ORIGINAL ARTICLES

Article received on November 7, 2016 and accepted for publishing on February 14, 2017.

Management of burning mouth syndrome (BMS) in patients with diabetes mellitus

Elena C. Coculescu[1], Ioanina Părlătescu[1], Carmen Gheorghe[1], Șerban Țovaru[1], Bogdan I. Coculescu[2,3]

Abstract: *Unlike the therapy of primary BMS, the treatment of secondary BMS benefits, in addition to symptomatic therapy, from the possibility of using means and methods to correct biological disturbances and/or morphological, psycho-emotional changes respectively. The use of these therapeutic means in secondary BMS is recommended to be established as a first step of therapeutic conduct. Their success is reflected in homeostasis restoring, correcting morphological and functional changes of the field, which frequently leads to no longer use prescription of symptomatic treatment.*

DEFINITION

The International Association for the Study of Pain (IASP) defines burning mouth syndrome (BMS) as a "distinct nosological entity" characterized by "oral sensation of burning or pain, persistent and non-remitting in time in the absence of clinical objective changes of the mouth mucosa" [1]. A relatively similar vision is supported by Grushka (2014). BMS defining a sensory sensation, the author admits that this is manifested mainly by: a) subjective characteristics: changes in taste perception; bilateral burning sensation associated with altered taste mouth; sensation of "dry mouth", although salivary flow is not reduced; perceived foreign body in the oropharynx and b) objective criterion: the oral tissues with clinically normal aspect. The author specifically mentions that the 4 subjective lists, encountered in BMS come forth from the absence of results after an objective clinical exam, a defining element for this condition [2].

EPIDEMIOLOGY

Setting the epidemiology of BMS is difficult and imprecise because there is no universally accepted definition. The various epidemiological studies often refer to different clinical entities in which oral mucosal lesions lack [3]. This disease has a high rate that varies according to the studies from 0.7% to 14.8 - 15% [3,4,5]. The prevalence of painful syndrome in the Service of Oral Pathology of the Faculty of Dental Medicine - "Carol Davila" University of Medicine and Pharmacy, Bucharest (Romania) is 16.23% [6].

Corresponding author Bogdan I. Coculescu
bogdancoculescu@yahoo.fr

[1] Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest
[2] Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania
[3] Center for Military Medical Scientific Research, Ministry of National Defence. Bucharest. Romania

ETIOLOGY. PREDISPOSING FACTORS

Pathogenic, sex, age, menopause can be considered contributing factors. Therefore:

1. Although it was observed in any age group between 27-87, BMS has a clear predisposition related to age. The average age of reporting the disease is 61 [2]. BMS rarely occurs before the age of 30 [7].

2. Sex is also placed between contributory factors. The women are 2.5 to 7 times more frequently affected than men.

3. The body functioning as a whole, at menopause, besides circulating electrolyte changes, it suffers from other disturbances such as:

a) Lipid disorders with consequences in the development of atherosclerosis;

b) exacerbated production of ROS/RNS, including liquid in the gingival sulcus (where ROS = reactive oxygen species, and RNS = reactive nitrogen species);

c) changes in the hormonal constellation at menopauses the quantity of estrogen become responsible for the development of female cardiovascular pathologies same as men.

Data from the literature considers that up to 90% of the female patients with BMS are around menopause, the onset of symptoms characteristic of peri-menopausal period taking place three years before and 12 years after climax [8].

The explanation for BMS distribution predominantly in women during perimenopause, according to Woda et al. (2009) is that BMS is the result of hormonal changes (hypo-estrogenism) in women during menopause, which often associates with metabolic disorders and neuropsychological chronic anxiety or stress. Mental disorder in menopausal women explains anxiety and depression from BMS [9].

4. Another pathogenic explanation takes into consideration the interrelationship taste-saliva-pain. Laboratory tests showed that female patients with disorders in climax present a growth of salivary phosphate concentrations, proteins, Na, K+, Ca2+ and Mg2+. The referred electrolyte disturbances trigger the disruption of the membrane potential, including those of the cells involved in collecting taste excitations or cells responsible for saliva secretion [10].

Certain hormonal changes (hypoestrogenemia, diabetes mellitus, hypothyroidism, thyroid dysfunction type) and functional morphological and immunological disorders affecting the endocrine glands were also among factors described as possible cause of this disorder [11]. Regarding the relationship between diabetes and BMS various assumptions were formulated, including the existence of metabolic changes in the mouth due to peripheral neuropathy, which can generate among other disturbances the hypo-function of the salivary glands, thus reducing the secondary salivary flow [3,12,13].

The mode of action of psycho-neuro-endocrine factor is even more difficult to explain since it has been shown that patients presenting BMS have a greater tendency to somatization and to develop psychiatric symptoms [11]. For this reason the theory was accepted that burning mouth syndrome is a form of neuropathic pain [14]. The neuropathy mechanism in the pathogenesis of BMS is still controversial, the expert literature admitting the possibility of dysfunction via peripheral or central reflex arc and cortical excitation [8,10].

BMS SYMPTOMS

Subjectively, patients describe the syndrome BMS as the presence of oral mucosa burning sensation, the most common manifestation present in the disease. Other features of the pain in this syndrome are itching sensation, numbness, impaired taste (taste "spicy"), dry mouth etc. As topography, the symptom is located almost constantly close to the lingual mucosa (especially in the front third) and the lip. Recently, Demarosi (2013) stresses however that it is not possible that all the oral mucosa could be involved without being identified any precise anatomic distribution [3].

Even since 2003, Scala et al. underlined the semiotic nature of BMS as being more complex, consisting of main and associated symptoms:

a) The main symptom is a triad, consisting of:

1. Pain in the oral mucosa: burning, stinging, tingling, swelling;

2. Dysgeusia (altered taste): the persistence of a certain flavor/taste perception alteration;
3. Xerostomia, with dry mouth.
b) Other associated symptoms: thirst, headache, pain in the temporomandibular joint (TMJ), tenderness/ pain during mastication and/or in some regions of the neck suprahyoid or shoulder level muscles [15].

The amount of positive clinical examination in the diagnosis and any associated distress, which act as causative factors in BMS syndrome

BMS diagnosis is essentially one of exclusion [16]. It is based on a historic and very thorough clinical examination. An accurate diagnosis requires careful investigation of BMS medical history of each patient (such as a preexisting condition at the oral mucosa level, malnutrition, cerebral dysfunctions or drug intoxication) [17,18].

1. The contribution of general clinical examination in the diagnosis of BMS

At their first visit at the dentist's, patients frequently report present disorders and diseases already diagnosed under therapy. When there is a suspicion of disease present and undiagnosed, the patient is advised to consult a physician in the respective domain [19].

2. The role of local clinical examination in the diagnosis of BMS

Local clinical examination often does not reveal any changes. Sometimes clinical examination can detect minor changes or variations of normality: fissured tongue, exfoliative glossitis, depapillations of various origins, geographic tongue or coated tongue [16].

If physical examination reveals the absence of clinically obvious lesions on the oral mucosa, it is reasonable to suspect that intraoral burning is a possible indicator of a systemic disorder [3].

Identifying the possibility of the existence of systemic diseases associated with or responsible for installing the BMS syndrome is by clinical examination and by performing general laboratory or laboratory tests [16].

THE MAIN THERAPIES EMPLOYED IN THE BMS

Based on a comprehensive assessment of the patient's disease state that integrates general clinical examination results, psychiatric/psychological balance and the local dental examination, a therapy in BMS is set. The characteristic of glossodynia treatment is its individualization and adapting to each individual case [19].

Primary stage in establishing BMS therapy requires the differentiation of the primary from the secondary. This is because if the balance sheet allowed the identification of predisposing and etiologic factors, therapy will target their harmful action through appropriate specific methods.

Clinical attitude to be adopted to establish the diagnosis and clinical form of BMS is summarized in figure 1. Schematic representation is useful because it allows to facilitate the understanding of therapeutic medical conduct to follow. According to Demarosi (2013), clinical, biochemical and hematological test results represent two phases of special importance in the etiological diagnosis of the BMS [3].

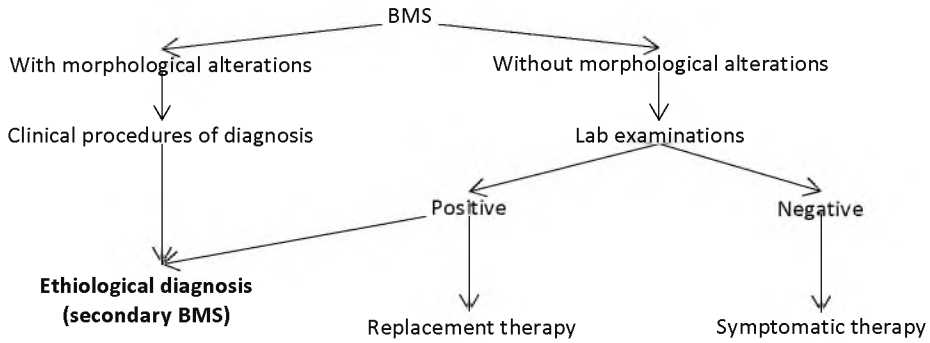
The therapy goals of the BMS syndrome are administered to target a triple purpose:
1) Improvement of symptoms;
2) Correction of biological and/or morphological disturbances (if there are), commonly referred to as correction therapy;
3) Changes in psycho-emotional therapy [3].

Symptomatic treatment

Symptomatic treatment is similar in both cases of BMS (idiopathic or secondary). While pain is a symptom of many chronic diseases, persistent pain should not be regarded simply as a symptom. Pain itself can become a disease where pain signals origins fail to be controlled due to deterioration of the pain alarm system, leaving the patient with persistent pain. Whatever the cause, chronic pain can transcend ordinary physical pain. Persistent pain interferes with daily life, other important relationships and puts a mark on the mind, body and spirit of the BMS patient. The pain and related problems (e.g., medication side effects, depression and anxiety) can be best managed

using a complex program of integrative treatments tailored to each patient. The name of integrative treatment derives from the means/method by which it is achieved, the approach of a "multi-modal" one.

Figure 1: The current clinical attitude in the presence of a case with BMS [3]



The method involves combining treatments from conventional medicine with those of complementary and alternative therapies. Scientifically, for the efficiency of the latter, evidence have been provided for both the quality and safety of the therapy. In this category, the treatment of patients with BMS can use homeopathic products, cognitive-behavioral methods, aromatherapy, herbal extracts, vitamins, dietary supplements, some combination of minerals etc. [21,22]. Also, acupuncture as an adjunctive therapy method is referred to in the expert literature as being beneficial for the relief of symptoms in patients with BMS [14].

Generally speaking, it is acceptable that the treatment of idiopathic BMS is essentially a symptomatic treatment. In the context of such therapy, the dentist has available a number of symptomatic therapies that can be administered by the general or local means with topical use. Some of these are summarized in the table shown above. The purpose of a symptomatic therapy aims at either improving the intensity of symptoms or halting the clinical manifestations. The results are uncertain, including failure.

Therapeutic strategies include benzodiazepines (clonazepam), tricyclic antidepressants (amitriptyline), opioids (gabapentin), selective inhibitors of serotonin receptors (paroxetine and sertraline), capsaicin topical/systemic, alpha-lipoic acid (neurological antioxidant) hydrochloride, benzydamine 0.15%, hormone replacement therapy, vitamin supplementation and/or zinc, iron and psycho-cognitive therapy [3].

Tricyclic antidepressants (amitriptyline/doxepin/ nortriptyline) are extremely useful for patients with chronic pain. Although developed for the treatment of depression, they have a spectrum of biological activities depending on the dose, including inducing analgesia in a variety of clinical conditions. Although the mechanism is not known, the analgesic effect of antidepressants have a more rapid onset and occurs at a dose lower than that typically necessary to treat depression. The maximum effect is achieved by tricyclic antidepressants in patients with chronic pain who are not depressed, reduced pain being a certainty. Anticonvulsants (carbamazepine) and tranquilizers (clonazepam) are particularly useful for patients with neuropathic pain [23].

Capsaicin, a substance extracted from red peppers, is used for its revulsive and analgesic action. Capsaicin is specifically detected by the "transient receptor potential vanilloid receptor" (TRPV1) distributed in the oral mucosa. The explanation is that the capsaicin molecule is a selective agonist vanilloid receptors TRPV1. Binding means stimulating the receptor, which is found in the nociceptors (pain receptors) in the oral cavity. Overstimulation of TRPV1 receptors make them become "desensitized", no longer able to respond to the stimuli that normally cause pain in patients with peripheral neuropathic pain [24].

Topical application of capsaicin has been shown to sometimes be useful in some pain syndromes, in particular for relieving the symptoms of herpes neuralgia or diabetic polyneuropathy hyperalgesia [25].

Similar conclusions on the effectiveness of topical application of capsaicin (0.02%/0.002%) in BMS are made by Silvestre et al. (2012) and Spanemberg et al. (2011) [26,27].

Other authors speak of the efficacy of capsaicin. Spadari et al. (2014) reported a success rate of over 70% for each control visits after 1, 3, 6 and 12 months of topical therapy (as by rinsing the mouth with a solution of capsaicin 3 times/day) [28].

Among the most widely used symptomatic therapies for BMS are salivary substitutes, from the most simple and economical specific physiological solution to gel. Their use is motivated by the fact that xerostomia is a frequent syndrome in patients with BMS [3].

Grushka (2014) suggests that treatment involves a combination of several BMS drugs that act together, increasing each other's effect (they are given together as dose so that a low-dose should enhance the action). From such an attitude, "low dose" can achieve favorable results on major symptoms present in patients. Achieving success involves on the one hand an individualized (personalized) therapy, on the other successive explorations, to identify the effective drug combination. Based on the results of his studies, Grushka (2014) admits that ⅔ of the patients respond to the treatment aimed at suppressing the effects of benzodiazepine receptor agonists group GABA-A and inhibition of pain. The combination drug likely to complete such a success is a triad of medications: clonazepam 0.5 mg before bed + 10 mg amitriptyline + gabapentin 100-300 mg 3-4 times +/or 25-75 mg Pregabalin 3-4 times daily. Again Grushka (2014) states that zinc therapy is effective in taste changes, prescribing zinc gluconate 50 mg 1-3 times a day for a period of 3-4 months [2].

In conclusion, according to the expert literature, the current level of knowledge about the disease does not include any certainly effective treatment for primary BMS.

Treatment of secondary BMS

According to Ţovaru et al. (2015), for the treatment of secondary BMS the major objectives are:

• detection and treatment of general factors involved in the emergence of glossodynia (anemia, vitamin B deficiency, diabetes, autoimmune disorders of the digestive tract, disorders during menopause, and esophageal reflux caused by gastric hyperacidity);

• detection and removal of the local causes of BMS (incorrect prostheses, changed vertical dimension of the lower floor of the face, improper dental alloys, chronic mucosal infections – for example, Candida – contact allergies, dry mouth, migratory glossitis;

• detection and treatment of coexisting psychiatric disorders (anxiety neurosis or depression, with stress, chronic states of conflict, emotional pressure, cancer-phobia) [19].

Achieving this objectives requires expert advice and patient's hospitalization for the neuropsychological disorder, often lasting for years.

Etiological treatment

A priori, BMS secondary treatment is etiologic, addressed to fight against the general and local factors that maintain the syndrome. The success of etiologic therapy is dependent on the precision with which the causative factor was identified [8,19]. Thus, in the case of the presence of allergic contact reactions, simply removing the suspected allergen (e.g., the material / dental alloy) determines remission of the symptoms of BMS.

If the necessary examinations revealed the presence of anemia, therapy should be prescribed to correct hemoglobin assets and deposits of iron and vitamin B12. Completion of these deposits is mandatory because suppressing the substitute anti-etiological treatment after restoration of erythrocyte hemoglobin level, allows a recurrence of anemia after a certain period of time.

Etiological treatment is required in other cases of BMS secondary diseases such as diabetes mellitus, gastric ulcer, gastro-esophageal reflux disease, mycosis, and the burning mouth is one of the manifestations of

these disorders [3].

Psychological and psychiatric treatment

The second place in the treatment of secondary BMS is psycho-pharmaceutical correction. Frequently, symptomatic treatment [3] is no longer resorted to.

Psychological and psychiatric treatment in the syndrome of secondary BMS is applied not only to the patients with psychiatric disorders or behavioral disorders diagnosed during the first medical checkup, but also to patients who do not respond to dental treatment. For this purpose, patients are directed to consult a specialist who would in fact perform a reassessment if the psychotherapeutic treatment is not appropriate to be set [3,29].

Specialized treatment is achieved by two means:

a) psychotherapy (psychological exam);

b) with drugs, therapy monitored by a psychiatrist;

Psychological treatment aims at controlling and alleviating the mental disorders that occurred. Typically, psychological treatment complements the psychiatric one, but it is the first to start with, especially in patients who have problems with mental BMS, such as those with dental treatment failure. Results of consequent studies have concluded that pharmacological products such as benzidamine-HCl solution, sucralfate, antihistamines, lidocaine, capsaicin have not shown significant improvement statistically [2,3,16].

Frequently followed conduct is the psychoanalytic association with administration of specific psychotropic medication (anxiolytic, antidepressant). The usefulness of psychotherapy is to reduce symptoms, if there is a psychological component to glossodynia [19].

Counselling treatment

BMS syndrome treatment conduct includes counselling, preferably applied by a physician demonstrating empathy for the patient. The purpose of counselling is to provide the patient information and explanations about the sickness, benignity of the lesion, its correlation with notions of its correlation with field (age and sex). These patients should always know that their disorders are often related to stress and that if they make it go away, at least in part their suffering can diminish [3].

The doctor should always have the status of patients with BMS, the suffering and disease, so they have to devote the necessary time to communicate and discuss the patients' problems. This is because one of the major concerns of patients with BMS is to undergo a treatment to alleviate the symptoms [3].

During counselling sessions the BMS patient will be informed about the need to respect therapeutic indications, even if obvious improvements do not occur. Also, we will clarify that for the relief of symptoms, duration of treatment is for months/years.

Starting from his own medical experience, Demarosi (2013) states that patients rarely comply with prescribed BMS treatment, the recommended therapy is often performed incorrectly and doctor visits are random. Simultaneously, the patient will be clearly advised that the outcome of the treatment consisting in improvement or even the disappearance of the disease is often only temporarily effective [3].

Since the treatment of BMS is generally unsatisfactory even if it is appropriate, and the pain is chronic, it is necessary that patients be counselled with correct information on expectations that are to be understood realistically. Otherwise, the patient loses confidence in his regular doctor and becomes psychotic, going from doctor to doctor.

EVOLUTION AND PROGNOSIS IN BMS SYNDROME

Sardella et al. (2006) in a retrospective study of 18 months showed that 28.3% of the BMS (basic form) cases registered moderate improvement, 49% not any significant change, 18.9% of the cases presented a worsening of symptoms in patients who have not received any treatment. Spontaneous complete remission is rare and has been reported by the same team in 3% of cases investigated over a period of 5 years [30,31].

Cure rates measured in glossodynia of type I and II were almost comparable (61% versus 59%). 70% of all

cases that have not responded to treatment present associated psychiatric disorders [19].

Idiopathic nonspecific painful syndromes are most rebellious to treatment. Some cases even exclude any possibility of allopathic treatment, in which case additional treatment, such as acupuncture is resorted to (14). Frequently, the results of acupuncture are not always stable, and in some cases a patient can get addicted to this kind of treatment [19].

In other words, where allopathic treatment + psychological + counseling fail, acupuncture may be used with relative efficacy and limited duration, which requires to repeat the complementary procedure.

In another study, a group of 91 patients with BMS symptoms were analyzed and it was concluded that in a small number of patients symptoms may resolve spontaneously within five years from the onset. Moreover, a partial improvement was observed in 38.4% of these cases under various treatments (for example, clonazepam in local administration). This rate of improvement is greater (up 61.7%) when patients were administered clonazepam locally associated with psychotherapy [32].

Fenelon et al. (2014), evaluating the results of short-term therapy with clonazepam versus amitriptyline in the pain relief of BMS highlighted that after 6 weeks of treatment there was an improvement in the symptoms of pain in both situations, noting that the effect of amitriptyline was lower than that of clonazepam. To explain such particularity of the therapy, the authors imply a slow onset of action of the first drug. After 3 months, the results were similar in the two groups of patients evaluated [33].

Under treatment against pain, proton pump inhibitor, hydratation and regime during hospitalization the symptoms disappear. However the hepatic cytolysis worsens with the progressive growth of alanine aminotransferase to values of 916 U/L, hence anti-helminthic treatment is delayed.

Enchinococcal infection caused by the larval form of *Echinococcus granulosus* remains an important health issue worldwide. Hepatic hydatid cyst is the most frequently encountered form (50-93 % of the cases) and left untreated these grow and lead to: developing fistulae in adjacent organs, rupture in the peritoneal cavity, produce daughter cysts or dye (rarely)[1]. Clinical manifestations appear after the cyst is larger than 10 cm in diameter and only a third of the patients experience symptoms.

Even though biological finding are nonspecific, elevated bilirubin and alkaline phosphatase may appear. Leukocytosis may appear due to infection of the cyst and eosinophilia is present only in a quarter of patients [2].

Despite the fact that ultrasonography remains the main pillar in the diagnosis of the disease, computed tomography and serology help improve the accuracy of diagnosing liver hydatidosis. WHO Ultrasound classification of echinococcal cysts helps establish the treatment: 1 (unilocular, anechoic cyst with double line sign), 2 (multiseptate honey comb cyst), 3a (cyst with detached membranes), 3b (cyst with daughter cysts in solid matrix), 4 (heterogenous contents and no daughter cysts) and 5 (solid plus calcified wall). CE4 and 5 are inactive.

On the other hand Gharbi classification also divides in 5 types: type I cysts consist of pure fluid; type II has a fluid collection with a split wall; type III cysts contain daughter cysts (with or without degenerated solid material); type IV has a heterogeneous echo pattern; and type V has a calcified wall. Therefore our case presents a hepatic hydatid cyst stage CE2 after WHO classification and type III after Gharbi classification.

Uncomplicated and small lesions (under 5 cm) CE1, 2 and 3 can be treated with oral albendazole (10-15 mg/kg/day) and close monitoring. However, large CE1 and CE3 cysts need treatment with both albendazole and PAIR (percutaneous aspiration, introduction of scolicide and reaspiration), performed after initiation of albendazole.

Primary surgical treatment has been replaced with less invasive methods since the relapse rate can reach 20%. In patients with complicated cysts, surgery is the treatment of choice. CE 4 and 5 only need to be monitored [1,3].

References:

1. Komiyama O., Nishimura H., Makiyama Y., Iida T., Obara R., Shinoda M., Kobayashi M., Noma N., Abe O., De Laat A., Kawara M., Group cognitive-behavioral intervention for patients with burning mouth syndrome, J Oral Sci., 2013, 55(1):17-22.

2. Grushka M., Oral sensory phantoms and other strange phenomena, Conference of "Carol Davila" University of Medicine and Pharmacy, June 2014, Bucharest, Romania.

3. Demarosi F., Sindrome della bocca urente - manuscript, 2013.

4. Rodriguez-de Rivera-Campillo E., López-López J., Evaluation of the response to treatment and clinical evolution in patients with burning mouth syndrome, Med Oral Patol Oral Cir Bucal, 2013, 18(3):e403-e410.

5. Mendak-Ziółko M., Konopka T., Bogucki Z.A., Evaluation of select neurophysiological, clinical and psychological tests for burning mouth syndrome, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 2012, 114(3):325-332.

6. Coculescu E.C., Ţovaru Ş., Coculescu B.I., Epidemiological and etiological aspects of burning mouth syndrome, Journal of Medicine and Life; 2014, 7(3):305-309.

7. Klasser G.D., Epstein J.B., Oral burning and burning mouth syndrome, J Am Dent Assoc., 2012, 143(12):1317-9.

8. Gurvits G.E., Tan A., Burning mouth syndrome, J Gastroenterol., 2013, 19(5):665-672.

9. Woda A., Dao T., Grémeau-Richard C., Steroid dysregulation and stomatodynia (burning mouth syndrome), J Orofacial Pain, 2009, 23:202-10.

10. Manole G., Clinical Physiology (2nd volume) [in Romanian], C.N.I. Coresi Publisher, Bucharest, Romania, 2007.

11. López-Jornet P., Camacho-Alonso F., Andujar-Mateos P., Sánchez-Siles M., Gómez-Garcia F., Burning mouth syndrome: an update, Med Oral Patol Oral Cir Bucal, 2010, 15:e562-8.

12. Minor J.S., Epstein J.B., Burning mouth syndrome and secondary oral burning, Otolaryngol Clin North Am., 2011, 44(1):205-19.

13. Souza F.T., Santos T.P., Bernardes V.F., Teixeira A.L., Kummer A.M., Silva T.A., Abreu M.H., The impact of burning mouth syndrome on health-related quality of life, Health Qual Life Outcomes, 2011, 9(1):57.

14. Sardella A., Lodi G., Tarozzi M., Varoni E., Franchini R., Carrassi A., Acupuncture and burning mouth syndrome: a pilot study, Pain Pract., 2013, 13(8):627-32.

15. Scala A., Checchi L., Montevecchi M., Marini I., Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med., 2003, 14:275-291.

16. Coculescu E.C., Radu A., Coculescu B.I., Burning mouth syndrome: a review on diagnosis and treatment, Journal of Medicine and Life, 2014, 7(4):512-515.

17. Brecht S., Courtecuisse C., Debieuvre C., Croenlein J., Desaiah D., Raskin J., Petit C., Demyttenaere K., Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry, 2007, 68:1707–1716.

18. Kim Y.D., Lee J.H., Shim J.H., Duloxetine in the treatment of burning mouth syndrome refractory to conventional treatment: A case report, J Int Med Res., 2014, 42(3):879-883.

19. Ţovaru Ş., Ţovaru M., Demarosi F., Mihai L., Pârlătescu I., Bold A., Gheorghe C., Vlădăreanu A.M., Pitru A., Streinu-Cercel A., Coculescu E., Medicine and Oral Pathology (2nd volume) [in Romanian], Quintessence Publisher, Bucharest, Romania, ISBN 978-973-88795-1-5, 2015.

20. Coculescu E.C., Manole G., Coculescu B.I., Purcărea V.L., Burning mouth syndrome: controversial place as a symptom of Oro-dental pathology, Journal of Medicine and Life, 2015, 8(Special Issue):34-37.

21. Cassidy J.T., Juvenile rheumatoid arthritis. In ED Harris Jr, et al. eds., Kelley's Textbook of Rheumatology, 7th ed., Philadelphia: Elsevier Saunders, vol. 2, 1579-1596, 2005.

22. Ailioaie L.M., Contributions to therapy of pain in chronic juvenile arthritis by physical and alternative medicine [in Romanian], Thesis of doctorate (summary), Faculty of Medicine, "Gr. T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, 2012.

23. Fauci A.S., Braunwald E., Isselbacher K., Wilson J., Martin J., Kasper D., Hauser S., Longo D., Harrison: Principles of Internal Medicine (1st volume) [in Romanian], 14th Edition, Teora Publisher, Bucharest, Romania, 2003.

24. European Medicines Agency, Qutenza capsaicin - summary of the European public assessment report (EPAR) for the public [in Romanian], Ref. doc.: EMA/535073/2015, 2015, http://www.ema.europa.eu/docs/ro_RO/document_library/EPAR_-_Summary_for_the_public/human/000909/WC500040448.pdf

25. Mungiu O.C. (under redaction), Treaty of Algesiology [in Romanian], Polirom Publisher, Iaşi, Romania, 2002.

26. Silvestre F.J., Silvestre-Rangil J., Tamarit-Santafé C., Bautista D., Application of a capsaicin rinse in the treatment

of burning mouth syndrome, Med Oral Patol Oral Cir Bucal, 2012, 17(1):e1-4.

27. Spanemberg J.C., Rodriguez-Archilla A., Ceballos-Salobreña A., Coppola M.C., de Araújo L.M.A., Burning mouth syndrome: topical application of 0.002% capsaicin (Capsicum frutescens L), Revista Brasileira de Ciências da Saúde, 2011, 9(28): 1-5.

28. Spadari F., Azzi L., Porrini M., Rossi M., Tagliabue A., Tettamanti L., Burning mouth syndrome and topical capsaicin: a clinical experience, In Conference: 12th Biennial Congress of the European Association of Oral Medicine, 11-14 September 2014, Gloria Hotels and Resort Antayla, Turkey, Oral Diseases, 2014, 20(s2): 13.

29. Sardella A., An up-to-date view on burning mouth syndrome. Minerva Stomatol., 2007, 56(6):327-40.

30. Sardella A., Lodi G., Demarosi F., Bez C., Cassano S., Carrassi A., Burning mouth syndrome: a retrospective study investi gating spontaneous remission and response to treatments, Oral Dis, 2006, 12:152-155.

31. Zakrzewska J.M., Multi-dimensionality of chronic pain of the oral cavity and face, J Headache Pain., 2013, 14(1):37. doi: 10.1186/1129-2377-14-37.

32. Rodriguez-de Rivera-Campillo E., López-López J., Evaluation of the response to treatment and clinical evolution in patients with burning mouth syndrome, Med Oral Patol Oral Cir Bucal, 2013, 18(3):e403-e410.

33. Fenelon M., Quinque E., Catros S., Arrivée E., Fricain J.C., Evaluation of pain-relieving effect of amitriptyline versus clonazepam in BMS, In Conference: 12th Biennial Congress of the European Association of Oral Medicine, 11-14 September 2014, Gloria Hotels and Resort Antayla, Turkey, Oral Diseases, 2014, 20(s2):16.