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Burning Mouth Syndrome: A State of the Art Review for the Oral Healthcare Provider

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Burning Mouth Syndrome (BMS) is a neurosensory disorder that affects the oral mucosa by causing a burning or stinging pain of varying degrees in different individuals. It is difficult to diagnose the condition as it does appear in conjunction with any clinical or laboratory abnormalities. The psychological and psychiatric issues involved along with the oral symptoms make oral healthcare provision in such individuals a challenging task. This review presents the oral healthcare provider an insight into the peculiar nature of BMS and the oral healthcare management of patients with BMS.

Keywords: Burning mouth syndrome, dental management, glossodynia, oral burning, burning mouth.

Burning Mouth Syndrome (BMS) is a neurosensory disorder wherein patients present with a complaint of stinging or burning sensation that affects the oral mucosa, although the clinical examination and laboratory data do not correlate to the symptoms[1]. It was first described by Fox in 1935 as a chronic orofacial pain disorder which was not accompanied by any oral mucosal lesions[1]. BMS is also known as stomatodynia[1], glossalgia, glossodynia, glossopyrosis, stomatopyrosis, burning tongue, sore tongue, sore mouth, scalded mouth syndrome, oral dysaesthesia and burning mouth condition[1]. The use of such multiple and heterogeneous terms stands testimony to the fact that there is confusion and uncertainty among researchers and oral healthcare providers regarding this condition.

In order to bring some agreement among researchers regarding the exact nature of BMS, multiple definitions have been proposed. The International Association for the study of Pain[2] defines BMS as a pain condition that lasted for at least 4-6 months, was located on the tongue or other mucosal membranes in the oral cavity and did not coincide with any clinical or laboratory findings. The International Headache Society[3] defines BMS as a pain condition characterized by intraoral burning or a dysesthetic sensation, that recurs daily, lasts more than 2 hours/day, has been present for more than 3 months, in absence of any clinically evident causative lesions in the mouth. The American Academy of Orofacial Pain[3]defines BMS as a pain condition with burning sensation

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in the oral mucosa, despite there being no clinical findings or abnormalities in laboratory testing or imaging.

The disorder is frequently associated with other symptoms (subjective dryness of mouth, dysaesthesia and alterations in taste) and the complexity surrounding the condition of the patient (psychosocial and psychiatric disorders) has lead to some authors preferring to use the term 'burning mouth syndrome' (BMS) to refer to this condition.

Epidemiology

BMS prevalence has been reported to be in the range from 0.7-15% of the population, mainly based on the type of criteria used in the reporting studies[4].The condition is predominantly observed in women after menopause, generally 50-60 years of age, while in men the reported ratio is approximately 5-7 times lesser[4]. Prevalence of BMS has been observed to increase with age in both genders.This condition unreported in children or adolescents, while being rare in people under 30 years of age[4]. Grouping of BMS patients by occupational, educational or social factors is unavailable.

Classification

Lamey and Lamey and Lewis classified BMS into3 subtypes based on pain experiencesacross a 24 hour period[5]. **Type 1:** burning is present every day, not present on waking, but occurs as the day proceeds, being at maximum by evening. This subtype encompasses 35% of BMS patients and may be associated with systemic disorders (nutritional deficiencies and endocrine disorders)[5].**Type 2:** burning is present daily, on awakening, and often causes difficulty in night sleep. This subgroup encompasses 55% of BMS patients and is associated with mood changes, altered nutritive choices and social isolation (possibly a result of altered sleep pattern)[5]. **Type 3:**burning present intermittently, occuring on unexpected days, affectinguncommon areas such as the floor of the mouth, buccal mucosa and pharynx. This subtype encompasses 10% of BMS patients, frequently associated with anxious behaviour and allergy (particularly to food taste enhancers)[5].

Gremeau-Richard *et al*[6]classified BMS into a peripheral orcentral type based on the reaction to alingual nerve block usinga local anesthetic. Jaaskelainen[7] classified BMSinto 3 categories according to neuropathicpain experience. **First**: intraoral mucosal peripheral small fibre neuropathy (affects 50%–65% of BMS patients), **Second**: subclinical major trigeminal neuropathy (affects 20%–25% of BMS patients), and **Third**: central neuropathy that may have resulted from decreased activiyu of basal ganglial dopaminergic neurons, in turn being caused by deficient dopaminergic top-down inhibition (affects 20%–40% of BMS patients).

Scala *et al*[8] proposed a more practical approach in categorizing BMS by dividing patients into two groups, primary/essential/idiopathic BMS with no other evident conditionand secondary BMS that results from other clinically identifiable conditions.It is evident from this classification that when secondary BMS results from a pre-existing abnormality or etiology, symptoms must either improve or disappear following the treatment of such a condition. Cerchiari *et al*[9] proposed a classification based upon the associated risk factors namely: idiopathic, psychogenic, local and systemic.

Etiology

To date, the precise etiology for primary BMS has remained unknown. The best explanation for its cause is multifactorial, most probably involving a combination of neurophysiologic and psychological factors. Numerous psychological, systemic and local conditions have been reported to be related to secondary BMS. **Table 1**[10-16]

Pathophysiology

Psychogenic factors play a predominant role in the pathophysiology of BMS[17]. Peripheral and central neuropathies also appear to be involved, varying in balance between individuals[17]. Genetic and environmental factors influence the differences in pain experience between individuals[17].

Physical trauma to the chorda tympani nerve, resulting in inhibitoryloss on cranial nerve VII has been proposed as a possible cause of burning in BMS[18]. Evidence in favour of this theory is the fact that burning pain reduction is observed in patients upon mastication, chewing gum, or candy sucking, thereby indicating taste buds stimulation by food may exert a central inhibitory effect on the cranial nerve VII sensory system, thereby decreasing the pain[18]. A study using functional MRI to assess BMS patients reported decreased thalamic function in the brain of BMS patients, thereby strengthening this theory[19].

The mechanism of BMS in post-menopausal women seems to be a result of decrease in estrogen levels, with a corresponding increase in follicle-stimulating hormone (FSH). This leads to burning in the oral mucosa since the oral mucosa contains estrogen receptors while also histologically resembling the vaginal mucosa and responds to estrogen decrease in a manner similar to post menopausal symptoms. Another mechanism could be a higher number of nociceptive neurons in the spinal nucleus of cranial nerve VII, leading to altered neuron expression and pain/burning symptoms[1, 5].

Peripheral small fibre neuropathy involving small somatic nerve fibres results in pain, burning, tingling and numbness in the oral cavity, with symptoms usually worst at night[20]. Such neuropathy can result from many medical conditions such as metabolicdisorders, decrease in vitamin B12 levels, viral disease and autoimmune disease (Sjogren's syndrome). When such damage involves the autonomic small nerve fibres, symptoms include dry eyes/mouth, an association often observed in BMS patients[20]. There is also evidence of increased nerve growth factor (NGF) in the saliva of BMS patients, suggesting destruction of native nerve fibres and establishment of nociceptive fibres, especially in the papillae and subepithelial layers of the tongue[21].

Central dopaminergic system involvement with inherent sympathetic and parasympathetic dysfunction has been implicated in the development of symptoms of BMS in a subset of patients. Supporting evidence for this mechanism comes from positron emission tomography studies that have shown decreased dopamine levels in the central nervous system[5].

The possible mechanisms by which autoimmune disorders cause BMS may be via stimulation of T-cells, leading to cytokine secretion,whichpromotes an inflammatory response, whereas stimulation of B-cells results in release of autoimmune antibodies, which damage antigens present in the peripheral nerves[22]. Support for this mechanism comes from immunologic studies in BMS patients which has shown changes in levels of salivary and plasma immune factors such as higher IL-6 and IL-8, lowered serum IL-2 and tumor necrosis factor alpha, elevated salivary IL-6, tryptase and lowered salivary SIgA)[5].

Krief *et al*[23]analyzed whole saliva samples from BMS patients by proteomic profilingand proposed that neurotrophin signaling pathway was involved in the development of BMS.They suggested that the amplification of P75NTR activity stimulated neural apoptosis, thereby decreasing the sub-papillary nerve fibre density in the oral cavity.

Clinical features

The presenting feature is oral mucosal pain that is typically described as burning, scalding, tingling, or a numbing sensation[24]. The pain has been described as being continuous nature with spontaneous acute exacerbations. There is no clearly identifiable cause apart from stress and psychological issues. The pain typically involves the anterior 2/3rds of the tongue in a bilateral and symmetrical fashion. Other areas of the oral cavity affected are the dorsum and lateral borders of the tongue, anterior hard palate, lip mucosa and gingiva, often involving multiple locations together. Less frequently, pain may appear at locations such as the oral mucosa, floor of the mouth, soft palate and oropharynx[24].

Pain in absent at waking, increases in intensity as the day progresses and reaches its peak at late afternoon or evening. However, pain is absent at night in a majority of BMS patients, although all find it difficult to go to sleep[24]. In a majority of patients (>50%), no particular triggers can be identified and the symptoms appear spontaneously. However, in a subset of patients (17-33%), the start of symptoms can be coincident with conditions such as development of respiratory infection, dentistry or medicines. Other patients identify the start of symptoms directly with stress associated with unpleasant event or development in their lives[24].

Some patients are affected by dysgeusia (persistent metallic/bitter/altered taste). Xerostomia or subjective feeling of dry mouth is a common complaint along with increased thirst, headache, temporomandibular joint symptoms, and tenderness/pain in the muscles of the neck, shoulder and suprahyoid muscles[1]. These patients often exhibit mood changes such as be anxious, irritable and depressed.

Dysphagia and atypical facial/ dental pain may also be present in some patients. Others may develop disorders of oral perception, such as

roughness, stickiness, irritated lingual papillae, pruritus, halitosis and ill-tolerated prostheses that were previously well tolerated. Patients may also be affected by concomitant symptoms such as frequent headaches, weakness/fatigue, inability to concentrate, inability to sleep and almost always presenthealth disorders of unrelated nature[24].

Diagnosis

In the absence of any specific diagnostic tests or oral mucosal lesions, BMS is predominantly a diagnosis of exclusion of all other probable causes. Disorders that can present with symptoms similar to BMS are Sjogren's syndrome, lichen planus, diabetes mellitus, candidal infection, deficiencies of minerals such as iron/folate/zinc or vitamin B-complex[24].

Laboratory studies that must be conducted include [1] Serum glucose levels or Hb A1C levels to evaluate glycemic control [2] Serum iron/ferritin, vitamin B12 and folate levels to evaluate anemias [3] Antinuclear antibodies such as antiRo/SS A, antiRo/SS B and rheumatoid factor, to rule out connective tissue disorders like Sjögren's syndrome [4] Complete blood count [5] Cytological smears when candidal infection is suspected [6] Saxon's test to measure salivary flow rates [7] Skin patch tests to rule out any allergic reaction [8] MRI imaging when any central nervous system pathology is suspected (usually when BMS symptoms are accompanied by numbness/ dysaesthesia)[25] [9] Taste evaluation to check whole mouth threshold and any altered burning sensation on ethanol application[57] [10] Thyroid profile.

Recently, Tan *et al*[26] conducted a functional MRI study wherein BMS patients exhibited decreasedamount of gray matter in the bilateral ventro-medial prefrontal cortex (VMPFC) and an increase in connectivity between this region and the bilateral amygdale. The functional connectivity also indicated the duration of BMS symptoms in patients. This could be utilized as a potential neuromarker in future. Ji *et al*[27] identified three potential protein biomarkers, alpha-enolase, IL-18, and KLK13 through quantitative salivary proteomic analysis which could serve as a non invasive diagnostic tool in BMS patients.

When the intra oral clinical examination is unremarkable and laboratory investigation results or clinical history fail to elicit a possible cause for the oral pain/burning, a diagnosis of primary BMS is established.

Management

The first step in management of BMS is to decipher whether a patient has primary or secondary BMS. Secondary BMS patients must have their underlying conditions diagnosed and treated. Primary BMS patients are primarily treated based on their symptoms. Before initiating a management strategy, clinicians must talk and reaffirm to their patients the nature of the disease and discuss the benefits of intended medications or possibility of pain relief. Patients must be educated about the need for a multidisciplinary team approach, probability of needing multiple changes in medications prescribed until an effective treatment module is achieved.

At present, clinicians have at their disposal 2 treatment strategies in the management of BMS. First approach is of behavioural strategies, which includes abortion of parafunctional habits (clenching, bruxism, tongue thrusting), replacement of potentially irritating oral healthcare products such as alcohol containing mouthwashes with non-alcohol containing alternatives and the use of oral healthcare products (tooth paste, tooth whitening gels, anticalculus agents) without added flavouring agents (cinnamon) or irritating components (sodium lauryl sulphate)[5]. Patients are advised to discontinue use of breath fresheners[28]. Local irritants such as ill fitting dentures, sharp restoration edges and sharp edges of dentition are corrected. Patients are advised to avoid eating acidic foods such as pineapple, tomato, orange, lemon, tamarind, spices etc as well as to stop consumption of alcohol and smoking. Approaches to life style practices such as active exercises, yogasana, and tai chi may be advised as a measure to reduce stress. Habit braking appliances may be fabricated in order to desensitize patients to reduce oral burning[29]. Specific behavioural strategies such as cognitive behavioural approaches[30] and/or group psychotherapy[31] have shown promise in mitigating pain levels in BMS and may be considered with professional assistance.

Second approach is that of medical management of BMS, either with topical agents, systemic agents or a combination of both. These agents shall be described with the level

of evidence (LOE)[32] that is presently available to analyze their utility in BMS. **Table 2** Topical agents include anxiolytics such as clonezepam (1a)[33], local anesthetics such as bupivacaine (1b)[34], antidepressants such as 5% doxepin (5)[1], atypical analgesics such as 0.02% capsaicin (1b)[35], non steroidal anti-inflammatory agent such as 0.15% benzydamine hydrochloride (5)[1], antimicrobials such as lysozyme and lactoperoxidase (2b)[36], mucosal protectotants such as sucralfate, aloe vera, lycopene enriched virgin olive oil (2b)[37], artificial sweeteners such as sucralose (2b)[38], immunosuppressant such as cyclosporine (2b)[39], low level laser phototherapy (1b)[40] and botulinum toxin A[41].Recently, Lecor *et al*[42] demonstrated that significant pain reduction could be achieved by use of an oral rinse of 0.5 % Methylene blue (four times a day) for 7 days, an effect that lasted 3-6 months.

Systemic therapies include use of antioxidants such as alpha lipoic acid (1a)[43], tricyclic antidepressants such as amitriptyline, nortriptyline (2b)[44], selective serotonin reuptake inhibitor or SSRI such as paroxetine (2b)[45], serotonin noradrenaline reuptake inhibitor or SNRI such as duloxetine (2b)[46] and milnacipran (2b)[47], benzodiazepines such as clonazepam (1a)[48], anticonvulsants such as pregabalin (4)[49]andgabapentin (2b)[50], antipsychotics such as olanzapine (4)[51] and amisulpride (4)[52], histamine receptor antagonist such as lafutidine (2b)[53], dopamine agonists such as pramipexol (4)[54], salivary stimulants such as pilocarpine and

Table 1. Etiological Factors In Burning Mouth Syndrome

Local	Hyposalivation, xerostomia (subjective and drug induced), alteration in taste, oral infections (bacterial, viral or fungal) oral mucosal abnormalities (lichen planus, geographic tongue, scalloped/ fissured tongue, black hairy leukoplakia, oral parafunctional habits (bruxism, clenching, tongue thrusting), mechanical (denture irritation), chemical (galvanism), allergy (mercury, polymethylmethacrylate)
Systemic	Nutritional deficiencies of vitamins (folic acid, vitamin B complex) and minerals (zinc, iron) Post menopausal changes, hormonal deficiencies Drug induced, such as angiotensin converting enzyme or ACE inhibitors (captopril, enalapril, lisinopril), angiotensin receptor blockers (eprosartan, losartan), anti-retrovirals (efavirenz), anti-epileptics (topiramate), selective serotonin reuptake inhibitors (fluoxitine), benzodiazepines (clonazepam) and anticoagulants (warfarin) Autoimmune (connective tissue disorders), gastrointestinal (gastroesophageal reflux disease), diabetes and thyroid disorders Genetic
Psychological	Anxiety/depression, somatization, aberrant personality traits, oral cancer phobia

Table 2. Levels of Evidence According to Oxford Centre for Evidence Based Medicine

Level of Evidence	Description
1a	Systematic review with homogeneity of RCTs
1b	Individual RCT with narrow confidence interval
1c	All or none studies
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study, including low quality RCT (< 80% follow up)
2c	"Outcomes" research, ecological studies
3a	Systematic review withhomogeneity of case-control studies
3b	Individual case control study
4	Case series and poor quality cohort/case control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT- randomized controlled study

cevimeline (5)[5], herbal supplements such as Hypericum perforatum or St John's wort (2b)[5] and Catuama (2b)[5], transcranial magnetic stimulation (2b)5, transcranial direct current stimulation (2b)[5], acupressure (2b)[5] and auriculotherapy (2b)[5].

Dental considerations

Patients with BMS present the oral healthcare provider a unique challenge in providing oral care and improving their quality of life. As most of the BMS patients tend to be post menopausal women, the treating oral healthcare professional must be aware that menopause tends to reduce the relative anchorage of teeth[24]. Therefore, as a primary step in the oral health management of BMS patients, prevention of any irreversible damage by maintaining flawless oral hygiene habits must be inculcated, specifically targeted at removal of plaque and tartar from the mouth minimum twice a day[55]. In patients who experience hyposalivation or xerostomia, ample regular intake of water at sips, sugar free sweets or chewing gum is encouraged to stimulate salivation[24]. Adequate oral hygiene aids such as interproximal brushes, dental floss and chlorhexidine digluconate mouthwash reduce dental plaque buildup, lower periodontal problems and prevents dental caries, particularly root caries[55]. It is advisable to use fluoride containing toothpastes, varnishes or gels to preventdental caries.

A fraction of BMS patients may be sensitive to dental restorative components. Therefore, it may be advisable to carry out allergen patch testing to identify such patients and avoid using the implicated dental restorative or impression materials.[56] Nickel is a component of the alloy used in fabrication of metallic or porcelain fused to metal crowns. Nickel and titanium ions leaching from dental cast alloys and dental implants have been identified as a possible causative factor for oral burning in BMS patients.[56] Use of metal free crowns and alternatives to dental implants as a choice for tooth replacement must be considered in such patients.

Denture materials may elicit a burning response in sensitive BMS patients.[57] Change in denture material is indicated in such patients. Other problems related to denture wear may also contribute to oral burning sensation. Inadequate denture retention and stability result in abnormal activity in the tongue which is a habit patients develop in an effort to retain dentures in the mouth[24]. An inadequate freeway space and denture extensions may increase the load on the denture bearing areas, resulting in oral burning sensation.[58] Correction of such deficiencies in dentures or fabrication of new dentures must be undertaken to improve oral symptoms.

Dental amalgam fillings have been shown to induce BMS symptoms in sensitive individuals[24]. Replacement of such restorations with suitable alternative filling materials is indicated in such individuals. Anxiety and stress related to dental treatment can exacerbate symptoms of BMS and complicate restorative procedures wherein the patient is required to remain still in the dental chair. Such instances can be managed by the "4 S" rule or the so-called "4 S" principle[59]. This principle involves removal of four of the principle sensory triggers for dental anxiety when in the dental office, such as sight (air motor, syringe), sounds (air motor), sensations (vibrations from tooth cutting), and smells (eugenol and cut dentin). Needles may be replaced with computer assisted anesthetic delivery via a plastic handpiece at fixed slow flow rates, thereby making the local anesthetic delivery less traumatic[59]. Alternatively, electronic dental anesthesia can be utilized to achieve tissue anesthesia[59]. Methods to carry out restorative treatment without the sound or vibrations of air turbines include atraumatic restorative treatment, alumina powder stream powered air abrasion, diamond-coated ultrasonic tips, chemo-mechanical caries removal agents and laser assisted cavity preparation[59]. A rubber dam must be used to isolate the teeth being treated and prevent root canal irrigating solutions such sodium hypochlorite or acid etching gels from contacting soft tissues of the mouth[60].

It has been shown that in patients with BMS, pain and disability increase as the day progresses, and are influenced by anxiety[61]. Therefore, an early morning appointment would be beneficial to take advantage of the fact that patients are in their best physiologic state early in the morning as well as that burning symptoms are least in the morning. Minimal waiting room time decreases the anxiety associated with dental treatment by allowing patients less time to focus on negative stimuli. Additionally, longer waiting times give them an to recall the negative stimuli[59].

Nagao *et al*[62] reported the use of an oral care gel (REFRECARE-H®), a therapeutic dentifrice containing hinokitiol in a BMS patient. This gel was found to useful in removal of dental stains, oral debris and was effective in the prevention of halitosis and gum problems. More importantly, it was found to improve symptoms such as oral discomfort, tingling pain, halitosis, sleep disturbances, depression, and jitteriness in the patient. Use of such a gel for local application can significantly improve oral healthcare and general well being in BMS patients.

CONCLUSION

Adequate knowledge of the condition of BMS, its management strategies and dental considerations are mandatory for successful oral health care provision. BMS patients may suffer from concomitant mental or physical conditions that have to be kept in mind while providing oral healthcare. Multidisciplinary approach involving the oral healthcare provider, physician, dietitian and endocrinologist provides the best possible outcome for appropriate oral healthcare needs in BMS patients.

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