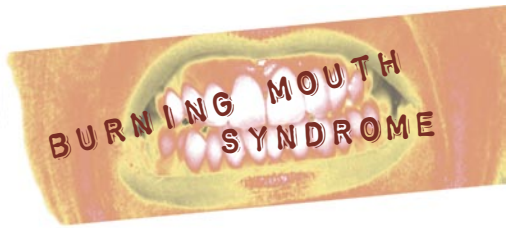

Burning Mouth Syndrome: An Update on Diagnosis and Treatment Methods

Piedad Suarez, DDS, and Glenn T. Clark, DDS, MS

ABSTRACT

Burning mouth syndrome is characterized by both positive (burning pain, dysgeusia and dysesthesia) and negative (loss of taste and paraesthesia) sensory symptoms involving the lips and tongue, mainly the tip and anterior two–thirds. BMS patients report a persistently altered (metallic) taste or diminished taste sensations. Acidic foods such as tomatoes and orange juice cause considerable distress. Most of the common laboratory tests suggested for BMS patients will be negative as well. BMS is best subcategorized as primary BMS, no other evident disease, and secondary BMS, which is defined as oral burning from other clinical abnormalities. The presence of BMS is very uncommon before the age of 30; 40 years for men. The onset in women usually occurs within three to 12 years after menopause, and is higher in women who have more systemic disease. Quantitative assessment of the sensory and chemosensory functions in BMS patients reveals that the sensory thresholds (significantly higher) are different than in controls.

Tongue biopsies have shown that there is a significantly lower density of epithelial nerve fibers for BMS patients than controls. The above data generally support the idea that BMS is a disorder of altered sensory processing which occur following the small fiber neuropathic changes in the tongue. BMS patients frequently have depression, anxiety, sometimes diabetes, and even nutritional/mineral deficiencies, but overall these co-morbid diseases do not fully explain BMS. The management of BMS is still not satisfactory, but because BMS is now largely considered to be neuropathic in origin, treatment is primarily via medications that may suppress neurologic transduction, transmission, and even pain signal facilitation more centrally. Finally, spontaneous remission of pain in BMS subjects has not been definitely demonstrated. The current treatments are palliative only, and while they may not be much better than a credible placebo treatment, few studies report relief without intervention.

Imagine the frustration of having a continuous painful disorder that cannot be definitively diagnosed with any known test or X-ray, interferes with eating, becomes progressively worse with time, has no known cause, and for which there is no highly effective treatment. This is what patients with burning mouth syndrome deal with every day of their lives. BMS typically has a spontaneous onset, although its intensity will increase gradually over time. It is characterized by both positive (burning pain, dysgeusia and dysesthesia) and negative (loss of taste and paraesthesia) sensory symptoms. The primary location for these symptoms are the lips and tongue, mainly the tip and anterior two–thirds. BMS patients complain also of sensory discomfort in the hard palate and alveolar ridges.

Conversely, the buccal mucosa and the floor of the mouth are almost never involved.[1] At least for the tongue, the anatomic distribution of the burning pain in BMS patients corresponds to a great degree where taste bud density

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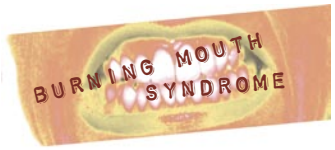


is greatest in the mouth. For example, Miller examined taste bud density on the tongue and found that taste bud density was 4.6 times higher on the tip than the mid-tongue region.[2] However, since taste buds are not commonly located on the inner lip mucosa, anterior hard palate or alveolar ridges, this association between taste buds and BMS is not absolute. Nevertheless, most BMS patients report a persistently diminished taste or altered (metallic) taste sensations. Acidic foods such as tomatoes and orange juice cause considerable distress with an increase in burning sensations. These descriptions vary but often include a stinging-burning sensation as if they have scalded the mucosa. Finally, in spite of the vividly described irritated or raw feeling in their oral tissues, most of the time, the tissues appear normal to visual inspection. Most of the common laboratory tests suggested for BMS patients (described later) will be negative as well.[3]

BMS has various synonyms such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral dysesthesia. These terms are used to emphasize the quality and/or the location of pain in the oral cavity. The International Association for the Study of Pain has identified BMS as a distinctive named entity characterized by oral burning pain episodes lasting at least four to six months.[4] The International Classification of Disease (version 9) has assigned the term glossodynia, which included the subterms glossopyrosis and painful tongue a specific identity code number (ICD-9 #529.6).[5]

A recent paper suggested that a subpopulation of BMS cases presents with a common triad of symptoms including idiopathic sensorial disturbance of burning mouth, taste disturbance (dysgeusia), and dry mouth.[6] Another paper suggested three subgroups with type 1 being characterized by burning pain increasing throughout the day and reaching its peak in the evening. Type 2 was characterized by complaints of continuous sensory disturbances, and type 3 had intermittent symptoms with free-pain periods during the day.[7] The most pragmatic method of grouping BMS is by dividing patients into the primary BMS sufferers (no other evident disease) and secondary BMS sufferers (defined as oral burning from other clinical abnormalities). In fact, using this classification scheme, one paper examined 69 BMS patients (83 percent female) and asked them to fill out both the Multidimensional Pain Inventory and Symptom Checklist 90-Revised.[8] They found that the primary BMS patients and the secondary BMS patients showed no differences with respect to age, pain duration, pain intensity, or levels of psychologic distress. The only substantial difference was that if the associated clinical abnormality was treatable, then the burning sensations would improve in the secondary BMS group, whereas the primary BMS group did not demonstrate remarkable symptom cessation with treatment.

In spite of the vividly described irritated or raw feeling in their oral tissues, most of the time, the tissues appear normal to visual inspection.

Epidemiology

Burning mouth symptoms are reported in up to 4 percent of adults, and this percentage increases with age being more prevalent in the fifth to seventh decade. One study surveyed 669 men and 758 women randomly selected from 48,500 individuals between the ages of 20 and 69, and reported 53 individuals (3.7 percent) exhibited BMS (11 men or 1.6 percent and 42 women or 5.5 percent).[9] The presence of BMS is very uncommon before the age of 30; 40 years for men. The onset in women usually occurs within three to 12 years after menopause and is higher in women who have more systemic disease.[10] Another epidemiologic study surveyed U.S. adults and estimated the overall prevalence of burning mouth to be 0.7 percent of the adults up to age 65.[11] This study was repeated on a subset of more than 5,800 individuals aged 65 or older in southern Florida.[12] They reported a prevalence of 1.7 percent for burning mouth pain in this elderly group. Clearly the differences in these prevalence figures are related to sampling bias in surveyed populations and disease definition being used.

Quantitative Sensory Testing in BMS

The frequent occurrence of numbness, pain and dysesthesia in BMS has prompted researchers to perform a quantitative assessment of the sensory and chemosensory functions in these patients. Until recently, researchers have not consistently found a statistically significant alteration in the sensory perception (touch and temperature) of BMS patients. For example, one study carefully examined 20 BMS patients versus 20 controls for different abilities to perceive different shapes of objects with

their tongue.[13] No systematic disparity was evident in the two groups regarding object size perception ability. Of course, detecting the shape of objects with one's tongue is not the only test of sensory acuity. Several years ago researchers used argon laser stimulation to examine 23 BMS subjects versus 23 age-matched controls for differences in their sensory and pain thresholds.[14] This study used brief laser stimulation to six test sites (tongue tip, lower lip mucosa and skin, buccal mucosa, anterior hard palate, and dorsum of the hand).

They reported the sensory thresholds were significantly higher and the ratios between pain and sensory thresholds significantly lower in patients with BMS at all tested sites. The resulting widespread sensory threshold differences seen in this study argues for a centrally mediated sensory amplification abnormality. Another study used an objective electrophysiological examination of the trigeminal-facial nerve system using the blink reflex response in 11 BMS subjects and 10 controls.[15] They reported BMS patients have clear-cut alterations in their blink response to applied stimulation. Finally, a study examined evoked brainwave potentials following lingual nerve stimulation in 22 BMS patients with pain, 10 BMS patients with reported numbness, and six controls.[16] They found that pain thresholds were significantly lower and evoked potential response latencies were significantly different (i.e., shorter) in the BMS with pain group. The latencies in the BMS with numbness group were significantly longer. Overall, these sensory data suggest that peripheral and/or central nervous system changes are clearly present in BMS but they do not pinpoint where in the somatosensory system changes are to be found.

Biopsy Evidence of BMS changes

Until recently, the primary site of pathology in BMS was not identified; therefore, no diagnostic test was available for this disorder. However, a new study investigated the innervation of the epithelium of the tongue in 12 chronic BMS cases and nine healthy controls using tongue tissue biopsies to assess whether damage of peripheral nerve fibers underlies the pathogenesis of the disease.[17] These researchers used immunohistochemical and microscopic methods to examine for nerve damage in the tongue. They reported a significantly lower density of epithelial nerve fibers for BMS patients than controls. The authors described epithelial and subpapillary nerve fibers changes suggestive of axonal degeneration. They concluded that BMS is caused by a trigeminal small-fiber sensory neuropathy.

BMS patients frequently report a positive taste sensation, which they describe as a persistently altered (metallic) taste.

Taste Changes and BMS

Dysgeusia is a term used to describe a distorted gustatory perception or persistent gustatory sensation in the absence of gustatory stimulants.[18] As mentioned earlier, BMS patients frequently report a positive taste sensation, which they describe as a persistently altered (metallic) taste. They also have a diminished ability to detect bitter flavors, and spicy and acidic foods increase their burning sensations. One recent study examined 50 patients with BMS (study group) and 50 healthy subjects (control group), and analyzed their ability to taste three flavors: bitter, acid, and spicy substances.[19] They found that taste sensation was normal in all controls, but in 30 of the BMS patients, they had a diminished response to bitter taste. The use of a spicy substance, pepper sauce, applied to the tongue produced a strong burning to the tongue in 28 patients of the BMS group but the same response was only seen in 10 of the controls.

Another study examined 180 subjects with complaints of BMS, xerostomia, and taste disturbances versus 90 age- and gender-matched healthy controls.[20] They also reported that the BMS patient group had clear-cut taste acuity differences compared to the controls with more of the BMS patients reporting sweet abnormality than with the other three taste substances: salt, bitter, and sour. Lastly, a study examined taste acuity in 73 BMS patients (57 women and 16 men) and 52 control subjects (38 women and 14 men) who were age- and gender-matched to the BMS group.[21] They used various concentrations of sweet, salty, sour, and bitter solutions, and asked subjects to rate the intensity and quality of each solution. They found that the 57 women in the BMS group gave lower intensity ratings for salty and sweet test solutions than the 38 women controls. They also found no group differences for these women on sour or bitter test solutions, but the men in this study showed no group differences on any of the substances tested. The above studies document that taste is consistently altered, although not in a consistent direction in BMS patients.

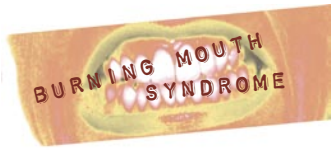


Table 1

Primary and Secondary BMS

Presumed Etiology	Clinical Presentation
PRIMARY BMS TREATMENT	
Nerve atrophy	**Focal neuropathic pain involving small fiber atrophy of the oral tissues.**
SECONDARY BMS TREATMENT	
Dry mouth (xerostomia)	Several medications cause decreased salivary flow (tricyclic antidepressants, central nervous system depressants, lithium, diuretics, and medications used to treat high blood pressure). It can also occur with aging or Sjögrens syndrome.
Oral infection	Yeast infections (thrush) have been seen in BMS patients and may be related to immune dysfunction (e.g., HIV), uncontrolled diabetes, poorly maintained/cleaned denture and certain immunosuppressive medications.
Autoimmune mucosal Rxns	Lichen planus and geographic tongue are conditions that are usually painless but sometimes cause a mucosal Rxns stomatitis and a sore, patchy tongue.
Nutritional deficiencies	Being deficient in nutrients, such as iron, zinc, folate (vitamin B-9), thiamin (vitamin B-1), riboflavin (vitamin B-2), pyridoxine (vitamin B-6) and cobalamin (vitamin B-12), may affect oral tissues and cause a burning mouth. These deficiencies can also lead to vitamin deficiency anemia and oral stomatitis.
Allergies	The mouth burning may be due to allergies or reactions to foods, food flavorings (especially cinnamon), other food additives, fragrances, dyes, or other substances. Similarly, direct chemical irritation and allergic reactions to dental materials may be a factor in burning mouth syndrome.
Reflux of stomach acid	The sour- or bitter-tasting fluid that enters the mouth from the upper gastrointestinal tract may cause irritation and pain.
Certain medications	Angiotensin-converting enzyme (ACE) inhibitors, used to treat high blood pressure, may cause side effects that include a burning mouth.
Endocrine disorders	Endocrine disorders such as diabetes and underactive or overactive thyroid are known to produce peripheral neuropathic pain and generalized hyperalgesia.

Since metallic dysgeusia is a common early symptom of a BMS disorder, it would be appropriate to review a recent article that describes medication induced dysgeusia.[22] This recent paper reported that the most commonly reported medications linked to metallic dysgeusia are those used to treat bacterial infections, psychosis, arthritis, and hypertension. Specifically, they found case reports for metallic dysgeusia linked with tetracycline, lithium carbonate, D-penicillamine, and catopril.[23-27] The Doty and Bromley review paper in 2004 also pointed out that sometimes the underlying medical problems for which medications are being prescribed are the real problem, especially when the disease affects the brain (e.g., epilepsy, migraines, hypothyroidism, schizophrenia).[28] Lastly, one 1985 paper described a link between metallic dysgeusia and Crohn's disease that is manifesting oral effects as well as the usual intestinal changes.[29]

In summary, metallic dysgeusia is not well understood, but in the absence of medications or a brain disease causing it, the possibility remains that it may be related to damaged peripheral nerves, especially considering the information already presented about small sensory fiber neuropathic changes in the tongue. The hypothesis that pain

Table 2

Diagnostic Test Used as Part of the BMS Diagnostic Process

Complete blood cell count (CBC)	This common blood test provides a count of each type of blood cell in a given volume of blood. The CBC measures the amount of hemoglobin, the percentage of blood that's composed of red blood cells (hematocrit), the number and kinds of white blood cells, and the number of platelets. This blood test may reveal a wide variety of conditions, including infections and anemia, which can indicate nutritional deficiencies.
Other blood tests	Because nutritional deficiencies are one cause of a burning mouth, running a test on the blood levels of iron, zinc, folate (vitamin B-9), thiamin (vitamin B-1), riboflavin (vitamin B-2), pyridoxine (vitamin B-6) and cobalamin (vitamin B-12) is important. Also, because diabetes causes neuropathic pain, a check may be done of the fasting blood sugar level.
Allergy tests	While it is not common, occasionally, testing to see if the patient may be allergic to certain foods, additives or even substances in dentures can be ordered through an allergist.
Oral swab culture or cytologic smear	If a fungal infection is suspected, a small tissue sample (biopsy) or an oral swab of the mouth for culture and examination may be ordered.
Tongue tissue biopsy	With the recent suggestion that small nerve fibers are depleted in the affected area, some special tests may be ordered when a biopsy is taken.

and taste pathway are both affected and interact is reasonable and certainly worthy of further testing, especially if an animal model could be developed.

Other Local Oral Factors and BMS

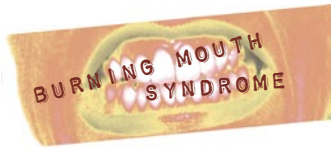
Many local and systemic precipitating factors have been suggested beyond the salivary changes and sensory dysfunction changes previously mentioned. The local factors included other diseases that may cause burning sensations such as oral candidal infections, autoimmune mucosal reactions like lichen planus and geographic tongue, and tissue trauma from ill-fitting dentures. Of course, there are always case reports of burning-type pain occurring from oral carcinomas that invade the trigeminal nerve and from a variety of local oral mucosal tissue irritants.[30] These local oral conditions have been seen often enough to suggest that some cases of BMS are secondary BMS cases.[31] Estimates are that more than one-third of all BMS patients presenting for diagnosis have multiple causes and the most common causes of secondary BMS are listed in **Table 1**.

Other Common Co-morbid Systemic Diseases

Various systemic conditions have been associated with BMS, including diabetes, hormonal changes and nutritional/mineral deficiencies. Because the condition is more prominent in female patients over age 40, most suffering from BMS are perimenopausal or postmenopausal at this stage in life.[32] Whether or not the hormonal changes in women that occur with menopause is causally related to BMS is not clear. One study examined this issue by looking at the effect of hormonal replacement therapy, HRT, on BMS. They found that HRT helped in 15 of 27 of their postmenopausal women with BMS.[33] Unfortunately, this study was an open label study and not a randomized, blinded, placebo-controlled study and thus the data are not convincing proof of a causal link between hormone alterations and BMS. Patients with BMS often have high blood glucose levels, but this does not occur on a consistent basis so no causal relationship has been demonstrated.[34] Next, nutritional deficiencies (vitamins B-1, B-2, B-6, B-12, iron, folic acid, zinc, etc.) is yet another reported systemic abnormality associated with BMS. Like hormonal status and diabetes, these suggested nutritional deficiencies are not consistently supported by the literature. Nevertheless, local and systemic factors must be ruled out before final diagnosis of BMS is made. The common diagnostic tests used for BMS are listed in **Table 2**.

Psychological Factors

Various psychological disorders, including depression, anxiety and soma-



tization, have been mentioned as playing a role in BMS.[35] One study examined 25 patients with a diagnosis of primary BMS and 25 age- and gender-matched patients with organically based painful disorders of the mouth and reported a positive psychiatric diagnosis in 44 percent (11/25) of the BMS patients but only in 16 percent (4/25) of the non-BMS controls of the patients with BMS. This study involved an interview by a psychiatrist and a questionnaire that screens for psychiatric disorders. While 44 percent seems a high number when compared to other chronic pain patients, this rate is not unusual or even high. For example, the same 28-item psychiatric screening questionnaire (general health questionnaire (GHQ-28)) used in the prior study was given to 31 consecutive primary BMS subjects. These authors found that although 51.9 percent of the patients showed evidence of psychiatric illness using the GHQ-28 questionnaire, this rate was similar or lower than what had been reported for other chronic pain subjects, except those attending a psychiatric clinic.[36] Anxiety is another often-reported feature of BMS patients and one study examined 74 BMS using a psychiatric interview plus the Hamilton's Depression and Anxiety Scales, HADS.[37]

This study reported a positive psychiatric diagnosis (mostly depression) was established in 38 of the 74 cases (51.4 percent). The HADS questionnaire data suggested that when anxiety was present, it strongly influenced the psychiatric condition of these patients. Findings of an elevated rate of positive findings when a systematic psychometric analysis of BMS patients is performed was confirmed again in a recent study, which examined 32 BMS patients and 32 matched control subjects using a comprehensive, reliable, and validated inventory.[38] Like the studies previously mentioned, results showed highly significant differences between the BMS group and the non-BMS controls with regard to several personality factors. Unfortunately, findings of high levels of anxiety, depression or even somatization tendencies are not unusual or unique to BMS patients.

Chronic pain patients in general have elevated findings when compared to age- and gender-matched nonpain patients. The question remains whether the pain is etiologically related to these personality characteristics or visa versa. In fact, recently, a report on 33 BMS patients suggested that psychological factors are not consistently elevated over control subjects in this population.[39] These authors used the revised Symptom Checklist (SCL-90R) and the Multidimensional Pain Inventory (MPI) on their BMS cases and compared the resulting data to data from population samples that included both non-BMS chronic pain patients and a normal nonclinical sample. They concluded the BMS patient scores were not significantly elevated on the measures of depression, anxiety, and somatization. They did note that 21 percent of the BMS cases (7/33) had a substantially elevated psychologic distress. Of course, the presence of co-morbid psychological disease would suggest treatment of these problems but is not evidence of causality.

Unfortunately, findings of high levels of anxiety, depression or even somatization tendencies are not unusual or unique to BMS patients.

Current Etiologic Theories

Searching for the causal link is one of the more difficult endeavors in science. It is a well-known scientific principle that association does not prove causality. Unfortunately, many authors have not made this point clear when reporting on clinical findings that are seen in association with BMS symptoms. For example, it is just as likely that the observed elevated depression and anxiety traits and the elevated somatic focus on their burning pains is an effect of the pain symptoms and not a causative factor. The same could be said about diabetes, menopause, candida infections and their relationship to BMS. For example, it is just as likely that the patients do not clean their mouth as well because of the burning and this causes candida overgrowth.

Other local factors and systemic factors could also be coincidental findings that may have no specific relationship to the causation of the BMS. To establish a causal link between two factors, one must have good consistency of data. This means that the association is present in all cases, no matter how many ways it is studied. The association should be strong and it should account for most of the variability seen in the data. There should be a positive dose-response relationship between the two associated factors. This means that when you have a small amount of the predictor, you see only a small amount of outcome. As the predictor increases so does the outcome response. A bio-

logically plausible explanation must be available regarding how the predictor variable causes the outcome and the suggested association must be independently verified.

Given the mentioned caveats, there are two current hypotheses for BMS worth discussing. The first deals with the interplay of sensory and taste systems which innervate the tongue. The anterior two-thirds of the tongue send taste sensations centrally via the chorda tympani nerve. Nontaste sensations are supplied by the trigeminal nerve (lingual branch). The essential theory is that burning mouth pain symptoms occur when there is an abnormal interplay between lingual nerve function and chorda tympani function.[40,41] These authors have further speculated that there is a specific group of patients at risk for developing burning mouth pain who have a large number of fungiform papillae. They speculate that individuals with increased fungiform papillae innervation (labeled as supertasters) are more at risk for disturbance of the balance between these two nerves (trigeminal and chorda tympani). In other words, if there is damage to the chorda tympani nerve over time, they have the greatest potential to develop pain and taste alterations (dysgeusia). At present, this theory is lacking definitive data that a high prevalence of BMS patients are indeed supertasters.

Their second theory is similar but does not require a disturbed interplay between taste nerves and sensory nerves. It is based on two new studies that suggest that BMS is due to small fiber neurologic damage in the oral cavity. Of course, the idea that a neuropathic change may underlie BMS is not new, but strong evidence supporting this idea has been lacking. The first study of significance is one that examined 52 BMS patients using quantitative sensory tests (QST) in addition to the blink reflex (BR) recordings.[42] They suggested that while BMS patients have different types of neural change (some with diminished neural responses and some with elevated neural responses, the majority (90 percent) of those tested had some form of an altered sensory thresholds or reflex reaction. The other critical study supporting a neuropathic etiology for BMS is by Lauria et al. (2005) and it was described earlier in the section on biopsy evidence for BMS. In combination, the QST and the tongue biopsy data suggest that small diameter nerve fibers progressively deteriorate causing the BMS symptoms.

Altered central nociceptive signal processing is an expected consequence with all neuropathic disease processes, not just BMS.

Finally, neuropathic pain phenomena are not limited to peripheral neural changes altering transduction and transmission of impulses into the brain. Most neuropathic disorders also have ongoing altered central modulation of nociceptive information as an integral part of the disease process. In this regard, two additional studies have examined BMS patients for more central neural changes, specifically on dopamine receptors in the basal ganglia.[43] The study measured dopaminergic function of the putamen in 10 BMS patients and 14 healthy controls using positron emission tomography. They reported that the presynaptic dopaminergic function was significantly decreased (between 17 percent and 20 percent) in the putamen of the BMS patients compared to control subjects. The above data was supported by a subsequent study using a more specific ligand which specifically bound to dopamine D1 and D2 receptors in these patients.

Again, they examined 10 BMS cases and 11 healthy controls. They concluded from the ligand uptake data that a decline in endogenous dopamine levels in the putamen was present in burning mouth patients.[44] The number of available striatal D2 receptors are thought to dictate the extent of central pain suppression.[45] All in all, these studies suggest that brain function changes occur along with peripheral nerve changes and support the idea that central modulation of sensory signal occurs in BMS cases. In fact, altered central nociceptive signal processing is an expected consequence with all neuropathic disease processes, not just BMS.

Management

In 2003, a systematic review of the treatment literature for BMS was conducted.[46] These authors examined Medline publications and conference proceedings up to September 2001 which contained quality research on interventions used for the treatment of BMS in comparison to a placebo. The authors identified several trials that tested antidepressants, cognitive behavioral therapy, analgesics, hormone replacement therapy, and vitamin complexes used to provide relief of the burning and discomfort in BMS. They found that none of the trials examined was able to provide conclu-

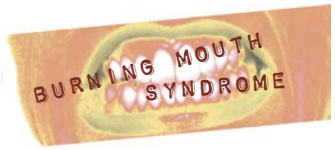


Table 3

Medications for BMS

Medications (class of drug)	Common Dosage Range	Prescription	Mechanisms of Action/ FDA Approval Status
Nortriptyline (tricyclic antidepressant)	10 to 75 mg per day	10 mg at bedtime; increase dosage by 10 mg every four to seven days until oral burning is relieved or side effects occur.	Tricyclic antidepressants inhibit the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine. This drug is approved for use of the symptoms of depression, but is used off-label for neuropathic pain.
Oral clonazepam (benzodiazepine)	0.25 to 2 mg per day	0.25 mg at bedtime; increase dosage by 0.25 mg every four to seven days until oral burning is relieved or side effects occur. As dosage increases, medication is taken as full dose or in three divided doses.	Mechanism is unknown, although it is believed to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS. This agent is approved by the FDA for seizures and for panic disorders. It is used off-label for neuropathic pain and BMS in particular.
Topical clonazepam (benzodiazepine)	1 mg tablet tid, after meals	Let tablet dissolve and hold fluid in mouth in area of most intense burning for three minutes, then spit.	Same as above
Gabapentin (anticonvulsant)	300 to 2,400 mg per day	100 mg at bedtime; increase dosage by 100 mg every four to seven days until oral burning is relieved or side effects occurs. As dosage increases taken in three divided doses.	Anticonvulsant action is unknown, gabapentin is known to prevent seizures as do other marketed anticonvulsants. This drug is FDA-approved for partial seizures and for post-herpetic neuralgia pain.
Pregabalin (anticonvulsant)	100 mg PO tid	100 mg PO tid	This is a new drug that is being suggested for use in neuropathic pain patients. Its mechanism of action is thought to be similar to gabapentin. It is approved by the FDA as an adjunctive agent in adult patients with partial onset seizures and for post-herpetic neuralgia and diabetic neuropathy.
Topical lidocaine (anesthetic)	Viscous gel 2%	5 ml qid. Rinse for two minutes and expectorate.	This agent is a sodium channel-blocking agent and provides analgesic effects when applied topically. It is FDA-approved as a topical anesthetic agent but its use is specified as an aid for minor surgeries or skin abrasions.

Evidence Basis for Use
No published evidence for BMS but used commonly for neuropathic pain.
Open clinical trials show some efficacy for BMS. No randomized, blinded placebo-controlled study (note exception below).
RBCT is available showing this approach is helpful in many BMS patients and is better than placebo.
Case report data suggests this agent may be helpful in some patients. No RBCT study performed.
No data for BMS is yet available, but it should work similar to gabapentin and it thought to have better pharmacokinetics. No RBCT study performed.
No data for BMS is yet available. No RBCT study performed.

(Table continues on Page 620)

sive evidence of high effectiveness. They reported that cognitive behavioral therapy may be beneficial in reducing the intensity of the symptoms, that the clinician needs to provide support and understanding when dealing with BMS sufferers, and that psychological interventions help patients cope with symptoms. A random, controlled test demonstrating benefit when compared to placebo suggests that psychotherapy or cognitive therapy sessions of one hour per week over 12 to 15 weeks have beneficial effects on reducing BMS pain intensity for up to six months.[47] An additional study showed some improvement resulting from psychotherapy over two months with significant improvement when combined with alpha lipoid acid therapy.[48]

Even though definitive curative treatments cannot be demonstrated in randomized, controlled, blinded trials, the current standard of practice for neuropathic pain disorders involves medications that may suppress neurologic transduction, transmission, and even pain signal facilitation more centrally. The most common medications used in BMS cases are presented in **Table 3**. These medications include but are not limited to tricyclic antidepressants, clonazepam, trazodone, serotonin-norepinephrine reuptake inhibitor (duloxetine), sodium channel-blocking agents, antipsychiotic medications (olanzapine, amisulpride), anticonvulsants (gabapentin, pregabalin) and alpha-lipoic acid, a nutritional supplement (alpha-lipoic acid).[49-52]

Among these medications, the most widely accepted treatment for BMS is clonazepam. This drug has been evaluated in open-label studies on BMS with reported positive results.[53] Recently, a randomized, double-blind, placebo-controlled multicenter clinical trial was performed on the efficacy of topical clonazepam for BMS.[54] This study reported on 48 patients (four men and 44 women) who were given either a placebo tablet or a 1 mg tablet of clonazepam to suck on and hold the saliva in the area of burning for three minutes, then spit. This was done three times per day for 14 days. They reported that pain intensity decreased significantly more in the clonazepam group and blood levels of clonazepam were extremely low. They hypothesized that clonazepam, which is classified both as an anticonvulsant and an anxiolytic agent, acts locally to disrupt the mechanism(s) underlying stomatodynia.

The newer drugs, on which there is preliminary data assessing efficacy for possible use in BMS, include gabapentin and alpha-lipoic acid. Gabapentin was approved by the Food and Drug Administration in the United States in May 2002 for treatment of postherpetic neuralgia. Even before this, gabapentin has been used off-label for many types of neuropathic pain disorders including BMS. A meta-analysis of gabapentin shows it to be a promising medication in the treatment of sustained continuous pain, but no good, high-quality study has examined it specifically for BMS.[55] A recent case report showed that at least in one patient, this medication was helpful at reducing burning pain.[56] Another agent that has been suggested as potentially helpful in BMS is alpha-lipoic acid. This is a common nutritional supplement that is promoted for its pain-suppressing effect on diabetic neuropathic pain. The best study on alpha-lipoic acid involved assessment of the short-term effect (three weeks) of 600 mg of alpha-lipoic acid per day for diabetic polyneuropathy.[57] This study was a multicenter, randomized double-blind placebo-controlled trial on

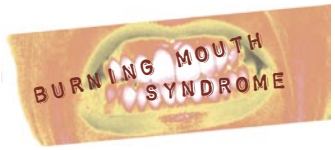


Table 3

Medications for BMS *(continued)*

Medications (class of drug)	Common Dosage Range	Prescription	Mechanisms of Action/ FDA Approval Status
Alpha-lipoic acid (antioxidant)	200 mg tid	200 mg tid for two months in association with gastroprotector.	This agent is not a drug and it is described as an antioxidant. It is not regulated by the FDA and therefore requires no prescription since it is considered a nutritional supplement.
Duloxetine (serotonin, norepinephrine reuptake inhibitor)	60 mg PO qd	Start with 30 mg for one week then increase to 60 mg qd	Mechanism unknown. The antidepressant and pain inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. This agent is approved by the FDA for major depression and for treatment of diabetic neuropathic pain.
Tramadol (analgesic, non-narcotic)	50 mg taken up to 4/d	50 mg in the evening is the starting dose, but if needed, the dose can be increased up to four tablets per day or more (depending on side effects).	While it is classified as a nonopioid medication, most consider tramadol as an opiod since it does bind to opioid receptors. It also inhibits reuptake of norepinephrine and serotonin similar to tricyclic antidepressants. It is FDA-approved for moderate to severe pain relief.
Hydrocodone (narcotic analgesic)	5/500	One tablet q6h	Used primarily for chronic pain control. It is FDA-approved for moderate to severe pain relief.
Olanzapine (atypical anti-psychotic agent)	5 mg/day	5 mg once a day	Antipsychotics decrease unusually high levels of brain activity. This drug is FDA-approved for schizophrenia.
Amisulpride (atypical anti-psychotic agent)	50 mg/day	50 mg tablets up to three times per day. Maximum dose not to exceed 400 mg/d	Same as above, but not available in the United States.

509 outpatients with neuropathic pain symptoms in the feet. The subjects were randomly assigned to receive either 600 mg alpha-lipoic acid once daily intravenously, 600 mg alpha-lipoic acid three times a day orally for six months, or a placebo in various sequences. Using the total symptom score as an outcome, the study found no significant difference between the alpha-lipoic acid group and the placebo group. In contrast, in BMS patients, there was one double-blind, randomized controlled study that involved 60 BMS patients who were given either alpha-lipoic acid or an inert control substance.

This study reported significant improvement in the alpha-lipoic acid group compared with placebo with the majority showing at least some improvement after two months.[58] Finally, a three-treatment randomized, single-blind comparison study examined amisulpride (50 mg/day), paroxetine (20 mg/day) and sertraline (50 mg/day) over an eight-week period on 76 BMS patients. The study demonstrated beneficial effects on reducing BMS pain intensity for all three agents although amisulpride was the fastest acting of the three agents and no subject assigned to this agent stopped participation in the study.[59] No serious

Evidence Basis for Use
RBCT shows that this agent is helpful for BMS.
No RBCT study performed so no data specific to BMS available.
One RBCT study showed that tramadol was ineffective for BMS.
No RBCT study performed so no data specific to BMS available. Obviously this is a powerful pain-relieving agent.
Only a single case report has reported it is helpful for BMS. No RBCT study performed to date.
One RBCT study showed that amisulpride was ineffective for BMS.

adverse events were reported, and the incidence of side effects did not differ among the three groups. It is interesting to note that amisulpride is an antipsychotic that is disinhibitory at low doses (<10 mg/kg), with specific dopamine D2 and D3 receptor-blocking and little effect on other receptors.[60] Unfortunately, this study had no placebo-control condition and amisulpride is not available in the United States.

Prognosis

In spite of the many behavioral and medication-based treatments, the management of BMS is still not satisfactory, and there is no definitive cure, although help is provided with these methods. Untreated BMS represents a disorder with a very poor prognosis in terms of quality of life, and the patient's lifestyle may worsen when psychological dysfunctions occur. Spontaneous remission of pain in BMS subjects has not been definitely demonstrated, the current treatments are palliative only, and while they may not be much better than a credible placebo treatment, few studies report relief without intervention. ■■■■

References / 1. Ship JA, Grushka M, et al, Burning mouth syndrome: An update. *J Am Dent Assoc* 126(7):842-53, July 1995.

2. Miller IJ Jr., Variation in human fungiform taste bud densities among regions and subjects. *Anat Rec* 216(4):474-82, December 1986.

3. Grushka M, Epstein JB, Gorsky M, Burning mouth syndrome. *Am Fam Physician* 65(4):615-20, Feb. 15, 2002.

4. Merskey H, Bogduk N, (eds), Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms/prepared by the Task Force on Taxonomy of the International Association for the Study of Pain, second ed., Seattle, IASP:742, 1994.

5. ICD-9 CM http://eicd.com/ accessed June 2, 2006.

6. Nagler RM, Hershkovich O, Sialochemical and gustatory analysis in patients with oral sensory complaints. *J Pain* 5(1):56-63, February 2004.

7. Lamey PJ, Lewis MA, Oral medicine in practice: Burning mouth syndrome. *Br Dent J* 167:197-200, Sept. 23, 1989.

8. Danhauer SC, Miller CS, et al, Impact of criteria-based diagnosis of burning mouth syndrome on treatment outcome. *J Orofac Pain* 16(4):305-11, Fall 2002.

9. Bergdahl M, Bergdahl J, Burning mouth syndrome: Prevalence and associated factors. *J Oral Pathol Med* 28(8):350-4, September 1999.

10. Ben Aryeh H, Gottlieb I, et al, Oral complaints related to menopause. *Maturitas* 24(3):185-9, July 1996.

11. Lipton JA, Ship JA, Larach-Robinson D, Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc* 124(10):115-21, October 1993.

12. Riley JL III, Gilbert GH, Heft MW, Orofacial pain symptom prevalence: Selective sex differences in the elderly? *Pain* 76(1-2):97-104, May 1998.

13. Lamey PJ, Hobson RS, Orchardson R, Perception of stimulus size in patients with burning mouth syndrome. *J Oral Pathol Med* 25(8):420-3, September 1996.

14. Svensson P, Bjerring P, et al, Sensory and pain thresholds to orofacial argon laser stimulation in patients with chronic burning mouth syndrome. *Clin J Pain* 9(3):207-15, September 1993.

15. Jaaskelainen SK, Forssell H, Tenovuo O, Abnormalities of the blink reflex in burning mouth syndrome. *Pain* 73(3):455-60, December 1997.

16. Gao S, Wang Y, Wang Z, Assessment of trigeminal somatosensory evoked potentials in burning mouth syndrome. *Chin J Dent Res* 3(1):40-6, May 2000.

17. Lauria G, Majorana A, et al, Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. *Pain* 115(3):332-7, June 2005.

18. Deems DA, Doty RL, et al, Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg* 117(5):519-28, May 1991.

19. Femiano F, Gombos F, et al, Burning mouth syndrome (BMS): Evaluation of thyroid and taste. *Med Oral Patol Oral Cir Bucal* 11(1):E22-5, January 2006.

20. Hershkovich O, Nagler RM, Biochemical analysis of saliva and taste acuity evaluation in patients with burning mouth syndrome, xerostomia and/or gustatory disturbances. *Arch Oral Biol* 49(7):515-22, July 2004.

21. Formaker BK, Frank ME, Taste function in patients with oral burning. *Chem Senses* 25(5):575-81, October 2000.

22. Doty RL, Bromley SM, Effects of drugs on olfaction and taste. *Otolaryngology Clin North Am* 37(6):1229-54, December 2004.

23. Magnasco LD, MagnascoAJ, Metallic taste associated with tetracycline therapy. *Clin Pharm* 4:455-6, 1985.

24. Coulter DM, Eye pain with nifedipine and disturbance of taste with captopril: A mutually controlled study showing a method of postmarketing surveillance. *Br Med J* 296:1086-8, 1980.

25. Greenberg AJ, Kane JM, et al, Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med* 321:1489-93, 1989.

26. Hochberg MC, Auranofin or D-penicillamine in treatment of rheumatoid arthritis. *Ann Int Med* 105:528-35, 1986.

27. Coulter DM, Eye pain with nifedipine and disturbance of taste with captopril: A mutually controlled study showing a method of postmarketing surveillance. *Br Med J* 296:1086-88, 1988.

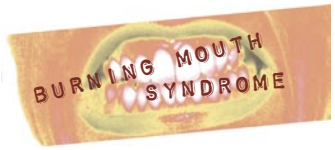
28. Frank ME, Smith DV, Electrogustometry: A simple way to test taste. In: Smell and taste in health and disease, pp. 503-514. Getchell TV, Doty RL, et al, (eds) Raven Press, New York, 1991.

29. Frankel DH, Mostofi RS, Lorincz AL, Oral Crohn's disease: Report of two cases in brothers with metallic dysgeusia and a review of the literature. *J Am Acad Dermatol* 12(2 Pt 1):260-8, February 1985.

30. Zegarelli DJ, Burning mouth: An analysis of 57 patients. *Oral Surg Oral Med Oral Pathol* 58(1):34-8, July 1984.

31. Scala A, Checchi L, et al, Update on burning mouth syndrome: Overview and patient management. *Crit Rev Oral Biol Med* 14(4):275-91, 2003.

32. Gorsky M, Silverman S Jr., Chinn H, Burning mouth syndrome: A review of 98 cases. *J*



Oral Med 42(1):7-9, January-March 1987.

33. Forabosco A, Criscuolo M, et al, Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. *Oral Surg Oral Med Oral Pathol* 73(5):570-4, May 1992.

34. Basker RM, Sturdee DW, Davenport JC, Patients with burning mouths. A clinical investigation of causative factors, including the climacteric and diabetes. *Br Dent J* 145(1):9-16, July 4, 1978.

35. Browning S, Hislop S, et al, The association between burning mouth syndrome and psychosocial disorders. *Oral Surg Oral Med Oral Pathol* 64(2):171-4, August 1987.

36. Zilli C, Brooke RI, et al, Screening for psychiatric illness in patients with oral dysesthesia by means of the general health questionnaire--28-item version (GHQ-28) and the irritability, depression and anxiety scale (IDA). *Oral Surg Oral Med Oral Pathol* 67(4):384-9, April 1989.

37. Rojo L, Silvestre FJ, et al, Psychiatric morbidity in burning mouth syndrome. Psychiatric interview versus depression and anxiety scales. *Oral Surg Oral Med Oral Pathol* 75(3):308-11, March 1993.

38. Al Quran FA, Psychological profile in burning mouth syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97(3):339-44, March 2004.

39. Carlson CR, Miller CS, Reid KI, Psychosocial profiles of patients with burning mouth syndrome. *J Orofac Pain* 14(1):59-64, Winter 2000.

40. Grushka M, Epstein JB, Gorsky M, Burning mouth syndrome and other oral sensory disorders: A unifying hypothesis. *Pain Res Manag* 8(3):133-5, 2003.

41. Bartoshuk LM, Snyder DJ, et al, Taste damage: previously unsuspected consequences. *Chem Senses* 30 Suppl 1:i218-i9, 2005.

42. Forssell H, Jaaskelainen S, et al, Sensory dysfunction in burning mouth syndrome. *Pain* 99(1-2):41-7, September 2002.

43. Jaaskelainen SK, Rinne JO, et al, Role of the dopaminergic system in chronic pain--a fluorodopa-PET study. *Pain* 90(3):257-60, Feb. 15, 2001.

44. Hagelberg N, Forssell H, et al, Striatal dopamine D1 and D2 receptors in burning mouth syndrome. *Pain* 101(1-2):149-54, January 2003.

45. Hagelberg N, Martikainen IK, et al, Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. *Pain* 99:273-9, 2002.

46. Zakrzewska JM, Forssell H, Glenny AM, Interventions for the treatment of burning mouth syndrome: A systematic review. *J Orofac Pain* 17(4):293-300, Fall 2003.

47. Bergdahl J, Anneroth G, Perris H, Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: A controlled study. *J Oral Pathol Med* 24(5):213-5, May 1995.

48. Femiano F, Gombos F, Scully C, Burning mouth syndrome: Open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. *Med Oral* 9(1):8-13, January-February 2004.

49. Ehrnrooth E, Grau C, et al, Randomized trial of opioids versus tricyclic antidepressants for radiation-induced mucositis pain in head and neck cancer. *Acta Oncol* 40(6):745-50, 2001.

50. Woda A, Navez ML, et al, A possible therapeutic solution for stomatodynia (burning mouth syndrome). *J Orofac Pain* 12(4):272-8, Fall 1998.

51. Tammiala-Salonen T, Forssell H, Trazodone in burning mouth pain: A placebo-controlled, double-blind study. *J Orofac Pain* 13(2):83-8, Spring 1999.

52. Gick CL, Mirowski GW, et al, Treatment of glossodynia with olanzapine. *J Am Acad Dermatol* 51(3):463-5, September 2004.

53. Grushka M, Epstein J, Mott A, An open-label, dose escalation pilot study of the effect of clonazepam in burning mouth syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86(5):557-61, November 1998.

54. Gremeau-Richard C, Woda A, et al, Topical clonazepam in stomatodynia: A randomized placebo-controlled study. *Pain* 108(1-2):51-7, March 2004.

55. Scheinfeld N, The role of gabapentin in treating diseases with cutaneous manifestations and pain. *Int J Dermatol* 42(6):491-5, June 2003.

56. White TL, Kent PF, et al, Effectiveness of gabapentin for treatment of burning mouth syndrome. *Arch Otolaryngol Head Neck Surg* 130(6):786-8, June 2004.

57. Ziegler D, Hanefeld M, et al, Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A seven-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-lipoic acid in diabetic neuropathy. *Diabetes Care* 22(8):1296-301, August 1999.

58. Femiano F, Scully C, Burning mouth syndrome (BMS): Double-blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med* 31(5):267-9, May 2002.

59. Maina G, Vitalucci A, et al, Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: A single-blind study. *J Clin Psychiatry* 63(1):38-43, January 2002.

60. Schoemaker H, Claustre Y, et al, Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. *J Pharmacol Exp Ther* 280(1):83-97, January 1997.

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