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Review Article

Burning Mouth Syndrome: Pharmacotherapeutic Update

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Abstract

Background: Burning mouth syndrome BMS is defined as an intraoral burning or dysaesthesia sensation with daily recurrence for more than two hours daily and over than three months duration, in the absence of any lesion based on Headache Classification Committee of the International Headache Society (IHS). It affects about 3.9% of the population with female predilection in which studies showed that it affects 12%-18% of postmenopausal women. Studies have suggested that there is a psychological component in BMS symptoms. Management of BMS mostly aims toward eliminating the symptoms by prescribing topical and systemic medications. Different pharmacologic categories are available for use and few new types of drugs have been introduced recently. The main objective of this review is to present the currently available therapeutic options for BMS.

Methods: A literature review was conducted on PubMed, Medline, Cochrane Database on thepharmacotherapeutictreatment options of idiopathic BMS published to January 2023 using the following keywords ; burning mouth syndrome and treatment or therapeutic or management or therapy or systemic medications or topical medications.

Results: All articles matched the search criteria were included in this narrative review.

Conclusion: A variety of therapeutic modalities are available for BMS and pharmaceutical intervention appears to be the firts line approach for some patients. Dentists and other healthcare professionals should stay updated on therapeutic advances in this field to provide better management for their patients.

INTRODUCTION

Burning mouth syndrome BMS is defined as an intraoral burning or dysaesthesia sensation with daily recurrence for more than two hours daily and a duraion over three months, in the absence of any lesion based on The International Headache Society's Headache Classification Committee (IHS) ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition," 2018). BMS is used to be known as stomatodynia or glossodynia. ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition," 2018) It affects about 3.9% (Tan et al., 2022) of the population with female predilection, more specifically affecting 12-18% of postmenopausal women in some studies. (Sun et al., 2013) The hard-palate, lower lip, oral mucosa, and anterior two-thirds of the tongue bilaterallycan all experience burning; however, the tongue tip is the most commonly afflicted area.(Ferensztajn et al., 2013; Imamura et al., 2019) Generally, the patient presents with multiple complaints other than burning, which include pain, tingling, swelling, stinging, altered taste (dysgeusia), and xeros-

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tomia (Imamura et al., 2019), which can be accompanied by paresthesia. (Ferensztajn et al., 2013; Imamura et al., 2019) Symptoms may fluctuate, but usually the intensity of the symptoms increases throughout the day and peaks in the evening. (Tan et al., 2022)

BMS is considered a type of idiopathic orofacial pain in which the cause is not identified yet, and the exact pathogenesis is still uncertain; however, it is believed that the peripheral and central neuropathological pathways are involved (previously called primary BMS). ("International Classification of Orofacial Pain, 1st edition (ICOP)," 2020) Moreover, studies have suggested that there is a psychological component in BMS, (Imamura et al., 2019) in which depression and anxiety could have a role in triggering and progression of BMS.(Imamura et al., 2019) BMS should be diagnosed only when all other local and systemic etiologies are excluded. Those factors might include nutritional deficiencies (vitamin B12, zinc, iron, anemia, and folate), medication-induced (AEC inhibitors), systemic disorders (such as diabetes and hypothyroidisim), and infectious etiologies (fungal, viral and bacterial).Table 1 ("International Classification of Orofacial Pain, 1st edition (ICOP)," 2020; Sun et al., 2013) When any of the previously mentioned factors caused this condition, it was used to be called secondary BMS.

Table 1: Local and systemic etiologies that should be ruled out be-fore considering BMS diagnosis.

Local factors	Systemic factors
Parafunctional habits (clenching,bruxism)Food allergiesInfectious diseases (fungal, bacterial , or viral)	Nutritional deficiencies (vitamin B12, zinc, folate, iron)AnemiaHormonal imbalance/endocrinal disorders (diabetes, hypothyroidism)Salivary gland dysfunctionMedications (ACE inhibitors)

According to the Orofacial Pain International Classification (ICOP), the clinical diagnosis of BMS is achieved in the presence of normal oral mucosa and the absence of any possible local or systemic causes. The diagnostic criteria for oral pain should include persistent discomfort with a duration of more than 2 hours each day for a period exceeding 3 months. The pain should be burning and felt superficially in the oral mucosa. More impratantly, the symptoms are not better accounted by another ICOP or ICHD-3 diagnosis. ("International Classification of Orofacial Pain, 1st edition (ICOP)," 2020)

Management of BMS is primarily symptomatic. Clinical professionals must first ascertain weather the patient's symptoms are compatible with primary or secondary BMS. The later necessitates accurate identification and management of the underlying cause. The etiology of primary BMS remains unclear, and therapeutic strategies are predicated on the patient's symptoms . Burning Mouth Syndrome can be managed through pharmaceutical, psychological, or a combination of both approaches. Systemic and topical medications have been employed in the management of BMS with differing levels of efficacy. Psychological or psychiatric intervention may be considered when symptoms fail to respond to pharmacotherapy. In the context, cognitive-behavioral therapy, which assists patients in developing pain-coping strategies, was found to be effective in alleviating complaints. Many topical and systemic medications are available for use and fall into different pharmacologic categories. The remaining sections of this review will focus only on the most currently available therapeutic options for BMS.

MATERIALS AND METHODS

A literature review was done on PubMed, Med-line, and Cochrane Database on the therapeutic options of idiopathic BMS published until January 2023. The following keywords were used: “burning mouth syndrome and treatment or therapeutic or management or therapy or systemic medications or topical medications”. This review includes systematic reviews, randomized -controlled clinical trials with or without a placebo and review papers. Moreover, a manual search was made and included any potentially relevant studies to this review article. All articles were published in the English language.

DRUG SELECTION

The course, progression, remission,and prognosisof BMS are still undetermined. Pharmacotherapeutic options for treating BMS include anticonvulsants, benzodiazepines, antidepressants, and other supplements.(Coculescu et al., 2014) Novel therapeutic non-pharmaceutical modalities, such as lasers, acupuncture, cognitive behavioral therapies, yoga, and group psychotherapy are also available. The treatment can be topical, systemic, or a combination of both. Many factors should be taken into consideration before medication selection, including the patient's age, medical history, existing medications, anticipated side effects, and tolerance. Generally, the management of BMS aims to reduce the peripheral sensitization in the mucus membrane of the oral cavity whether by applying the medicines topically or using them systemically to provide that purpose.

Benzodiazepines

Clonazepam is the most common benzodiazepine employed, possessing both anxiolytic and anticonvulsant effects.(Ferensztajn et al., 2013) It has been used systemically and topically(disintegrating tablets, oral rinse), and there have been randomized, double-blind clinical trials that have demonstrated its efficacy in lowering burning sensation in people with BMS.. (Feren-

sztajn et al., 2013; Heckmann et al., 2012; Rodriguez de Rivera Campillo et al., 2010; Salih Levent Çınar, 2018) The mechanism of action of systemic benzodiazepines is still unclear, but it has been proposed that it could affect the activity of the neurotransmitter gamma-aminobutyric acid (GABA). The GABA-A receptor has different subunits with alpha (A) subunit that is considered the most important one to BMS. It is believed that the A1 and A2 subunit are responsible for the sedative effects and some of the anticonvulsive properties and mediating the anxiolytic and myorelaxant effects, respectively.(Edinoff et al., 2021) It was proposedthat GABA is found in the taste pathways and the loss of its inhibitory function has a role in mediating oral pain seen in burning mouth syndrome.(Bartoshuk et al., 2005)Thus, binding of Benzodiazepine to GABA receptors enhances the activity of the GABA, resulting in depressed neural transmission in the motor cortex, leading to anxiolytic effect and relief of oral pain.(Bartoshuk et al., 2005) (Edinoff et al., 2021)

When used topically, the activation of GABA receptors on the tongue can alter the mechanical sensitivity and decrease pain in BMS as well.(Cui et al., 2016; Tan et al., 2014) Dentists should be mindful of the side effects that include dizziness, tolerance, and drug withdrawal symptoms(anxiety, panic, return of symptoms), which can be seen following sudden discontinuation of the medication, especially in elderly patients. Generally, clinical judgment determines the optimal dose keeping into consideration severity of symptoms and the patient's tolerance. A meta-analysis on the efficacy of clonazepam for treating burning mouth syndrome has shown that systemic form can cause dependence. (Cui et al., 2016) Thus, dose tapering is suggested towards the end of the treatment.(Cui et al., 2016) It has been highly recommended to consider the combined systemic and topical clonazepam administration as an effective regimen for treating BMS.(Sun et al., 2013) That will help to avoid high doses of systemic clonazepam. Also,a study showed rapid relief of oral symptoms with the use oftopical clonazepamalonebut a shorter duration of action compared to oral clonazepam.(Rodriguez de Rivera Campillo et al., 2010)Within 10 minutes of dissolving the clonazepam tablet intraorally, patients had symptom relief, however pain reoccurred within 3-4 hours.(Rodriguez de Rivera Campillo et al., 2010) So the orally disintegrating tabletscould be considered in some instances whensystemic adverse effects are highly expected. The systemic clonazepam should be started with 0.25 mg at bedtime for a week, and the dose could be increased to twice or three times daily on a weekly basis until the symptoms resolve but not exceeding a maximum of2 mg/ day.(Sun et al., 2013)

Because clonazepam is metabolized by cytochrome P450 3A4 (CYP3A4), it is contraindicated in patients using drugs that have cytochrome P450 and 3A4 inhibition properties such as azole antifungals, calcium channels blockers, and some antibiotics (erythromycin, clarithromycin in particular). Grapefruit juice could also theoretically increase its blood levels.(Hersh & Moore, 2004) The potential interaction between these medications and benzodiazepine will result in increased benzodiazepine levels in the blood, which may lead to excessive drowsiness and psychomotor impairment.Tables (2&3)

Anticonvulsants

Gabapentin is an anticonvulsant that works by enhancing the central GABA pathway. This action is thought to decrease peripheral neuropathic pain and it has shownimprovement in BMS pain as well. (Tan et al., 2022) It is widely used for neuropathic pain suchas diabetic neuropathy and postherpetic neuralgia,and it has minimal adverse effects and is generally tolerated by the patients. (Wiffen et al., 2017) Thus, it wasproposedto use gabapentin in the treatment of BMS.The administration of 300 mg of gabapentin in BMS patients daily for 2 months showed relatively favorable results in a double-blind, placebo-controlled trial; however, more effective results were noted when combining gabapentin with alpha lipoic acid.(Lopez-D'alessandro & Escovich, 2011) In general, the dose can start at 300 mgand can be increased by 300 mg every 2-3 days until symptoms are relieved or adverse effects are encountered.(Wiffen et al., 2017)A daily maximum dosage of 3600 mg should not be exceeded to avoid serious side effects.(Martin & Forouzanfar, 2011) Gabapentin can lead to renal impairment at higher doses; thus significant caution should be applied when used in patients with chronic kidney diseases. Tables (2&3)

Antidepressants

Tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) are among the antidepressant drug classes that have been utilized to treat BMS. The mechanism of action of TCA is complex. The analgesic mechanism is believed to involve the inhibition of serotonin and noradrenaline reuptake, leading to elevated synaptic levels of serotonin and/or norepinephrine in the central nervous system. However, they act on multiple receptor systems, causingsignificant side effects, including the anticholinergic impact that may cause decreased salivation and cardiac stimulation.(Fleuret et al., 2014; Nasri-Heir et al., 2015) Amitriptyline, nortriptyline, and desipramine have been used for treatment of otherneuropathic pain disorders, including diabetic neuropathies, chronic orofacial pain, post-herpetic neuropathy, and also in cases of BMS.(Fleuret et al., 2014)

Amitriptyline is one of the commonly used TCA for the treatment of BMS. In previous studies,10–40 mg/day of amitriptyline has been recommended for adult patients with BMS.(Fenelon et al., 2017; Jaaskelainen & Woda,

2017) Although the required dose for burning pain relief is lower than that needed for depression, Amitriptylinetolerability has been decreased due to reported side effects especially in older patients. In a study by Suga et al, the therapeutic dose of amitriptyline in three groups of older patients with burning mouth syndrome was assessed, and 90% of the participants reported side effects like drowsiness, xerostomia, and constipation. However, 76% of the thirty-two analyzed patients reported improving burning symptoms with amitriptyline.(Suga et al., 2019) In general, Amitriptylinecan still be effective at lower dose which also minimizes the risk of adverse events.

Doxepin is a tricyclic antidepressant (TCA), and it has been approved by the Food and Drug Administration FDA to treat depression, anxiety, and moderate pruritus.(Epstein et al., 2006; McCleane, 2000) Doxepin rinse has been highly recommended for the treatment of radiotherapy-induced oral mucositis due to its opioid analgesic effects and the suggested dose was to have the patient swish and spit 5 ml of doxepin suspension (5 mg/mL) 3-6 times/ day. (Jayakrishnan et al., 2015) Doxepin has also been used topically for neuropathic pain, including BMS with great success based only on expert opinion.(Feller et al., 2017) The mechanism of action of the topical form is unkown but it could be explained through its potential action on pain suppression in cutaneous nociceptors as a sodium channel blocker and production of local anesthetic activity. (Jayakrishnan et al., 2015)

Owing to the significant side effects associated with TCAs, SSRIs are considered a superior alternative in BMS, exhibiting fewer adverse effects and enhanced tolerance.(Fleuret et al., 2014) SSRIs are available in many forms and are widely used for the therapy of chronic pain conditions such as sertraline, citalopram, paroxetine, and fluoxetine. Although few studies show direct effect for SSRI on reduction of BMS symptoms, the overall effect of this drug has been generally positive. A study showed a decrease in pain within 12 weeks of paroxetine in about 80% of BMS patients with only minor transient side effects.(Yamazaki et al., 2009) Another study has demonstrated that citalopram effectively lowered pain intensity associated with BMS.(Pakfetrat et al., 2019) A recent study showed that fluoxetine therapy decreases pain intensity in BMS patients along with improving their psychological status. (Zoric et al., 2018) Despite the fact that the previously mentioned studies have suggested the benefit of using SSRI in the management of BMS patients, more clinical trials are needed to conclude the exact effect of SSRI on chronic pain conditions.

Duloxetine is a SNRI and has been widely used with success for the management of painful diabetic peripheral neuropathy.(Dworkin et al., 2010) Moreover, its use as a therapeutic option for burning mouth syndrome has been documented with limitations due to a lack of evidence of benefits for BMS. (Nagashima et al., 2012) However, it has been showing fewer adverse events than TCA and SSRI, including gastrointestinal disturbances mainly. (Nagashima et al., 2012) Tables (2&3)

Other local and systemic medications

Alpha Lipoic Acid (ALA) is a compound that naturally occurs and is found in the body and vegetables like potatoes and broccoli. It is considered an antioxidant that works by reducing free radicals and exerting activity in nerve repair. It is known to elevate the concentration of intracellular glutathione, which in turn triggers the nervestextquotesingle rebuilding mechanisms and stimulates the production of the nerve growth factor.(Ferensztajn et al., 2013) It's effect on BMS patients is still controversial. However, multiple studies have shown positive results of ALA (600 mg/-daily) in the management of BMS (Spanemberg et al., 2012) with better results when used in conjunction with gabapentin.(Ferensztajn et al., 2013; Spanemberg et al., 2012) In general, ALA can be used in combination with other drugs to adjunct the effect. This may benefit the patients by reducing the doses and frequency of the prescribed medication, resulting in fewer possible side effects. The use of antipsychotic medicines such as olanzapine and amisulpride also has been reported in the literature and have shown improvement of BMS symptoms in two cases.(Ueda et al., 2008) The administration of 50 mg /day of amisulpride for 24 weeks was effective and well tolerated by BMS patients.(Nasri-Heir et al., 2015; Rodriguez-Cerdeira & Sanchez-Blanco, 2012) Tables (2&3) Capsaicin is the most used topical agent for BMS which is composed of peppermint. It acts on TRPV1 (Transient receptor potential vanilloid), which is a potent calcium receptor. When TRPV1 is activated at the peripheral terminal fiber endings, this will lead to the release of neuropeptides including substance Pand calcitonin-gene-related peptide (CGRP). (Tan et al., 2022)These neuropeptides are essential in nerve survival and have a role in the onset of hyperalgesia, pain and inflammation. (Imamura et al., 2019) It was found that prolonged exposure to capsaicin depletes substance p and calcitonin-gene-related peptide (CGRP), resulting in desensitizing peripheral nociceptors, and reducing pain and burning sensation in cases of BMS. (Yilmaz et al., 2007) Capsaicin is available topically as a cream and in oral rinse formulations of 0.025% or 0.02%, which may be used 3-4 times daily.(Miziara et al., 2015) Numerous research have looked into the effectiveness of topical capsaicin and they demonstrated significant positive outcomes on BMS with no remarkable reported side effects.(Miziara et al., 2015; Petruzzi et al., 2004) However, the initial burning that can be encountered by patients is widespread and can affect patient compliance, and patients should be warned about it.(Nasri-Heir et al., 2015) A number of studies have looked into the effectiveness of the use of systemic capsaicin (0.25% capsules /three times a day) to reduce pain intensity in BMS patients. The outcome has been

Table 2: Topical medications used to treat BMS with suggested doses and references.

Medication classification	Medication	Dose	Reference
Benzodiazepine	Clonazepam disintegrating tablets 0.5 mg	1-3 times/day	(Rodriguez de Rivera Campillo et al., 2010)
Antidepressant	Doxepin suspension (5mg/mL)	3-6 times/day	(Jayakrishnan et al., 2015)
Other	Capsaicin rinse (250 mg/50 mL)	Three times/day	(Marino et al., 2010)

Table 3: Systemic medications used to treat BMS with suggested doses and references.

Medication classification	Medication	Dose	Reference
Anticonvulsant	Gabapentin	300-3600 mg /daily	(Wiffen et al., 2017)
Benzodiazepine	Clonazepam	-0.25-0.5 mg daily for 1 week ;Increase to 3 times daily , a maximum of 2 mg/ day	(Heckmann et al., 2012)(Salih Levent Çınar, 2018)
Antidepressant	Amitriptyline	25 mg at bedtime ; increase 25 mg every 3 to 7 days not exceeding 125 mg	(Moore et al., 2012)
	Desipramine	100 -150 mg daily	(Hearn et al., 2014)
	Nortriptyline	10 mg daily at bedtime; increase to 75 mg daily	(Derry et al., 2015)
	Paroxetine	10-20 mg/day; increase to a maximum of 30 mg/day	(Yamazaki et al., 2009)
	Fluoxetine	20-40 mg/day with titration	(Zoric et al., 2018)
	Citalopram	10 -20 mg with titration	(Pakfetrat et al., 2019)
	Duloxetine	20-40 mg/day	(Nagashima et al., 2012)
Others	Alpha lipoic acid	200 mg 3 times/day with tongue protector	(Spanemberg et al., 2012)

positive, however ,gastric pain has been reported as a side effect. (Petruzzi et al., 2004) In a study by Marino et al, topical capsaicin (250 mg/50 mL), lactoperoxidase lysozyme and α-lipoic acid (ALA) 800 mg/d were compared to placebo and the results showed significant symptoms improvement. (Marino et al., 2010) Tables (2&3)

On the other hand, lidocaine and 0.15% benzydamine hydrochlorate possess both anesthetic and anti-inflammatory properties and have been used with minimal efficacy due to the temporary relief of symptoms.(Salerno et al., 2016; Sun et al., 2013) Comparably, one randomized, double-blind, clinical study showed that topical application of 0.5 ml of Aloe vera at 70% has shown to be effective in reducing BMS symptoms when used three times daily combined with a tongue protector. (Lopez-Jornet et al., 2013)Tables (2&3)

In general, as discussed earlier, no specific guideline on the selection of topical and systemic pharmacotherapeutics is currently available in the litrature. The medication selection is based mostly on available randomized controlled trials RCT results. However, a recent systematic literature analysis of randomized controlled trials (RCTs) on the efficacy of topical drugs for treating BMS found that there is insufficient convincing evidence on the short- and long-term results to either support or oppose the use of any particular topical treatment for BMS management. (Goncalves et al., 2022) A similar systematic review and meta-analysis on the systemic medications showed variable levels of evidence for the effectiveness of some systemic treatments for BMS. (Farag et al., 2021) Also, a recent systematic review on treating BMS concluded that topical capsaicin and clonazepam, along with other non-pharmacotherapeutic options such as cognitive behavior therapy and laser therapy, showed favorable outcomes in both short- and long-term assessment. (Tan et al., 2022) Furthermore, a slight improvment in pain score was observed with the administration of alpha lipoic acid (ALA); nevertheless, its beneficial effects were more pronounced in long-term evaluations. (Tan et al., 2022) Overall, this suggests that more RCTs with standardized outcome measures are needed.

CONCLUSION AND RECOMMENDATION

BMS is a multifactorial disorder with several questions remaining unanswered concerning its etiology. Treating patients with BMS requires a multidisciplinary approach including medical and psychosocial therapy. However, further studies are necessary to establish a long-term prognosis. Different therapeutic modalities are available for management of BMS but pharmaceutical intervention may be the first line approach for some patients . Dentists and other healthcare professionals should remain updated on therapeutic advances in this field to provide better management for their patients.

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