

Burning mouth syndrome: Current concepts

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Abstract

Burning mouth syndrome (BMS) is a chronic pain condition. It has been described by the International Headache Society as “an intra-oral burning or dysesthetic sensation, recurring daily for more than 2 h/day for more than 3 months, without clinically evident causative lesions.” BMS is frequently seen in women in the peri-menopausal and menopausal age group in an average female/male ratio of 7:1. The site most commonly affected is the anterior two-thirds of the tongue. The patient may also report taste alterations and oral dryness along with the burning. The etiopathogenesis is complex and is not well-comprehended. The more accepted theories point toward a neuropathic etiology, but the gustatory system has also been implicated in this condition. BMS is frequently mismanaged, partly because it is not well-known among healthcare providers. Diagnosis of BMS is made after other local and systemic causes of burning have been ruled out as then; the oral burning is the disease itself. The management of BMS still remains a challenge. Benzodiazepines have been used in clinical practice as the first-line medication in the pharmacological management of BMS. Nonpharmacological management includes cognitive behavioral therapy and complementary and alternative medicine (CAM). The aim of this review is to familiarize healthcare providers with the diagnosis, pathogenesis, and general characteristics of primary BMS while updating them with the current treatment options to better manage this group of patients.

Key Words: Burning mouth syndrome, neuropathic pain, orofacial pain

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INTRODUCTION

Burning mouth syndrome (BMS) is an intraoral chronic pain condition characterized by intra-oral burning sensation. According to the International Headache Society, BMS is described as “an intra-oral burning or dysesthetic sensation, recurring daily for more than 2 h/day for more than 3 months, without clinically evident causative lesions.”^[1]

The International Association for the Study of Pain defines BMS as “burning pain of the tongue and/or other oral mucous membrane in the absence of clinical signs or laboratory findings.”^[2]

TERMINOLOGY/CLASSIFICATION

Various synonyms such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral

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dysesthesia have been used to describe the burning sensation. Moreover, several classifications have been proposed in the literature in an attempt to better categorize this syndrome. Lamey and Lewis suggested classifying BMS as three different subtypes according to the variations in pain level over 1 day as follows: BMS type 1: Burning increasing throughout the day and reaching its peak in the evening. BMS type 2: Characterized by the complaint of continuous sensory disturbances. BMS type 3: Intermittent symptoms with pain-free periods during the day.^[3] Recently Scala *et al.* have proposed the terms: “Primary BMS” (idiopathic/essential condition where no local or systemic cause for the burning can be identified) and “secondary BMS” (an organic local or systemic cause for the intra-oral burning sensation is present).^[4] For the remainder of this article essential/idiopathic BMS will be discussed as “BMS.”

EPIDEMIOLOGY/CLINICAL PRESENTATION

Due to the shortage of universally accepted diagnostic criteria, accurate BMS epidemiological data are difficult to collect. Currently, the prevalence of BMS in the general population is estimated to be 0.7% to 15%.^[5] The management of BMS is still a challenge. The prognosis is poor, and the literature reports complete spontaneous remission in only 3% of the patients within 5 years after the onset of BMS.^[6,7] This chronic pain condition predominantly affects middle-age women in the peri- and post-menopausal period, though men can also be affected in an average female/male ratio of 7:1.

The most affected site is the anterior two-thirds of the tongue, followed by the palate although multiple oral sites may be involved.^[8,9] The onset can be spontaneous (and increases gradually in intensity) or after a precipitating event which can include dental procedures (e.g., dental cleaning, insertion of a denture). Patients usually report no pain or that the burning sensation presents its lowest intensity upon awakening, starting after the first meal of the day.^[10] Once initiated, it is continuous, reaching the maximum intensity by late evening. Although waking up during sleep due to the pain is uncommon, BMS patients present with a decrease in sleep quality and sleep disorders might increase the risk of BMS.^[11,12]

Along with the burning sensation, the patient may also report associated symptoms such as alteration in taste (dysgeusia or “taste phantom”) and oral dryness (xerostomia), reflecting changes involving taste and oral somatosensory perception. Bitter and metallic tastes are the “taste phantom complaints” most commonly reported. Other changes in somatosensory perception can also include a feeling of “roughness,” “sandiness,” and dry mucosa although the salivary flow is normal.^[13,14]

Stress, fatigue, and speech might increase the intraoral burning sensation while eating and leisure time might decrease the burning sensation.^[10] The constant intraoral burning pain severely affects the patient’s quality of life.^[16] As in any chronic pain condition, irritability, depression, and decrease of sociability are commonly reported among BMS patients; however, their role in the pathogenesis of BMS remains unclear.^[17,18] As, most healthcare providers are not aware of BMS and furthermore this condition is not common, patients may think they have a malignant disorder, and consequently experience cancer-phobia. Therefore, it is very important to clarify to the patient that BMS is a benign condition, yet difficult to manage.

ETIOLOGY

To date, BMS etiology remains unclear and not fully understood. Patton *et al.* suggested that in a large percentage of patients, BMS probably involves interactions among local, systemic, and psychogenic factors.^[19] A review of the literature shows that some authors believe BMS etiology could be related to local factors such as saliva composition, mucosal blood flow, inflammation, and changes in cell morphology.^[20-23] However, the most recent literature presents a growing body of evidence suggesting that BMS has a neuropathic etiology.^[24-27] Jääskeläinen *et al.* and Hagelberg *et al.* demonstrated the involvement of the dopaminergic system in BMS patients.^[28,29] Lauria *et al.* observed through tongue biopsies morphological changes reflecting axonal degeneration and hypothesized that trigeminal small-fiber sensory neuropathy is involved in BMS etiology.^[30] Woda *et al.* proposed that neurodegeneration associated with the drastic decline of neuro-steroids following the concomitant falls of gonadal and adrenal steroids as a possible mechanism for BMS.^[31] Zidverc-Trajkovic *et al.* found that levels of calcitonin gene related peptide, which is implicated in the development of pain and hyperalgesia were not elevated in saliva of BMS patients and proposed that trigeminal nerve degeneration may be the underlying cause of BMS.^[32]

Recently, the role of the gustatory system in BMS has been implicated as shown by the following facts. Seventy percent of BMS patients report “phantom taste” which is a disorder of the gustatory system.^[33,34] Eating often relieves the burning sensation (particularly sweets), suggesting that the decrease in pain might be related to the stimulation of the gustatory system.^[35] It is notable that the most commonly affected site in BMS is the anterior two-thirds of the tongue, which is also where the largest number of taste buds is located.^[36,37] Moreover, an association between taste and oral pain has been described previously in the literature.^[38,39]

Grushka and Bartoshuk suggested that taste alterations could be explained by damage to any special sensory nerve responsible for carrying taste, that is, glossopharyngeal, vagus, chorda tympani, and greater petrosal nerve. According to them, damage to any nerve that supplies taste affects the central inhibitory mechanism normally present between them. The authors propose that as this inhibition also occurs between the chorda tympani and lingual nerves, damage to the first consequently results in exacerbation of general sensation, such as pain, carried by the latter. Eliav *et al.*, using quantitative sensory testing, demonstrated the hypofunction of the chorda tympani nerve in BMS patients, providing support for this hypothesis.^[40] Furthermore, Nasri-Heir *et al.*, 2011 demonstrated that BMS patients with complaints of longer durations presented with a significantly elevated tingling/taste electrical detection threshold ratio, indicating a possible neurodegenerative process, pointing to the hypofunction of the chorda tympani.^[41]

An additional theory supporting the role of the gustatory system in BMS pathophysiology suggests that individuals genetically endowed with a large number of fungiform papillae for which the taste sensation is innervated by the chorda tympani (“supertasters”) might be more predisposed to develop BMS.^[10] Therefore, there is greater potential for loss of inhibition, in these individuals, if damage to the chorda tympani occurs. However, Nasri-Heir *et al.*, and Camacho-Alonso *et al.* (2012) did not find any significant difference between the numbers of fungiform papillae in BMS subjects compared to controls.^[41,42] Nevertheless, these findings do not negate the role of fungiform papillae in the pathogenesis of BMS.

Recently, Jääskeläinen, based on neurophysiologic, psychophysical, neuropathological, and functional imaging studies results concluded that several neuropathic mechanisms, mostly subclinical, act at different levels of the neuroaxis and contribute to the pathophysiology of BMS.^[43] According to the author, there are at least three distinct, subclinical neuropathic pain conditions that may overlap in BMS patients. The first subgroup (50–65%) is categorized by peripheral small diameter fiber neuropathy of intraoral mucosa. The second subgroup (20–25%) comprises of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be separated with detailed neurophysiologic examination; however, cannot be distinguished clinically from the other two subgroups. The third subgroup (20–40%) is included in the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia. Thus, BMS patients may benefit from treatments that would specifically target the mechanism involved in each individual case. Nonetheless, BMS etiology is still not fully understood and further research is necessary.

DIAGNOSIS

It is essential that the healthcare provider is able to differentiate primary BMS from secondary BMS. When the cause can be identified as in the case of secondary BMS, it should be treated and the symptoms should successfully disappear. The diagnosis of BMS is based on the exclusion of all possible local and systemic factors that are known to cause burning mouth sensation. Local causes that may cause burning can include but are not limited to:

- Fungal infections (e.g., arising from poor hygiene, secondary to systemic conditions such as diabetes, or immunosuppression and xerostomia)
- Mechanical trauma (e.g., from poorly fitting prostheses, sharp edges of teeth, rough restorations)
- Thermal injury (e.g., from hot foods, liquids)
- Chemical injury (e.g., from abrasive toothpastes, root canal irrigating solutions).
- Hyposalivation/xerostomia (e.g., consequence of radiation therapy, or salivary gland disorders)
- Parafunctional habits (e.g., clenching, tongue thrusting)
- Oral mucosal lesions (e.g., secondary to systemic conditions such as lichen planus or local lesions like benign migratory glossitis [geographic tongue])
- Allergic contact stomatitis (e.g., secondary to denture base materials, e.g., monomer and other dental materials [Table 1]).

Systemic conditions that can cause oral burning include:

- Deficiencies due to iron, zinc, folate, and Vitamins B1, B2, B6, B12
- Endocrine disorders, e.g. diabetes and thyroid imbalance
- Immunological disorders as Sjögrens syndrome
- Gastroesophageal reflux disease
- Medications that augment/induce burning (e.g. angiotensin converting enzyme inhibitors) or have xerostomia as their side effect [Table 2].

Table 1: Substances that may cause intra-oral allergic reaction

Chemicals	Where it can be found
Zinc, cobalt, mercury, gold, and palladium	Dental materials
Nickel sulfate	Dental materials Stainless steel Food (e.g., shrimp and chocolate milk)
Sodium lauryl sulfate	Toothpaste
Fragrance mix	Oral care products
Balsam of Peru	Oral care products Citrus fruits Spices Cough medicine and lozenges
Cinnamic alcohol	Cinnamon and products with cinnamon flavor

Jensen and Barkvoll 1998; Steele *et al.*, 2012; Lynde *et al.*, 2014; Coculescu *et al.*, 2014

As part of a thorough workup, it is very important to collect a detailed history of presenting illness including location of the pain; onset (spontaneous or related to a precipitating factor); intensity and its variations throughout the day; frequency; duration (greater or lesser than 3 months to establish chronicity); aggravating factors (e.g., type of food, talking, stress); and alleviating factors (e.g., eating/not eating, type of food, relaxation). Medical history and review of systems should be carefully evaluated, for conditions such as anemia, diabetes, thyroid disease, or whether the patient is undergoing menopause or has the immunologic disease.^[44] Moreover, all past and current medications, which have a potential to cause intraoral burning as a direct/indirect side effect, should be recorded (e.g., angiotensin converting enzyme inhibitors).

A thorough and careful intra-oral exam should be performed looking for clinical signs that could explain the burning sensation including candidiasis, xerostomia, parafunctional habits. The possibility of thermal or chemical injury should be ruled out. Examination should also include looking for intraoral clinical signs of systemic diseases such as lichen planus.

Laboratory studies should be part of the diagnosis process and should include:

- Basic metabolic panel: Glucose serum levels to rule out diabetes or hemoglobin A1C levels to indicate if diabetes is under control
- Iron serum levels/ferritin, Vitamin B₁₂ and folate levels to rule out associated anemias
- Antinuclear antibodies, antiRo/SS-A, antiRo/SS-B and rheumatoid factor, to rule out Sjögren's syndrome
- Complete blood count to evaluate the patient's general health status

Table 2: Medications that possibly cause hyposalivation/xerostomia as a side-effect

Medications	Examples (generic)
Tricyclic antidepressant	Amitriptyline, nortriptyline
Antipsychotic	Carbidopa/levodopa, chlorpromazine
Antihistaminic	Phenergan
Bronchodilator	Tiotropium, formoterol
(anticholinergic and β-2 agonist)	
Decongestant	Oxymetazoline
Antidepressant	Venlafaxine
Skeletal muscle relaxant	Tizanidine
Antihypertensives	Furosemide, clonidine, lisinopril, verapamil
Chemotherapy	Cyclophosphamide
Protease inhibitor (for HIV)	Reyataz, Norvir, Kaletra
Opioid	Hydrocodone, oxycodone
Benzodiazepine	Diazepam
Triptan	Rizatriptan

Atkinson *et al.*, 1989; Fox 1998; Bergdahl and Bergdahl 2000; Saleh *et al.*, 2015

- Cytological smears if Candidiasis is suspected
- Salivary flow rates to rule out xerostomia
- Skin patch tests can be ordered if an allergic reaction is suspected.

If BMS symptoms are associated with numbness or dysesthesia, ordering a magnetic resonance imaging study is prudent to rule any underlying central nervous system pathology.^[15]

On the follow-up visit, the information collected from the history, physical exam and laboratory exams are evaluated to identify possible local or systemic etiology. The successful treatment of such causes should result in remission of the burning mouth sensation. When no local or systemic cause is identified, the oral burning is the disease itself and therefore, the patient will receive the BMS diagnosis.

TREATING BURNING MOUTH SYNDROME

The management of BMS still remains a challenge. Knowledge of the etiology and pathophysiology is still limited.^[19] It is difficult to target the treatment of a condition, where the mechanism involved is not fully understood.

Furthermore, it is important to emphasize that the health care provider needs to be knowledgeable to receive a BMS patient in their office. They are usually anxious, depressed, tired and frustrated due to previous unsuccessful treatments, numerous visits to multiple health care providers with limited knowledge of their condition, and promises of “cure” not kept. They are frightened because no diagnosis is given and they are often financially drained from numerous expensive and unsuccessful treatments. It is very important to be patient with them, listen to their complaints and above all, believe in their complaint.^[45]

Although the literature presents several studies, there is only limited evidence to guide clinicians in the management of patients with BMS. Treatment can be divided into pharmacological and nonpharmacological approaches.

Pharmacologic

Systemic

Benzodiazepines have been used in clinical practice as the first-line medication for treatment of BMS and the literature supports its efficacy. Studies have shown a decrease of pain levels with clonazepam, a gamma amino butyric acid (GABA) agonist. GABA is a neurotransmitter possibly involved with taste,^[46] reinforcing the evidence that BMS is probably a neuropathic pain condition involved with the gustatory system. Grushka *et al.* reported a 70% reduction in pain levels with the oral administration of clonazepam, 0.5–1.5 mg/day in divided doses to a maximum of 3 mg/day.^[47] Heckmann *et al.*,

demonstrated in a double-blind randomized controlled study that treatment with clonazepam 0.5 mg/day significantly reduced pain levels in BMS patients compared to controls after 9 weeks of treatment. However, there was no follow-up.^[48] Interestingly, Ko *et al.* (2012) evaluated the outcome predictors affecting the efficacy of clonazepam and they found that those with greater symptom severity of taste disturbance and xerostomia at baseline, showed better therapeutic results after clonazepam therapy than those without those complaints; and patients with tongue symptoms had a significantly decrease in pain compared to those with intraoral symptoms excluding the tongue.^[49]

The use of anticonvulsants in BMS is controversial. White *et al.*, reported favorable results in an open label study using gabapentin 300 mg/day in BMS patients.^[50] However, Heckmann *et al.*, 2006, did not confirm their results.^[51] Antidepressants also have been used to treat BMS patients. Tricyclic antidepressants (TCA) have been demonstrated to be beneficial in relieving the pain in low doses of 10–40 mg/day. Nevertheless the side effect of decreased salivary flow is undesirable, specifically in BMS patients.^[14]

Medications that act on the reuptake of serotonin and noradrenaline, such as selective serotonin reuptake inhibitor (SSRI) have also been used in the management of BMS. Yamazaki *et al.*, demonstrated in an open label, noncomparative, prospective study using paroxetine (SSRI) with an initial dosage of 10–20 mg/day, increased to a maximum of 30 mg/day, about 80% of patients experienced pain reduction within 12 weeks.^[52]

Serotonin noradrenaline reuptake inhibitor is thought to be associated with less frequent and milder adverse reactions relative to TCAs. Ito *et al.*, found a significant decrease in pain levels after 12 weeks of treatment with milnacipran 15 mg/day to 100 mg/day.^[53] Kato *et al.*, in a 12-week open study confirmed the improvement reporting that at least 50% reduction on the visual analog scale was achieved in BMS patients after treatment.^[54] However, Sugimoto 2011 suggested that a randomized, double-blind, placebo-controlled multi-institution trial of milnacipran is necessary to establish the effectiveness of milnacipran in BMS treatment.^[55] Nagashima *et al.*, 2012 reported a decreased in pain levels using duloxetine initial dose 20 mg/day up to 40 mg/day for 12 weeks.^[56]

The literature also reports the improvement of BMS symptoms using atypical antipsychotics as olanzapine.^[57] In a pilot study using amisulpride (antipsychotic, specific blocker of dopamine D₂ and D₃) 50 mg/day for 24 weeks, Rodriguez-Cerdeira and Sanchez-Blanco found that it is effective and well-tolerated as a short-term treatment.^[58] It is mainly efficacious at the beginning

of the treatment. However, double-blind placebo-controlled trials are needed.

Maina *et al.* in a single blind randomized study compared the effect of paroxetine 50 mg/day, sertralina 50 mg/day, and amisulpride 50 mg/day. After 8 weeks, they concluded that amisulpride and SSRIs are equally effective and well-tolerated in the short-term treatment of BMS. Amisulpride is associated with shorter response latency in comparison with SSRIs.^[59]

Grushka, 2005 has suggested that the combination of medications such as benzodiazepines, gabapentin, and TCA could be more efficient in treating BMS. According to the author, low doses of several medications might be more effective, as this reduces the undesirable side effects provoked at higher doses.^[60]

Femiano *et al.* based on the possibility that BMS may be related to free toxic radicals, suggested in a series of studies that the use of lipoic acid as a successful alternative treatment for BMS. Alpha-lipoic acid (ALA), is a potent antioxidant, with neuroprotective effects.^[61–63] However, other studies performed by Carbone *et al.*; López-Jornet *et al.*, Cavalcanti and da Silveira^[64–66] did not confirm their results.

López V. *et al.* (2009) demonstrated in a randomized placebo double-blind study that ALA used in combination with gabapentin is more efficacious than ALA or gabapentin alone because they target different nociceptive mechanisms.^[67]

In a pilot study, Petruzzi *et al.*, used systemic capsaicin 0.25% 3x day and had a significant reduction in pain levels though 32% reported major gastric pain.^[68]

Recently, Toida *et al.*, reported in a randomized controlled trial a significant improvement in pain levels of BMS patients using lafutidine, 10 mg twice daily for 12 weeks, lafutidine is a histamine H₂ receptor antagonist that has a sensitive effect on capsaicin-sensitive afferent neurons. According to the authors, oral administration of lafutidine is safe and effective in reducing oral burning symptoms.^[69]

Topical

The use of topical clonazepam has been suggested in the literature. Woda *et al.*, in a study with 25 patients, dissolved clonazepam 1.0 mg, 3 times/day for 3 min in the mouth with 66% of patients reporting a reduction in symptoms, and 29% reporting partial reduction in symptoms after 6 months.^[70] Gremeau-Richard *et al.* (2004), in a randomized placebo-controlled study instructed the patients to suck a tablet of 1 mg of clonazepam (or placebo) and hold their saliva near the pain location without swallowing for 3 min and then to

spit. This protocol was repeated 3 times a day for 14 days. The authors then concluded that topical administration of clonazepam improves intraoral burning sensation in some but not in all BMS patients.^[71] Rodríguez de Rivera Campillo *et al.* also reported benefits of using clonazepam topically.^[72]

Besides clonazepam, topical capsaicin can also be used as a substitute, although the initial burning provoked when applied is undesirable by the BMS patient, and therefore, it is difficult to obtain the patient's compliance.^[73] Silvestre *et al.* in a prospective, double-blind crossover study concluded that capsaicin rinse (0.02%) for one week was effective however its use presents some limitations.^[74]

The use of benzydamine as a mouth rinse is also controversial. Sardella (1999) in a double-blind, randomized longitudinal study found no significant efficacy between placebo/benzzydamine hydrochloride 0.15% oral mouthwashes 3 times a day for 4 weeks/no treatment group.^[75]

Nonpharmacological

Cognitive behavioral therapy has been shown to improve the symptoms in BMS. Bergdahl *et al.* showed that CBT reduced the symptom intensity in BMS patients for 6 months.^[76]

Miziara *et al.* demonstrated that in patients who were treated with group therapy there was a 70% improvement in the BMS group as compared to the placebo group. Groups sessions seem to serve as a support group where patients share information about their symptoms and fears, improve their understanding of the disease, helping them accept and be compliant with the recommended treatment.^[77] Cognitive behavioral intervention can increase knowledge of the causes and treatment of BMS, helps to provide skills to self-monitor the condition and to introduce strategies to manage the constant, persistent pain. This was confirmed by Komiyama *et al.* where they showed that pain intensity and disturbance to daily life significantly decreased from the first to the second session.^[78]

Complementary and alternative medicine (CAM) might be another option for BMS patients. In a study reported by López-Jornet *et al.* on 82 BMS patients, 40 (24%) already included CAM in their treatment plan. 39.3% found it to be effective.^[79] Acupuncture has been raised as another option for BMS treatment.^[80,81] However, more studies are needed to study its effectiveness in the management of BMS. The use of laser therapy remains controversial in treating BMS.^[82,83]

CONTROL OF LOCAL FACTORS AND DIET

It is important to note that primary and secondary BMS can occur concurrently. As BMS affects older individuals is important

be aware that as this population usually presents with several comorbidities and usually take medications (that could have unfavorable side effects including intraoral burning sensation) the two conditions can occur simultaneously.^[84] Therefore, it is very important to identify and control local factors in BMS patients. Xerostomia, candidiasis, local trauma provoked by dentures or sharp dentition and restorations, and parafunction could amplify and perpetuate the intraoral burning sensation.^[85]

Moreover, any factor including foods/habits that can add to or exacerbate symptoms should be managed or avoided, such as eating acidic foods (i.e., pineapple, tomato, orange, lemon, etc.), alcohol and smoking, mouth rinses with alcohol and toothpaste with abrasive substances.

FUTURE DIRECTIONS

Although there are still many questions to be answered, the current research on this challenging chronic pain condition looks encouraging. The use of quantitative sensory testing by means of electric taste/tingling detection threshold ratio has been demonstrated to be a reliable tool to support clinicians on making a diagnosis of BMS.^[40,41] Limitations include the high cost of the device.

Recently, there is an increased interest in using saliva for BMS biomarkers.^[22,86,87] Saliva is a natural oral fluid, easy to collect through a noninvasive and nonstressful method. It is inexpensive and easy to store and ship. This makes the oral fluid a valuable diagnostic tool. However, more research is necessary to validate this method.^[87]

The involvement of TRPV1 (transient receptor potential channel) and nerve growth factor (NGF), which are both involved in the generation of chronic pain, has been demonstrated in BMS. Therefore, selective TRPV1 and NGF blockers may provide a new therapy in the future.^[88]

CAM has become an increasingly popular method of treating chronic pain either alone or as a complement to traditional medical approaches while presenting with no undesirable side effects.^[79] Therefore, it may be a valuable tool to manage BMS.

Finally, future research should focus on developing a uniform definition and diagnostic criteria, developing profiles for groups at risk for developing BMS, elucidating the mechanisms involved and designing better studies involving various treatment options with long-term follow-ups.^[19]

CONCLUSIONS

BMS remains a challenge to clinicians and researchers. To date, there is no specific management for BMS. Patients should be

made aware that the symptoms might not totally resolve even after long-term treatment. The support, attention and concern of the healthcare provider combined with patient education are fundamental components to successful management. Perhaps symptoms will not entirely disappear, but certainly, the quality of life can be enhanced.

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