INTRODUCTION

Many different terms have been used to describe a condition whereby the tongue or other intraoral areas develop “burning” type pain. If this affects the tongue it may be termed glossodynia, glossopyrosis or, less frequently, glossalgia. If it is more widespread, burning mouth syndrome (BMS), primary burning mouth, stomatodynia, and oropyrosis have been used. Although there is some controversy as to whether glossopyrosis can be differentiated from oropyrosis,1 current literature suggests that these oral complaints can be viewed as similar entities that may encompass only the tongue, lips, gingiva, palate, buccal mucosa, or a combination of these mucosal regions. Inherent in the diagnosis is an understanding that there are several systemic and local conditions that can lead to a sensation of burning pain in the mouth. If one of these conditions is responsible for causing the pain, after successful treatment of the underlying condition the burning pain will resolve.

This article focuses on descriptions, etiologic theories, and management of primary BMS, a condition for which underlying causative agents have been ruled out.

DEFINITION

BMS is a chronic disorder for which there are no standardized validated diagnostic criteria. Various approaches to developing a consistent definition have been attempted by several organizations. The American Academy of Orofacial Pain2 uses that of Sardella and colleagues,3 in which the condition is described as a burning sensation in the oral mucosa occurring in the absence of clinically apparent mucosal abnormalities or laboratory findings, often perceived as painful; intrinsic to this definition is that the clinician has not observed any clinical abnormality in the oral cavity and that laboratory testing has ruled out systemic involvement.

The International Headache Society (ICHD-II)4 describes Burning Mouth within Central Causes of Pain as an intraoral burning sensation for which no medical or dental cause can be found, and with the following diagnostic criteria: (1) pain in the mouth present daily and persisting for most of the day; (2) oral mucosa is of normal appearance; and (3) local and systemic diseases have been excluded, with an additional comment specifying that pain may be confined to the tongue (glossodynia). This condition has also been described by terms that
include stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral dysesthesia.\textsuperscript{5–7}

**CLINICAL CHARACTERISTICS**

BMS is characterized by a burning sensation or other dysesthesia, with normal appearance of the oral mucosa. Multiple sites in the oral cavity may be affected, with the tongue being the most common; however, other areas of the intraoral mucosa may also be involved. BMS pain is usually bilateral and does not follow peripheral nerve distributions.

The pain associated with the condition has been described as continuous, with an intensity that is moderate to severe. Its daily pattern may fluctuate, often being better in the morning and more aggravating toward the evening; it rarely affects sleep. Associated symptoms may include alterations of taste (dysgeusia, hypogeusia) and smell, dry mouth (xerostomia) despite normal salivation, altered salivary composition,\textsuperscript{8,9} and paresthesia. Mild food and noncarbonated beverages may improve the burning symptoms, but extremes of spice or temperature may worsen it.\textsuperscript{10}

The diagnosis of primary BMS is purely clinical, and is based on patients’ description of symptoms as well as on the exclusion of any systemic or local factors that may give rise to secondary burning sensations within the oral mucosa (and consequently a different diagnosis). These factors include endocrinopathies such as hypothyroidism,\textsuperscript{11,12} diabetes,\textsuperscript{13} oral candidiasis,\textsuperscript{14} decreased salivation, secondary effects of drugs, and nutritional deficiencies.\textsuperscript{15,16} Secondary BMS symptoms disappear with treatment of the underlying cause.

**EPIDEMIOLOGY**

Several investigators have described BMS based on person, place, and time. The data from which clinical information has been obtained are limited to cross-sectional studies and convenience samples with heterogeneous composition, owing to the need for consensus on the diagnostic criteria. Population-based information is based on national surveys. Although symptom improvement has been reported over time,\textsuperscript{17} there are no longitudinal data on the natural history or onset of the condition.

The prevalence of BMS symptoms in adults has been estimated at from 0.7% to 7.9%.\textsuperscript{18,19} Symptoms worsen with an increase in age, have a female gender preference, and have been associated with menopause.\textsuperscript{20–23} Some investigators have reported a prevalence as high as 40% on convenience samples.\textsuperscript{24}

**CLASSIFICATION**

A conventional and practical classification presented in the literature on burning mouth divides this condition into primary and secondary. As presented in Table 1, secondary BMS is associated with a preexisting condition or cause, and once such a condition is treated the symptoms improve or disappear.

**ETIOLOGY**

The etiology and pathophysiology of primary BMS have remained largely unknown. Data from several experimental models support the hypothesis that primary BMS is a neuropathic condition.\textsuperscript{23} The role of the peripheral and/or central nervous system(s) is supported by studies involving quantitative sensory testing and functional imaging methods.\textsuperscript{23} Table 2 illustrates the sensory neuropathic changes that have been associated with BMS.

Secondary burning mouth, unfortunately, has been associated with several local and systemic conditions (see Table 1). The clinical concern is that ruling out each of these possible related conditions to allow diagnosis of primary burning mouth is costly and time consuming. The role of the various causative factors is unknown, so it is difficult to develop a reasonable and solid scientifically supported protocol. In several studies, complete blood counts were done on all patients complaining of BMS; there is no indication, however, that abnormalities in complete blood count are associated with a burning sensation in the mouth. In patients with low but normal nutritional findings, there is no indication that additional supplementation of the nutritional substances will be absorbed, nor is there information regarding “how much is enough” for patients. A thorough clinical examination demonstrating normal appearance of mucosal tissues along with a careful review of systems may be indicated for clinically ruling out the various risk indicators associated with secondary burning mouth. Though not tested to date, it would be very illustrative to determine the rate of abnormal findings on laboratory testing in the presence of a normal examination and negative review of systems.

**PSYCHOLOGICAL FACTORS**

It has been postulated that patients with BMS may have distinct psychological characteristics. Conditions such as depression, anxiety, and somatization\textsuperscript{8,25} have been described in this population. In
addition, BMS patients are subjected to elevated psychological stress that is not necessarily associated with stressful life events. Intensity of burning sensation, however, is apparently not influenced by severity of psychological symptoms.\textsuperscript{26,27} It has not been well documented whether the rate of occurrence of these psychological conditions is unique to BMS or consistent with other chronic pain conditions. In addition, these psychological conditions could be comorbidities, modifiers of the burning mouth condition, or a behavioral consequence of having BMS. Although the role of occurrence of these psychological conditions is unique to BMS or consistent with other chronic pain conditions. In addition, these psychological conditions could be comorbidities, modifiers of the burning mouth condition, or a behavioral consequence of having BMS. Although the role

<table>
<thead>
<tr>
<th>Theoretical Model</th>
<th>Description</th>
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<tr>
<td>Dysfunction of the chorda tympani</td>
<td>Abnormal interplay between lingual and chorda tympani nerves</td>
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<tr>
<td>Small afferent fiber atrophy</td>
<td>Small fiber neurologic damage in the oral cavity</td>
</tr>
<tr>
<td>Upregulated TRPV1 receptor (Transient Receptor Potential Vanilloid type 1)</td>
<td>Increased number of heat and capsaicin receptors in nerve fibers, leading to release of sensory neuropeptides, promoting neurogenic inflammation</td>
</tr>
<tr>
<td>Central nervous system pain pathway and dopamine receptor</td>
<td>Altered central modulation. Decreased dopaminergic function. Decreased endogenous dopamine levels</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>BMS associated with lichen planus due to elevated expression of CD14 mRNA and decreased levels of TLR-2 mRNA in saliva</td>
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of psychiatric disorders in the pathophysiology of BMS is still unknown, these disorders must be actively elucidated because of their impact on quality of life.\(^28\) Screening for psychiatric disorders may be relevant, because of its impact on treatment outcomes.\(^29\) Appropriate management includes referral to health professionals who can assist these patients with their mental health status to provide a better quality of life.\(^30,31\)

**MANAGEMENT OF BURNING MOUTH**

Several systematic reviews that address the management of BMS have been published.\(^7,32,33\) These reviews have highlighted the lack of randomized clinical trials that are available, as well as the limitations of many treatments when compared with placebo. Table 3 lists randomized controlled trials of various oral and systemic therapies along with the side effects of treatment. With treatment regimens that range from topical, over-the-counter products to systemic medications with potentially significant side effects, the clinician is faced with treatment dilemmas that may not be easily answered even with the help of systematic reviews. This section considers a stepped treatment protocol, which highlights potential side effects and benefits of several published therapies.

When assessing treatment success, the calculation of number needed to treat (NNT) has been used to quantify relative success. The NNT, though originally designed to demonstrate reduction of adverse outcome based on providing an intervention,\(^34\) has been used in determining the success of treatments for neuropathic pain.\(^35\) In this calculation, the “success” of a treatment for pain needs to be defined, and previous reports have used more than 50% pain relief as a reasonable clinically relevant outcome.\(^35,36\) This value, unfortunately, has not generally been reported in publications assessing treatments for BMS. Instead, statistically significant changes in pain in comparison with placebo have been used. Using a percent absolute risk reduction, calculated from subtracting the percent event rate with a drug from the percent event rate with the placebo, allowed Patton and colleagues\(^37\) to calculate some values of NNT for treatments for BMS. Wherever available, the NNT for a treatment for burning mouth is reported in this section.

**Nonprescription Treatments**

\(\alpha\)-Lipoic acid has been used for diabetic neuropathy for many years, with support for its use in multiple studies including a meta-analysis comprising more than 1250 patients.\(^38\) Because of its use with diabetic neuropathy, a protocol was developed and tested for BMS. A double-blind, randomized controlled trial using 200 mg of \(\alpha\)-lipoic acid 3 times a day yielded significant improvement over placebo, with an NNT of 3.3.\(^39\) Because of this and other supportive articles, Patton and colleagues classified \(\alpha\)-lipoic acid as a “Class I” treatment whereby the benefit far outweighs the risk of use, with recommendation for administration of the treatment.\(^37\) Subsequent to their review, additional studies have not yielded a statistical difference over placebo.\(^40–42\) What should be appreciated in these studies, however, is the high rate of success of placebo and the large variations in pain response for both placebo and active trial groups. In general, all 3 of these studies yielded a decrease of 2 points on an 11-point visual analog scale (VAS), which in one of the studies yielded a 50% pain reduction in 30% of the patients.\(^40\) In this study, however, Carbone and colleagues reported a greater than 50% pain reduction with 25% of patients on placebo, and similar or superior reductions in VAS occurred in the placebo groups in the other 2 studies. From a treatment standpoint, \(\alpha\)-lipoic acid supplementation may help a limited number of patients, but not at a higher rate than placebo. As the risk is limited in otherwise healthy individuals and the cost of treatment is consistent with other nutritional supplements, a 2-month regimen could be considered in patients who otherwise would be considered for higher-cost or higher-risk treatment regimens.

Capsaicin, administered both topically and systemically, has been used for the treatment of BMS and other neuropathic conditions. Systemically administered capsaicin has showed success compared with placebo\(^43\) in treating BMS, but carries a high risk of gastric pain (32% of subjects in the active treatment arm). Until recently, the lack of randomized controlled trials limited the ability to compare topical capsaicin results with those for placebo. Topical capsaicin had reported success in case trials,\(^34,45\) and recent randomized controlled trials now indicate that it decreases pain rating when compared with placebo.\(^46,47\) Adverse effects of capsaicin include an increase in burning sensation, which can lead to noncompliance. For treatment of post-herpetic neuralgia pain on dermal sites, pretreatment of the area with topical anesthetic was able to increase compliance in patients using a high-dose capsaicin patch.\(^48\) In addition, animal research combining local anesthesia and capsaicin indicates that this may allow a more selective targeting of pain receptors in the trigeminal system.\(^49\) Further research in these areas may provide
<table>
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<tr>
<th>Treatment</th>
<th>Warnings/Side Effects</th>
<th>Rate of Success</th>
<th>Reference</th>
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<tbody>
<tr>
<td>α-Lipoic acid</td>
<td>Hypoglycemic reactions; gastric upset</td>
<td>&gt;50% pain reduction: 10/34 patients (no difference from placebo)</td>
<td>Carbone et al, 40 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean reduction of 2 points on 0–10 VAS (no difference from placebo)</td>
<td>López-Jornet et al, 31 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean reduction of 20 points on 0–100 VAS (no difference from placebo)</td>
<td>Cavalcanti et al, 42 2009</td>
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<td></td>
<td></td>
<td>“decided improvement or resolution” 26/30 patients (significant difference from placebo)</td>
<td>Femiano et al, 39 2002</td>
</tr>
<tr>
<td>Capsaicin (topical)</td>
<td>Increased burning</td>
<td>Statistically significant mean reduction of 2 points on a 0–10 VAS with active treatment (no statistical difference seen with placebo)</td>
<td>Silvestre et al, 47 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean reduction of 3 points on 0–10 VAS (significant difference from placebo)</td>
<td>Marino et al, 46 2010</td>
</tr>
<tr>
<td>Capsaicin (systemic)</td>
<td>Gastric pain (32% in treatment arm)</td>
<td>VAS reported as significantly lower in the treated group compared with placebo. Unable to determine mean change</td>
<td>Petruzzi et al, 43 2004</td>
</tr>
<tr>
<td>Clonazepam (systemic 0.5 mg/d)</td>
<td>Dizziness, drowsiness, emotional liability</td>
<td>VAS reported as significantly lower than baseline in active group (mean reduction 3 points on a 0–10 VAS), but placebo group also had significant reduction (1.5 points on VAS). No statistical comparison between active and placebo treatment</td>
<td>Heckmann et al, 54 2012</td>
</tr>
<tr>
<td>Clonazepam (topical, 1 mg TID dissolve and expectorate)</td>
<td></td>
<td>Significant difference from placebo with mean reduction of 2 points on 0–10 scale VAS over 2 wk with active treatment. Mean reduction in VAS with placebo 0.6</td>
<td>Gremeau-Richard et al, 52 2004</td>
</tr>
<tr>
<td>Gabapentin (systemic)</td>
<td>Dizziness, drowsiness</td>
<td>Odds ratio for possibility of improvement or resolution: 7 times higher for α-lipoic acid 5.7 times higher for gabapentin 13.2 times higher for combination α-lipoic acid and gabapentin</td>
<td>López-D’Alessandro et al, 57 2011</td>
</tr>
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*Abbreviation: VAS, visual analog scale.*
evidence for the clinical practice of mixing capsaicin with benzocaine for oral delivery in BMS and oral neuropathic pain. With relatively low cost and low risk in the topical formulation, capsaicin has demonstrated some success in 2 clinical trials, and should be considered for patients with BMS. Although no published studies have examined the use of capsaicin with topical anesthetic, this clinical practice could help with compliance and is starting to receive support for use with other types of neuropathic pain in other body sites.

Investigators have evaluated the use of St John’s wort (*Hypericum perforatum*), but there is no evidence to support the use of this herbal compound as a treatment modality for BMS.50

**Prescription Treatments**

Clonazepam, a benzodiazepine used for seizure control and panic disorder, has undergone off-label use for BMS for many years. It has been used systemically,51 topically (dissolve and expectorate),52 and in combination.53 Reported success rates in non–placebo-controlled regimens, using as the benchmark improvement of pain of greater than 50%, are as high as 80%.53 In an earlier study, 70% of patients reported at least “some” reduction in pain; however, 27% of these patients elected to stop use of clonazepam for reasons that included its side effects.51 A recent randomized controlled trial of systemic clonazepam demonstrated a significant reduction in pain with the active drug; however, there was also a significant reduction in pain with placebo.54 Concerns with clonazepam include dizziness and drowsiness55 (of particular concern in an elderly population), as well as potential withdrawal effects. Though a recognized treatment in management of BMS, the lack of randomized controlled trials with clonazepam demonstrating a benefit beyond placebo and the risks associated with systemic use may warrant reserving this treatment for those who do not respond to other therapies.55

Gabapentin, also used for seizure control and post-herpetic neuralgia, is used extensively in neuropathic pain. An early case report indicated its potential for success in BMS,56 but a subsequent open-label trial did not demonstrate pain reduction over the course of the up to 6-week study.57 A more recent randomized controlled trial that tested α-lipoic acid, gabapentin, and the combination of the two demonstrated an improvement in burning in 55% of those using α-lipoic acid alone, 50% improvement in those using gabapentin alone, and 70% improvement in those using a combination of α-lipoic acid and gabapentin.58 Gabapentin as a single-use drug does not appear to have a high rate of success in BMS, but it may be helpful in combination with other treatments.

Tricyclic antidepressants (TCA) and serotonin-norepinephrine reuptake inhibitors (SNRI) have demonstrated pain relief in neuropathic pain.59 Using diabetic neuropathic pain, amitriptyline yielded an NNT of 3 for at least 50% reduction of pain.60 Placebo-controlled studies in BMS for these drugs, however, are lacking. In patients with BMS, a retrospective analysis demonstrated some success with TCAs in burning mouth,51

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**Fig. 1.** Algorithm for the treatment of burning mouth syndrome (BMS). ROS, review of systems.
and a case report documented success with an SNRI. Concerns with the use of these medications include dry mouth for amitriptyline (possibly compounding the oral complaints), significant cardiac rhythm issues, and sedation. The combination of potential side effects in an older population along with limited indications of their effectiveness limits the recommendation for use in BMS at this time.

**Biobehavioral Therapy**

Cognitive behavioral therapy (which focuses on how beliefs and thoughts can influence behavior), used alone or in combination with other therapies for BMS, has shown success in reducing its intensity. Based on the evidence at the time, this therapy was recommended by Patton and colleagues as a treatment that should be performed. A randomized controlled trial of group psychotherapy versus a placebo tablet resulted in a higher percentage of improvement in the patients receiving group therapy (70.8% improved) as opposed to those receiving placebo medication (40% improved). With indications that biobehavioral therapy may increase the success achieved by other treatments or demonstrate improvement as a stand-alone therapy, it should be considered for use, especially in individuals whose medical conditions increase the risks associated with alternative therapies.

**SUMMARY**

Many of the current etiologic theories of primary BMS focus on neuropathology. Unfortunately, not all treatment modalities that seem helpful in other neuropathic conditions appear to be successful in BMS. These patients are often a challenge to manage, especially in a standard clinical surgery practice. Patients often do not report complete symptom resolution frustrating even the best-intentioned clinician.

Given the controversial nature of the disorder, a stepped treatment protocol initially using low-risk treatments followed by combination protocols appears to have the most support in the literature. Because of the relatively low prevalence of primary BMS, research should focus on developing multicenter trials that follow standard diagnostic protocols and use randomized controlled trials, to develop treatment protocols for clinical use. In the interim, the clinician may provide some relief from this difficult-to-manage condition using the best available information.

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*Chlorhexidine rinse, with or without alcohol, has not been published as a treatment. Anecdotally, this has provided relief for some patients and has allowed avoidance of higher-risk and higher-cost therapies.

**Fig. 2.** Treatment protocol for burning mouth syndrome. BID, twice a day; QD, once a day; QID, 4 times a day; Rx, treatment; TID, 3 times a day.
REFERENCES


Crow & Gonzalez