

# Burning Mouth Syndrome



Shehryar Nasir Khawaja, BDS, MS<sup>a,c,\*</sup>, Omar F. Alaswaini, DDS<sup>b</sup>,  
Steven J. Scrivani, DDS, DMedSc<sup>c</sup>

## KEYWORDS

• Burning mouth syndrome • Chronic pain • Dysesthesia • Pain • Neuropathic

## KEY POINTS

- Burning mouth syndrome (BMS) is a chronic, intraoral burning or dysesthetic sensation that recurs daily.
- For diagnosis of BMS, it is essential to rule out any local or systemic causes of burning pain or dysesthesia.
- The pathophysiology of BMS remains elusive. However, it seems to have neuropathic, endocrinological, and psychosocial components.
- There are no universally accepted guidelines for the management of BMS. Clonazepam, as topical and/or systemic intervention with alpha-lipoic acid, can be offered as first-line therapy.

## CASE REPORT

A 67-year-old woman presented to the clinic with the chief complaint “I have a burning pain in my mouth.” The patient reported constant burning pain over the tip of her tongue, lower and upper lips, and behind her upper teeth (anterior hard palate). Her symptoms started around 4 months ago without any apparent reason. In the beginning, the intensity of symptoms was minimal; however, gradually the severity of symptoms has increased. She has no pain when she wakes up in the morning, but the symptoms start and reach full severity within a couple of hours. Hereafter, they remain constant until bedtime. She rates her pain as 7 on a 0 to 10 numeric verbal pain rating scale, where 0 indicates no pain and 10 suggests the worst pain experience. The pain is aggravated by alcohol, acidic or spicy foods, and anything hot or mint flavored. She gets relief from sucking on ice or having anything cold. In addition to pain, she feels that her tongue is raw or burnt, and the texture of anterior teeth feels rough. She has an intermittent spontaneous metallic taste, and her mouth always feels dry.

<sup>a</sup> Orofacial Pain Medicine, Shaukat Khanum Memorial Cancer Hospitals and Research Centres, Lahore and Peshawar, Pakistan; <sup>b</sup> Orofacial Pain Program, Tufts University, School of Dental Medicine, 1 Kneeland St, Boston, MA 02111, USA; <sup>c</sup> Tufts University, School of Dental Medicine, Boston, MA, USA

\* Corresponding author. Shaukat Khanum Memorial Cancer Hospital and Research Center, 7A Block R-3, Phase 2, M.A. Johar Town, Lahore, Punjab 54782, Pakistan.

E-mail address: [khawajashehryar@gmail.com](mailto:khawajashehryar@gmail.com)

There were no additional associated sensory or motor alterations or autonomic symptoms.

Her medical history was significant for hypercholesterolemia for which she takes rosuvastatin 10 mg once a day. She was not aware of any allergies to medications. Her family history was significant for diabetes mellitus and heart disease. She had discontinued drinking alcohol 2 months ago because it aggravated her oral symptoms. She had no history of smoking or substance abuse. There was no history of psychiatric disease. She had retired from an office job 2 years ago and lived with her husband and 2 dogs.

On physical examination, her pulse rate was 72 beats/min, and her blood pressure was 125/76 mm Hg. Her respiratory rate was 17 breaths per minute, and her temperature was 36.4°C. During the examination, she was oriented to time, place, and person. There was no asymmetry, atrophy, swelling, lymphadenopathy, or lesions on inspection of the head, face, and neck regions. The vertical and horizontal mandibular range of motion was within normal limits and was achieved without pain. The patient reported no pain on palpation of the masticatory muscles, temporomandibular joint, posterior mandibular area, or submandibular region. No palpable joint sounds or abnormal movement patterns were observed during mandibular motion. The cervical range of motion was within normal limits, and the patient did not report any pain on palpation of the cervical muscles.

Intraoral examination revealed normal, moist, and pink-colored oral mucosa. Tongue movements were normal, the uvula was in the midline, and the soft palate was mobile. No lesions, discolorations, or swelling were observed, and salivary flow was clear and adequate. There was mild pooling of saliva on the floor of the mouth. There were no calculi or plaque deposits. The right mandibular and maxillary third molars were missing. Class I amalgam restorations were present in the right mandibular first molar, left mandibular first and second molars, and left maxillary first molar. The rest of the dentition was sound.

Cranial nerve (CN II-XII) examination revealed no gross discrepancies. The spinal nerves (C2-T1) were grossly intact. Testing of complex motor skills revealed normal coordination. Deep tendon reflexes of the biceps, triceps, and brachioradialis were normal. The panoramic radiograph in the closed-mouth position did not show any disease. A working diagnosis of burning mouth syndrome was made. Before presenting to the pain clinic for assessment, the patient had a thorough evaluation by her primary care physician. She had a complete blood cell count, thyroid function test, liver function test, vitamin D, HbA<sub>1c</sub> (glycated hemoglobin), cholesterol assessment, and serum electrolyte test. In addition, she had completed a 10-day course of fluconazole 100 mg once a day for a presumptive diagnosis of oral candida infection. The tests were within normal physiologic limits, and fluconazole therapy did not improve her symptoms.

The patient was prescribed clonazepam 0.5 mg at night. She was advised to suck the tablet for 5 minutes and expectorating the tablet afterward. Likewise, the patient was advised to start alpha-lipoic acid 300 mg twice a day. Laboratory studies (vitamin B<sub>12</sub> and serum folate) were ordered and were within normal limits. A definitive diagnosis of burning mouth syndrome was made.

At the 6-week follow-up, the patient reported that the severity of symptoms had reduced, and she had mild pain. The spontaneous episodes of metallic taste perception had diminished, and the roughness she felt over the teeth had improved. She was advised to start swallowing the clonazepam tablet after sucking on it for 5 minutes. At the subsequent 6-week follow-up, the patient reported that she had been pain free for nearly 3 weeks. However, she continued to have sensitivity to spicy foods. She was advised to continue using clonazepam and alpha-lipoic acid and avoid spicy foods or any other potential irritants.

## INTRODUCTION

Burning mouth syndrome (BMS) is a chronic pain disorder affecting the oral cavity. BMS has previously been referred to as stomatodynia, glossodynia, oral dysesthesia, or primary BMS.<sup>1,2</sup> The inclusion of the word “syndrome” in the nomenclature is controversial. In a recent expert-based Delphi-style investigation, 88% of the field experts believed that BMS was not a syndrome.<sup>3</sup> Nonetheless, the International Classification for Orofacial Pain (ICOP) has used the nomenclature of BMS.<sup>4</sup> For uniformity of understanding and care, this is the terminology used in this article.

Likewise, there have been multiple operational definitions and diagnostic criteria proposed for BMS, making for a diagnostic challenge. It has been reported that it may take on average 13 months from the reported onset of symptoms to a definitive diagnosis. Likewise, a patient may seek care from 3.1 caregivers during this period.<sup>5</sup>

More recently, a committee from the International Network for Orofacial Pain and Related Disorders Methodology developed a set of Research Diagnostic Criteria for Burning Mouth Syndrome (RDC/BMS) based on the ICOP guidelines.<sup>6</sup> These criteria are currently in beta version and undergoing field testing.

This variation in definition and diagnostic criteria between studies has resulted in limited understanding of the epidemiology, pathophysiology, and management of BMS.

## EPIDEMIOLOGY

The prevalence of BMS has been reported to range from 0.1% to 4.6% in the general population.<sup>1,7</sup> This range is likely due to dissimilarities in the operational definitions of BMS, differences in the diagnostic criteria, and the population investigated.<sup>6,7</sup> In general, BMS is most prevalent in postmenopausal women. The estimated men to women ratio of prevalence is between 1:3 and 1:7. Nonetheless, the prevalence increases in both genders with age.<sup>1,2</sup>

## DIAGNOSTIC CRITERIA AND CLASSIFICATION

In the ICOP, BMS has been defined as pain or dysesthesia recurring every day for more than 2 hours for 3 months or more with no evident causation on clinical examination and/or investigation. The ICOP diagnostic criteria of BMS are summarized in **Box 1**. The classification system further divides BMS into BMS without somatosensory changes and BMS with somatosensory changes. These changes can be assessed using either qualitative or quantitative somatosensory testing.<sup>4</sup>

Recently, a Delphi-style expert-based standardized approach to diagnose BMS through a research diagnostic framework was published. RDC/BMS are based on the ICOP definition. The purpose of these guidelines is to operationalize the ICOP BMS definition by creating a structured assessment and clinical examination.

Previously, the presence of symptoms of burning pain or dysesthesia in the oral cavity attributed to any underlying systemic or local causes was referred to as secondary BMS. However, this term is no longer valid or acceptable.<sup>4</sup> Nonetheless, conditions that may mimic BMS are listed in **Box 2**.

## PATHOPHYSIOLOGY

The exact cause of BMS remains elusive. Clinical and animal-based investigations examining etiologic and pathophysiological associations suggest that the cause of BMS has neuropathic, endocrinological, and psychosocial components.

**Box 1****The International Classification of Orofacial Pain, 1st edition, diagnostic criteria for burning mouth syndrome**

Diagnostic criteria:

- A. Oral pain fulfilling criteria B and C.
- B. Recurring daily for greater than 2 h/d for greater than 3 months.<sup>a</sup>
- C. Pain has both the following characteristics:
  1. Burning quality
  2. Felt superficially in the oral mucosa
- D. Oral mucosa is of normal appearance, and local or systemic causes have been excluded.
- D. Not better accounted for by another ICOP or Internal Classification of Headache Disorders-3 diagnosis.<sup>b</sup>

<sup>a</sup> Before 3 months, if all other criteria are fulfilled, code as *Probable burning mouth syndrome*.<sup>b</sup> A diagnosis of *burning mouth syndrome* implies that quantitative sensory testing has not been performed. Once it has, either of the 2 subtypes: *burning mouth syndrome without somatosensory changes* or *burning mouth syndrome with somatosensory changes* should be diagnosed.

*Data from International Classification of Orofacial Pain, 1st edition (ICOP). Cephalalgia. 2020;40(2):129-221.*

**NEUROPATHIC MECHANISMS**

It has been proposed that the sensory portions of trigeminal and glossopharyngeal nerves interact with the gustatory fibers of the chorda tympani nerve. This interaction takes place via both peripheral and central mechanisms.<sup>8-10</sup>

In BMS, there is evidence that small fibers in the epithelium of the tongue undergo atrophy.<sup>9,11,12</sup> Similarly, it has been reported that the number of fibers innervating the taste buds are reduced and that trigeminal innervation of the fungiform papillae varies, which can cause the afferent nerve impulses to decrease.<sup>9,10</sup>

**Box 2****List of conditions that may mimic burning mouth syndrome**

- Psychosomatic disorders (anxiety, somatization)
- Systemic illness (diabetes, Sjögrens, or thyroid or hepatic illness)
- Nutritional deficiencies such as, iron, zinc, magnesium, or vitamin B (B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub>)
- Medications (antihypertensive agents such as angiotensin-converting enzyme inhibitors, hormonal replacement therapies, antihistamines)
- Dry mouth
- Inflammatory disorders (stomatitis, lichen planus, geographic tongue)
- Trauma or injury (noniatrogenic)
- Surgical or iatrogenic injury
- Radiation- or chemotherapy-induced pain
- Infections (fungal, bacterial, or viral)
- Autoimmune disorder or systemic illness (diabetes, or thyroid or hepatic illness)
- Hypersensitivity or allergic reaction
- Pain attributed to malignant lesion (cancer-related pain)

The loss of input from the chorda tympani nerve fibers diminishes the disinhibitory action on the trigeminal or glossopharyngeal nerve, which results in overcompensation from the latter; causes modification in the mutual modulation at the level of nucleus tractus solitarius, amygdala, and medial pain system; and triggers deafferentation-hyperactivity changes in the somatosensory regions of the trigeminal system.<sup>8,9,13,14</sup> Likewise, studies using quantitative sensory testing have suggested that the thermal and pain detection thresholds vary among patients with BMS. However, the pain tolerability has consistently been reported to be reduced, suggesting temporal summation (induced by central sensitization).<sup>9,15</sup>

## ENDOCRINOLOGICAL MECHANISMS

Gonadal hormones are essential for maintaining tongue epithelium thickness and keratinization.<sup>9</sup> After menopause, a reduction in the synthesis of ovarian steroids may cause adrenal steroid deficiency or dysfunction.<sup>16</sup> This deficiency or dysfunction can diminish the neuroprotective effects of steroids on neural tissues, which may directly or indirectly generate pain-related behaviors through peripheral and central mechanisms.<sup>9,16</sup> In patients with BMS, tongue epithelium thickness is reduced, and there may be a loss of keratinization.<sup>9</sup> Furthermore, as stated earlier, the clinical symptoms of BMS suggest that patients have peripheral and central sensitization.

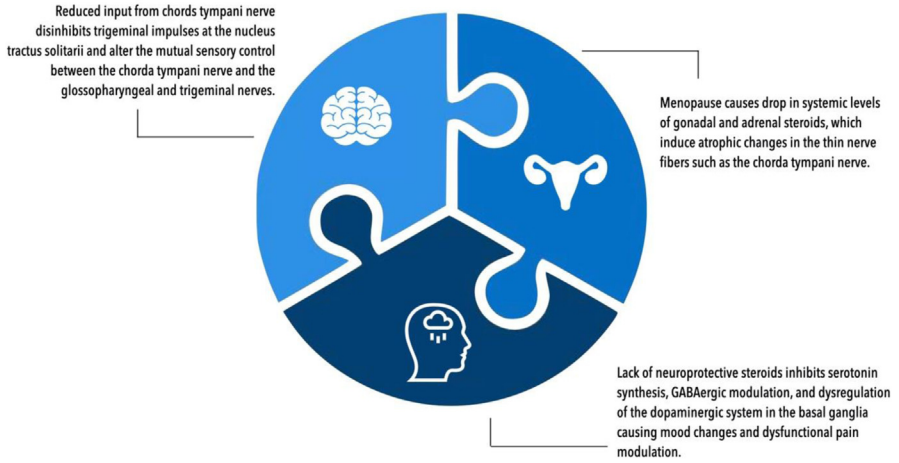
Ovariectomy has been shown to result in upregulation of glial cell line-derived neurotrophic factor (GDNF) family ligands and their receptors.<sup>17</sup> Levels of artemin, a member of the GDNF family, was reported to be raised in the tongue epithelial cells of patients with BMS.<sup>18</sup> Moreover, transgenic overexpression of artemin resulted in increased expression of TRPV1 (transient receptor potential cation channel, subfamily V, member 1) and TRPA1 (transient receptor potential cation channel, subfamily A, member 1), which was associated with increased sensitivity to capsaicin and mustard oil and lingual nerve atrophy. These changes are similar to the characteristics of nerve atrophy seen among patients with BMS.<sup>9,18,19</sup>

It has been hypothesized that the lack of neuroprotective steroids leads to hypofunction of minor salivary glands, which may induce latent oral dryness and preclinical inflammation of oral mucosa. These peripheral changes may generate burning pain and dysesthesia and account for the subjective feeling of oral dryness.<sup>9</sup>

## PSYCHOSOCIAL MECHANISMS

The prevalence of anxiety and depression increases postmenopause, and there is a high comorbidity of anxiety and depression in BMS.<sup>20</sup> Among patients with depression and anxiety, there is reduced synthesis of neuroprotective steroids in the hippocampus, amygdala, and medial prefrontal cortex. Similar areas have been reported to have altered brain activity in patients with BMS.<sup>9</sup>

The high prevalence of psychological distress among patients with BMS may be explained by the role of neuroprotective steroids on mood. Dysregulation of gonadal hormones can lead to psychological distress.<sup>9,21</sup> Neuroprotective steroids, such as progesterone metabolites, modulate  $\gamma$ -aminobutyric acid (GABA<sub>A</sub>) receptors and result in mood changes.<sup>22</sup> Allopregnanolone can exert an anxiolytic effect by positive modulation of GABA<sub>A</sub> receptors and negative modulation of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>9</sup> Similarly, progesterone and estrogen can regulate the endogenous anxiolytic effects of serotonin and allopregnanolone.<sup>9</sup> Overall, in postmenopause, there is reduced serotonergic neurotransmission, reduced GABAergic inhibition, and less efficient HPA axis activity, which increases the risk of developing anxiety and depression. Correspondingly, mental stress induces downregulation of



**Fig. 1.** A schematic of the suspected pathophysiology of burning mouth syndrome. A pathologic event, such as infection, trauma, or an allergic reaction can theoretically induce atrophic changes in the thin nerve fibers such as the chorda tympani nerve.

the hypothalamic-pituitary-gonadal (HPG) and HPA axes by modulating the GABA<sub>A</sub> receptor, further reducing gonadal hormone levels.<sup>9</sup>

## SUMMARY

A pathologic event, such as infection, trauma, or an allergic reaction, or a physiologic phenomenon such as menopause that reduces systemic levels of gonadal and adrenal steroids, can induce atrophic changes in the thin nerve fibers such as the chorda tympani nerve, innervating the oral mucosa; this causes predominance of the trigeminal nerve, which may clinically produce dysgeusia. Moreover, reduced input from the chorda tympani nerve fibers can disinhibit trigeminal impulses at the nucleus tractus solitarii and alter the mutual sensory control between the trigeminal, the chorda tympani, and the glossopharyngeal nerves, which may clinically present as burning pain or dysesthesia. Furthermore, lack of neuroprotective steroids inhibits serotonin synthesis, GABAergic modulation, and dysregulation of the dopaminergic system in the basal ganglia. These alterations produce mood changes and dysfunctional pain modulation. Collectively, persistent pain (and concurrent psychological distress) suppresses the function of the pain modulation system (Fig. 1).

## CLINICAL FEATURES AND SYSTEMIC ASSESSMENT

BMS diagnosis requires a comprehensive history and clinical examination, including laboratory investigations to rule out any local and systemic causes of symptoms.

Most patients report pain rather than dysesthesia.<sup>1,2,23</sup> However, in some cases, both may be present. The quality of pain or dysesthesia is often described as burning, tender, tingling, hot, stinging, scalding, numbness, discomfort, raw, unpleasant, or annoying.<sup>2,23</sup> The intensity of pain varies from mild to severe. On average, it can be approximately  $6 \pm 2$  (on a 0 to 10 numeric verbal pain rating scale). However, in some cases, pain can be 10 of 10 in intensity. In some patients, oral intake of food or liquids and talking help alleviate pain intermittently for a few minutes. However, in others, foods or beverages and hot, spicy, acidic, minty, or alcoholic drinks may exacerbate the symptoms.<sup>2,23</sup>

In BMS, symptoms are distributed bilaterally, and the most common locations of pain are the tip and the anterior two-thirds of a tongue. Nonetheless, in most of the patients, more than one site of pain is present. Other areas involved are the hard palate, labial, or buccal mucosa.<sup>1,2,23</sup> The pain is often spontaneous in onset and can last for years. The likelihood of spontaneous remission is rare.<sup>1,2</sup> The pattern of pain varies among patients. In some patients, pain increases toward the end of the day. In others, the intensity of the pain remains constant, or the pain may present intermittently for minutes/hours throughout the day. Nonetheless, it occurs daily for at least 2 hours.<sup>1,2,23</sup>

In more than two-thirds of the patients, primary symptoms of pain or dysesthesia are associated with at least one secondary symptom.<sup>23</sup> The patient may report alteration of taste perception in the presence of taste stimulation (dysgeusia) or an abnormal taste (bitter or metallic) occurring in the absence of stimulation of taste (phantom taste). Similarly, primary symptoms may present with a subjective feeling of oral dryness (xerostomia) or alteration in sensory perception, such as feeling that the tongue or oral mucosa has a sandpaperlike texture or that the surfaces or size of teeth are different.<sup>1,2,23</sup>

The clinical examination is normal and does not correspond to the symptoms. There are no local or systemic causes that may explain the symptoms in the oral mucosa.<sup>1,2</sup> The RDC/BMS has proposed an extensive list of investigations at baseline to rule out secondary causes (Box 3).<sup>6</sup> This list is not exclusive, and other tests may be added depending on the outcome of the history and examination. In addition, recent guidelines have proposed quantitative or qualitative sensory testing of the oral cavity to subclassify BMS. However, the clinical significance of this is unknown.

The presence of BMS has a negative effect on the patient's quality of life.<sup>24</sup> Furthermore, patients with BMS have a high prevalence of psychiatric disorders such as anxiety, depression, and somatization; significantly higher adverse early life experiences; cancer phobia; gastrointestinal problems; and chronic fatigue syndrome.<sup>1,2,20</sup>

## MANAGEMENT

There are no universally accepted guidelines for the management of BMS. Nonetheless, over the last couple of years, multiple systematic reviews and meta-analyses have been published, which have provided a better understanding of the effectiveness of the interventions.

Management should commence with a detailed review and explanation of BMS. Patients should be given detailed instructions regarding the possible pathophysiology and management strategies for BMS in a manner that they can understand. Furthermore, expectations of therapy should be addressed. This educational session alone may help alleviate primary and secondary symptoms associated with BMS.<sup>25</sup>

Clonazepam is a benzodiazepine that is an effective topical and systemic intervention for the management of BMS.<sup>23</sup> It is often used as the first-line therapy. Until recently, most of the evidence for the effectiveness of clonazepam was based on case series and retrospective analyses. However, recent systematic reviews and meta-analyses have shown that clonazepam has a significant therapeutic effect in BMS.<sup>7,25</sup> Clonazepam is routinely used between 0.5 and 2 mg single dose at night because of the sedative effect.<sup>23</sup> The beneficial effect of topical therapy has been shown to take place without any systemic absorption. Likewise, in studies in which clonazepam was used both as topical and systemic therapy, it was observed to have a synergistic effect. Similar observations have been reported in studies in which

**Box 3****List of investigations proposed by the research diagnostic criteria for burning mouth syndrome to be completed at baseline for all patients**

- Complete blood cell count/full blood count (mean corpuscular hemoglobin/mean corpuscular volume/white cell count/hemoglobin)
- Vitamin B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub>; iron; folate
- Serum iron, ferritin, total iron-binding capacity
- Zinc and magnesium
- Glycated hemoglobin (HbA<sub>1c</sub>)
- Thyroid function test
- Liver function test
- Erythrocyte sedimentation rate or C-reactive protein
- Autoantibodies test (Anti-Ro and anti-La, anti-nuclear antibodies, and extractable nuclear antigen antibodies)
- Serum homocysteine level
- Swab or smear for gram staining

*Data from* Currie CC, Ohrbach R, De Leeuw R, et al. Developing a research diagnostic criteria for burning mouth syndrome: Results from an international Delphi process. *J Oral Rehabil.* 2021;48(3):308-331.

clonazepam has been used with other therapies, such as alpha-lipoic acid (ALA), N-acetyl cysteine, and gabapentin.<sup>7,25,26</sup> Clonazepam has an agonistic effect on peripheral and central GABA<sub>A</sub> receptors subunits  $\alpha$ 1 and  $\alpha$ 2. In chronic mental distress, the GABA<sub>A</sub> receptor configuration changes, which results in the expression of the  $\alpha$ 4,  $\alpha$ 5, and  $\gamma$  subunits to undergo a significant increase and the expression of the  $\alpha$ 1 and  $\alpha$ 2 subunits to decrease significantly. Benzodiazepines have a poor affinity for the  $\alpha$ 4,  $\alpha$ 5, and  $\gamma$  subunits, which are highly sensitive to neuroprotective steroids.<sup>27</sup> Correspondingly, in the studies in which the participants had a poor response to clonazepam the patients were found to have a significant level of psychological distress (anxiety and/or depression).<sup>28</sup> The use of clonazepam is commonly associated with drowsiness, dizziness, feeling tired or depressed, memory issues, or gait problems.<sup>29</sup> Furthermore, the use of benzodiazepines accounts for nearly half of the total emergency visits due to toxicity associated with the use of sedatives. Owing to its high potential for misuse and overdose, it is categorized as a schedule IV drug under the Controlled Substance Schedule.<sup>29,30</sup> Furthermore, investigations have suggested that benzodiazepine and opioid cotreatment is associated with increased long-term mortality risk.<sup>29</sup> It may be valuable to involve the patient's primary care physician in caring for such patients.

The systemic use of gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRI) has been reported to be beneficial in the management of BMS.<sup>2,23</sup> SNRIs have been used to manage cases refractory to clonazepam, which might be due to the neurosteroidergic effects of these medications at low nonserotonergic doses in the brain. Like clonazepam, gabapentinoids are classified as schedule IV (and schedule V in some states) controlled substances.<sup>31</sup> The use of gabapentinoids, tricyclic antidepressants, and SNRIs is commonly associated with drowsiness, dizziness, memory clouding, and gastrointestinal and genitourinary side effects.<sup>32-34</sup>

ALA, an antioxidant, has extensively been investigated either alone or as an adjunct to a pharmacologic agent or cognitive behavioral therapy for the management of BMS. The regimen consists of 200 to 800 mg in single or divided doses a day for up to 8 weeks. The short-term ( $6 \pm 2$  weeks) results are inconsistent; some studies showed significant relief in symptoms, and others suggested a nonsignificant effect. On the contrary, studies that investigated long-term (10 weeks or more) effects of using ALA reported significant benefits. The use of ALA may result in minor side effects, including but not limited to gastrointestinal complaints such as heartburn and headaches.<sup>35</sup>

Herbal Catuama, a herbal compound, has been shown to be helpful in the management of BMS. This compound has been shown to result in a significant reduction in burning after 8 and 12 weeks.<sup>7,36</sup> Herbal Catuama is, relative to controlled substances, a safe intervention and has a low risk of causing sleep issues or weight gain. When used topically or systematically, capsaicin, a TRVP1 (transient receptor potential vanilloid subtype 1) agonist, has been reported to significantly improve symptoms associated with BMS. However, the topical use of the modality was associated with aggravation in burning sensation, and systemic therapy was associated with gastric pain.

Psychotherapy alone or in combination with ALA has been shown to result in pain reduction in patients with BMS. Recently, a systematic review and meta-analysis on the effectiveness of photobiomodulation (low-level laser therapy) in BMS management determined that photobiomodulation results in pain reduction.<sup>37</sup> However, the investigators concluded that more evidence was still required.

There is anecdotal evidence for symptomatic relief using a 1:1 mixture of diphenhydramine (elixir) and kaolin-pectin (solution), local anesthetic (viscous or jelly lidocaine, or benzocaine gel), or Magic mouthwash/Miracle mouthwash (a combination of local anesthetic, antihistamine, antacid, simethicone, or corticosteroid).<sup>30</sup> Beneficial effects of treating subjective oral dryness in BMS have not been studied.

## SUMMARY

BMS is a chronic intraoral pain disorder that is associated with burning pain or dysesthesia. The prevalence of secondary symptoms such as alteration in taste perception, phantom taste, xerostomia, or alteration in sensory perception differs between patients, resulting in a varying clinical presentation. In BMS, there are no organic local or systemic causes for symptoms. BMS has a negative impact on the quality of life, and the patients often have comorbid psychological disorders. Clonazepam is often used as the first-line therapy. However, other modalities have been shown to have a beneficial effect. There are no universal guidelines on the management of BMS primarily due to the lack of standardized definition, diagnostic criteria, and reporting of outcomes in published studies. Nonetheless, recent advances such as the release of the ICOP and RDC/BMS, and the development of an expert and patient-driven set of core outcome measures for randomized controlled trials for BMS may help answer these important questions in the future.

## CLINICS CARE POINTS

- The patient reported near-constant burning pain over the tip of her tongue, lower and upper lips, and behind upper teeth (anterior hard palate) for nearly 4 months.
- The pain was associated with feelings of the tongue being raw or burnt, the texture of anterior teeth feeling rough, intermittent spontaneous metallic taste, and dry mouth.

- The oral mucosa was of normal appearance, and no local or systemic causes for burning pain were identified.
- The patient partially responded to topical clonazepam and systemic ALA therapy. However, after switching her to systemic clonazepam therapy, the patient reported significant pain relief.

## DISCLOSURE

The authors have nothing to disclose.

## REFERENCES

1. Fortuna G, Napenas J, Su N, et al. Oral dysesthesia. In: Farah CS, Balasubramaniam R, McCullough MJ, editors. Contemporary oral medicine. Cham, Switzerland: Springer International Publishing; 2018. p. 1–25.
2. Klasser GD, Grushka M, Su N. Burning Mouth Syndrome. *Oral Maxillofacial Surg Clin North Am* 2016;28(3):381–96.
3. Chmieliauskaite M, Stelson EA, Epstein JB, et al. Consensus agreement to rename burning mouth syndrome and improve ICD-11 disease criteria: an international Delphi study. *Pain* 2021;162(10):2548–57.
4. International Classification of Orofacial Pain, 1st edition (ICOP). *Cephalalgia* 2020;40(2):129–221.
5. Mignogna MD, Fedele S, Lo Russo L, et al. The diagnosis of burning mouth syndrome represents a challenge for clinicians. *J Orofac Pain* 2005;19(2):168–73.
6. Currie CC, Ohrbach R, De Leeuw R, et al. Developing a research diagnostic criteria for burning mouth syndrome: Results from an international Delphi process. *J Oral Rehabil* 2021;48(3):308–31.
7. Farag AM, Kuten-Shorrer M, Natto Z, et al. WWOM VII: Effectiveness of systemic pharmacotherapeutic interventions in the management of BMS: A systematic review and meta-analysis. *Oral Dis* 2021. <https://doi.org/10.1111/odi.13817>.
8. Felizardo R, Boucher Y, Braud A, et al. Trigeminal projections on gustatory neurons of the nucleus of the solitary tract: A double-label strategy using electrical stimulation of the chorda tympani and tracer injection in the lingual nerve. *Brain Res* 2009;1288:60–8.
9. Imamura Y, Shinozaki T, Okada-Ogawa A, et al. An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives. *J Oral Rehabil* 2019;46(6):574–87.
10. Eliav E, Kamran B, Schaham R, et al. Evidence of chorda tympani dysfunction in patients with burning mouth syndrome. *J Am Dent Assoc* 2007;138(5):628–33.
11. Yilmaz Z, Renton T, Yiangou Y, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. *J Clin Neurosci* 2007;14(9):864–71.
12. Beneng K, Yilmaz Z, Yiangou Y, et al. Sensory purinergic receptor P2X3 is elevated in burning mouth syndrome. *Int J Oral Maxillofac Surg* 2010;39(8): 815–9.
13. Boucher Y, Simons CT, Faurion A, et al. Trigeminal modulation of gustatory neurons in the nucleus of the solitary tract. *Brain Res* 2003;973(2):265–74.
14. Corson JA, Erisir A. Monosynaptic convergence of chorda tympani and glosso-pharyngeal afferents onto ascending relay neurons in the nucleus of the solitary

- tract: A high-resolution confocal and correlative electron microscopy approach: Convergence in the rNTS. *J Comp Neurol* 2013;521(13):2907–26.
15. Grushka M, Sessle BJ, Howley TP. Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. *Pain* 1987;28(2):169–84.
  16. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). *J Orofac Pain* 2009;23(3):202–10.
  17. Hernández-Aragón LG, García-Villamar V, Carrasco-Ruiz M, et al. Role of Estrogens in the Size of Neuronal Somata of Paravaginal Ganglia in Ovariectomized Rabbits. *Biomed Res Int* 2017;2017:1–12.
  18. Shinoda M, Takeda M, Honda K, et al. Involvement of peripheral artemin signaling in tongue pain: possible mechanism in burning mouth syndrome. *Pain* 2015;156(12):2528–37.
  19. Eliott CM, Malin SA, Koerber HR, et al. Overexpression of artemin in the tongue increases expression of TRPV1 and TRPA1 in trigeminal afferents and causes oral sensitivity to capsaicin and mustard oil. *Brain Res* 2008;1230:80–90.
  20. Kim JY, Kim YS, Ko I, et al. Association Between Burning Mouth Syndrome and the Development of Depression, Anxiety, Dementia, and Parkinson Disease. *JAMA Otolaryngol Head Neck Surg* 2020;146(6):561.
  21. Walf AA, Frye CA. A Review and Update of Mechanisms of Estrogen in the Hippocampus and Amygdala for Anxiety and Depression Behavior. *Neuropsychopharmacol* 2006;31(6):1097–111.
  22. Gunn BG, Cunningham L, Mitchell SG, et al. GABAA receptor-acting neurosteroids: A role in the development and regulation of the stress response. *Front Neuroendocrinol* 2015;36:28–48.
  23. Khawaja SN, Bavia PF, Keith DA. Clinical Characteristics, Treatment Effectiveness, and Predictors of Response to Pharmacotherapeutic Interventions in Burning Mouth Syndrome: A Retrospective Analysis. *J Oral Facial Pain Headache* 2020;34(2):157–66.
  24. Souza FT, Santos TP, Bernardes VF, et al. The impact of burning mouth syndrome on health-related quality of life. *Health Qual Life Outcomes* 2011;9(1):57.
  25. Kim M, Kim J, Kho H. Treatment outcomes and related clinical characteristics in patients with burning mouth syndrome. *Colorectal Dis* 2021;27(6):1507–18.
  26. Han S, Lim JH, Bang J, et al. Use of a combination of N-acetylcysteine and clonazepam to treat burning mouth syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2021;132(5):532–8.
  27. Locci A, Pinna G. Neurosteroid biosynthesis down-regulation and changes in GABA receptor subunit composition: a biomarker axis in stress-induced cognitive and emotional impairment. *Br J Pharmacol* 2017;174(19):3226–41.
  28. Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, et al. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): A randomized crossover trial. *Pain* 2010;149(1):27–32.
  29. Xu KY, Hartz SM, Borodovsky JT, et al. Association Between Benzodiazepine Use With or Without Opioid Use and All-Cause Mortality in the United States, 1999–2015. *JAMA Netw Open* 2020;3(12):e2028557.
  30. Kaufmann CN, Spira AP, Alexander GC, et al. Emergency department visits involving benzodiazepines and non-benzodiazepine receptor agonists. *Am J Emerg Med* 2017;35(10):1414–9.
  31. Peckham AM, Ananickal MJ, Sclar DA. Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance. *Risk Manag Healthc Policy* 2018;11:109–16.

32. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Exp Clin Psychopharmacol* 2015; 23(1):1–21.
33. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 2007;151(6):737–48.
34. Quintero GC. Review about gabapentin misuse, interactions, contraindications and side effects. *J Exp Pharmacol* 2017;9:13–21.
35. Femiano F, Gombos F, Scully C, et al. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis* 2000;6(5):274–7.
36. Spanemberg JC, Cherubini K, de Figueiredo MAZ, et al. Effect of an herbal compound for treatment of burning mouth syndrome: randomized, controlled, double-blind clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113(3):373–7.
37. Spanemberg JC, Segura-Egea JJ, Rodríguez-de Rivera-Campillo E, et al. Low-level laser therapy in patients with Burning Mouth Syndrome: A double-blind, randomized, controlled clinical trial. *J Clin Exp Dent* 2019;11(2):e162–9.