

Burning mouth syndrome: a review of etiology, diagnosis, and management

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Burning mouth syndrome (BMS) is a chronic condition characterized by a burning sensation of the oral cavity and is often associated with taste disturbances and xerostomia. It primarily affects menopausal or postmenopausal women. Idiopathic or primary BMS can occur spontaneously and without any identifiable precipitating factors. When BMS is associated with systemic factors, it is defined as secondary BMS. While the exact etiology of BMS is still unknown, the condition appears to be multifactorial, and numerous local, systemic, and psychological factors have been associated with it. Primary BMS is a diagnosis of exclusion and can only be reached after all potential causes of secondary burning pain have been eliminated. Management strategies include reassurance of the patient as well as pharmacologic agents such as clonazepam, supplements such as α -lipoic acid, and psychological therapy.

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Burning mouth syndrome (BMS) is a chronic, orofacial pain condition described as a constant, painful, and burning sensation of the oral mucosa that occurs in the absence of obvious organic pathosis. Therefore, BMS is a diagnosis of exclusion, and local and systemic factors must be ruled out. According to the International Headache Society, BMS is defined as “an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions.”¹ Other terms previously used for BMS are *glossodynia*, *glossopyrosis*, *oral dysesthesia*, and *stomatodynia*.

This review will describe the epidemiology, clinical features, etiology, diagnosis, pathophysiology, and management of primary and secondary BMS.

Epidemiology

The true prevalence and incidence of BMS have not been determined, and studies report wide variation.² A Swedish study assessing the prevalence of BMS found that 4% of 1279 participants reported having BMS.³ In a retrospective study, 149 patients from Minnesota were diagnosed with BMS over a 10-year period, and the overall prevalence of BMS in Olmsted County was 0.10%.⁴ The reported prevalence of BMS varies because of loose diagnostic criteria and differing characteristics of populations sampled. Well-controlled studies have shown the prevalence to range from 1% to 3.7%, which is probably the most reliable estimate.^{5,6}

BMS predominantly affects menopausal or postmenopausal women, usually aged between 50 and 70 years, and is seldom diagnosed in patients younger than 30 years.^{4,5} Prevalence increases significantly with age, and rates of 12% and 18% have been reported in postmenopausal women.^{5,7}

Clinical features

Oral burning pain, dysgeusia, and xerostomia are the 3 cardinal symptoms characterizing BMS.⁸ Patients may further report feeling a scalding sensation over affected sites. This symptom is usually localized to the anterior two-thirds of the tongue but can also affect the lips, palate, gingiva, buccal mucosa, and oropharynx.^{9,10} The sensation can also be described as *numbness*, *tingling*, *prickling*, or simply *uncomfortable*. These symptoms typically present bilaterally.

The intensity of the pain ranges from mild to severe, and it may vary during the day. In general, patients experience mild or no pain on awakening. As the day progresses, the pain gradually increases in intensity. By the evening, most patients report severe pain. However, the pain does not usually interfere with sleep. There is a subset of patients who experience unceasing symptoms throughout the day, while another subset has daily but only intermittent symptoms.¹⁰ As a result, BMS has been classified into 3 types (Table).¹¹⁻¹³

Table. Types of burning mouth syndrome (BMS).¹¹⁻¹³

Attribute	Type 1	Type 2	Type 3
Prevalence among patients with BMS	35%	55%	10%
Clinical characteristics	<ul style="list-style-type: none"> • Persistent pain throughout day • Pain typically absent in the morning and worse in the evenings 	<ul style="list-style-type: none"> • Daily pain • Lasts all day 	<ul style="list-style-type: none"> • Intermittent pain • Affects sites not usually affected by BMS (ie, floor of mouth, throat, buccal mucosa)
Associated conditions and characteristics	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Anxiety or other psychological comorbidities • Most resistant of the 3 BMS types to treatment 	<ul style="list-style-type: none"> • Certain food allergies

BMS occurs spontaneously and without any specific precipitating factor in more than 50% of patients.¹⁴ Nearly one-third of patients report their burning pain is related to a dental procedure, medical illness, or medication use.⁷ A cause-and-effect relationship between these incidents, however, has not been identified. Examination findings in patients with BMS show no evidence of oral lesions or other oral mucosal abnormalities.^{2,7,8,15}

Dysgeusia and xerostomia are concomitant symptoms that are often reported. Dysgeusia—a distortion in the perception of taste, a persistent metallic or bitter taste, or both—is reported in 11%-69% of patients.^{5,15} Other symptoms can include chemosensory anomalies, mood changes, or disturbances in personality traits.¹⁶

The prevalence of xerostomia ranges from 39% to 66% in patients with BMS.^{5,15,16} Interestingly, patients who complain of xerostomia do not usually exhibit objective findings of it. Lee and colleagues found that patients with BMS had a decreased unstimulated salivary flow rate compared with control participants.¹⁷ However, no differences were observed in stimulated salivary flow rate between the BMS and control groups. Furthermore, salivary scintigraphy revealed no differences in salivary gland function between BMS patients with hyposalivation and BMS patients without hyposalivation.¹⁷

Etiology and diagnosis

The International Headache Society lists the following diagnostic criteria for BMS¹:

- A. Oral pain fulfilling criteria B and C
- B. Recurring daily for > 2 hours per day for > 3 months
- C. Pain has both of the following characteristics:
 1. burning quality
 2. felt superficially in the oral mucosa
- D. Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
- E. Not better accounted for by another ICHD-3 [International Classification of Headache Disorders, 3rd edition] diagnosis.

The exact etiology of BMS remains unknown and appears to be multifactorial. Nonetheless, various local, systemic, and

psychological factors have been associated with it (Box).¹⁸⁻²⁰ When BMS is associated with any of these factors, it is defined as secondary BMS. If no causative factor is identified, it is defined as primary (or idiopathic) BMS. In the presence of causative systemic factors, the diagnosis of primary BMS may only be rendered if the symptoms persist after the management of the underlying systemic condition.¹⁹ Similarly, if a local causative factor is present, a diagnosis of primary BMS is only rendered when symptoms persist after removal of that local factor.¹⁹ Consequently, primary BMS is a diagnosis of exclusion and can only be reached after all potential causes of secondary burning pain have been eliminated.²⁰

Secondary BMS has multiple causes. The most common oral disease that can present with burning pain in the mouth is oral candidiasis. A fungal culture may be taken to confirm the diagnosis, and a trial of antifungal medication can also be helpful. In addition, oral mucosal diseases such as erosive lichen planus, recurrent aphthous stomatitis, or other vesiculobullous diseases may present with burning symptoms in the mouth. However, these disorders usually present with characteristic lesions affecting the mucosa.

Systemic conditions can also cause secondary BMS. To identify these potential factors, clinicians should perform a thorough review of the patient's medical history and medications as well as a detailed review of systems. Systemic diseases associated with burning pain in the mouth include hypothyroidism, diabetes mellitus, hematologic deficiencies, nutritional deficiencies, and autoimmune disorders. The following tests can be helpful in the diagnosis of secondary BMS: complete blood count with differential; fasting blood glucose; hemoglobin A_{1c}; thyroid panel; estradiol; iron; ferritin; vitamins B₁, B₂, B₆, and B₁₂; folate; zinc; antibodies to *Helicobacter pylori*; and autoantibodies (ie, antinuclear antibody, rheumatoid factor, and anti-Sjögren syndrome antigens A and B).^{19,20}

Because xerostomia can be an important contributing factor to symptoms of burning in the mouth, another diagnostic test includes evaluation of salivary gland function. Sialometric studies that determine the presence of salivary gland hypofunction can also be performed. Finally, minor salivary gland biopsy is another test to rule out lymphocytic infiltration or other salivary gland diseases that can cause xerostomia.²¹

Box. Secondary causes of burning mouth syndrome.¹⁸⁻²⁰**Local factors**

- Infections:
 - Fungal
 - Bacterial
 - Viral
- Salivary gland disorders:
 - Dysfunction
 - Hyposalivation
- Irritants:
 - Ill-fitting oral prosthesis
 - Physical or chemical irritants
- Oral lesions:
 - Recurrent aphthous stomatitis
 - Benign migratory glossitis
 - Erosive lichen planus
 - Mucous membrane pemphigoid
 - Pemphigus vulgaris
 - Other vesiculobullous autoimmune conditions

Systemic factors

- Endocrine disorders:
 - Diabetes mellitus
 - Thyroid disorders
 - Other hormonal disorders
- Deficiencies in:
 - Vitamin B₁₂
 - Folate
 - Iron
 - Zinc
- Systemic diseases:
 - Sjögren syndrome
 - Gastroesophageal reflux
 - Peripheral neuropathy
- Medications:
 - Angiotensin-converting enzyme inhibitors
 - Angiotensin receptor blockers

Psychological factors

- Anxiety
- Depression
- Cancer phobia
- Personality disorder

Additionally, a subset of patients with BMS present with pain that may be related to hypofunction of the dopaminergic system in the basal ganglia, suggesting the existence of changes within the central nervous system.^{24,27,28}

Management

BMS is a complex condition to manage (Chart). The differentiation between primary and secondary BMS is critical and is the initial step for proper diagnosis. Secondary BMS is treated by managing the underlying etiology. Primary BMS can be more challenging to manage, largely due to a poor understanding of its pathogenesis. While there is no completely effective treatment protocol or established guideline, studies have shown some pharmacologic and nonpharmacologic approaches that may be helpful in the management of this condition.²

In management of primary BMS, ruling out secondary causes is the first step. Patients must be educated and assured about the benign nature of primary BMS, especially since most are fearful of a more ominous underlying systemic pathology. It is equally important for the practitioner to set realistic treatment expectations. Clinicians should communicate to the patient that BMS is a chronic pain condition. As such, symptoms can be managed, but complete resolution may not be achieved.

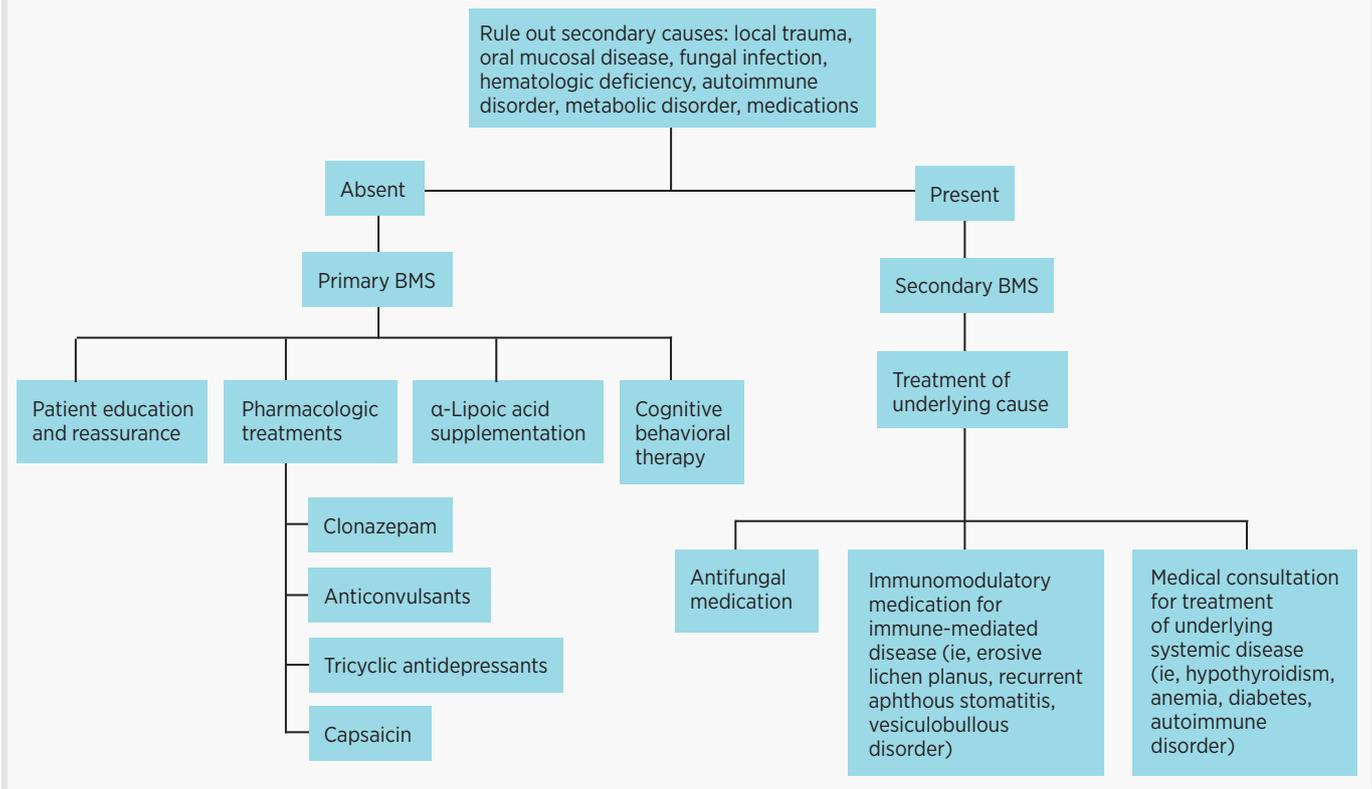
Since evidence suggests that the pathophysiology of primary BMS involves neuropathic alterations, the pharmacologic management of BMS is similar to the management of other neuropathic pain conditions. Studies have evaluated the efficacy of various medications, categorized as anxiolytics, anticonvulsants, antidepressants, and analgesics, for the management of primary BMS.^{2,29,30} Dietary supplements, physical barriers, capsaicin, low-level laser therapy, acupuncture, electromagnetic radiation, and cognitive behavioral therapy (CBT) have also been studied.^{29,30} First-line pharmacologic agents include clonazepam and the antioxidant α -lipoic acid (ALA). Anticonvulsants, such as gabapentin, and tricyclic antidepressants are second-line medications. Topical anesthetics, such as 20% benzocaine, may provide temporary relief.³¹

A recent systematic review found that evidence was low for all interventions used in the management of primary BMS; management becomes difficult because of this lack of evidence.³⁰ The best evidence shows that clonazepam (topical or systemic) is the preferred treatment option because of its effect on the peripheral γ -aminobutyric acid (GABA) A receptor. It has been shown that nerve fibers on the tongue have a high expression of GABA_A receptors.³² Consequently, GABA_A receptor activation results in altered mechanical sensitivity in these fibers. Benzodiazepines such as clonazepam are GABA_A agonists that promote the inhibitory actions similar to the GABA neurotransmitter.³³ Benzodiazepines act on peripheral and central receptors, allowing central serotonergic modulation and reduction of central neuronal hyperactivity.³³ In the peripheral nervous system, it is thought that benzodiazepines may reduce the disinhibition of the chorda tympani nerve, thereby moderating the trigeminal nerve activation that is responsible for the burning sensation.³⁴ Clonazepam has been shown to be more effective in managing symptoms than with other benzodiazepines, possibly because it has a longer half-life that would diminish withdrawal side effects.³³

Pathophysiology

Although the exact mechanisms involved in the pathophysiology of primary BMS are still unknown, there is evidence that BMS may be a neuropathic condition, affecting the peripheral and central nervous systems.²²⁻²⁷ Patients with BMS present with changes in the peripheral nervous system, such as a significantly lower density of intraepithelial nerve fibers, fewer fibers penetrating the oral mucosal epithelium, and upregulation of factors associated with neuropathic pain conditions, namely, transient receptor potential subfamily V member 1 (TRPV1) ion channels, purinoreceptor 3, and nerve growth factor.²⁵⁻²⁷ This evidence suggests that BMS is a small-fiber trigeminal neuropathy.

Chart. Management of burning mouth syndrome (BMS).



A meta-analysis evaluating the efficacy of topical and systemic clonazepam for primary BMS included 3 randomized controlled trials and 2 case-control studies, involving a total of 195 patients.³³ Clonazepam was found to be effective in the management of BMS as both short-term and long-term therapies. Studies also showed that both topical and systemic administration were effective.³³ Topical clonazepam administration would be the preferred method initially, since fewer adverse effects are associated with it.³³

The dose-effect relationship between clonazepam administration and symptom relief is unclear. For treatment with clonazepam taken orally, most clinicians start by prescribing 0.25 mg and gradually titrate to 1.00-1.50 mg per day in 3 divided doses.^{35,36} In the swish and spit method of administration, the recommended interval for rinsing is 3 minutes. Common adverse effects of clonazepam include drowsiness, dry mouth, and fatigue.^{35,37,38}

A retrospective study evaluated patients who rinsed with 0.5 mg/mL or 0.1 mg/mL of clonazepam for 5 minutes.³⁶ Patients were instructed to spit out the medication after rinsing and repeat the process 2-4 times per day. The median improvement of symptoms was 75.0% in patients using the 0.5-mg/mL dosage, compared with 32.5% for those in the 0.1-mg/mL group.³⁶ Heckmann et al performed a double-blind, randomized controlled trial comparing the efficacy of 0.5 mg of clonazepam per day to that of a placebo.³⁹ Twenty patients were enrolled, and significant reductions in pain were reported in the patients treated with clonazepam. However, no changes in mood, depression, salivary flow, and taste perception were seen.³⁹

Anticonvulsants, such as gabapentin and pregabalin, have also been used in the management of primary BMS. However, high-quality studies are lacking. These medications are usually used for neuropathic pain; because primary BMS is considered to be neuropathic, clinicians sometimes prescribe these drugs. Gabapentin and pregabalin are calcium channel blockers. They bind to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, thereby suppressing nerve activity.^{40,41} They also enhance the inhibitory effects of GABA.⁴¹ One case report showed symptom improvement with 50 mg of pregabalin per day.⁴² White et al also reported the case of a patient who benefited from 900 mg of gabapentin per day.⁴³

One double-blind, randomized controlled study evaluated the efficacy of 600 mg of ALA per day, 300 mg of gabapentin per day, and a combination of both.⁴² While the combination group achieved the greatest benefit, 50% of the group taking only gabapentin also achieved pain relief.⁴² In a study by Ito et al, 5 patients who had previously failed to respond to serotonin-norepinephrine reuptake inhibitors responded to 50-150 mg of pregabalin per day.⁴⁴ However, Heckmann et al performed a pilot study on the use of 900-2400 mg of gabapentin per day over 2-6 weeks for primary BMS and found little to no therapeutic effect.⁴⁵

ALA is a mitochondrial coenzyme that has antioxidant and neuroprotective properties and the potential to stimulate the production of neural growth factors.⁴⁶ Further, it is the most studied treatment option for BMS and is considered to be a first-line treatment option for primary BMS.⁴⁵ Studies have found

that patients reported greater improvement in symptoms with ALA compared with placebo.^{31,46}

Variations among studies, small sample sizes, and short follow-up periods make it difficult to assess the true effect of ALA on BMS.⁴⁶ Despite this, ALA is considered to be a reasonable treatment option because of its minimal adverse effect profile. Headache and gastric irritation were the most common adverse effects reported in 1 study, but no significant differences were identified between the ALA and placebo groups for these effects.⁴⁶ Dosing regimens vary between 200 and 800 mg of ALA per day.³¹

Capsaicin is a compound found in chili peppers that has medicinal properties in treatment of chronic pain. It binds to TRPV1, a nociceptor located on polymodal C fibers.⁴⁵ While capsaicin increases the production of inflammatory mediators and causes hyperalgesia on initial application, repeated application causes prolonged activation of TRPV1. This activation renders the receptor dysfunctional, leading to impaired nociception in that site.⁴⁷

Studies have shown benefit with topical and systemic administration of capsaicin.³¹ Jørgensen & Pedersen evaluated 2 concentrations of capsaicin gel, 0.01% and 0.025%, which were applied topically to the dorsal surface of the tongue 3 times a day for 2 weeks.⁴⁷ Eleven of 22 patients found the capsaicin gel beneficial, and no statistically significant differences were found between concentrations.⁴⁷ Azzi et al reported findings from a preliminary investigation of capsaicin oral rinse for BMS.⁴⁸ They prescribed it for 2 groups, 1 with neuropathic etiology and 1 with psychogenic comorbidities, over 1 year. Among the group with neuropathic symptoms, 78% reported a benefit from the oral rinse compared with 20% of the group with psychogenic symptoms.⁴⁸ Common side effects of capsaicin include nausea, dyspepsia, and an initial increase in pain when the compound is applied topically.^{31,47}

Psychological therapies such as CBT have been used in patients with neuropathic pain and, therefore, may be another treatment option for patients with BMS. Group psychotherapy and CBT have been shown to reduce pain intensity in most patients when implemented once a week for 3 or 4 months.² However, a Cochrane review of approaches for management of chronic neuropathic pain included 2 studies investigating the role of psychological therapies, 1 of which studied patients with BMS.⁴⁹ The authors concluded that psychotherapy did not result in any significant improvements.⁴⁹ While randomized controlled trials show limited benefit, other studies still report improvement with CBT.^{50,51} Thus, although high-quality evidence is lacking, CBT remains an option and seems to be more effective when it is targeted toward patients who exhibit pain catastrophization and comorbidities such as anxiety and depression.^{50,51}

In summary, there are several treatment options for patients with primary BMS. Evidence supports clonazepam, ALA, and CBT, either alone or in combination, as the treatment modalities that are useful in relieving symptoms.³¹ However, treatment results often vary from patient to patient because of clinical presentation and medical history.

Conclusion

BMS is a chronic orofacial pain condition that presents challenges in diagnosis and management. To accurately diagnose BMS, the clinician must first rule out any possible local or systemic causes for oral burning. Increasing evidence indicates that BMS may be a condition resulting from dysfunction of the peripheral and central nervous systems, similar to other neuropathic pain conditions. Educating the patient about the nature of this condition and setting realistic expectations for pain management are crucial parts of the treatment plan.

Treatment of BMS secondary to underlying local, systemic, and psychological factors is targeted toward eliminating the associated cause. The approach to managing primary BMS is usually a combination of pharmacologic (eg, clonazepam) and nonpharmacologic (eg, CBT) modalities. Appropriate referral of patients with BMS to an orofacial pain specialist is necessary to establish the correct diagnosis, provide the appropriate management, and avoid unnecessary office visits and inappropriate treatments.

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