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Burning Mouth Syndrome: Recognition, Understanding, and Management

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Burning mouth syndrome (BMS) is defined by the International Association for the Study of Pain [1] as burning pain in the tongue or other oral mucous membrane associated with normal signs and laboratory findings lasting at least 4 to 6 months [2,3]. The International Classification of Diseases (version 9) has assigned the term glossodynia, which includes the adjunctive terms glossopyrosis and painful tongue, a specific identity code number (529.6) [4]. The International Headache Society in the International Classification of Headache Disorders II (ICHD-II) [5] classifies BMS in the category of cranial neuralgias and central causes of facial pain within the subcategory of central causes of facial pain. BMS (ICHD-II:13.18.5) is described as an intraoral burning sensation for which no medical or dental cause can be found. It is further noted that pain may be confined to the tongue (glossodynia) with associated symptoms that include subjective dryness of the mouth, paresthesia, and altered taste. Diagnostic criteria for BMS from ICHD-II are listed in Box 1. These definitions and classifications show the difficulty for the patient and the practitioner evaluating these individuals: the patient is experiencing continuous burning pain in the mouth without any obvious clinical signs, but the practitioner is unable to definitively diagnose these symptoms even with the use of diagnostic testing or imaging. This article aids the oral and maxillofacial surgeon in recognizing, understanding, and managing BMS.

Historically, BMS has been referred to by many names based on the quality or location of pain in the oral cavity. Some of these are: glossodynia, glossopyrosis, glossalgia, stomatodynia, stomatopyrosis, sore tongue, burning tongue, scalded mouth syndrome, oral dysesthesia, burning mouth condition, and burning mouth syndrome [6,7]. From these numerous descriptions it is not clear whether the oral mucosa appeared normal and, therefore, if these terms were describing BMS. The use of these multiple terms attests to the confusion and uncertainty that exists in the scientific literature and in clinical practice. This confusion has led to some discussion regarding the proper nomenclature for this condition. There is debate as to whether burning mouth is a syndrome or a disorder [6,8,9]. By definition, a syndrome (a disease unto itself) is a collection of several simultaneous signs and symptoms of varying intensity, which in the case of BMS is a normal-appearing oral mucosa with a burning sensation, a feeling of oral dryness, and taste disturbances [6,10–12]. A disorder is defined as a condition manifesting symptoms of other diseases, such as the complaint of dry mouth being the cause of the burning sensation often reported by patients who have BMS [9]. If burning mouth is a symptom of other local, systemic, or psychogenic diseases then this is referred to as oral burning disorder; otherwise the term burning mouth syndrome is used, making it a diagnosis of exclusion.

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Box 1. Diagnostic criteria for burning mouth syndrome

Pain in the mouth present daily and persisting for most of the day
Oral mucosa is of normal appearance
Local and systemic diseases have been excluded

Data from International Headache Society. The international classification of headache disorders. 2nd edition. Cephalalgia 2004; 24(Suppl 1):9–160.

Epidemiology

The prevalence of burning mouth symptoms reported from international studies ranges from 0.6% to 15% [8]. The considerable variation in prevalence among these studies may be because of different definitions of BMS leading to different criteria for the selection of the populations. Bergdahl and Bergdahl [13] performed a questionnaire survey study regarding oral burning complaints in a group of 1427 randomly selected subjects (669 male and 758 female) from 48,500 Swedish individuals between the ages of 20 and 69 years. All individuals who reported oral burning were clinically examined. It was found that 53 individuals (3.7%), 11 men (1.6%) and 42 women (5.5%), were classified as having BMS. In men, no BMS was found in the age groups of 20 to 39 years, whereas the prevalence in the 40- to 49-year-old age group was 0.7%, which increased to 3.6% in the 60- to 69-year-old age group. In women, no BMS was found in the 20- to 29-year-old age group, but in the age group 30 to 39 years the prevalence was 0.6% and increased to 12.2% in the 60- to 69-year-old age group. It seems the prevalence of BMS increases with age in both males and females, with this syndrome mainly affecting females in the fifth to seventh decade [13,14]. In an epidemiologic study conducted in the United States, the overall prevalence of burning mouth was found to be 0.7% in adults up to age 65 [15]. Interestingly, Riley and colleagues [16] repeated this telephone interview study in a subset of 5800 individuals aged 65 or older and reported a prevalence of only 1.7% for burning mouth pain. The difference between the lower prevalence of BMS in the Riley and colleagues study as compared with others may be related to methodologic errors, such as sampling bias, interview technique, question format, and lack of clinical examination. BMS usually first presents 3 years before to 12 years following menopause [3] and rarely before the age of 30 [13,17]. The ratio between females and males varies from 3:1 to 16:1 [3,18–21]. These gender differences may be explained by biologic, psychologic, and sociocultural factors; however, these factors are yet to be defined. It seems from these epidemiologic studies that menopausal females have a particularly high incidence of burning mouth. Despite these findings, no significant differences have been found between BMS and control subjects in any of the following factors: the number of years since menopause, the occurrence of surgical menopause, the use of hormone replacement therapy (HRT), the number of years of treatment with HRT, and the number of years passed since completion of HRT [3,22,23]. Santoro and colleagues [24] retrospectively studied the clinical and therapeutic experience of 28 patients who had BMS. They found that in a cohort of postmenopausal patients who had estrogen receptors of the oral mucosa (determined on biopsy of the buccal mucosa), hormone-replacing therapy had a positive effect on their symptoms. There has been only one study conducted on the prevalence of BMS in relation to ethnicity (Table 1). No studies have reported prevalence of burning mouth by social, educational, or occupational groups.

Table 1
Prevalence of burning mouth syndrome by demographic group

Demographic variable	Estimated prevalence (per 100,000)	Prevalence (%)
Ethnicity		
White, non-Hispanic	693	19
Black, non-Hispanic	531	15
Hispanic	786	22
Other non-Hispanic	1598	44
Age group		
18–34	609	19
35–54	696	21
55–74	757	23
75+	1184	36

Data from Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124(10):115–21.

Classification

There have been several proposed classification schemes to better characterize and define BMS. One such classification [6,25] contains three subtypes according to variations in pain intensity over 24 hours. Type 1 is characterized by patients having burning every day. The burning is absent on waking but presents as the day goes on, being maximal in the evening. This type may be linked to systemic disorders, such as nutritional deficiencies and endocrine disorders [26]. Approximately 35% of patients who have BMS give such a history. Type 2 is characterized by burning that occurs every day, is present on awakening, and often makes falling asleep at night difficult. This subgroup of patients often report mood changes, alterations in eating habits, and decreased desire to socialize, which seem to be attributable to an altered sleep pattern [2,27]. Approximately 55% of patients who have BMS describe such a history. Type 3 is characterized by intermittent burning, present only on some days, with burning affecting unusual sites, such as the floor of the mouth, buccal mucosa, and throat. These patients frequently display anxiety and allergic reactions, particularly to food additives [28]. About 10% of patients who have BMS report this pattern of symptoms. A demographic study by Killough and colleagues [29] comparing BMS populations in the United Kingdom and United States has reported on identical prevalence rates using these subtypes within these two populations. The authors of this classification system believe that it is valid because they believe this system has prognostic significance and also indicates the necessity for specialist investigation to identify allergic components to the burning. This classification is not universally accepted, however, nor is it considered essential for management of the patient who has BMS.

A more pragmatic approach in classifying patients who have BMS is to divide patients into either primary (essential/idiopathic) BMS (no other evident disease) or secondary BMS (oral burning from other clinical abnormalities). Danhauer and colleagues [30] examined 69 patients who had BMS (83% female) with an average age of 62 years, pain duration of 2.45 years, and visual analog scale pain rating of 49 mm (rated from 0 to 100 mm). All patients completed the Multidimensional Pain Inventory (MPI) and Symptom Checklist 90-Revised (SCL-90R) questionnaires and had a clinical examination. The investigators found that there were no differences between the patients who had primary and secondary BMS with respect to age, pain duration, pain intensity, or levels of psychologic distress. There were substantial differences in burning symptom cessation with treatment; the patients who had secondary BMS improved if the underlying clinical abnormality was treated, whereas the primary BMS group did not report such positive results.

Symptomatology

Most individuals who have BMS describe their symptoms in the oral mucosa using the following words: burning, tender, tingling, hot, scalding, numb, and annoying. BMS is characterized by positive (burning pain, dysgeusia, and dysesthesia) and negative (taste loss and paresthesia) sensory symptoms [31]. The pain is mainly located bilaterally and symmetrically in the anterior two thirds of the tongue (71%–78%) followed by the dorsum and lateral borders of the tongue, the anterior aspect of the hard palate, and the labial mucosa of the lips, often occurring in multiple sites [3,10,20,32]. Other less commonly reported sites include the buccal mucosa, floor of the mouth, hard and soft palates, and the throat. The sites of pain do not seem to affect the course of the disorder or the response to treatments [28,33]. More than half the patients who have BMS experience a spontaneous onset of symptoms without any identifiable triggering factor [11,34]. About 17% to 33% of the patients attribute the onset of their symptoms to a previous illness, such as an upper respiratory tract infection, previous dental procedure, or medication use (including antibiotic therapy) [34–36], suggesting the possibility of neurologic alterations preceding the onset of burning in some patients [37–39]. Other individuals claim the onset of symptoms relates to traumatic life stressors [11,20,34]. Typically, the symptoms occur continuously for months or years without periods of cessation or remission [34], with some reports suggesting an average duration of 2 to 3 years [40,41]. There have been reports [34] of complete/partial remission (with or without intervention) in approximately 50% of patients and a complete spontaneous remission in approximately 20% of patients within 6 to 7 years of onset. The remission of symptoms, be it complete or partial, is often characterized by a change in pain pattern from a constant to an episodic form [34,42]. Contrary to these findings, Sardella

and colleagues [43], in an investigation to specifically evaluate the spontaneous remission rate in BMS, reported that a complete spontaneous remission was observed in only 3% of the patients within 5 years after BMS onset.

The pattern of daily symptoms is reportedly constant for the individual patient, with approximately one third of patients experiencing symptoms both day and night [3,13,20]. Most patients report minimal symptoms on awakening, after which the symptoms gradually increase during the day to culminate in the evening [2,3]. About one third of the patients have difficulty with sleep onset and some may awaken during the night because of the burning pain [20,44]. It has been suggested that these sleep disturbances and the presence of ongoing pain may explain the increased incidence of mood changes, irritability, and affective motivational disturbances among patients who have BMS [2,27]. The intensity of the burning pain has been described as moderate to severe and in some cases it is comparable to the intensity of toothache pain in regard to severity but not quality [27]. In most patients, the burning sensation intensifies in the presence of personal stressors, fatigue, and acidic foods (tomatoes and orange juice), and in about half the patients the intake of food or liquids and distraction seem to reduce or alleviate the symptoms [3,31]. It is unclear what the effects of tobacco, ethanol, or dietary factors are on the symptoms of BMS. Patients who have BMS have a significantly higher incidence of dry mouth, thirst, and taste disturbances, but they do not differ from healthy controls regarding changes in oral mucosa or dental problems [3,11,45,46]. More than two thirds of patients complain of dry mouth [3,10,13] and taste disturbances that manifest as a persistent alteration in taste (bitter or metallic) or a change in taste intensity [47]. Taste disturbances have been objectively demonstrated in patients who have BMS using electrical stimuli [48,49] and oral tastants [3,42,50] at threshold and suprathreshold levels. In contrast to these studies, Bergdahl and Bergdahl [51], in reviewing perceived taste disturbances from a large population-based study, found only a weak correlation between burning mouth and taste disturbances with perceived taste disturbances being more prevalent in females than males. Additionally, most studies have not objectively demonstrated decreased salivary flow rates despite the subjective complaints of dry mouth and thirst [26,36,52,53]. There have been several studies that have shown qualitative changes in salivary composition, however [36,53,54]. Furthermore, patients had no greater prevalence of medical conditions, such as diabetes, arthritis, or cardiovascular and gastrointestinal disorders, when compared with age- and sex-matched controls [3].

Patients who have BMS have more nonspecific health complaints and more severe menopausal symptoms as compared with healthy controls [3]. Headaches, dizziness, neck and back pain, dermatologic disorders, irritable bowel syndrome, anxiety, depression, personality disorders, and other psychiatric disorders are reported more frequently in these patients [20,35,45,46,55,56]. Many of these studies are unclear as to whether these symptoms are risk factors for development of BMS or a consequence of the syndrome, indicating a need for longitudinal cohort studies.

Etiology

The cause of BMS is currently unknown. The etiology is presumed to be multifactorial involving the interaction between biologic (neurophysiologic mechanisms) and psychologic factors [12]. A considerable number of local, systemic, and psychologic factors have been found related to BMS; however, several of these factors should be considered as conditions important to the differential diagnosis of oral burning rather than as an etiologic factor for BMS (Box 2).

Local factors

Various and multiple local factors have been implicated as causes of BMS. Some of these are: xerostomia, which is the subjective sensation of dry mouth and is found to be a frequent complaint (25% of patients who have BMS) [19,26,40] and may also include drug-induced xerostomia [40,48]; hyposalivation, which denotes objectively reduced salivary flow measured by sialometry [11,21,26]; taste disturbances involving either an alteration in taste perception, a persistently altered taste, or a combination [3,47,57]; oral infections involving bacterial, viral, or fungal (candidiasis) infection [58–62]; oral mucosal diseases, such as lichen planus [48]; parafunctional oral habits, such as clenching, bruxing, or tongue posturing [43,63]; mechanical and chemical irritations, such as galvanism and denture-related problems [26,64]; and allergic reactions [26,65]. Additionally, mucosal findings, such as benign migratory glossitis (geographic tongue), scalloped

Box 2. Reported etiologic factors for burning mouth syndrome

Local
Denture factors
Dental treatment
Mechanical factors
Parafunctional habits
  Clenching
  Bruxism
  Tongue posturing
  Myofascial pain
Allergic contact stomatitis
  Dental restorations
  Denture materials
  Foods
  Preservatives, additives, flavorings
Neurologic
  Referred from tonsils or teeth
  Trigeminal neuropathy
  Acoustic neuroma
Infection
  Bacterial
  Fungal
  Viral
Hyposalivation
  Radiation therapy
  Salivary gland disorders

Systemic
Deficiencies
  Iron (anemia)
  Vitamin B_{12}
  Folate
  Zinc
  B complex vitamins
Endocrine
  Diabetes
  Thyroid disease
  Menopause
  Hormonal deficiencies
Hyposalivation
  Connective tissue disease
  Sjögren syndrome
  Sicca syndrome
  Drug-induced
  Anxiety or stress
Medication
  Angiotensin converting enzyme (ACE) inhibitors
  Antihyperglycemic
Esophageal reflux

Psychologic
Depression
Anxiety
Obsessive compulsive disorder
Somatoform disorder
Cancerphobia
Psychosocial stressors

tongue, and fissured tongue, have also been considered [10,40,66]. Interestingly, Grushka [3] reported no significant differences on clinical examination between BMS and control subjects who had any intraoral soft or hard tissues findings. It is possible that the discrepancy between this study and the studies that found higher prevalences of oral changes may be attributable to the subjective nature of the diagnoses or may have developed as a result of the BMS rather than being the cause.

Systemic factors

There are many and varied systemic factors that have been considered as etiologic factors. Some of these are autoimmune, gastrointestinal, and endocrine disorders, such as connective tissue diseases, gastroesophageal reflux disease, diabetes, and thyroid disorders [11,18,31,42,67–70]; hormonal deficiencies and menopausal alterations [3,18]; drug-induced factors, especially involving angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, and lisinopril [71,72]; and nutritional deficiencies involving vitamins and minerals, especially those associated with anemia (iron and vitamin B_{12} deficiency), zinc, and vitamin B complexes [73,74]. Despite some evidence from these studies supporting a possible association of these systemic factors as etiologic agents, there is much inconsistency within the literature [3,10,19,26,75–77]. Additionally, although more than 58% of people who have BMS display abnormal immunologic features, such as elevated rheumatoid factor and antinuclear antibody [78], no consistent relationship has been found between BMS and a connective tissue disorder. Other studies have reported a relationship between other facial pains [64], pains in other parts of the body [64], and headache pain [3] as being more frequent in patients who have BMS. The meaning and relevance of this association remains unclear, however.

Psychologic factors

Psychologic phenomena, such as alterations in states of anxiety and depression, somatization, and certain aberrant personality traits, are common findings in patients who have BMS [41,79–81]. At least one third of patients may have an underlying psychiatric diagnosis [40]. A phobic concern regarding cancer is also found in 20% of patients [26] and is often manifested as repeated self-examination by the patient [6]. Although BMS may be a somatic symptom of depression, the association does not always equate to a causal relationship. Carlson and colleagues [82] used the MPI and SCL-90R on 33 BMS cases and compared the data to those from population samples that included patients who had non-BMS chronic pain and a normal nonclinical sample. They concluded that there was no evidence for significant clinical elevations on any of the SCL-90R subscales, including depression, anxiety, and somatization. Moreover, patients reported significantly fewer disruptions in normal activities as a result of their oral burning pain than did a large sample of patients who had chronic pain. They did note that 21% of the BMS cases had substantially elevated psychologic distress. The presence of comorbid psychologic issues suggests the need for treatment of these problems but this is certainly not evidence of causality. Depression and psychologic disturbances are common findings in the chronic pain population and may be the result of the constant pain or may contribute to the cause, intensity, and urgency of complaint. Studies have reported similarities between the personality characteristics of chronic oral pain patients and other chronic pain populations [27]. In addition, many of the medications used to treat these psychologic conditions can cause side effects, such as dry mouth and taste alterations, that may induce or exacerbate BMS symptoms.

Salivary features

Xerostomia is a frequent complaint in patients who have BMS. No differences were identified in studies comparing the flow rates of whole saliva and parotid saliva between patients who had BMS and healthy controls [53,54,83–87]. There are many causes of xerostomia or hyposalivation, with the intake of certain medications being the most common causative factor. Because patients who have BMS take more medications, most likely because of issues regarding anxiety and depression, then it seems reasonable that this may account for the complaint of dry mouth in these individuals [69,88]. In a study by Lamey and colleagues [84] it was shown that stimulated parotid saliva flow rates were reduced in patients who had BMS who were taking antidepressants but normal in nonmedicated patients who had BMS.

Other possibilities for dry mouth symptoms found in BMS populations may be altered sensation or alterations in saliva composition or viscosity [89]. Some sialochemical studies in patients who have BMS have reported no alterations in the protein composition of whole or parotid saliva when compared with healthy age- and sex-matched controls [83,85,86]. Contrary to these findings, several studies have demonstrated, in stimulated and unstimulated whole saliva and stimulated parotid saliva, significant alterations in salivary compositions, such as proteins, immunoglobulins, inflammatory mediators, and phosphates, along with differences in salivary ions, pH, buffering capacity, electrical resistance, and conductance [46,54,87,90–94]. It has also been found that altered salivary composition is a common finding, possibly as a result of altered sympathetic tone at the time of menopause [22]. Although the significance of these findings is unknown, it is possible that these alterations represent a selective rather than a gross change in salivary flow rate related more to age or disease than BMS [95–97]. It does not seem that studies examining salivary flow rates or saliva composition in samples collected from the submandibular, sublingual, or minor salivary glands have been performed in the BMS population even though the location of BMS symptoms is frequently affected by areas exposed to the contents from these glands.

Evolving etiologic theories

The pursuit of a causal relationship is an extremely difficult task in science and association does not prove cause and effect. This distinction has not been purely adhered to as is evidenced by the vast array of potential etiologic factors reported by the many authors discussing BMS. For example, the observed elevated levels of psychologic issues, such as depression and anxiety, may be an effect of the chronic pain condition rather than a causative factor. Additionally, other local and systemic factors may purely be coincidental findings that are devoid of a cause-and-effect

relationship. Suarez and Clark [31] stated that to establish a causal link between two factors, one must have good consistency of data, meaning that the association investigated must be present in all cases regardless of the number of ways in which it is studied. They further comment that a biologically plausible explanation must be available regarding how the potential etiologic factor causes the outcome, and the suggested association must be independently verified. Using these criteria, there seem to be two current hypothetical etiologic theories for BMS, both involving neurologic processes.

Taste and sensory system interactions

Taste to the anterior two thirds of the tongue is innervated by a branch of cranial nerve (CN) VII (facial) by way of the chorda tympani nerve. Somatosensory innervation to this same area is supplied by a branch of CN V (trigeminal), the lingual nerve. The theory is that burning mouth pain symptoms occur when there is an abnormal interplay between the sensory function of these nerves within either the peripheral or central nervous systems [98,99]. This theory proposes that certain individuals, labeled as supertasters because of the high density of fungiform papillae present on the anterior aspect of the tongue, are more at risk for developing burning mouth pain. 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 [100,101]. Although supertasters may be at increased risk, those who are not supertasters may also develop symptoms of BMS following damage to taste wherein disinhibition of sensory input leads to burning symptoms. Svensson and colleagues [102] showed that patients who had BMS perceived a significantly more intense burning pain in the oral mucosa following exposure to capsaicin (the chemical irritant found in chili peppers) than did a matched control group. It has also been reported that 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 [103]. A study by Eliav and colleagues [104] supports the concept of abnormal interplay between taste and sensory innervations by way of the chorda tympani and lingual nerves. Their study was composed of 48 patients: 22 patients had BMS, 14 had burning symptoms related to other diseases and were diagnosed as having secondary burning mouth syndrome, and 12 were healthy volunteers. The results of the study indicated an elevated electrical taste/tingling detection threshold ratio (lingual nerve) and taste detection threshold (chorda tympani) in the patients who had BMS, with 82% of these patients demonstrating chorda tympani dysfunction. This finding led to the conclusion that taste alteration may result in sensory hyperfunction. Additionally, the authors believe that this continuous input of pain may generate alterations in central nervous system processing and lead to pain that spreads beyond the affected nerve distribution. The taste and sensory system interaction theory speculates that damage (mechanical, chemical, or biologic) to the chorda tympani nerve impairs the normal ability of this nerve to inhibit sensations of pain from CN V. This impairment creates a type of disinhibition manifesting as 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) as observed in patients who have BMS [105]. It has also been suggested that interactions between taste and oral pain are not limited to BMS but may involve other orofacial pain complaints because patients who have persistent idiopathic facial pain also display taste damage [106]. Presently, this theory is lacking definitive data that a large proportion of patients who have BMS are indeed supertasters, and this theory is also unable to account for all the various manifestations that are clinically seen in the BMS population.

Neural alteration

Peripheral

The theory that alterations to the peripheral nervous system are an etiologic factor for BMS has been proposed in several studies. Jaaskelainen and colleagues [107] evaluated the possible neuropathic mechanisms underlying BMS by means of objective electrophysiologic examination of the trigeminofacial system. They studied the blink reflex response in 11 patients who had BMS and 10 controls with both groups undergoing a thorough clinical oral and neurologic examination. As a group, the patients who had BMS displayed definite alterations in their blink response to applied stimulation. The authors concluded from these

results that a possible pathologic involvement of the nervous system may be present in the BMS population. Forssell and colleagues [108] used quantitative sensory tests in addition to the blink reflex in 52 patients who had BMS. They found, based on electrophysiologic findings, that these patients in general have different types of neural changes (some with enhanced and some with reduced neural responses). Overall, the majority (90%) of those tested had some form of altered sensory threshold or blink reflex reaction. These studies suggest that peripheral or central nervous system alterations are present in BMS; however, they do not provide a definitive location for where in the somatosensory system these changes have occurred. The first study [109] to investigate whether damage of peripheral nerve fibers underlies the pathogenesis of BMS studied the innervation of the tongue epithelium. This study examined 12 patients who had clinically definite BMS for at least 6 months whereby superficial biopsies of the lateral aspect of the anterior two thirds of the tongue were performed on all patients who had BMS and 9 healthy controls. Immunohistochemical and confocal microscope colocalization studies were performed with cytoplasmatic, cytoskeletric, Schwann cell, and myelin markers for pathologic changes. Patients showed a significantly lower density of epithelial nerve fibers than controls, with a trend toward correlation with the duration of symptoms. Epithelial and subpapillary nerve fibers showed diffuse morphologic changes reflecting axonal degeneration. It was concluded that BMS is caused by a trigeminal small-fiber sensory neuropathy. Small-fiber neuropathy refers to a subtype of peripheral neuropathies characterized by the impairment of thinly myelinated A-delta and unmyelinated C fibers. This conclusion implies that both somatic and autonomic fibers may be involved, thus leading to sensory and autonomic neuropathies [110].

Central

Evidence from several studies alludes to a more centrally mediated alteration in modulation of nociceptive processing as an etiologic factor. These studies involve the dopaminergic function in the striatum (putamen and caudatus), which is part of the basal ganglia in the midbrain. The basal ganglia is purported to be involved in the processing and sensorimotor gating of nociceptive information. These studies indicate that inhibition of the nigrostriatal dopaminergic system is reduced in patients who have BMS compared with healthy controls resulting in reduced central pain suppression. It was also found that BMS participants involved in these studies displayed no signs of motor dysfunction or psychiatric disorders, which supports the hypothesis that pain sensation in BMS is exclusively a nociceptive projection [111–113]. Overall, these studies suggest that brain function in the processing of nociceptive input is altered in BMS cases. This theory was further evaluated in a study assessing the pathophysiology associated with BMS with the use of functional magnetic resonance imaging. Areas of brain activation following thermal stimulation of the trigeminal nerve in eight female patients who had BMS were compared qualitatively and quantitatively to matched pain-free controls. The authors concluded that patients who had BMS displayed brain activation patterns similar to those of patients who had other neuropathic pain conditions and seemed to process painful stimulation differently than pain-free individuals [114]. It has also been shown that areas in the brain that respond to taste are identical to those areas activated in response to pain, suggesting that taste and pain share overlapping neural substrates [115].

From these studies, it seems apparent that there are both central and peripheral mechanisms and a combination of such may be involved in the etiologic process leading to BMS. Additionally, it should be considered that these factors are not purely evident in all BMS cases, because BMS presents in multiple variations and themes.

Diagnosis

Taking a thorough and comprehensive history is the key to diagnosis of BMS. Important information to be ascertained by the practitioner relates to the past and current symptoms (pain, dry mouth, taste, and so forth), their duration, intensity, character, location, onset, and factors that improve or worsen the pain and its course. A numeric or visual analog scale measuring the patient's pain intensity and dry mouth should be used. Information should be obtained about current and past health status, including chronic systemic disorders, allergies, and immunologic disorders, and previous and current medications. This history should also include information on previous or current psychosocial stressors and psychologic well being. The diagnosis is based on the clinical characteristics and presenting symptomatology supplied by the patient. Important clinical characteristics that would provide

a diagnosis of BMS are: a sudden or intermittent onset of pain usually localized to the tongue, hard palate, and lips; bilateral presentation; a persistent and often progressive increase in pain during the day often not present on awakening and the remission of pain with eating (although some foods may exacerbate the pain) and sleeping; presence of abnormal or altered tastes (usually metallic or bitter); subjective sensations of a dry mouth and intraoral areas of roughness, irritation, or swelling; and parafunctional habits [116]. The clinical examination is more to rule out any possible local factors that may be responsible for the oral burning complaints. The clinical examination should therefore include an extraoral and intraoral examination of temporomandibular joint function; inspection and palpation of the masticatory muscles, oral mucosa, tongue mobility, and dental hard and soft tissues; and evaluation of any prosthetic devices. Objective measurements of salivary flow rates (whole stimulated and unstimulated saliva) and taste function should be taken [117]. Neurologic imaging and consultation should be a consideration if patients present with more complex, confounding, or atypical symptoms, including sensory, motor, and autonomic changes, to rule out any neurodegenerative disorders or central nervous system pathology. Additional clinical tests may be requested to rule out any local and systemic factors that may be responsible for the symptomatology (Box 3). As previously stated, BMS is a diagnosis of exclusion.

Box 3. Clinical tests for burning mouth syndrome

- Hematologic tests: Complete blood count/differential, glucose, thyroid studies, nutritional factors, autoimmune panel
- Oral cultures: fungal, viral, or bacterial if infections suspected
- Imaging: MRI, CT scans, and nuclear medicine, if deemed necessary to rule out systemic considerations
- Salivary flow rates for whole unstimulated (0.3–0.4 g/min) and stimulated (0.75–2.0 g/min) saliva
- Salivary uptake scans if low salivary flow rates and Sjögren syndrome suspected
- Allergy testing if needed, especially for a dental panel and allergens
- Trial of discontinuation of certain medications, including ACE inhibitors
- Psychometric tests: SCL- 90R, MPI, Hospital Anxiety and Depression Scale, and Beck Depression Inventory
- Gastric reflux studies

In a study by Mignogna and colleagues [118] it was reported that the average delay from onset of the symptoms to definitive diagnosis was 34 months. This delay in diagnosis may not only cause the oral pain to interfere chronically with normal daily lifestyle and sleep pattern but also could have a significant emotional impact on patients. The authors also found the average number of medical and dental practitioners consulted by each patient over this period (who initially misdiagnosed BMS) was 3.1. It is unclear whether this situation is the consequence of the complex and largely unknown nature of BMS or the expression of inadequate knowledge among the physicians and oral health care providers about non-dental orofacial pain conditions.

Burning mouth syndrome management

There is little research evidence to provide clear recommendations for management of patients who have BMS. Initially, the clinician must determine if the patient is suffering from primary (essential/idiopathic) BMS or secondary BMS in which symptoms are attributable to underlying local or systemic conditions, such as mucosal disease (ie, lichen planus, candidiasis), hormonal disturbances, psychosocial stressors, vitamin or nutritional deficiencies, diabetes, dry mouth, contact allergies, galvanism, parafunctional habits, cranial nerve injuries, or medication side effects [119]. Secondary BMS requires appropriate diagnosis and treatment of the underlying condition to manage symptoms. In primary BMS the cause is unclear, so treatment options are based on patients' symptomatology, often yielding unsatisfactory results. A retrospective study evaluated 53 patients who had BMS for at least 18 months. Various treatment modalities were administered, for which moderate improvement was reported in 28.3% of the subjects and spontaneous remission occurred in 3.7%. All other patients reported no change or worsening symptoms of BMS a mean of 5 years after having been diagnosed with the condition [43]. Three

Table 2
Summary of treatment interventions

Treatment (class of drug)	Dosage	Prescription	Evidence for use	Notes
Behavioral interventions				
Cognitive behavioral therapy			Two RCTs indicate decreased BMS symptomatology.	
Topical therapy				
Clonazepam (benzodiazepine)	1 mg tablet tid	Let tablet dissolve and hold fluid in mouth in area of most intense burning for 3 minutes, then expectorate.	One RCT indicates decreased BMS symptomatology.	This agent is approved by the FDA for seizures and panic disorders. It is used off-label for neuropathic pain and BMS in particular.
Lidocaine (anesthetic)	Viscous gel 2%	5 mL qid. Rinse for two minutes and expectorate.	No published evidence for BMS	This agent is FDA approved as a topical anesthetic agent but its use is specified as an aid for minor surgeries or skin abrasions.
Topical capsaicin	0.025% cream	Apply tid to qid	No published evidence for BMS	
Topical doxepin	5% cream	Apply tid to qid	No published evidence for BMS	
Systemic therapy				
Nortriptyline, amitriptyline (tricyclic antidepressants)	10–75 mg or more per day	10 mg at bedtime; increase dosage by 10 mg every 4–7 d until oral burning is relieved or side effects occur	No published evidence for BMS but used commonly for neuropathic pain	This drug is approved for treating the symptoms of depression, but it is used off-label for neuropathic pain.
Paroxetine, sertraline (SSRIs)	Paroxetine: 20 mg/d; sertraline: 50 mg/d	Paroxetine: maximum 50 mg/d; sertraline: maximum 200 mg/d	One RCT indicates decreased BMS symptomatology.	This agent is approved by the FDA for major depression and is used off-label for chronic pain.
Amisulpride, levosulpiride (atypical antipsychotic agents)	50 mg/d	50 mg tablets up to three times per day. Maximum dose not to exceed 400 mg/d	One RCT for amisulpride and open trial for levosulpiride indicate decreased BMS symptomatology.	This drug is FDA approved for schizophrenia. It is not available in the United States.

(*continued on next page*)

Table 2 (*continued*)

Treatment (class of drug)	Dosage	Prescription	Evidence for use	Notes
Clonazepam (benzodiazepine)	0.25–2 mg/d	0.25 mg at bedtime, increase dosage by 0.25 mg every 4–7 d until oral burning is relieved or side effects occur. As dosage increases, medication is taken as full dose or in three divided doses.	Open trial indicates decreased BMS symptomatology. No RCTs have been performed.	This agent is approved by the FDA for seizures and panic disorders. It is used off-label for neuropathic pain and BMS in particular.
Gabapentin (anticonvulsant)	300–2400 mg/d	100 mg at bedtime; increase dosage by 100 mg every 4–7 d until oral burning is relieved or side effects occur. As dosage increases, medication is taken in three divided doses.	One RCT indicates no decrease in BMS symptomatology. One case report suggests this agent may decrease burning in some patients.	This drug is FDA approved for partial seizures and for postherpetic neuralgia pain.
Alpha-lipoic acid (antioxidant)	200 mg tid	200 mg tid for 2 mo. Also prescribe gastroprotector.	Multiple RCTs indicate decreased BMS symptomatology.	This agent is considered a nutritional supplement.
Capsaicin (atypical analgesic)	0.25% capsules tid	0.25% capsules tid for 1 mo	One RCT indicates decreased BMS symptomatology.	It is not available in the United States.

Abbreviation: FDA, US Food and Drug Administration.

Data from Suarez P, Clark GT. Burning mouth syndrome: an update on diagnosis and treatment methods. J Calif Dent Assoc 2006;34(8):611–22.

approaches or combinations of these can be considered part of the management strategy.

Behavioral interventions

One randomized controlled trial (RCT) examined the effect of cognitive therapy on resistant BMS compared with a placebo program. Thirty participants underwent 12 to15 sessions of cognitive therapy lasting 1 hour once a week, and 30 individuals in the placebo group underwent motivational input three times during the 12- to 15-week period. The study showed a statistically significant reduction in pain intensity for those receiving cognitive therapy compared with placebo immediately following the therapy and a further reduction at the 6-month follow-up [120]. Another study showed some improvement of BMS resulting from psychotherapy treatment over 2 months, with significant improvement when combined with alpha-lipoic acid therapy (ALA) (600 mg/d) [121]. It seems from these studies that the practitioner may consider the involvement of a behavioral medicine practitioner as part of a multidisciplinary approach when managing patients who have BMS.

Topical medications

Three studies have assessed the efficacy of topical therapies on BMS symptomatology. A double-blind RCT was performed to evaluate the efficacy of topical clonazepam, a γ-aminobutyric acid (GABA) receptor agonist, compared with placebo. Patients were instructed to suck on a tablet containing either 1 mg clonazepam or placebo three times a day. After 14 days, the decrease in pain was significantly more

pronounced in the clonazepam compared with the placebo group. Sixty-six percent of patients who had BMS reported reduced pain intensity after 14 days, with residual partial improvement after 6 months in 29% [122]. In addition, benzydamine (not available in the United States) is a nonsteroidal drug with analgesic, anti-inflammatory, and antimicrobial properties that also has topical anesthetic properties. A small, double-blind RCT of benzydamine hydrochloride 0.15% oral rinse (15 mL used three times a day) compared with a placebo oral rinse solution and a no-treatment group was unable to demonstrate any statistically significant difference between the three groups at the end of the 4-week period. No adverse events were reported [123]. Furthermore, a single open-label RCT indicated topical lactoperoxidase oral solution (Biotene mouthwash) used five to six times daily for 60 days compared with placebo was not effective [124].

Systemic medications

Numerous studies have assessed systemic therapies for treatment of BMS, including antidepressants, anticonvulsants, GABA receptor agonists, and vitamin complexes. A prospective, randomized, single-blind study without placebo comparison was performed to compare the efficacy of amisulpride (not available in the United States), an antipsychotic medication, and selective serotonin reuptake inhibitor (SSRI) antidepressants sertraline and paroxetine in patients who had BMS. After 8 weeks of treatment, all three treatment regimens resulted in a significant improvement in BMS symptomatology [125]. In another study, 44 patients used levosulpiride (not available in the United States), an antipsychotic and antidepressant drug, at a dose of 100 mg daily (50 mg capsule, twice daily) for 8 weeks. Seventy two percent of the patients reported a partially effective result and 28% of the patients reported no benefit to the medication. This study did not include a control group [126]. Additionally, a double-blind, randomized, placebo-controlled study evaluated the efficacy of trazodone, a serotonin antagonist antidepressant medication, compared with placebo. After 8 weeks of trazodone 200 mg/d, the authors reported no statistically significant differences compared with placebo at any time point [127].

Thirty patients who had burning mouth symptoms ranging from 1 month to 12 years received clonazepam 0.25 mg/d, which was titrated on a weekly basis by 0.25 mg until symptoms resolved or to a maximum dosage of 3 mg/d in three divided doses. All subjects used clonazepam for a minimum of 2 months. Mild to moderate improvement of burning mouth symptoms was reported in 70% of the patients. Although using a convenience sample and providing evidence of effect, the strength of these data is limited by the lack of a control group [128]. Another study assessed 15 patients who had BMS prescribed gabapentin, an anticonvulsant medication, at a starting dose of 300 mg/d, slowly titrated up to a maximum of 2400 mg/d. Subjects were treated for 2 to 6 weeks. Gabapentin had no effect on pain ratings, mood scale, Beck Depression Inventory scores, or chemosensory functions following therapy [129]. Contrary to this, a case report suggests that gabapentin may be effective in reducing burning mouth symptoms [130].

ALA is the trometamol salt of thioctic acid and a potent antioxidant mitochondrial coenzyme. ALA may protect against damage mediated by reactive oxygen species and may be neuroprotective [131]. In patients who have BMS, multiple double-blind and open-label RCT studies conducted at one center have evaluated the efficacy of 600 mg ALA given daily compared with placebo [121,124,131,132]. In a Cochrane Database systematic review [133] these studies were unable to be pooled because of variation in the results. Regardless, all four trials showed a statistically significant improvement in BMS symptomatology with ALA. Another study compared ALA in patients who had BMS who had taken tranquilizer medication for treatment compared with those who had never used tranquilizers. Patients who were treated with tranquilizers responded poorly to therapy with ALA compared with those who had not received previous psychotropic therapy [134]. Given the subjective nature of the outcome assessment for all of these studies, the results should be interpreted with caution.

A triple-blind trial of systemic capsaicin was administered as 0.25% capsules three times per day for 4 weeks and compared with placebo. Results indicated that treatment with systemic capsaicin induced a statistically significant reduction of burning symptoms at the end of the study period. This study was limited by nonrandom allocation to the study groups, however, so results should be interpreted with caution [135]. Furthermore, a single open-label RCT indicated systemic bethanechol (which stimulates the parasympathetic system) 5 mg three times daily for 60 days

compared with placebo was not effective at improving symptoms of BMS [124]. In persisting cases of BMS, combinations of more than one agent with different mechanisms of action have been discussed, but no trials have been conducted.

It is apparent that a range of treatments has been used to alleviate symptoms of BMS resulting in an assortment of outcomes. The varying therapies, with different mechanisms of action, represent numerous suspected etiologies of the condition. Treatment interventions are summarized in Table 2.

Summary

Diagnosis and management of patients who have BMS is not an easy task. The scientific literature is ambiguous and equivocal about the classification, epidemiology, etiologic factors, clinical presentation, diagnosis, and management strategies regarding this condition. There is little evidence-based material to assist the practitioner when dealing with these individuals. There is no doubt that innovative and interdisciplinary research is required to elucidate and expand on the knowledge of the etiology and pathogenic factors involved in BMS. Oral and maxillofacial surgeons should therefore be cautious in diagnosis of a BMS case as to whether or not this individual should be managed within his or her scope of care, because the complaints represent a chronic pain condition wherein medical management is indicated and surgical approaches contraindicated. If there is uncertainty then the oral and maxillofacial surgeon may be wise to refer to an oral medicine/orofacial pain practitioner to assist in the management of these complex patients.

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