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Burning mouth syndrome – a burning enigma

Sindrom pekućih usta – goruća enigma

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Abstract. Burning Mouth Syndrome (BMS) is a chronic pain condition characterized by an intraoral burning sensation and an absence of oral mucosal lesions and disturbances in laboratory findings. Burning symptoms usually affect the anterior two-thirds of the tongue, its lateral borders, hard palate and labial mucosa, but other oral cavity sites may also be affected. Taste alterations and a decrease in the salivary flow rate frequently accompany the burning symptoms. This condition mostly affects peri- and postmenopausal women. To date, the etiology of BMS remains unclear. This unknown etiology means that no appropriate treatment is currently available. A large number of the treatments and medications have been tried for BMS, but treatment management remains unsatisfactory in some patients. The purpose of this article is to present current knowledge on the treatment of BMS.

Key words: burning mouth syndrome; etiopathogenesis; management; stomatodynia; stomatopyrosys

Sažetak. Sindrom pekućih usta (SPU) kronično je bolno stanje koje je karakterizirano osjećajem žarenja u usnoj šupljini bez vidljivih promjena na sluznici i poremećaja u laboratorijskim nalazima. Simptomi žarenja obično zahvaćaju prednje 2/3 trećine i lateralne površine jezika, tvrdo nepce, labijalnu sluznicu, ali može biti zahvaćena bilo koja regija u usnoj šupljini. Simptomi žarenja obično su praćeni promjenom osjeta okusa te smanjenim lučenjem sline. Ovo stanje najviše pogađa žene u peri- i postmenopauzi. S obzirom na to da je etiologija SPU-a nepoznata, ne postoji niti odgovarajuće liječenje. Dostupno je više različitih terapija i lijekova za SPU, međutim, liječenje kod pojedinih pacijenata i dalje je bez-uspješno. Svrha ovog rada je prikazati trenutno znanje o liječenju SPU-a.

Ključne riječi: sindrom pekućih usta; etiologija; liječenje; stomatodinija; stomatopiroza

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INTRODUCTION

Every dentist, and most likely every general practitioner, has come across a patient complaining of a burning sensation in the oral cavity. The pain or burning symptom is regularly accompanied any one of the numerous diseases affecting the oral cavity, including visible clinical pathological signs. When dealing with patients experiencing burning mouth syndrome (BMS), no clinical alterations are noticeable. These patients should be extensively screened, taking into account the possibility of odontogenic pain, injury or infection of the oral mucosa, bone lesions, salivary gland disorders, temporomandibular disorders or trigeminal neuralgia. Excluding some of the above-mentioned issues requires frequently applying a number of diagnostic methods and techniques. The problem is that having conducted all the tests, there is no justified reason for burning sensations in the mouth which often leads to frustration in patients.

CLASSIFICATION AND ETIOLOGY

Literature provides several definitions of BMS. The International Association for the Study of Pain (IASP) defines BMS as "a chronic condition characterized by a burning sensation of the oral mucosa for which no cause can be found"[1]. The definition given by the International Headache Society (IHS) describes BMS as "an intraoral burning sensation or dysesthesia, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions"[2]. Moreover, BMS is an "idiopathic disorder in terms of burning or pain of the oral cavity in people with a clinically normal oral mucosa, without odontogenic or general medical causes"[3]. Accordingly, Scala et al. suggested two clinical forms of BMS, primary and secondary. Primary or idiopathic BMS is defined as a burning symptom in the oral cavity without any local or systemic causes involving central or peripheral neuropathologic mechanisms, while secondary BMS is a result of local, systemic and psychological disturbances[4]. However, BMS may also be the sum of a number of diseases with overlapping symptoms.

Besides the mentioned classification, Lamey and Lewis proposed three BMS subtypes according to the variation in pain intensity over a 24-hour period. In type 1, burning symptoms are absent in the morning but gradually increase towards the end of the day. Type 2 involves patients with constant pain during day and night, and type 3 involves patients with pain-free intervals[5]. Jääskelänien classified BMS into three subgroups with overlapping features in some patients. The first subgroup (50–65 %) is characterized by peripheral fiber neuropathy of the oral mucosa, the second subgroup (20–25 %) refers to a pathology involving the lingual, mandibular or trigeminal system, and the third central pain subgroup (20–40 %) involves hypofunction of dopaminergic neurons[6]. Subsequently, it becomes clear that there is still no universally accepted classification system for BMS and no definitive diagnostic criteria.

Burning mouth syndrome (BMS) is characterized by intraoral burning sensation with clinically healthy oral mucosa and an absence of disturbances in laboratory findings. Etiology of BMS still remains poorly understood. So far, there is no proper medical treatment for this condition.

Despite numerous proposed factors, the etiology of BMS is still enigmatic, and data from literature often show controversial assertions. Aggravating circumstance in BMS research and treatment has its origin in the fact that symptoms may be caused by a large number of local and systemic disorders which can be identified and treated (e.g., hormonal or nutritional disturbances). The most commonly implicated systemic predisposing factors include postmenopausal disorders, diabetes and nutritional deficiencies (lack of B1, B2, B6, B12, folic acid or serum iron). However, results of published studies on the proposed systemic factors are conflicting[7].

In the literature, several available theories endeavor to explain the etiopathogenesis of BMS. Scala et al.[4] stated that BMS is a specific set of chronic oral symptoms that have their origin in the activation of neuropathic mechanisms, where the activation is caused by unknown factors ("primary BMS") or any of a wide range of

diseases ("secondary BMS"). In both groups, the etiologic role of psychogenic factors has not been sufficiently clarified. Forssell et al.[8] have found altered sensory dysfunction associated with fiber neuropathy in almost 90 % of BMS patients. Several studies have shown that thresholds for thermal sensory stimuli are altered in primary BMS when measured with an appropriate small thermo diode on the mucous membrane of the tongue. Most of those studies have shown negative sensory signs, thermal hypoesthesia on harmless thermal modality in most BMS patients. A significant increase in the detection of the pain threshold to hot – hypoalgesia, or the threshold detection of harmless sensation to cold and hot – hypoesthesia has been shown[9].

Some studies have shown a common disfunction within A delta fibers to a cold sensation. In addition, some patients with primary BMS may exhibit positive sensory signs: decreased toleration of hot or allodynia for a warm sensation or decreased threshold for a hot sensation. The fact that primary BMS may exhibit different types of thermal QST disturbances might explain controversies stemming from previous research. Profiling the QST disorder in each individual patient relative to correct reference values offers a more informative approach to researching the pathology of the small fiber system in primary BMS[9]. Due to the frequent subjective disturbances with taste sensation in BMS patients, the suggestion is that the timpani cord that transmits the tasty afferent fibers from the oral mucosa may have been damaged. Another theory expounds that BMS is a phantom pain due to releasing inhibitory control of taste fibers in the intraoral somatosensory system[9]. Taste sensations are analyzed using sensory testing. These studies have shown an increase in detection thresholds for taste after electrical stimulation of the tongue mucosa in primary BMS, indicating hypofunction of A delta fibers in the chorda tympani that transmits taste sensation[10]. Disrupted interaction between sensory functions of the trigeminal and facial nerves is well known, and some people, mainly females, due to a large number of fungiform papillae present on the anterior 2/3 thirds of the tongue, are at greater risk of developing burning sensations[11,12]. Axonal degeneration of epithelial and subpapillary nerve fibers in the oral mucosa have been detected using immunohistochemical and microscopic scanning[13]. A change in the nigrostriatal dopaminergic system resulting in reduced central pain suppression has been reported[14], as well as disturbances in autonomic innervation and blood flow in the tongue[15]. Woda et al. stated that anxiety and stress may lead to disruption of gonadal, adrenal and neuroactive steroid levels in skin and mucosa[16]. The correlation between burning symptoms in BMS and saliva composition has also been investigated[17,18]. According to this theory, the assumption is that quantitative and qualitative salivary changes may possibly alter the salivary lubricant function and oral mucosa perception[17]. An exceptionally old theory, based on little or poor evidence, presents BMS as a consequence of psychogenic disorders. This has not been supported in acceptable scientific evidence[19,20]. Although many cases of improvement due to psychotropic medications do exit, it remains unclear whether anxiety or depression is a primary or secondary event in oral burning symptoms. Today, there is significantly more evidence in favor of interpreting psychogenic disorder as a secondary event in BMS patients, and which develops as a result of long-lasting symptoms and a series of consecutive unsuccessful attempts at treatment.

EPIDEMIOLOGY

Most of the affected patients are peri- and postmenopausal women. Data from the literature shows a prevalence of up to 12-18 % (6=9) for BMS in postmenopausal women. The female/male ratio is 7:1[21]. Psychological, biological and sociocultural factors explain this gender difference. Furthermore, in most of the cases. BMS occurs within an age group of 38 -78 years of age and is an extremely rare condition in patients under 30 years of age[4,22]. The real epidemiology of BMS is difficult to establish due to non-universal diagnostic criteria and a low awareness of BMS among dentists and general health practitioners.

CLINICAL FEATURES

Patients usually report a burning sensation in the anterior 2/3rd of the tongue, lateral borders of

the tongue, hard palate and labial mucosa, but other sites of the oral cavity may also be affected. Burning symptoms are spontaneous and present every day, with a lower intensity in the morning and a gradual deterioration towards the end of the day. Rarely are burning symptoms present during the night. A typical diagnostically significant feature is symptom reduction when patients consume food or drinks. The strongest intensity of symptoms on the visual analogue scale is described as moderate in about 50 % of BMS patients. A certain proportion of the patients report that burning symptoms occur after certain dental procedures (obtaining a prosthetic replacement, tooth extraction) or an illness (e.g., the flu). In more than 70 % of BMS patients, taste disturbances, most commonly bitter, metallic or both, are present[23]. Furthermore, approximately 2/3 of the patients have dry mouth[4]. In approximately 3 % of patients, burning symptoms disappear spontaneously five years after first appearing[24]. Constant intraoral burning sensations seriously affect the patient's quality of life[25]. Ching et al.[26] reported that in patients with BMS, a significantly higher prevalence of geographic tongue was established in comparison to the control group. Gao et al.[27] reported that tongue thrusting onto the frontal teeth, lip sucking, periodontal disease, smoking and depression were underlying disturbances in BMS patients.

Many studies in the literature have noted some nonspecific health issues in BMS patients, such as headaches, irritable bowel syndrome, temporomandibular joint pain, musculoskeletal disorders, dermatological and psychiatric disorders[28]. The main BMS comorbidities according to recent literature are sleep disturbances, anxiety and depression, Parkinson's disease and thyroid dysfunction[29-35]. Hypochondria and cancerophobia, especially in patients with positive family history of head and neck cancer, may be associated with BMS, which suggests more probable unresponsiveness to the BMS treatment[4].

Published literature asserts that BMS patients have mood and even personality changes. Many researchers have found that BMS patients had cases such as children with disabilities, chronic diseases and child deaths more frequently in their anamnestic data. Many BMS patients were refugees. Lamb et al.[36] reported that 50 percent of the BMS patients had psychological disorders. Browning et al.[37] and Ship et al.[38] reported that more than 45 percent of the BMS patients have a psychiatric diagnosis, mostly depression and anxiety. Nicholson et al.[39] reported that in six out of ten BMS patients, psychiatric diagnosis was establish based on a psychiatrist's review. The same authors pointed out the need for psychiatric evaluation of BMS patients. Shoenberg[40] stated that stress due to the death of a close person or divorce is associated with BMS and that treatment of such patients should also include treating the underlying depression. Contrary to these studies are Rojo et al.[41] who have not established any common psychological disorder in BMS patients, although reporting that 50 % of BMS patients have some kind of psychological disorder. Trikkas et al.[42] found that BMS patients (25 patients) were more unfriendly, introverted or extroverted with respect to the control group (25 patients) and also had more neurotic and psychosomatic morbidity scores compared to control subjects.

Hammaren et al.[43] concluded that BMS is associated with anxiety and depression, while Lamey et al.[44] think that anxiety, depression and cancerophobia stem from an underlying BMS condition. Given the findings that BMS patients experience increased anxiety and depression compared to control groups and other subjects with painful conditions, it appears that these conditions may be causing BMS. However, it remains unclear whether psychological disorders are an underlying condition in BMS patients or whether they result from unpleasant daily burning symptoms.

The opinion is that viewing BMS solely as bodily manifestation of anxiety, depression or other psychological disorders is not recommended.

However, BMS patients may also suffer from a number of other diseases such as gastrointestinal problems, chronic fatigue, headaches, pain in other parts of the body, and often suffer from cancerophobia. The literature describes how cancerophobia, chronic fatigue and sleep disorders may be emotional forerunner to anxiety, while gastrointestinal diseases may be a physical forerunner to anxiety. Furthermore, chronic stress,

depression and chronic anxiety are highly indicative of the "functional painful conditions" group to which BMS belongs, including irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. Furthermore, chronic stress, anxiety and depression may lead to changes in cortisol secretion, which helps in the emergence of pain syndromes and so on BMS in a way that disturbed cortisol secretion destroys neural cells[44].

Sensitive individuals may also to experience emotional stress as a burning sensation. Interestingly, a high percentage of BMS patients are hospitalized due to psychiatric illness before the onset of BMS symptoms. There is currently a large number of BMS patients who receive psychiatric treatment. However, apparently burning symptoms decrease in a large number of BMS patients after psychotherapy, especially cognitive behavioral therapy[45]. In addition to this treatment, low-dose anxiolytic use reduces in most BMS patients burning symptoms. Studies have shown that selective serotonin reuptake inhibitors (SSRIs) and amisulpride may reduce burning symptoms[46].

Amenábar et al.[47] have shown that patients with BMS have more positive results in anxiety tests compared to control groups and a higher level of salivary cortisol.

Al Quran[48] has investigated personality profiles based on questionnaires measuring five dimensions of personality in 32 BMS patients and 32 control subjects. The same author has reported that BMS patients were more neurotic, anxious, hostile, depressed, less self-confident and more impulsive and vulnerable than the control group[48].

Pokupec et al.[49] have investigated anxiety and depression in 120 BMS patients and reported an improvement of 7.5 to 8.8 % in their anxiety findings, with depression completely disappearing in some patients after undergoing treatment with anxiolytics, antidepressants or autogen training. The visual analogue scale has shown that symptoms decrease from 6.9 – 7.8 before treatment to 2.1 – 3 after treatment. Before treatment, patients described having common symptoms, while after completing at treatment they said they rarely had symptoms. De Souza et al.[50] reported a common prevalence of psychiatric disorders in BMS patients, although the effect of those disorders in the etiopathogenesis of BMS remains unclear. The same authors[51] used the visual analogue scale and five psychometric scales in 30 BMS patients and 30 control subjects. They found that BMS patients had higher scores on the Hamilton and Beck's scale and concluded that BMS patients have a particular psychologic profile and should be treated in an appropriate way or referred to a psychologist or psychiatrist.

Furthermore, Bergdahl et al.[51] concluded that changes in personality and psychological functioning may point to the fact that burning sensations are a consequence of psychosomatic problems in patients, and recommended reviews of patients by psychologists or psychiatrists depending on the severity of the psychopathology.

The objective of Bogetto et al.[52] was to determine the types and frequency of psychiatric disorders occurring in unison with BMS in 102 BMS patients. Although psychiatric diagnoses were never established in 29 BMS patients (28.4 %), different psychiatric comorbidities were found in the rest of the 73 BMS patients. The most common psychiatric diseases were depression and anxiety with no differences in clinical symptoms between patients with or without psychiatric comorbidities. The severity of personal events, not their frequency is remarkably connected with the BMS findings.

Soto-Araja et al[53] found that anxiety and depression were the most common psychiatric diseases in BMS patients according to the Anxiety Hospital and Depression Scale.

Abetz and Savage[54] reported the existence of evidence that BMS patients have at least some psychological difficulties and that somatoform pain disorder is suggested as a mechanism attributed to BMS. Furthermore, factors such as personality, stress, anxiety and depression, as well as other psychological and even psychiatric illnesses play an important role in BMS. The same authors[54] stated that in treating BMS patients, physiological and psychological factors should be considered and that patients themselves should admit to having certain psychological disorders, which

is usually the most difficult issue related to BMS treatment.

The results of different studies have shown that BMS patients are more anxious and depressed compared to the general population as are patients with organic orofacial pain.

Matsuoka et al.[55] reported a higher level of catastrophizing and anxiety in BMS patients as control subjects. Furthermore, catastrophizing in BMS patients was associated with pain intensity, including response to stress as well as psychological and social difficulties. The same authors (55) concluded that in Japanese BMS patients, catastrophizing is a more significant cognitive factor than cancerophobia. This frequent finding of catastrophizing in BMS patients was confirmed by Andabak Rogulj et al[5]. In their study, catastrophizing was significantly present in 30 percent of patients. Patients with stronger catastrophizing had a poorer quality of life. Examining the catastrophizing disorder reveals patients with negative behavioral patterns and for whom further psychological intervention may reduce or eliminate negative cognitive factors and improve submission of chronic painful conditions, such as BMS.A previous study[57] has shown parafunctional habits in BMS patients related to anxiety. Parafunctional habits point to certain exogenous factors like stressful situations, alcohol abuse, certain type of personality, psychiatric and neurological disturbances. This may be a consequence of the interaction between the limbic and motoric system with possible involvement of the dopaminergic system.

Furthermore, it has become evident that certain BMS patients suffer from cancerophobia[14,55]. Some authors[58,59] stated that cancerophobia is presented in almost 45 – 74 % of BMS patients but it is unclear whether cancerophobia affects burning symptoms.

Femiano et al.[60,61] found that hypothyroidism may be responsible for burning sensations and taste disturbances in patients with strong taste sensations. The same authors concluded that the thyroid hormone status should be obtained for BMS patients.

Furthermore, Bergdahl et Bergdahl[62] found that BMS patients more often have diabetes. Otherwise, data providing a correlation between BMS and diabetes exists which also includes metabolic changes in the mouth due to peripheral neuropathy[63,64].

The association between BMS and dry mouth is also interesting. Dry mouth has been established in 46 – 67 % of BMS patients. In patients, dry mouth often reflects a subjective feeling of dryness instead of objective hyposalivation. The dry mouth sensation in BMS patients may be associated with depression and medications like psychotropic drugs, anticholinergics, diuretics and other types of drugs[57].

A recent study of Poon et al.[65] showed that BMS patients had a significantly lower amount of unstimulated saliva whereas the amount of stimulated saliva was not statistical lower. The same authors[65] concluded that hyposalivation may be involved in the pathogenesis of BMS which in turn may be positively affected by use of sialogogues. Nagler et Hershkovich[66] did not find a significant difference in unstimulated saliva between BMS patients and control subjects. The same results were also been reported by Zhao et al[66]. Lee et al.[67] reported that the amount of unstimulated saliva was significantly lower in BMS patients in comparison with control subjects, while the difference in the amount of stimulated saliva was not significant. Furthermore, there was no difference in scintigraphy findings among BMS patients in terms of whether they have a normal amount of saliva or hyposalivation.

Imura et al.[18] found hyposalivation and increased saliva viscosity in BMS patients. They also reported a lower level of salivary IgA.

DIAGNOSIS

Today, most researchers insist that term burning mouth syndrome should only be used upon excluding a local and general health pathology, while cases of burning oral sensations that accompany various diseases are considered only a symptom as part of the overall symptomatology associated with the disease (e.g., anemia). A detailed clinical examination and thorough anamnesis coinciding with laboratory testing are necessary. Several diagnostic tests have been proposed in the literature but are not used in

everyday practice due to lack of evidence regarding their use.

Zavoreo et al. evaluated 20 patients with BMS and 20 control subjects with chronic pain in the lumbosacral region using transcranial sonography of the brain parenchyma, substantia nigra, midbrain raphe and brain nucleus. The results of this pilot study revealed hypoechogenicity of the substantia nigra and midbrain raphe, and hyperechogenicity of the brain nucleus in BMS patients when compared to the controls. This finding might reflect central disturbances in patients with BMS[68].

As mentioned earlier, BMS comorbidities are anxiety and depression. Accordingly, Sikora et al. conducted a study using self-reported STAI (State-Trait Anxiety Inventory) and BDI (Beck Depression Inventory) questionnaires to evaluate anxiety and depression in a total of 93 subjects. Patients were divided in two groups: a BMS group of 43 participants and a control group of 50 participants. Higher average total scores of state anxiety, trait anxiety and depression were detected in the BMS group. They found a statistically significant difference for state anxiety scores and BDI scores between the BMS group and control group. The authors concluded that BMS patients are more anxious and depressed compared to the control group, as well as the fact that the feeling of anxiety lasts for a longer period of time after BMS symptoms first occur[69].

Furthermore, Boras et al measured salivary and serum levels of substance P (SP), neurokinin A (NKA) and calcitonin gene related peptide (CGRP) in the 26 female patients with BMS (age group 51-78 years, mean age 65.69 years), and in the 22 female controls (age group 24-82 years, mean age 49.72 years). They found no significant differences between the groups in salivary SP, NKA and CGRP and in the serum SP and CGRP. However, a significantly lower level of serum neurokinin A in BMS patients may reflect an inefficient dopaminergic system[70].

The conclusion is that a diagnosis of BMS is made by exclusion, since there is no diagnostic test for assessing this condition and no possibility of detecting any morphological abnormalities of the oral mucosa[71].

MANAGEMENT

Without clear evidence and due to links to many causal conditions, BMS treatment poses a serious clinical problem. The absence of clinically visible mucosal damage makes diagnosing and treating these patients a complicated matter. There is still no effective therapeutic agent for treating BMS. This fact was confirmed by a Cochrane Review that endeavors to identify effective treatment for BMS patients in randomized controlled trials (RCTs) which were conducted prior to December 2015. The systematic review included 23 RCTs with 1121 participants (83 % females) analyzed. The authors concluded that there is insufficient evidence to support or disapprove the use of any interventions in the treatment of BMS due to a very low number (1/23) of clinical trials with low risk of bias[72]. BMS prognosis is poor in a significant number of patients, and this groupof patients are a large consumer of health insurance funds. Treatment involves the participation of physicians from different disciplines, and pharmacotherapy often has no effect on burning symptoms[73].

Various treatment options have been proposed for BMS. Three medications have demonstrated a positive outcome in RCTs. However, the lack of study design uniformity and inconsistent use of a standard placebo were present in these studies. These supportive treatment options are systemic and topical capsaicin (depletion of substance P), topical clonazepam (pain inhibition via GABA receptors) and alpha-lipoic acid (an antioxidant, effective in the case of diabetic neuropathy)[74]. The efficacy of 0.5 mg/mL topical clonazepam solution for managing BMS was recorded in a retrospective study[75]. The same authors found that 0.5 mg/mL or 0.1 mg/mL topical clonazepam solution was safe and well tolerated in the treatment of BMS[76]. As a supportive treatment option in treating BMS, tricyclic antidepressants (nortriptyline and amitriptyline) in small dosages (analgesic effect) are also prescribed to the BMS patients[4].

Additionally, in two studies, milnacipran was used in patients with BMS. In 12 patients with BMS, the does was increased (from 15 mg till 60

mg daily) during a period of 12 weeks and the results for depression improved based on the Hamilton scale. However, no changes in BMS symptoms and scores on the visual analogue scale were noticed[77]. Ito et al.[78] prescribed 100 mg milnacipran to BMS patients and reported significant improvement in BMS symptoms.

Zinc was tested on 276 patients with BMS and Cho et al.[79] reported zinc deficiency in more than 25 % of BMS patients. The same authors prescribed 14.1 mg daily of zinc supplements which significantly decreased BMS symptoms. However, Bhoopathi and Mascarenhas,[80] based on the literature review on zinc supplementation in BMS patients, failed to confirm these findings. Furthermore, topically applied sucralose in a 0.5 g dose lead to significant improvement of burning symptoms after 5-15 minutes of administering it.

Furthermore, Pelivan et al. treated 91 BMS patients with vitamin B1, B6 and B12 injections. The treatment protocol consisted of nine vitamin B injections, given every other day into the gluteal muscle (i.m.). Every injection contained 100 mg of vitamin B1 and B6 and 1 mg of vitamin B12. No laboratory vitamin B tests were performed. The authors reported a complete remission in 75 BMS patients, while 16 patients were given clonazepam 0.5mg twice a day. According to these results, the authors strongly support the use of vitamin B1, B6 and B12 in BMS patients due to their low price and potential benefit of the drug without unwanted side-effects[81]. Contrary to these findings, Hugoson et al. reported no benefit of administering vitamin B replacements in BMS patients, although most of the patients (15 out of 16) had low thiamine (B1) and/or riboflavin (B2) levels as well as normal levels of pyridoxine (B6)[82].

Furthermore, one of the treatments mentioned in the literature is acupuncture. The exact mechanism in which acupuncture acts on BMS patients remains unknown. The assumption is that acupuncture stimulates blood circulation and the release of neuropeptides. This was stated in study of Scardina et al., the authors reported a significant reduction of burning symptoms after three weeks of acupuncture therapy in 30 patients with BMS. Treatment response lasted for 18 months[83]. The effectiveness of acupuncture was also studied in 10 BMS patients. The treatment regimen lasted 8 weeks (20 sessions) and the results of the study reported a significant mean reduction in pain. No significant improvement in the overall score for quality of life was observed, although BMS patients better coped with symptoms[84].

The effectiveness of acupuncture as opposed to administering clonazepam in BMS patients was tested in a study conducted by Jurisic Kvesic et al.

Based on our long-lasting clinical experience, cognitive behavioral therapy and vitamin B injections might improve this condition in many cases. However, considering that there are cases resistant to the therapies offered so far, further well designed RCT's are needed to clarify this enigmatic condition.

The study was conducted on forty-two BMS patients who were randomly divided into two groups. The acupuncture group consisted of 20 participants. The treatment regimen was performed 3 times a week over 4 weeks, on points ST8, GB2, TE21, SI19, SI18 and LI4 bilaterally as well as GV20 in the midline, with each session lasting half an hour. The clonazepam group consisted of twenty-two participants and the treatment regimen included administering clonazepam once a day (0.5 mg in the morning) for 2 weeks and, after 2 weeks, two tablets (0.5 mg in the morning and in the evening) were administered for the next 2 weeks. Before and one month after commencing either therapy, participants completed questionnaires, i.e., visual analogue scale (VAS), Beck Depression Inventory (BDI), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, 36-item Short Form Health Survey (SF-36) and Montreal Cognitive Assessment (MoCA). The authors reported significant improvements in the scores of all outcome measured after treatment with acupuncture and clonazepam, except for MoCA, with no significant differences between the two treatment regimens in terms of scores from the performed tests. They concluded that acupuncture and clonazepam are similarly effective for BMS patients[85].

Table 1. Treatment modalities for BMS patients

Treatment	Modalities
Pharmacological	**Nonpharmacological**
Clonazepam Capsaicin Alpha lipoic acid (ALA) Antidepressants (paroxetine, duloxetine) Antipsyhotics (olanzapine, amisulpride) Medicinal plants (aloe verabarbadensis, catuama, hypericumperforatum) Histamine H2 receptor (lafutidine)	Low level laser therapy (LLLT) Acupuncture Cognitive behavioral therapy (CBT) Tongue protector

Another study tested the effectiveness of acupuncture as opposed to vitamin C. Forty-two participants with BMS were included in the study and divided in two groups. Acupuncture was performed on points ST8, GB2, TE21, SI19, SI18 and LI4 bilaterally as well as GV20 in the midline in 21 participants 3 times a week over 4 weeks. Each session lasted half an hour. In the other 21 participants, Vitamin C was given at a dose of 1 mg after lunch. Before and one 1 month after commencing the treatment regimens, the participants completed questionnaires, i.e., visual analogue scale, STAI, Hamilton and OHIP-CRO 14. Results of the study showed that acupuncture was efficient in BMS patients; however, vitamin C partially decreased the results of all performed tests, however without significance[86].

Treatment using low level laser therapy (LLLT) in BMS patients was also performed. In the study conducted by Sikora et al., forty-four patients with BMS were randomized into two groups: a study laser group (LLLT) and a sham laser group. LLLT was performed with the GaAlAs laser (830 nm) used in non-contact mode on the site in the mouth where burning symptoms were present. Study patients received 10 sessions (over a period of 10 days). Before and after commencing either therapy protocol, each participant filled out the visual analog scale (VAS) and oral health impact on the quality of life questionnaire (OHIP-CRO 14). Results of this study showed no significant differences between the groups before and after LLLT (switched on and off) in the quality of life (OHIP CRO 14 scores) ($p>0.05$). There was a significant decrease in pain symptoms (VAS) in both LLLT switched on and LLLT switched off groups ($p <0.05$). However, neither LLLT switched off or switched on treatment regimen improved the quality of life[87].

Lopez-Jornet et al.[88] reported that control of tongue thrusting together with topical lubricant significantly reduced burning mouth symptoms in patients. Kenchadze et al.[89] suggested that EEG biofeedback and neurofeedback along with psychotherapy significantly improved symptoms in patients with BMS.

Treatment modalities for BMS patients according to the literature are summarized in Table 1.[75,90-107] Furthermore, Kuten-Shorrer et al. evaluated the placebo effect in 12 published RCTs regarding the treatment of BMS. Despite limitations of the studies (study design, sample size, duration of therapy, placebo control), they found a positive placebo response in 6 out of 12 studies. They suggested utilizing standard protocol for future studies along with the use of a standard placebo substance and evaluation of treatment efficacy, as well as longer follow-up periods[108]. In addition, to eliminate limitations of the subjective outcome assessment by patient self-reporting, Green et al suggested including a third "no-treatment" group in future trials. The inclusion of third "no-treatment" group enables distinguishing between the natural course of burning symptoms and a real placebo effect[109]. Due to the limited number of clinical trials at low risk of bias, there is insufficient evidence in the Cochrane Review to support or refute the use of any interventions in managing BMS.

The first conversation with the patient is extremely important. Objective information and the current perspectives of BMS needs to be improved. Emphasizing that the symptoms are not related to malignancy is particularly important.

The interview should be structured as counseling with very strong psychological perspective. Therefore, one of the proposed therapeutic approaches in the literature is cognitive behavioral therapy (CBT)[107]. Bergdahl et al.[107] studied the effect of CBT in 30 patients with resistant BMS. The intensity of BMS, estimated using VAS, was significantly reduced after administering CBT and was further reduced in a follow-up period spanning 6 months. CBT is a talking therapy in which patients are encouraged to deal with symptoms, in order to effectively reduce emotional distress caused by chronic pain. The therapy provides detailed information about the condition, emphasizing impossibility for developing malignancy. Unlike other talking treatments, CBT deals with current patient problems, rather than focusing on issues from the past. The course of treatment usually lasts between 5 and 20 sessions (once a week or once every 2 weeks), with each session lasting 30 to 60 minutes. There is no standard length of CBT, it depends on the kind of problem and its severity. CBT may be performed by a variety of mental health professionals such as licensed psychologists, social workers and counselors[110].

CONCLUSION

Despite numerous studies, BMS remains a poorly understood condition in the practice of oral medicine. One of the reasons is due to the lack of a universally accepted definition of BMS. Furthermore, the literature describes a large number of treatment modalities. Considering the exceptionally low number of clinical trials with a low risk of bias, further well designed RCTs are needed for collecting more information on the etiopathogenesis as well as the diagnosis and treatment of BMS.

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