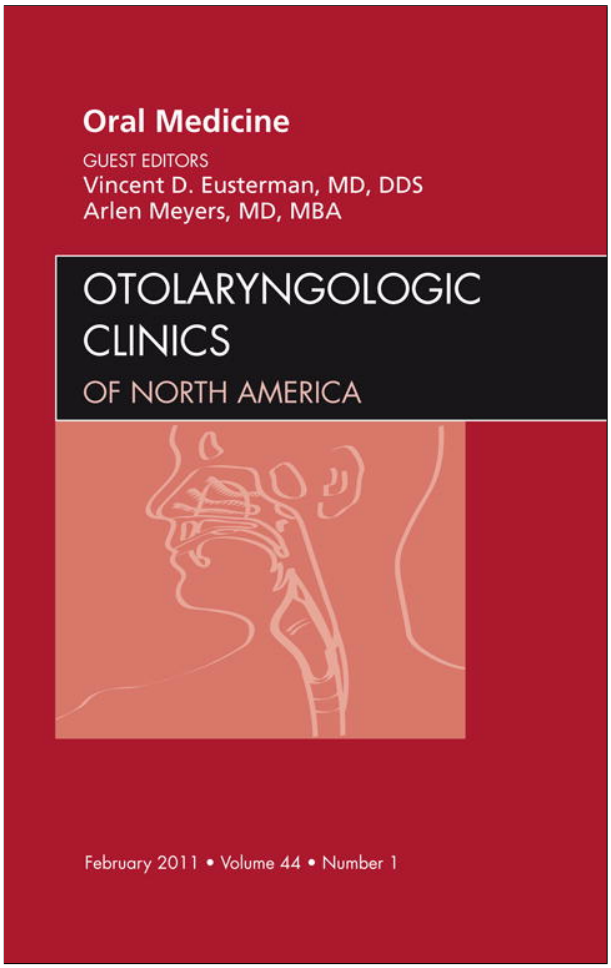

# Burning Mouth Syndrome and Secondary Oral Burning

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**KEYWORDS**

• Burning mouth syndrome • Glossodynia • Stomatopyrosis
• Neuropathy • Taste change • Xerostomia

Burning mouth syndrome (BMS) is an idiopathic condition causing a deep burning pain of the oral mucosa, despite an absence of identifiable dental or medical pathology, lasting at least 4 to 6 months.[1–7] BMS should be distinguished from secondary oral burning reported by patients with a variety of documented oral mucosal and medical conditions. BMS was first described by Fox[8] in 1935 and has gone by many aliases, including glossodynia, glossopyrosis, oral dysesthesia, sore tongue, stomatodynia, and stomatopyrosis.[9] The International Classification of Diseases (ICD-9) uses the term glossodynia with the descriptors glossopyrosis or painful tongue for code 529.6.[10] In this article BMS is used to refer to idiopathic oral burning not associated with oral mucosal or systemic conditions.

BMS is found in a 7:1 female to male ratio and approximately 90% of sufferers are perimenopausal women.[5] In one study of 130 patients, a burning sensation was noted in the tongue in 72%, in the hard palate in 25%, in the lips in 24%, and other sites such as buccal and labial mucosa, soft palate, and floor of mouth in 36%. Whereas some patients had burning confined to the tongue only, others had other or multiple sites of involvement.[11] Another study showed similar prevalence of tongue involvement, though with palate and lip involvement in only 5.7% of respondents.[12] In many cases symptomatic complaints are bilaterally distributed. Many patients also report

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associated symptoms of oral dryness and alteration in taste, such as a metallic bitter sensation, as well as worsening with stress, excessive speaking, or hot foods, and improvement with cold food, work, and relaxation.[5,7,13–15] Taste change and oral dryness may be associated with etiology in some cases. In general, BMS does not interfere with sleep, but may be present on waking or increase later in the day.[16] In the patients who report xerostomia, measurement of saliva may or may not confirm hyposalivation, suggesting that in some cases the sensation reported of dryness may be related to altered sensation and not a change in saliva.[14] Because of the lack of findings on physical examination, BMS may be a source of frustration for the caregiver, the patient, and significant others related to the patient.[1] This article surveys the current state of knowledge regarding BMS with the aim of assisting the practitioner in forming a strategy for diagnosis and management of this condition.

## EPIDEMIOLOGY

Several studies have attempted to assess the prevalence of BMS in various populations. The largest United States study surveyed more than 42,000 households for various types of orofacial pain, and estimated a BMS prevalence of 0.7%.[17] This method, of course, precluded examination to rule out other pathology and oral burning. A Swedish study in 1999 surveying 669 men and 758 women found a prevalence of 1.6% among men and 5.5% among women, with increasing prevalence with age up to more than 12% among the oldest women.[12] Patients in this study were brought in for examination if they reported burning mouth symptoms. In that study no BMS was found in men younger than 40 or in women younger than 30 years. Other studies have also confirmed that BMS is predominant in women,[6,18,19] especially in those who are perimenopausal.[20]

## ETIOLOGY

Although there is no confirmed cause of BMS, the general consensus, including that of the International Headache Society, is that the condition represents a neuropathy resulting in chronic pain.[7,21–23] Evidence in favor of this is seen both on histopathology and in neurologic testing. Current areas of debate regarding the etiology of BMS include its status as primarily a central or peripheral neuropathic phenomenon, and the role of dysguesia as a primary or secondary event. Also, the nature of associations between BMS, menopause, and psychiatric disease remains unclear. Finally, it is important to understand the wide variety of other conditions causing oral burning symptoms, ensuring that patients diagnosed with BMS are not in fact experiencing burning secondary to a potentially treatable mucosal or systemic condition.

### *Evidence for BMS as a Peripheral Neuropathy*

BMS is associated with unique histopathologic findings and alterations of levels of salivary neuropeptides. Lauria and colleagues[24] evaluated the innervation of the epithelium of the anterolateral tongue in 12 patients with BMS present for at least 6 months using 3-mm punch biopsies of the region. In addition, samples were obtained from 9 normal patients as a control. Immunohistochemical and confocal microscopy colocalization studies were performed with cytoplasmatic, cytoskeletal, Schwann cell, and myelin markers for pathologic changes. Of note, BMS patients showed a significantly lower density of epithelial nerve fibers than controls, with a trend toward correlation with the duration of symptoms. There was no correlation between density of fibers and severity of symptoms. Epithelial and subpapillary nerve fibers also showed diffuse morphologic changes reflecting axonal degeneration, demonstrating

that BMS is associated with a small-fiber sensory neuropathy or axonopathy of the tongue and that biopsy can be used to assess the diagnosis. The investigators note that these findings correlate with histologic findings in burning disorders of the lower limbs, and that the nociceptive stimulation of these fibers may be contributory to the accompanying dysguesia.[24] A recent study by Borelli and colleagues[25] examined the levels of salivary neuropeptides in 20 BMS patients and matched controls, and found significantly increased nerve growth factor peptide and tryptase activity in saliva of BMS subjects. Conversely, levels of substance P were shown to be significantly lower while neutrophil markers were unchanged. The investigators felt these substances might be useful biomarkers for diagnosis and monitoring of BMS.

There are alterations in trigeminal nerve function in BMS patients. Two studies by Jaaskelainen and colleagues examined alteration in function of the trigeminal nerve among BMS patients. Their 1997 article[23] reported on 11 patients with BMS for at least 1 year and 10 healthy controls. Following a thorough neurologic and laboratory evaluation to rule out any other contributory factors, the patients underwent electrophysiologic evaluation of the blink reflex and jaw reflex, and needle electromyographic evaluations of facial and masticatory muscles were performed on those with abnormal blink reflexes. Although all other testing was normal, there was a significant abnormality noted in the blink reflexes of patients with BMS, suggestive of trigeminal dysfunction. A follow-up study in 2002[21] confirmed the findings of abnormal blink reflexes in 52 BMS patients, and correlated them with quantitative thermal thresholds in 46 of the patients. Seventy-six percent of patients tested had thermal sensory abnormalities, the majority of those some variety of hypoesthesia. Less than 10% of all patients had entirely normal electrophysiological testing of the trigeminal nerve. Some potential mechanisms include neuropathy due to causes such as injury during procedures in the mouth and throat, and viral-induced neuropathy.

### *Evidence for BMS as a Central Neuropathy*

Central neuropathic mechanisms are also felt to be involved in BMS. Albuquerque and colleagues[26] demonstrated differences in perception of trigeminal pain between BMS and normal patients on functional magnetic resonance imaging (fMRI) in a 2006 study. In follow-up to their aforementioned work in trigeminal abnormalities in BMS, Jaaskelainen and colleagues[27] evaluated the nigrostriatal dopaminergic pathway in 10 BMS patients and 14 controls using modified positron emission tomography (PET). Findings of decreased uptake in the right putamen indicated decreased dopaminergic inhibition in BMS patients. Another study by the same group in 2003 found alterations consistent with a decline in endogenous dopamine levels in the putamen in BMS patients.[28]

### *Evidence for BMS as a Phantom Pain*

The role of dysguesia as a primary or secondary phenomenon in BMS remains a point of investigation. Whereas some have felt dysguesia is a secondary event arising from trigeminal dysfunction,[24] others question if loss of taste might be an inciting event, playing a primary role in the etiology of some cases of BMS.[29–31] It is hypothesized that BMS represents a central oral phantom pain secondary to damage to the gustatory system and disinhibition of central nociceptive regions.[29,31–34] Other taste phantoms may also be associated with a similar etiology.[35] Other supporting evidence is that anesthesia of the chorda tympani has been demonstrated to increase the contralateral pain response to capsaicin,[36] and that overlap exists between brain regions involved in taste and pain perception.[37] Supertasters, those with a genetic alteration causing increased number of fungiform papillae and an ability to taste the bitter compound phenylthiocarbamide,[38,39] may be at increased risk.[32,33] BMS patients

may also have a higher likelihood of taking medications interfering with taste.[31] Evidence that BMS is a form of oral phantom pain is both tantalizing and revealing, given the challenges experienced in treating the most common phantom sensation in otolaryngology, namely, tinnitus. Like tinnitus, BMS has an association with psychopathology and central and peripheral factors, as well as limited success with current medical therapies and a need for careful counseling of those affected.

### *Evidence for BMS as Variable Disorder with Subcategories*

One recent effort to investigate a central versus peripheral origin for BMS was a double-blind, randomized crossover trial comprising 20 patients with BMS. The patients underwent lidocaine and saline injection of the lingual nerve, and although the group overall showed no significant difference in response, central (n = 7) and peripheral (n = 13) subgroups were identified. In the peripheral group, there was a significant decrease in burning with lidocaine injection compared with saline, whereas the central group had a nonsignificant trend toward worse burning with lidocaine. In addition, the peripheral group had a trend toward improved response to clonazepam, and had significantly less evidence of concomitant psychiatric issues on a validated survey. The 2 groups identified in this small study should be considered in the design of future treatment trials.[40]

### *Contributions of Psychiatric and Hormonal Disturbances*

Several studies have investigated relationships between BMS and psychiatric disease.[6,41–49] Indeed, for several years BMS was felt by some to be primarily psychological in origin,[24] although studies were unable to demonstrate a link between its onset and a stressful life event.[46] Similar to other chronic pain patients, one group found an Axis I diagnosis in more than 50% of BMS patients, with depression predominating. Anxiety, when present, had an additional marked impact.[43] Another study assessed Axis II diagnoses in 70 BMS patients compared with a normal population and a group of patients with somatoform disorders. Whereas only 24% of the normal group had a personality disorder, 86% of the BMS patients and 88% of the somatoform patients had an Axis II disorder, although interestingly Cluster A predominated among BMS patients whereas somatoform patients had a higher incidence of Cluster B disorders.[42] Other potential psychogenic factors may include obsessive-compulsive disorder, depression, anxiety, and cancerophobia.[13] Psychopathology may also increase the likelihood of the patient's presentation and worsen the severity of the complaint, as is the case in chronic pain in general. So while considerable psychiatric comorbidity is present among BMS patients, this is felt to be usually a concurrent or secondary factor rather than its primary cause.

Menopause also has a definite but unclear relationship with BMS.[6,18,20,22] As mentioned earlier, up to 90% of patients with BMS are perimenopausal women.[5] Suggested explanations for this finding have included age-related changes, estrogen-related decreased perception of bitter tastes,[33] coexistence of depression and anxiety, and subtle mucosal changes. Pisanty and colleagues[50] relate the lack of evidence regarding the effects of estrogens on oral mucosa. Woda and colleagues[51] recently proposed that at menopause, the drastic decrease in gonadal steroids leads to altered production of neuroactive steroids, resulting in neurodegenerative changes of small nerve fibers of the oral mucosa and/or some brain areas involved in oral somatic sensations. These investigators posit that these neuropathic changes become irreversible and precipitate the burning pain, dysguesia, and xerostomia associated with BMS, which all involve small nerve fibers.

### *Distinguishing BMS from Secondary Oral Burning*

One difficulty in assessing the literature regarding BMS is that it is often unclear whether local and systemic underlying conditions have been adequately assessed and excluded. Danhauer and colleagues[52] examined patients with BMS and compared them with patients who had oral burning derived from other clinical abnormalities. These investigators concluded that although the 2 categories of patients may initially present with similar clinical and psychosocial features, they are distinguishable with careful diagnosis that often enables successful management of symptoms for each group. Failure to rule out secondary oral burning will result in inappropriate management strategies. Because of this, it is important to understand the potential causes of secondary oral burning and symptom presentation. In BMS, complaints of oral burning may decrease when eating or chewing; symptoms are typically bilateral in presentation and may be present at multiple oral sites. Secondary oral burning related to mucosal changes may be localized to areas of mucosal lesions, and is typically increased with eating, particularly spicy or acidic foods. Secondary oral burning associated with systemic conditions may be bilateral.

One classification divides etiology of secondary oral burning into factors related to the mouth (such as decreased salivary production), systemic factors, and psychological conditions.[12,49] Another article by Cerchiari and colleagues[13] goes into further detail and includes etiologic categories of local, systemic, psychogenic, and idiopathic. In cases identifying local or systemic factors, the definition of idiopathic BMS is not met. Local factors might include parafunctional behaviors such as tongue movements or habits causing mucosal irritation,[53] dental disease or galvanism, allergic reactions to dental materials, dentures, or other local factors,[54] stomatitis, and infectious conditions such as candidiasis. Possible systemic causes of secondary oral burning include salivary dysfunction, endocrine disturbances, nutritional disorders such as vitamin B complex, folate, iron, or zinc deficiencies, gastrointestinal disease including gastritis, reflux, or *Helicobacter pylori* infection, medication-related causes, other distinct cranial neuropathies, and possibly primary psychiatric disease.[13,31,55]

## PROGNOSIS

Limited studies have been done thus far to assess prognosis.[56] A retrospective review in 2006 including 48 women and 5 men with a mean age of 67.7 years (range 33–82 years) demonstrated a complete spontaneous remission in 3% of the patients within 5 years after the onset of BMS and moderate improvement in fewer than 30% of the subjects.[57] Other investigators have noted the tendency of BMS to persist for many years.[6]

## EVALUATION AND DIAGNOSIS

As mentioned earlier, the diagnosis of BMS is primarily one of exclusion. To that end, it is important to conduct a history and physical examination of a patient with the complaint of oral burning, with the goal of identifying any primary etiology. Laboratory studies should also be guided by this principle in a cost-effective manner. **Box 1** outlines components of a thorough evaluation for BMS.

## TREATMENT

The idea that BMS represents a form of chronic neuropathy is reflected in the most common approaches to clinical management. Recent reviews have examined evidence for various therapeutic interventions, including a 2004 Cochrane review[58]

**Box 1**
**Recommended evaluation for oral burning symptoms**

History

- Characteristics of the burning, including location, quality, severity, onset, duration, course over the day, aggravating/relieving factors: work, stress, foods, talking
- Associated symptoms: taste disturbances, oral dryness
- Medical history including ear disease, dental or oral disease, dentures, zoster, menopause, diabetes, thyroid disease, peripheral neuropathy, depression/anxiety
- Surgical history including oral, ear, and intracranial surgery
- Medications: angiotensin-converting enzyme inhibitors, antiretrovirals, tricyclic antidepressants, others (review side effect profiles)

Physical Examination Highlights

- General: age, gender, affect/mood
- Head: evidence of radiation or previous trauma or tumor
- Ears: examine for middle ear disease or evidence of surgery that might have damaged the chorda tympani
- Oral cavity: evaluate mucosa, dental health, salivary production, taste testing, tenderness to palpation, local anesthetic testing
- Neck: evaluate for goiter, lipodystrophy secondary to antiretrovirals, evidence of radiation
- Neurologic: peripheral neuropathy, complete neurologic examination

Laboratory Evaluation

- Full blood count
- Random blood glucose, Fasting blood glucose, hemoglobin A1c
- Alanine and aspartate transaminase
- Thyroid function (T3/T4)
- Serum iron, ferritin, total IgE, vitamin B6, B12, D
- Serum antinuclear antibodies, erythrocyte sedimentation rate
- Serum antibodies to *H pylori*
- Oral swab for *Candida*

and a more recent review by Buchanan and Zakrzewska.[56] Strategies that have thus far been investigated for treatment of BMS include clonazepam, α-lipoic acid, lafutidine, hormone replacement therapy, antidepressants, a variety of topical applications, anticonvulsants, medications for neuropathic pain, and psychiatric therapies. There are limited data on treatment approaches; although most represent small cohort studies, they do provide some guidance in treatment. **Box 2** summarizes current recommendations regarding management of BMS.

### *α-Lipoic Acid*

Three studies of α-lipoic acid (ALA) in BMS,[69–71] all by Femiano and colleagues, were included in the Cochrane review mentioned previously.[58] ALA is mitochondrial coenzyme with antioxidant effect that has been shown to be neuroprotective in previous studies of diabetic neuropathy.[64] The first study included 42 patients with BMS in

**Box 2**
**Current approach to management of BMS**

- Diagnosis: rule out local and systemic conditions that may cause oral burning; if present treat accordingly and assess outcome

  Treatment of hyposalivation or tongue/jaw habit if present[53]

- Medication trials

  First-line therapies

    Clonazepam[30,59,60]

    Paroxetine[61,62]

    Lafutidine if available (not currently approved by Food and Drug Administration [FDA])[55]

  Second-line therapies (poor evidence supporting)

    Sertraline[62]

    Amisulpride[62]

    Gabapentin[63]

  Not recommended: α-lipoic acid,[64–66] hormone replacement therapy[50]

- Counseling and possible referral for formal psychiatric intervention

  Cognitive behavioral therapy[67]

  Group psychotherapy[68]

an open placebo-controlled trial. Forty-two percent of patients in the ALA arm initially had "decided improvement" versus 0% of placebo, and overall 76% reported "any improvement" versus 14% of placebo. After the placebo arm was crossed over, 52% of those patients had "decided improvement" and 63% reported "any improvement."[70] The second study of ALA was done in a double-blind, randomized controlled fashion in 2002 and featured 60 patients split into 2 arms. After 2 months, there was "any improvement" in 97% of the ALA arm versus 40% of placebo, and "decided improvement or resolution" in 87% of the ALA arm versus 0% of placebo ($P<.0001$).[71] The third study compared ALA with bethanecol, Biotene, and placebo, using 4 groups of 20 patients with BMS. The study found ALA of remarkable benefit with minimal adverse effects as compared with the other arms. Further multi-institutional double-blind, randomized controlled trials were recommended.[69] It is unclear whether any of the patient data are duplicated in these 3 studies by the same authors published within a similar timeframe.[56]

Recently, 3 randomized, double-blinded, placebo-controlled studies of ALA for BMS have been published, all by investigators and institutions unrelated to the aforementioned studies and each other. The first recent study features 66 patients enrolled in a 3-arm trial (ALA, ALA with multivitamin, and placebo) with treatment of ALA, 400 mg twice daily for 2 months in both ALA groups.[65] Fifty-two patients completed the trial and responders were those who had at least a 50% decrease in pain scores measured by the Visual Analog Scale (VAS) at 2 and 4 months. The study showed a significant response to intervention in all 3 groups (including placebo), with about 30% of each group responding. A second recent study by Lopez-Jornet and colleagues[66] included 60 patients split into 2 groups (ALA 800 mg daily and placebo) with responses also measured on the VAS. Again, no significant difference was found

with ALA versus placebo. A third trial completed by 31 patients also failed to demonstrate the effectiveness of ALA over placebo.[72] These 3 well-designed trials cast serious doubt on the efficacy of ALA in the treatment of BMS.

### *Antidepressants*

Several studies have examined the use of antidepressant medications in BMS, although in a limited fashion. A single double-blind, randomized controlled trial of trazodone versus placebo has been reported.[73] This study, which was done in Finland in 1999, included 37 women and failed to show any effect over the 8-week trial period; the trazodone group showed significantly worse symptoms of drowsiness and dizziness versus placebo. An open-label, single-arm, dose-escalation pilot study of the effect of paroxetine (Paxil) in treatment of BMS reported 80% of patients with pain reduction after 12 weeks of paroxetine treatment, with only minor transient side effects. These results suggest that paroxetine may be useful in the treatment of patients with BMS.[61]

A third trial in 2002 compared 2 selective serotonin reuptake inhibitors, paroxetine and sertraline (Zoloft), and amisulpride, an atypical antipsychotic.[62] The study was single-blinded without a placebo arm. Overall, 76 patients without concurrent major depression were enrolled in the 8-week trial and assigned to sertraline 50 mg daily, paroxetine 20 mg daily, or amisulpride 50 mg daily. Results were assessed using a VAS as well as the Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety. Overall, 69.6% to 72.2% of patients responded, with mean VAS pain scores decreasing in all 3 arms from an initial range of 7.2 to 7.0 to a final range of 3.3 to 2.8 at week 8 ($P<.001$). Although no adverse events were noted in any arm of the trial,[62] paroxetine may cause congenital malformations when given in the first trimester,[74] and patients who do have concurrent major depressive disorder should be managed in coordination with a physician with appropriate experience in psychiatry.[56] Again, the study was limited by lack of a placebo arm.

### *Clonazepam and Chlordiazepoxide*

Inspired by earlier promising successful open-label studies of topical[59] and systemic[30] clonazepam (Klonopin) for BMS, a multicenter, double-blinded, randomized controlled trial of topical clonazepam versus placebo was conducted with 84 patients (40 women and 44 men) in France and published in 2004.[60] The prior studies assessed low-dose systemic clonazepam without topical contact and reported improvement in oral burning in the majority of patients. Patients in the study were instructed to suck a tablet (either 1 mg clonazepam or placebo) for 3 minutes and swishing the dissolved medicine around the painful oral sites without swallowing before expectorating the medicine. The therapy was given 3 times daily for a total of 2 weeks. Pain was rated on a standard zero to 10 numerical scale before and after the intervention. Pain scores decreased $2.4 \pm 0.6$ in the clonazepam group versus $0.6 \pm 0.4$ in the placebo group ($P = .014$). There was no significant difference in adverse events between placebo and control. Despite the finding in the same study that the swish and spit technique resulted in significantly lower blood levels of clonazepam versus swallowing a 1-mg tablet, Buchanan and Zakrzewska[56] remind physicians of the addictive potential of benzodiazepines.

One other study of lower quality that remains interesting is a large nonrandomized nonplacebo controlled trial of multiple medications in 130 BMS patients in 1991 that included 78 patients who were placed on chlordiazepoxide (Librium), a benzodiazepine relative.[11] Of these, 14% had complete resolution, 35% had marked benefit, 15% had slight benefit, and 36% showed no change. The study design, however,

was poor. By contrast, the cohort studies of clonazepam show more positive outcomes.[30,60] Of note, although both drugs bind to benzodiazepine receptors and enhance the action of γ-aminobutyric acid, clonazepam is used in the treatment of neuralgias and neuropathies, whereas chlordiazepoxide is not.[75,76] Given the likely neuropathic nature of BMS, the greater efficacy of clonazepam is perhaps unsurprising.

### *Gabapentin*

Gabapentin (Neurontin) has been of interest in BMS on account of the putative neuropathic nature of the illness (or some subset thereof), but evidence in the literature in support of its use is discouraging. A trial of gabapentin[34] cited by Grushka and colleagues[77] in one review article was unavailable through PubMed and the journal's Web site. Another article in support is a single case report.[78] More importantly, the only multipatient trial currently available is an open dose-escalation study, in which 15 patients took gabapentin at doses from 300 up to 2400 mg per day over a course of 3 weeks. No significant improvement in pain, mood scales, or Beck Depression Inventory scores was seen after the 3-week period. These data indicate that gabapentin should not be used for trials except after the failure of other medications. A larger randomized trial of this medication may confirm its lack of efficacy for BMS.[63]

### *Hormone Replacement Therapy*

The most recent Cochrane review of BMS[58] reports one trial of hormone replacement therapy. Pisanty and colleagues[50] conducted a blinded trial of estrone cream versus estrone and progesterone cream versus placebo in 1975. The 3 arms of the trial had 6, 9, and 7 patients, respectively. The results of the trial showed minimal effect, with no more than 25% of patients in any arm reporting improvement in the burning sensation. Many aspects of the trial were unclear, including criteria for diagnosis, baseline characteristics of the 3 groups, and whether randomization was performed. Buchanan and Zakrzewska[56] identified 3 other similarly poor-quality studies with unclear implications.

### *Lafutidine*

Lafutidine is a unique histamine H2-receptor antagonist (H2RA) that has a sensitizing effect on capsaicin-sensitive afferent neurons. Because of this it was felt to have potential for treatment of BMS, and in a randomized controlled trial 34 BMS patients switched blindly to lafutidine from their previous H2-blocker and 30 BMS controls remained on their original H2-blocker. Both groups also did azulene sulfonate rinses. Symptoms were scored using a VAS at 4, 8, and 12 weeks. The improvement rate was consistently higher in the lafutidine group than in the control group; the differences between the groups were significant ($P<.05$).[55] Lafutidine is not currently approved by the FDA and is not available in the United States at present.[79]

### *Other Medical Treatments*

Other treatments studied in the literature with minimal findings have included topical anesthetics, topical anti-inflammatory medications, capsaicin, sucralfate (Carafate), and St John's wort, among others. Oral habit appliances have been mentioned for use in patients with evidence of active tongue habits and lingual fasciculations; however, no clinical data are available. The topical anesthetic dyclonine hydrochloride was studied by Formaker and colleagues[33] in an open noncontrolled study of 33 patients. Of those, 12 had increased burning, 14 had no change, and 7 had improvement. A single trial in 1999 of benzydamine hydrochloride, a topical anti-inflammatory,

failed to show an effect.[80] Therefore, limited study to date does not support the use of locally applied anesthetic or analgesic agents for idiopathic BMS.

Two articles discuss the use of capsaicin in BMS,[81,82] but the results are unclear, as one article in Italian does not give any information about patient response to capsaicin in the English abstract,[82] while the other includes only 2 patients classified as BMS among many with neuropathic oral pain. Of those two patients who used the topical capsaicin 0.025% cream, one had symptom resolution and the other discontinued the study with minimal improvement.[81] A single small nonplacebo controlled study in 1997 of sucralfate found very mixed results in 14 patients with BMS, with improvement in 6 patients and worsening of symptoms in 4.[83] Another recent study investigated possible therapy for BMS with *Hypericum perforatum* (St John's wort) in a placebo-controlled, double-blind, randomized controlled trial comprising 39 patients.[84] Unfortunately, the study failed to show any significant reduction in pain with this treatment.

Although amitriptyline (Elavil) and nortripyline (Pamelor) have been cited as therapeutic options for BMS in the same review,[77] there does not appear to be any reason to support this beyond anecdotal evidence. Despite this, it seems to be a not unreasonable third-line medication to try with otherwise unresponsive patients, given the apparent neuropathic nature of the disease. The nonrandomized noncontrolled trial by Gorsky and colleagues[11] of BMS therapies mentioned earlier also included patients who were trialed on antifungal agents, amitriptyline, prednisone, pilocarpine, vitamin B complex, and diazepam. Aside from diazepam, on which 4 of 6 patients noted considerable improvement, the results of the other groups were uniformly poor.

### *Cognitive Behavioral Therapy and Group Psychotherapy*

Although there are various case reports in the literature,[85,86] only one randomized controlled trial has investigated cognitive behavioral therapy (CBT) for BMS. This trial from Umea University in Sweden included 30 patients split into 2 equal groups. The first group received CBT in the form of 12 to 15 sessions for 1 hour per week and the second attention and placebo group (APG) received a similar number of sessions, but without the CBT techniques. Pain was measured with a VAS (scale of 1–7). Pretreatment scores were similar between the 2 groups (CBT = 5.0, APG = 4.3). After treatment the CBT group showed an average score decrease of 3.6 versus an increase of 0.4 for the APG ($P<.001$). Weaknesses of the study included minimal information provided about other characteristics of the 2 groups and the lack of a validated pain scale.[67]

A recent study by Miziara and colleagues[68] investigated group psychotherapy as an additional modality for treatment of BMS. Of 44 diagnosed patients, 24 underwent group psychotherapy while 20 had placebo therapy. Improvement occurred among 71% of patients in the treatment group versus 40% in the placebo group ($P = .04$).

### *New Directions*

Several recent case reports and studies have emerged concerning possible novel therapies for BMS. A 2007 article describes a single patient with BMS who had adverse reactions to initial therapy with carbamazepine (Tegretol) and gabapentin, but resolved completely with topiramate (Topamax).[87] A noncontrolled trial was recently reported using levosulpiride, 100 mg daily for 8 weeks, in 44 patients.[88] Of the 39 patients who completed the study, 28 showed some improvement, although none had complete resolution. Those with improvement tended to be patients with a shorter history of symptoms. The study is limited by its lack of a control arm. A third report in 2008 describes a patient with severe BMS who failed multiple initial attempts

at therapy but who responded to pramipexol (Mirapex).[89] This case seems unusual, however, because the patient had relief of symptoms with tongue motion. Similarity to documented modulation of tinnitus with head and neck motions is curious,[90–92] and may represent a subcategory of BMS patients able to modulate the burning sensation. These reports, though intriguing, will require further investigation before they could be recommended as possible alternative therapies.

## SUMMARY

Patients who present for evaluation of oral burning symptoms require a thorough evaluation to distinguish between secondary oral burning and primary BMS. Ensuring that other confounding conditions have been addressed prior to diagnosis of BMS is key to preventing improper attempts at treatment. While the exact etiology of BMS remains unclear, it seems most likely a neuropathy, with variable central and peripheral contributions among individuals. It is hoped that future efforts for BMS will include larger randomized therapeutic trials of both medical and psychiatric therapies as well as continued research into its exact origin.

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