmann SMC, de Abreu MHNG, do Carmo MAV, Aguiar MCF. Risk factor in burning mouth syndrome: a case-control study based on patient records. Clin Oral Invest 2011;15(4):571-575. doi: 10.1007/s00784-010-0419-5.
18. Felice F, Gombos F, Esposito V, Nunziata M, Scully C. Burning mouth syndrome (BMS): evaluation of thyroid and taste. Med Oral Patol Oral Cir Bucal 2006;11:E22-25.
19. Dutt P, Chaudhary SR, Kumar P. Oral health and menopause: a comprehensive review on current knowledge and associated dental management. Ann Med Health Sci Res 2013;3(3):320-323.
20. Cherubini K, Maidana JD, Wiegert KL, Figueiredo MA. Síndrome da ardência bucal: revisão de cem casos. Rev OdontoCiência 2005;20(48):109-113.
21. Cavalcanti DR, Birman EG, Migliari DA, da Silveira FRX. Burning mouth syndrome: clinical profile of Brazilian patients and oral carriage of Candida species. Braz Dent J 2007;18(4):341-345.
22. Slebioda Z, Szponar E. Burning mouth syndrome – a common dental problem in perimenopausal women. PrzMenopauzalny 2014;13(3):198-202. Doi: 10.5114/pm.2014.43825.
23. Kim Y, Kim HI, Kho HS. Characteristics of men and premenopausal women with burning mouth syndrome symptoms: a case-controlled study. Headache 2014;54(5):888-98. Doi: 10.1111/head.12338.
24. Kamala KA, Sankethguddad S, Sujith SG, Tantradi P. Burning mouth syndrome. Indian J Palliat Care 2016;22(1):74-9. Doi: 10.4103/0973-1075.173942.
25. Lewis AK, Prime SS, Cohen SN. An overview of burning mouth syndrome for the dermatologist. ClinExpDermatol. 2016 Mar; 41(2):119-23. Doi: 10.1111/ced.12808.
26. Cowart BJ. Taste dysfunction: a practical guide for oral medicine. Oral Dis 2011;17(1):2-6. Doi: 10.1111/j.1601-0825.2010.01719.x.
27. Formaker BK, Frank ME. Taste function in patients with oral burning. Chem Senses 2000;25:575-581.
28. Bartoshuk LM, Snyder DJ, Grushka M, Berger AM, Duffy VB, Kveton JF. Taste damage: previously unsuspected consequences. Chemical Senses 2005;30 (suppl. 1):i218-i219. doi: 10.1093/chemse/bjh 192.
29. Hershkovich O, Nagler RM. Biochemical analysis of saliva and taste acuity evaluation in patients with burning mouth syndrome, xerostomia and/or gustatory disturbances. Arch Oral Biol 2004;49:515-522. Doi: 10.1016/j.archoralbio.2004.01.012.
30. Kolkka-Palomaa M, Jääskeläinen SK, Laine MA, Teerijoki-Oksa T, Sandell M, Forssell H. Pathophysiology of primary burning mouth syndrome with special focus on taste dysfunction: a review. Oral Dis 2015;11, doi: 10.1111/odi.12345.
31. Coculescu EC, Manole G, Coculescu BI, Purcarea VL. Burning mouth syndrome: controversial place as a syptom of oro-dental pathology. J. Med and Life. 2015; 8 Special Issue:34-37.
32. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological conditions with implications for management. J Oral Rehabilitation 2015;42(4):300-322.
33. Femiano F, Lanza A, Buonaiuto C, Gombos F, Cirillo N. Burning mouth disorder (bmd) and taste: a hypothesis. Med Oral Patol Oral Cir Bucal 2008; 13(8):e470-474.
34. Da Silva LA, Lin SM, Teixeira MJ, de Siqueira JTT, Jacob Filho W, de Siqueira SRDT. Sensorial differences according to sex and ages. Oral Dis 2014;20:e103-e110. Doi: 10.1111/odi.12145.
35. Just T, Steiner S, Pau HW. Oral pain perception and taste in burning mouth syndrome. J Oral Pathol Med 2010;39:22-27.
36. Nasri-Heir C, Gomes J, Heir GM, Ananthan S, Benoliel R, Teich S, Eliav E. The role of sensory input of the chorda tympani nerve and the number of fungiform papillae in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral RadiolEndod2011;112(1):65072. Doi: 10.1016/j.tripleo.2011.02.035.
37. Camacho-Alonso F, López-Jornet P, Molino-Pagán D. Fungiform papillae density in patients with burning mouth syndrome and xerostomia. Med Oral Patol Oral Cir Bucal 2012;17(3):e362-366.
38. Sinding C, Gransjoen AM, Schlumberger G, Grushka M, Frasnelli J, Singh PB. Grey matter changes of the pain matrix in patients with burning mouth syndrome. Eur J Neurosci. 2016 Apr; 43(8):977-1005. Doi; 10.1111/ejn.13156.
39. Küstner EC, Soares MSM. Boca ardiente y saliva. Medicina Oral 2002;7(4): 244-253.
40. Silva LA, Siqueira JT, Teixeira MJ, Siqueira SR. The role of xerostomia in burning mouth syndrome: a case-control study. ArqNeuropsiquiatr 2014; 72(2):91-98. Doi: 10.1590/0004-282X20130218.
41. Lee YC, Hong IK, Eun YG. Evaluation of salivary function in patients with burning mouth syndrome. Oral Dis 2015;21(3):308-313. Doi: 10.1111/odi.12270.
42. Imura H, Shimada M, Yamazaki Y, Sugimoto K. Characteristic changes of saliva and taste in burning mouth syndrome patients. J Oral Pathol Med 2015; doi: 10.1111/jop.12350.
43. Spadari F, Venesia P, Azzi L, Veronesi G, Costantino D, Croveri F, Farronato D, Tagliabue A, Tettamanti L. Low basal salivary flow and burning mouth syndrome: new evidence in this enigmatic pathology. J Oral Pathol Med 2015; 44(3):229-233. Doi: 10.1111/jop.12240.
44. López-Jornet P, Juan H, Pons-Fuster A. Mineral and trace element analysis of saliva from patients with BMS: a cross-sectional prospective controlled clinical study. J Oral Pathol Med 2014;43(2):111-116. Doi: 10.1111/jop.12105.
45. Boucher Y, Braud A, Dufour E, Agbo-Godean S, Baaroun V, Descroix V, Guinnepain M-T, Ungeheuer M-N, Ottone C, Rougeot C. Opiorphin levels in fluids of burning mouth syndrome patients: a case-control study. Clin Oral Invertig. 2016 Nov 10. Doi: 10.1007/s00784-016-1991-0.
46. De Souza FT, Kumer A, Silva MLV, Amaral TMP, Abdo EN, Abreu MHNG, Silva TA, Teixeira AL. The association of openness personality trait with stress-related salivary biomarkers in burning mouth syndrome. Neuroimmunomodulation 2015;22(4):250-255. Doi: 10.1159/000367714.
47. Simcic D, Pezelj-Ribaric S, Grzic R, Horvat J, Brumini G, Muhvic-Urek M. Detection of salivary interleukin-2 and interleukin-6 in patients with burning mouth syndrome. Mediators of Inflammation 2006;article ID 54632. 1-4. Doi: 10.1155/MI/2006/54632.
48. Patton LL, Siegel MA, Benoliel R, deLaat A. Manegement of burning mouth syndrome: systematic review and management recommendations. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 2007;103 (suppl 1):S39.e1-S39.e13.
49. Forssell H, Jääskeläinen S, Tenovuo O, Hinkka S. Sensory dysfunction in burning mouth syndrome. Pain 2002;99(1-2):41-47.
50. Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. Effect of lingual nerve block on burning mouth syndrome (stomatyodynia): a randomized crossover trial. Pain 2010;149:27-32.
51. Silvestre F-J, Silvestre-Rangil J, López-Jornet P. Burning mouth syndrome: a review and update. Rev Neurol 2015;60(10):457-463.
52. Shinozaki T, Imamura Y, Kohashi R, Dezawa K, Nakaya Y, Sato Y, Watanabe K, Morimoto Y, Shizukuishi T, Abe O, Haji T, Tabei K, Taira M. Spatial and temporal brain responses to noxious heat thermal stimuli in burning mouth syndrome. J Dent res. 2016 Sep; 95(10):1138-46.Doi: 10.1177/00220034516653580.
53. Siviero M, Teixeira MJ, de Siqueira JTT, de Siqueira SRDT. Central mechanisms in burning mouth syndrome involving the olfactory nerve: a preliminary study. Clinics (São Paulo) 2011;66(3):509-512. Doi: 10.1590/S1807-59322011000300026.

54. Khan SA, Keaser ML, Meiller TF, Seminowicz DA. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain 2014;155(8):1472-1480. Doi: 10.1016/j.pain.2014.04.022.
55. Koike K, Shinozaki T, Hara K, Noma N, Okada-Ogawa A, Asano M, Shinoda M, Eliav E, Gracely RH, Iwata K, Imamura Y. Immune and endocrine function in patients with burning mouth syndrome. Clin J Pain 2014 Feb. 30(2):168-173.
56. Tatullo M, Marrelli M, Scacco S, Lorusso M, Doria S, Sabatini R, Auteri P, Cagiano R, Inchingolo F. EurRevMedPharmacolSci 2012;16(9):1218-1221.
57. Afrin LB. Burning mouth syndrome and mast cell activation disorder. Oral Surg Oral Med Oral Pathol Oral RadiolEndod2011;111(4):465-472 doi: 10.1016/j.tripleo.2010.111.030.
58. Henkin RI, Goulíouk V, Fordyce A. Distinguishing patients with glossopyrosis from those with oropyrosis based upon clinical differences and differences in saliva and erythrocyte magnesium. Arch Oral Biol2012;205-210. Doi: 10.1016/j.archoralbio.2011.08.010.
59. Sardella A, Gualerzi A, Lodi G, Sforza C, Carrassi A, Donetti E. Morphological evaluation of tongue in burning mouth syndrome. Arch Oral Biol. 2012; 57(1):94-101. Doi: 10.1016/j.archoralbio.2011.07.007.
60. Lauria G, MajoranaA, Borgna M, Lombardi R, Penza P, Padovani A, Sapelli P. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 2005;115:332-337.
61. Wandeur T, de Moura SA, de Medeiros AM, Machado MA, Alanis LR, Grégio AM, Trevilatto PC, de Lima AA. Exfoliative cytology of the oral mucosa in burning mouth syndrome: a cytomorphological and cytomorphometric analysis. Gerontology 2011;28(1):44-48. Doi: 10.1111/j.1741-2358.2009.00319.x.
62. Puhakka A, Forssell H, Soinila S, Virtanen A, Röyttä M, Laine M, Tenovuo O, Teerijoki-Oksa T, Jääskeläinen. Peripheral nervous system involvement in primary burning mouth syndrome – results of a pilot study. Oral Dis. 2016 May; 22(4):338-44. Doi; 10.1111/odi.12454.
63. Abetz LM, Savage NW. Burning mouth syndrome and psychological disorders. Australian Dent J. 2009;54:84-93.
64. Shivpuri A, Sharma S, Trehan M, Gupta N. Burning mouth syndrome: a comprehensive review of literature. Asian J Oral MaxillofacSurg 2011; 23:161-166. Doi: 10.1016/j.ajoms.2011.06.002.
65. Balasubramaniam R, Klasser GD, Delcanho R. Separating oral burning from burning mouth syndrome: unravelling a diagnostic enigma. Aust Dent J 2009; 54(4):293-9. Doi: 10.1111/j.1834-7819.2009.01153.x.
66. Minor JS, Epstein JB. Burning mouth syndrome and secondary oral burning. OtolaryngolClin North Am. 2011;44(1):205-219, vii. Doi: 10.1016/j.otc.2010.09.008.
67. Nasri-Heir C, Zagury JC, Thomas D, Ananthan S. Burning mouth syndrome: current concepts. J Indian ProsthodontSoc2015;15(4):300-307. Doi: 10.4103/0972-4052.171823.
68. Souza PRM, Duquin RP, Göetze FM, Boff AL, Martins MB. Papilite lingual transitória – relato de caso. Scientia Medica (Porto Alegre) 2012;22(4):208-210.
69. Ching V, Grushka M, Darling M, Su N. Increased prevalence of geographic tongue in burning mouth syndrome complaints: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol2012;114(4):444-448. Doi: 10.1016/j.oooo.2012.04.006.
70. Terai H, Shimahara M. Tongue pain: burning mouth syndrome vs Candida-associated lesion. Oral Dis 2007;13(4):440-442.
71. Terai H, Shimahara M. Glossodynia from Candida-associated lesions, burning mouth syndrome, or mixed causes. Pain Med 201011(6):856-860. Doi: 10.1111/j.1526-4637.2010.00861.x.
72. Corsalini M, di Venere D, Pettini F, Lauritano D, Petruzzi M. Temporomandibular Disorders in Burning Mouth Syndrome Patients: An Observational Study. Int J Med Sci2013;10(12):1784-1789. Doi: 10.7150/ijms.6327.
73. Brailo B. et al. Oral burning symptoms and burning mouth syndrome-significance of different variables in 150 patients. Med Oral Patol Oral Cir Bucal 2006;11:E252-5.
74. Lin H-P, Wang YP, Chen HM, Kuo YS, Lang MJ, Sun A. Significant association of hematinic deficiencies and high blood homocysteine levels with burning mouth syndrome. J Formos Med Assoc 2013;112(6):319-325. Doi: 10.1016/j.jfma.2012.02.022.
75. Sun A, Lin H-P, Wang Y-P, Chen H-M, Cheng S-J, Chiang C-P. Significant reduction of serum homocysteine level and oral symptoms after different vitamin-supplement treatments in patients with burning mouth syndrome. J Oral Pathol Med 2013;42(6):474-479. Doi: 10.1111/jop.12043.
76. De Giuseppe R, Novembrino C, Guzzi G, Pigatto PD, Bamonti F. Burning mouth syndrome and vitamin B12 deficiency. J EurAcadDermatolVenereol 2011;25(7):869-870. Doi: 10.1111/j.1468-3083.2010.03769.x.
77. Cho GS, Han MW, Lee B, Roh J-L, Choi S-H, Cho K-J, Nam SY, Kim SY. Zinc deficiency may be a cause of burning mouth syndrome as zinc replacement therapy has therapeutic effects. J Oral Pathol Med 2010;39(9):722-727. Doi: 10.1111/j.16000-0714.2010.00914.x.
78. Nagel MA, Gilden D. Burning mouth syndrome associated with varicella zoster virus. BMJ Case Rep. 2016 Jul 5; 2016. Pii: bcr2016215953. Doi: 10.1136/bcr-2016-215953.
79. Bonenfant D, Rompré PH, Rei N, Jodoin N, Soland VL, Rey V, Brefel-Courbon C, Ory-Magne F, Rascol O., Blanchet PJ. Characterization of burning mouth syndrome in patients woth Parkinson's Disease. J Oral Facial Pain Headache. 2016 Fall; 30(4):318-322. Doi: 10.h11607/ofph.1691.
80. Boopathi V, Mascarenhas AK. Zinc-replacement therapy may not reduce oral pain in patients with zinc-deficient burning mouth syndrome (BMS). J Evid Based Dent Pract2011;11(4):189-190. Doi: 10.1016/j.jebdp.2011.09.016.
81. Becker S, Schmidt C, Berghaus A, Tschiesner U, OlzowyB, Reichel O. Does laryngopharyngeal reflux cause intraoral burning sensations? A preliminary study. Eur Arch Otorhinolaryngol2011;268(9):1375-1381. Doi: 10.1007/s00405-011-1543-9.
82. Koszewicz M, Mendak M, Konopka T, Koziorowska-Gawron E, Budrewicz S. The characteristics of autonomic nervous system disorders in burning mouth syndrome and Parkinson disease. J Orofac Pain 2012;26(4):315-320.
83. Coon EA, Laughlin RS. Burning mouth syndrome in Parkinson's disease: dopamine as cure or cause? J Headache Pain 2012;13(3):255-257. Doi: 10.1007/s10194-012-0421-1.
84. Frutos R, Rodríguez S, Miralles-Jorda L, Machuca G. Oral manifestations and dental treatment in menopause. Med Oral 2002;7(1):26-30,31-5.
85. Meurman JH, Tarkkila L, Tiitinen A. The menopause and oral health. Maturitas 2009;63(1):56-62. Doi: 10.1016/j.maturitas.2009.02.009.
86. Palacios-Sanchez MFP, Comín XJ, Sívoli CEG. Síndorme de boca ardiente: Estudio retrospectivo de 140 casos em una muestra de lapoblacióncatalana. Med Oral Patol Oral Cir Bucal 2005;10:388-393.
87. Vaidya R. Burning mouth syndrome at menopause: elusive etiology. J Mid-Life Health 2012;3(1):3-4.
88. Dahiya PK, Kumar R, Niti M, Gupta R, Chaudhary K. Burning mouth syndrome and menopause. Int J Prev Med 2013;4(1):15-20.
89. Suri V, Suri, V. Menopause and oral health. J Mid-life Health 2014; 5(3):115-119.
90. Das Neves de Araújo Lima E, Barbosa NG, dos Santos AC, Araúko Moura Lemos TM, de Souza CM, Trevilatto PC, da Silveira EJ, de Medeiros AM. Comparative analysis of psychological, hormonal, and genetic factors between burning mouth syndrome and secondary oral burning. Pain Med. 2016 Sep; 17(9):1602-11. Doi; 10.1093/pm/pnv087.
91. Castells X, Rodoreda I, Pedrós C, Cereza G, Lsporte J-R. Drugs points: dysgeusia and burning mouth syndrome by eprosartan. BMJ 2002;325:1277.
92. Sallort-Llorca C, Minguez-Serra MP, Silvestre FJ. Drug-induced burning mouth syndrome: a new etiological diagnosis. Med Oral Patol Oral Cir Bucal2008; 13(3):E167-170.
93. Soares MSM, Chimenos-Küstner E, Pifarrè CS, De Rivera-Campillo MER, López JL. Asociación de síndrome de boca ardientecon xerostomia y medicamentos. Med Oral Patol Oral Cir Bucal 2005;10:301-308.
94. Klasser GD, Epstein JB, Villines D. Diagnostic dilemma: the enigma of an oral burning sensation. J Can Dent Assoc 2011;77:b146.
95. Klasser GD, Epstein JB, Villines D. Management of burning mouth syndrome. J Can Dent Assoc2011;77:b151.
96. Friedman DI. Topiramate-induced burning mouth syndrome. Headache 2010; 50(8):1383-1385. Doi, 10.1111/j.1526-4610.01720.x.
97. Raghavan SA, Puttaswamiah RN, Birur PN, Ramaswamy B, Sunny SP. Anti-depressant-induced burning mouth syndrome – a unique case. Korean J Pain 2014;27(3):294-296. Doi: 10.3344/kkjp.2014.27.3.294.
98. Lamey PJ, Freeman R, Eddie SA, Pankhurst C, Rees T. Vulnerability and presenting symptoms in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral RadiolEndod2005;99:48-45.
99. Takenoshita M, Sato T, Kato Y, Katagiri A, Yoshikawa T, Sato Y, Matsushima E, Sasaki Y, Toyofuku A. Psychiatric diagnosis in patients with burning mouth syndrome and atypical odontalgia referred from psychiatric to dental facilities. Neuropsychiatric Dis Treat 2010;6:699-705. Doi: 10.2147/NDT.S12605.
100. Komiyama O, Obara R, Uchida T, Nishimura H, Iida T, Okubo M, Shimosaka M, Narita N, Niwa H, Shinoda M, Kobayashi M, Noma N, Abe O, Makiyama Y, Hirayama T, Kawara M. Pain intensity and psychosocial characteristics of patients with burning mouth syndrome and trigeminal neuralgia. J Oral Sci 2012;54(4):321-327.
101. Schiavone V, Adamo D, Ventrella G, Morlino M, De Notaris EB, Ravel MG,

Kusmann F, Piantadosi M, Pollio A, Fortuna G, Mignona MD. Anxiety, depression, and pain in burning mouth syndrome: first chicken or egg? Headache 2012;52(6):1019-1025. Doi: 10.1111/j.1526-4610.2012.02171.x.
102. De Souza FTA, Teixeira AL, Amaral TMP, dos Santos TPM, Abreu MHNG, Silva TA, Kummer A. Psychiatric disorders in burning mouth syndrome. J Psychosom Res 2012;72(2):142-146. Doi: 10.1016/j.jpsychores.2011.11.008.
103. Bathia MS, Bathia NK, Bathia NK. Psycogenic lingual paresthesia. J ClinDiagn Res 2015;9(5):VD04-VD05. doi: 10.1097/WNF.0000000000000093.
104. Marino RM, Picci RL, Ferro G, Carezana C, Gandolfo S, Pentenero M. Peculiar alexithymic traits in burning mouth syndrome: case-control study. Clin Oral Invest 2015; doi: 10.1007/s00784-015-1416-5.
105. Liu BL, Yao H, Zheng XJ, Du GH, Shen XM, Zhou YM, Tang GY. Low regional cerebral blood flow in burning mouth syndrome patients with depression. Oral Dis 2015;21(5):602-607. Doi: 10.1111/odi.12322.
106. Mignogna MD, Pollio A, Fortuna G, Leuci S, Ruoppo E, Adamo D, Zarrelli C. Unexplained somatic comorbidities in patients with burning mouth syndrome: a controlled clinical study. J Orofac Pain 2011;25(2):131-140.
107. Tokura T. Kimura H, Ito M, Nagashima W, Sato N, Kimura Y, Arao M, Aleksic B, Yoshida K, Kurita K, Osaki N. Temperament and character profiles of patients with burning mouth syndrome. J Psychomatic Res 2015;78(5):495-498.
108. Kontoangelous K, Koukia E, Papanikolaou V, Chrysovergis A, Maillis A, Papadimitriou GN. Suicidal behavior in a patient with burning mouth syndrome. Case Reports in Psychiatry 2014;. Article ID 405106. Doi: 10.1155/2014/405106.
109. Malik R, Goel S, Misra D, Panjwani S, Misra A. J Midlife Health 2012;3(1):36-39. Doi: 10.41030976.7800.98816.
110. De Souza FTA, Kummer A, Silva MLV, Amaral TMP, Abdo EN, Abreu MHNG, Silva TA, Teixeira AL. The association of openness personality trait with stress-related salivary biomarkers in burning mouth syndrome. Neuroimmunomodilation2015;22:250-255. Doi: 10.1159/000367714.
111. Davies SJC, Underhill HC, Abdel-Karim A, Christmas DM, Bolela-Alamanac BM, Potokar J, Herrod J, Prime SS. Individual oral symptoms in burning mouth syndrome may be associated differentially woth depression and anxiety. ActaOdontol Scand. 2016; 74(2):155-60. Doi: 10.3109/00016357.2015.1100324.
112. Galli F, Lodi G, Sardella A, Vegni E. Role of psychological factors in burning mouth syndrome: a systematic review and meta-analysis. Cephalalgia. 2016 Apr 27; pii: 0333102416646769. Doi: 10.1177/03331024166467769.
113. Sevrain M, Brenaut E, Le Toux G, Misery L. Primary burning mouth syndrome: a questionary study of neuropathic and psychological components. Am J ClinDermatolol. 2016 Apr; 17(2):171-8. Doi; 10.1007/s40257-015-0170-4.
114. Chainani-Wu N, Madden E, Silverman SJr. A case-control study of burning mouth syndrome and sleep dysfunction. Oral Surg Oral Med Oral Pathol Oral RadiolEndod2011;112(2):203-208. Doi: 10.1016/j.tripleo.2011.03.014.
115. Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E, Dell'Aversana G, Mignogna MD. Sleep disturbance in patients with burning mouth syndrome: a case-control study. J Orofac Pain 2013;27(4):304-313. Doi: 10. 11607/jop.1109.
116. Lee CF, Lin KY, Lin MC, Lin CL, Chang SN, Kao CH. Sleep disorders increase the risk of burning mouth syndrome: a retrospective population-based cohort study. Sleep Med 2014;15(11):1405-1410. Doi: 10.1016/j.sleep.2014.06.009.
117. López-Jornet L, Lucero-Berdugo M, Castillo-Felipe C, Zamora-Lavella C, Ferrantez-Pujante A, Pons-Fuster A. Assessment of self-reported sleep disturbance and psychological status in patients with burning mouth syndrome. J EurAcadDermatolVenereol2015;29(7):1285-1290. Doi: 10.1111/jdv.12795.
118. Prakash S, Ahuja S, Rathod C. Dopa responsive burning mouth syndrome: restless syndrome or oral variant of restless legs syndrome? J NeurolSci 2012; 320(1-2):156-160. Doi: 10.1016/j.jns.2012.07.007.
119. Brailo V, Firic M, Vucicevic Boras V, AndabakRogulj A, Krstevski I, Alajbeg I. Oral dis. 2016 Sep; 22(6):512-6. Doi; 10.1111/odi.12493.
120. Moisset X, Calbacho V, Torres P, Gremeau-Richard C, Dallel R. Co-ocurrence of pain sumptoms and somatosensory sensitivity in burning mouth syndrome: a systematic review. PLoS One. 2016 Sep 22; 11(9):e0163449. Doi; 10.1371/journal.pone.0163449.
121. López-Jornet P, Pagan DM, Mateos PA, Agudo CR, Pons-Fuster A. Circadian rhythms variations of pain in burning mouth syndrome. GeriatrGerontolInt 2015;15(4):490-495. Doi: 10.1111/ggi.12303.
122. Papagerakis S. Zheng L, Schnell S, Sartor MA, Somers E, Marder W, McAlpin B, Kim D, McHugh J, Papagerakis P. The circadian clock in oral health and diseases. J Dent Res 2014;93(1):27-35. doi: 10.1177/0022034513505768.
123. Chen Q, Xia J, Lin M, Zhou H, Li B. Serum interleukin-6 in patients with burning mouth syndrome and relationship with depression and perceived pain. Mediators of Inflammation 2007;article ID 45327, Doi: 10.1155/2007/45327.
124. Aggarwal A, Panat SR. Burning mouth syndrome: a diagnostic and therapeutic dilemma J ClinExp Dent 2012;4(3):e180-185. Doi: 10.4317/jced.50764.
125. Nasri-Heir G. Burning mouth syndrome. Alpha Omegan 2012;105(3-4):76-81.
126. Zakrzewska JM. Differential diagnosis of facial and guidelines for management. Br J Anaesthesia 2013;111(1):95-104.
127. Zakrzewska JM. Multi-dimensionality of chronic pain of the oral cavity and face. J Headache Pain 2013;11:37-47.
128. Kenchadze R, Iverieli M, Geladze N, Khachapuridze N, Bakhtadze S. Management of burning mouth syndrome taking consideration various etiologic factors. Georgian Med News 2013;218:49-53.
129. Scala A, ChecchiL, Montevecchi M, Marini I. Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14(4):275-291.
130. Coculescu EC, Radu A, Coculescu, BI. Burning mouth syndrome: a review on diagnosis and treatment. J Med Life 2014;7(4):512-515.
131. Jimson S, Rajesh E, Krupaa RJ, Kasthuri M. Burning mouth syndrome. J Pharm Bioallied Sci. 2015(suppl. 1):S19406. doi: 10.4103/0975-7406.155899. Review.
132. Silvestre-Rangil J, Silvestre F-J, Tamarit-Sanfé C, Bautista D. Burning mouth syndrome: correlation of treatment to clinical variables of the disease. Med Oral Patol Oral Cir Bucal2011;16(7):e890-4. doi: 10.4317/medoral.17224.
133. Yilmaz Z, Egbuniwe O, Renton T. The detection of small-fiber neuropathies in burning mouth syndrome and iatrogrenic lingual nerve injuries: use of quantitative sensory test. J Oral Facial Pan Headache.2016 Spring; 30 (2):87-98. Oi: 10.11607/ofph.1531.
134. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. Clinical Neurophysiology 2012; 123(1):71-77. Doi: 10.1016/j.clinph.2011.07-054.
135. Mendak-Ziólko M, Konopka T, Bogucki ZA. Evaluation of select neurophysiological, clinical and psychological tests for burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral RadiolEndod2012; 114(3):325-332. Doi: 10.1016/j.oooo.2012.04.004.
136. De Siqueira SRDT, TeixeiraMJ, de Siqueira JTT. Orofacial pain and sensory characteristics of chronic patients compared with controls. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;15(6):e37-e45.
137. Komiyama O, Nishimura H, Makiyama Y, Iida T, Obara R, Shinoda M, Kobayashi M, Noma N, Abe O, De Laat A, Kawara M. Groupcognitive-behavioralintervention for patientswithburningmouthsyndrome.J Oral Sci2013;55(1):17-22.