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UPDATE ON THE CHALLENGES OF TREATING BURNING MOUTH SYNDROME

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ABSTRACT: Burning Mouth Syndrome (BMS), an idiopathic oral disease and also neuropathy of trigeminal nerves appear in oral cavity with the burning sensation in tongue. Other presentation of BMS as its synonyms sore mouth, sore tongue, oral dysesthesia and scalding of mouth. This chronic debilitating oral condition has an obscure aetiology and pathogenesis, causing an abroad way to treat this disease. The medication for BMS must concern its local or systemic condition, which focusing on the relief of symptoms so the clinicians may able to improving the patients quality of life. The literature contains the summary of type drugs and supplements. Although effective therapies have been conducted in many concrete cases, a treatment modality offering efficacy in most cases of BMS, yet remains to be established. It is important to achieve an intensive knowledge to the physiopathological mechanism of BMS, and to compare and establish for developing drugs to improve the efficacy and safety profiles in the treatment of BMS.

Key words : Burning Mouth Syndrome, orofacial pain, clonazepam, vitamin B complex

INTRODUCTION

Burning mouth syndrome (BMS) (oral dysesthesia; glossodynia; stomatodynia) is a medical condition characterized by chronic orofacial pain without any mucosal abnormalities or other organic disease. The BMS epidemiology is uncertain, with an reported prevalence varying from 0.7% to 4.6%. The variety of prevalence across studies may related to the differences in inclusion criteria utilized in the research. The range for BMS is typically in the fifth to seventh decade of life and is more popular in women than men, with an approximate ratio of 3:1 to 16:1 (Klasser *et al*, 2008).

According to The International Headache Society (IHS) in the International Classification of Headache Disorders III (ICHD-3), BMS is classified into the category of painful cranial neuropathies and other pacial pain. In ICHD-3, the diagnostic criteria of BMS is (i) Daily occur periodically for >2 h per day for 3 months, (ii) Pain sensation has all of the following characteristics: burning condition and superficial sensation in the oral mucosa (iii) Oral mucosa is of normal appearance and clinical evaluation including sensory examination is normal and (iv) Not different than any ICHD-3 diagnosis. The postulated category of neuropathy of BMS may be due to a decrement of thermal pain tolerance and increased recgnition thresholds to intensity of heat pain found in BMS patients(Korczeniewska *et al,* 2019).

There are several classification of BMS. In the clinical settings, classification based on etiology is widely use. Based on etiology, BMS classified into primary/ idiopathic BMS used in idiopathic condition is indicated and secondary BMS when underlying local/systemic conditions founded. Based on their pathophysiology, BMS can be devided into three subgroups. The first (50-65 percent) is distinguished by peripheral small diameter fiber nerve damage of oral mucosa, the second (20-25 percent) is defined by subclinical lingual, mandibular, or trigeminal system pathology, and lastly the third (20-40%) is associated with central pain resulting from dopaminergic neuron hypofunction in the basal ganglia (Jaaskelainen, 2012).

Although, the enigmatic characteristic of BMS ethiopathogenesis, several study postulated that BMS may related to peripheral and central sensory neuropathy or neuropathic disproportion in taste and sensory systems.

Peripheral sensory neuropathy may be explained to research findings related to chorda tympani dysfunctions. The gustatory function is maintained by the chorda tympani (2/3 anterior of the tongue) and lingual nerve (1/3 posterior of the tongue and mechanical function) (Nasri Heir *et al*, 2011; Eliav *et al*, 2007; Bartoshuk *et al*, 2005). The damage towards chorda tympani may disrupt a homeostatic condition of gustation orchestrated by both systems, thus somatosensory system disinhibiton would occur. This condition may result in intensification of sensory stimulus perceived by trigeminal nerve, including pain thus chronic burning sensation may be perceived by patients. Other pathophysiology in BMS patients related to chorda tympani damage is "supertasters", the ability to taste bitter compound phenylthiocarbamide. This condition may explained the altered taste function in BMS patients. Small fiber peripheral neuropathy also been postulated mechanism, a study reported epithelial and subpapillary nerve fibers exhibit disperse morphological improvement suggesting axonal degeneration (Korczeniewska *et al*, 2019).

The central mechanism of BMS is proposed to be related with presynaptic abnormalities of the nigrostriatal dopaminergic mechanism. This system is related in central pain modulation. This mechanism is controlled by physiological levels of estrogens. BMS often associated with menopausal condition, and it may be associated with the dysfunction in central pain modulation (Gajjar *et al*, 2003). Central nervous system hypoactivity has been proposed to be an important aspect of BMS pathophysiology. Greater signal shifts in the right anterior cingulate cortex and bilateral precuneus were identified in BMS patients relative to controls (Albuquerque *et al*, 2006) and less volumetric activity in the brain was found in BMS patients relative to controls. Generally, the brain activity changes found in BMS patients are identical to those seen in people with other neuropathic pain disorders and tend to handle thermal painful stimulation to the trigeminal nerve in a way that is qualitatively and quantitatively distinct from that seen in pain-free persons.

The eliminations of underlying systemic/local conditons and relieving symptoms are the main principles in BMS management. But the selection of appropriate interventions remain problematic and challenging to clinicians. This conditions resulted from variable and elusive pathophysiology of BMS and very little evidence-based treatment available. Consensus in the therapy sequence of BMS is still unavailable, but the selection of pharmacologic agents is similar as neuropathic pain management. This review will discussed pharmacological intervention often used in symptomatic therapy of BMS (Korczeniewska *et al*, 2019).

Topical medication

2% Lidocaine gel

2% lidocaine gel is an amide drugs and a topical analgesic and anti-inflammatory, which is commonly used as a local anesthetic in dentistry (Sun *et al*, 2013). 2% lidocaine gel works on cell membranes to inhibit the production and distribution of nerve impulses by covering voltage gated sodium channels. The activity of local topical anesthetics that rely on peripheral factors such as ectopic discharges from sensitized nerves. Ectopic impulses from damaged peripheral nerves may be responsive to local anesthetic than regular impulses in intact nerves. That is the why topical lidocaine can be effective for patients with neuropathic pain (Okayasu *et al*, 2016). 2% lidocaine gel infiltrate to the cell membrane and disturbing the depolarization, then it's increasing the extracellular Ca. The drug binding in the Na canal and ion influx impaired. It's preventing normal depolarization of the membrane and blocking the conduction of potential action (Wolf and Otto, 2015).

The onset of 2% lidocaine gel is about 5 minutes, the duration of action is 45-90 minutes and the metabolism occurs in liver. Maximum dosage is 6 mg/kg weight. 2% lidocaine gel has several side effect, such as allergic reactions (hive, problems breathing, swelling of the face, lips or tongue), stinging, irritation, swelling or redness, dizziness, confusion, blurred vision and it does not cause any systemic side effect(Wolf and Otto, 2015).

Some studies suggested that topical lidocaine can be used for postherpetic neuralgia and trigeminal neuralgia therapy and burning mouth syndrome has been considered to be neuropathic pain. Recently, topical lidocaine was used as an emergency therapy for patiens with BMS. (Okayasu *et al*, 2013). This drug can be used to reduce pain and burning sensation in patients with burning mouth syndrome (BMS), but the analgesic effect is too short so it is not effective as a burning mouth syndrome therapy (Sun *et al*, 2013).

Benzydamine hydrochloride 0, 15%

Benzydamine hydrochloride is included in non-steroidal drugs with anti-inflammatory, analgesic, and anti-microbial properties. This drug has the effect of decreasing prostaglandin production by forming thromboxane which inhibits platelet aggregation and stabilizes cell membranes (Goswami *et al*, 2018). Benzydamine hydrochloride mouthwash has topical anesthetic effects that are helpful for pain control. Benzydamine hydrochloride mouthwash is used to reduce

signs of discomfort or burning symptoms in patients with BMS. However, the use of the drug has not been proven to be an effective treatment because of its short analgesic effect (Sun *et al*, 2013). One study showed that the use of a 0.15% benzydamine hydrochloride mouthwash (15 mL used three times a day) in a group compared to another group without treatment, showed an insignificant difference in results at the end of the 4-week study period (Nasri-Heir *et al*, 2015).

Aloe vera gel 70%

Aloe vera (AV) is a cactus-like plant which grows easily in hot, dry climates. It belongs to the Liliacea tribe, of which there are approximately 360 species. Just two varieties are commercially cultivated: *Aloe barbadensis* Miller and *Aloe aborescens*. The parenchymatous cells in the fresh leaves of aloe vera excrete colorless gelatinous gel (*i.e.*, Aloe vera gel) that contains 98-99 percent water and 1-2 percent active content (Nair *et al*, 2016).

Aloe vera gel has numerous pharmacological function like antimicrobial, antifungal, anti-inflammatory, antioxidant, antitumour, hypoglycaemic properties and immune stimulation. This is also commonly used as nutritious drinks, a moisturizer, a therapeutic agent in cosmetics, diabetic patients, sun burn, injuries and gastrointestinal disorders, there is no adverse impact (Nair *et al*, 2016).

Topical AV medications have been commonly used for treating a variety of disorders as they may interrupt the inflammatory response through disruption with the arachidonic acid cascade through cyclooxygenase. Study shows that magnesium lactate available in the gel can prevent the production of histamine that causes itching and irritation of the skin.8, 9 It also enhances the immune system and the synthesis of cytokines. Aloe vera is effective in inhibiting inflammatory reactions by the inhibition of IL-6 and IL-8, the reduction of leukocyte adhesion, an increase of IL-10 levels, and decrease of TNF alpha levels (Hekmatpou *et al*, 2019; Lo´pez-Jornet *et al*, 2012).

The parafunctional behavior (tongue rubbing, lip or cheek chewing) that lasts for long time result in neuropathic changes that eventually lead to a persistent burning feeling. Therefore, managementapproachescan reduce the development of an acute burning sensation to a chronic condition. Evidence indicates that the prescription of a tongue protector and of topical AV 70 percent (0.5 ml three times daily for 12 weeks) combined with the control of oral parafunctional habits is an appropriate initial solution for the oral pain associated with BMS (Lo´pez-Jornet *et al*, 2012). Topical use of this formulation is found to be effective for reducing the burning and pain feeling of tongue (Aravindhan *et al*, 2014).

This analysis demonstrated that the tongue protection and use of topical AV should be seen as an 'option initial strategy' to BMS treatment. Neuropathy therapies such as selective serotonin reuptake inhibitors or clonazepam can aso beintended for patients with BMS, who do not respond to this form of standard initial treatment regimen. (Lo´pez-Jornet *et al*, 2012)

Systemic Medication

Systemic Clonazepam

Benzodiazepines (BZD, BDZ, BZs) or called benzos, are *gamma-amino butiric acid* A (GABAA) receptor agonists that binds to peripheral and central receptors, increase the inhibition of brain stem serotonergic pain, andsuppress hyperactivity of central neurons that occur after differentiation. Although, the function of GABAA in peripheral tissue has not been known certainty, it can be hypothesized that changes in receptor density or ligand concentration are related to burning pain sensations and these changes can be triggered by neurosteroid loss. BMS is known to be a phantom pain syndrome, associated with lack of resistance that is generally innervated by the chorda tympani nerve in the brain area that collects afferent impulses from the cranial nerve IX and cranial nerve V. GABAA agonists are expected to combat the lack of inhibition and thereby reduce oral phantom pain. Clonazepam, one of the most widely used BZD, is a modulator of GABAA and anticonvulsant. Lastest study has found that clonazepam is more effective in managing BMS manifestations than other benzodiazepines. This is likely because clonazepam appears to bind to the BZD receptor, clonazepam has a good impact on the brain serotonergic pathway and has a longer half-life, resulting in fewer side effects. Through research which has been conducted, clonazepam topical and systemic is found effective for relieving symptoms of BMS, in short-term and long-term use (Cui *et al*, 2016).

Clonazepam is an anticonvulsant drug commonly used for epilepsy management at adult doses from 4 – 8 mg a day. The alternative use of this drug in lower doses is for the management of orofacial pain. Several studies using this drug have shown a reduction in BMS manifestation. One randomized controlled trial (RCT) study and one open-label study showed that taking clonazepam medications for 3 minutes and then salivating has been successful in reducing the pain related to BMS. It was also found that perorally dosage of clonazepam was

effective either (Amos, Yeoh and Farah, 2011). For BMS, the dosage of systemic clonazepam is 0.5 mg/1-5 times a day. Several side effects of clonazepam are sleepiness, ataxia (the loss full control of bodily movement), palpitations, skin rash, painful urination, anorexia, dry mouth, muscle weakness, diplopia, slurred speech, tremor, vertigo and lower blood pressure (Farah *et al*, 2019).

The GABAA receptors in the central nervous system (CNS) is the molecular target for the actions for BDZ. Gamma-aminobutyric acid is an amino acid neurotransmitter that has an inhibitory effect on CND neurotransmission. As a consequence, an improvement in the impact of GABA results in general repression of the CNS. As GABA binds to GABAA receptors, the result is an influx of chlorine ions into neurons through the ion channel created by the receptor. This is the chlorine influx that detrimental impact on neurotransmission. There is also a site for the attachment of BZD on the GABAA receptors apart from the GABA binding site. When both GABA and BZD are associated with a GABAA receptor, chlorine influx rises through the receptor's ion channel. Consequently, the effect of GABA on the GABAA receptors when it binds were increased by benzodiazepines. Subsequently, it should be remembered that BZD have no direct effect on the GABAA receptor, but benzodiazepine binding has no direct impacts on the infllux of chlorine ion if GABA is not bound to the GABAA receptor. The primary mode of action of Clonazepam is to promote GABAergic transmission in the brain by a direct effect on benzodiazepine receptors. GABA receptors are found in dorsal raphe neurons, and GABA serves to inhibit raphe cell firing.

An open-label study conducted by Grushka *et al* (1998) was performed to see systemic clonazepam effect of 0.25 mg/day for 30 BMS patients led to use clonazepam with an increase of 0.25 mg/week in case the symptoms persisted. Studies indicate that pain has reduced at low doses to 70% of patients with BMS. In 20 patients with BMS in a randomized double-blind clinical tria, systemic clonazepam (0.5 mg/day) was shown to be effective for reducing pain and burning sensation (Heckmann *et al*, 2012). Ko *et al* (2012) examined clonazepam therapy outcome predictors in 100 BMS patients who received instruction to take 0.5 mg of clonazepam for 4 weeks onceor twice daily. The study showed that clonazepam therapy predictors for outcomes in BMS patients may include psychological condition, seriousness of initial symptoms, and the existence of dry mouth and/or taste dysfunction. The combination of topical and perorally clonazepam medication was used by Amos *et al* (2011) to treat 36 BMS patients. dissolvement clonazepam tablets (0.5 mg/tablet, three times daily) orally before swallowing were instructed to the patients were followed up for 6 months. They have found that 80% of patients report pain relief over 50% and one-third of patients have total pain resolution, which mean that combined topical and systemic clonazepam successful to treat BMS (Sun *et al*, 2013).

Gabapentin

Gabapentin is an anticonvulsant drug often used in neuropathic pain (NP) management and categorized in the first-line treatment of NP. Gabapentin derived from GABA, but it has no effect on the GABAergic system. The gabapentin's action mechanism involves the relation to the alpha-2/delta-1 sub-of the voltage-calcium channels in many CNS and spinal cord regions, and this is enough to understand their therapeutic properties as analgesic, anxiolytic and anticonvulsant. Voltage-gated calcium channels located in the presynaptic portion and sensitive towards action potential. The activation of these channels will contribute to the release into the synaptic hollow of synaptic vesicles and neurotransmitters. Alpha-2/delta-1 subunit is responsible for the trafficking, localization, and stabilization of the channel in plasma membrane. In numerous neuropathic condition such as post-herpetic neuralgia, painful diabetic neuropathy, painful polyneuropathy and low back pain were stated to be efficacious treated with gabapentin. Conversely, a study reported low effectivity of gabapentin 300 mg/day for three weeks in reducing symptoms of BMS. This conditions may indicate that neuropathy is not the main pathophysiology of BMS, though a further study needed (Heckmann *et al*, 2006).

Amitriptyline

Amitriptyline is a dibenzocycloheptadiene tricyclic antidepressant (TCAs). This prevents the neuronal reuptake in the presynaptic neuronal membrane of serotonin (5-HT) and/or norepinephrine, thereby increasing its synaptic concentration in the CNS. This has affinity to varying degrees for receptors of muscarinic and histamine (H_1).

TCAs also act as á1-adrenergic receptors (In particular, norepinephrine decreases glutamanergic excitatory postsynaptic potentials by the activation of á1-adrenergic receptors), calcium channel blockers, potassium channel activators, modulate the adenosine system and increase GABA-B receptor function. They activate opioid receptors, inhibit the production of nitric oxide, prostaglandin E2 and have a variety of other actions that may inhibit neuropathic pain in a complex manner. So that persistence of having peripheral neuropathy could

be treated by silencing the excitation of NMDA receptors and act as antagonists. TCAs also modulate the inhibition of ectopic discharge of sodium during nerve damage, thereby it will be inhibiting the neuropathy pain. Systemic dose for depression in adults initially increases by 25 mg request, then rises by up to 150 mg daily in separate doses every other day by 25 mg. Optionally, 50-100 mg medication can be increased to a cumulative dose of 150 mg daily, by 25-50 mg at bedtime.In patients hospitalized: 100 mg daily may initially be raised to 200 mg daily, up to 300 mg daily, as needed.Treatment duration: 2-4 weeks up to 6 months after recovery to minimize recurrence. Elderly: preferring to 10-25 mg daily at night. According to patient tolerability and reaction, it can be increased to 100-150 mg daily. Caution should be taken on doses above 100 mg. The prophylaxis of adult migraine, which is initially given at 10-25 mg preferably in the evening, for oral intake for neuropathic pain. Every 3-7 days, it can gradually increase to 10-25 mg. Standard dose: ideally 25-75 mg daily at night. In divided doses dose greater than 75 mg can be given. Caution should be taken on doses above 100 mg. Initially 10-25 mg is given in the evening, for elderly is preferably. The reaction and tolerability of the patient can be slowly increased. Caution should be taken on doses above 75 mg.

Kawasaki *et al* (2018) shown an exemplary of how amitriptyline worked in patient with BMS and used the patient salivary flow as a marker of analgesic effects of amitriptyline on BMS. The changes of salivary flow of BMS patients may reliable and non-invasive estimation of clinical response to amitriptyline. They suggest that antidepressants inhibiting noradrenaline reuptake may enhance pain facilitation in brainstem (during chronic pain induction located in dorsal reticular nucleus of descending pain facilitation system), counteracting their analgesic effect at the spinal trigeminal nucleus caudalis in treatment resistant BMS patients. Amitriptyline also shown to affect the increase of viscous salivary flow due blocking the Acetylcholine of autonomic nerve neurotransmitter for serous flow and instead increasing Noradrenaline.

Vitamin B complex

Patients with BMS have reduced blood serum levels of vitamins B1, B2, B6 and B12. Low follic acid and iron levels in blood serum form another minor finding of nutrient deficiencies in BMS subjects.Hypomethylation takes place in the CNS in person with vitamin B12 deficiency. The inhibition of methionin synthase enzyme-dependent of B12 causes the proportion of S-adenosylmethionine (SAM) to S-adenosylhomocysteine to decrease. Deficiencies in the SAM component interfere with the methylation reaction in the myelin sheath. Methylation of homocysteine into methionine requires the presence of Vitamin B12 (Jaya and Dwicandra, 2017).

Vitamin B like thiamine (B1), pyridoxine (B6) and cyanocobalamin (B12) have antinociceptive effects in studies for acute and chronic pain linked with neuronal injury (Nelonda and Setiadhi , 2018). They play important roles in nutrition, nerve conduction, axonal transport, synthesis of neurotransmitters and excitation *via* cyclic guanosine monophosphate (c-GMP) signaling mechanism. The vitamin B or B12 supplementation was shown to increase the amount of Schwann cell and nerve fibers, as well as axon diameter, facilitating regeneration and proliferation of Schwann cells. Vitamin B complex or vitamin B12 supplementation was demonstrated.Vitamin B12 promotes axon regeneration and is closely linked to neuronal repair through the metabolism pathway of vitamin B12 (Altun and Kurutas, 2016).

Folate deficiency can be treated with additional oral folate 400 to 1000 mcg/day. This treatment is very successful in tissue regeneration. Values less than 200 pg / mL are a sign of vitamin B12 deficiency. People with this deficiency must have or develop BMS. Oral vitamin B12 has been approved as an effective and safe treatment. 500-100 mcg of intravenous vitamin B12 supplementation can usually help the condition of B12 deficiency and its symptoms (Kim and Kho, 2016; Krasteva *et al*, 2013).

Alpha Lipoic acid

Alpha lipoic acid (ALA) is one of the most effective drugs in the treatment of burning mouth syndrome. ALA is the trometamol salt of thioctic acid and a potent antioxidant that is produced naturally in the body. ALA can also be found in some foods such as potatoes, tomatoes and spinach (Palacios-Sanchez *et al*, 2015). ALA is fat and water soluble so it has good bioavailability. ALA is one of the safest drugs for treating BMS, because it can decrease oxidative damage in the nervous system. ALA was systemically administered at amounts of 400 to 800 mg, separated into 2 to 3 daily administrations, with most studies lasting 2 months.Only two studies documented patients with digestive disorder side effects (De Sousa *et al*, 2018).

ALA has a neuro-regenerative ability, because it crosses the hematoencephalic barrier and has a protective effect on the brain and nerve tissue (López-D'alessandro and Escovich, 2011). Oxidative stress has been suggested to lead to impaired nerve blood supply and endoneural oxidative damage. In cells containing mitochondria, ALA is reduced by NADH-dependent reaction to dihydrolipoic

acid. Both ALA and its reduced form are powerful antioxidants quenching reactive oxygen species (ROS). So it can protect the nerve from oxidative stress causing nerve damage. Furthermore, ALA increases the production of nerve growth factor (NGF) and intracellular glutathione levels (GSH) thus prevents oxidative stress, inflammation and nerve damage, which leads to peripheral neuropathy (Cynar *et al*, 2018).

Femiano *et al* used 600 mg/day ALA and psychotherapy in his study with a total of 48 patients, 5 patients (10%) reported minor improvement, 19 patients (40%) reported significant improvement and 15 patients (31%) totaly recovered from BMS.81% of patients handled with a combination of ALA + psychotherapy reported some progress. In his analysis of 54 women and 12 men, Carbone *et al* used 400 mg of ALA every day along with vitamins.But he failed to support a role for ALA in the treatment of BMS. López-D'alessandro and Escovich (2011) in their study of 20 patients, with a daily dose of 600 mg ALA for two months, there was a decrease in burning sensation in 55% of treated patients, and 7 times higher for patients given ALA than in the control group.

DISCUSSION

Management of BMS has multiple methods but little data to support or refute the various strategiesIn the light of various underlying conditions, it should be pointed out that there is no all-powerful treatment which can be successful in all BMS patients.This heterogeneity of this condition is the biggest barrier to the best treatment. BMS is a condition of multiple causative causes, including psychosomatic causes and chronic pain. Hence, the therapeutic response of patients varies depending on the prevailing individual influencing pathological causes, such as neuropathic elements, central sensitization and psychiatric comorbidities. The concerns are interconnected in such a complex way that medical issues can not be addressed completely by a single therapy (Tu *et al*, 2019).

Patients should be aware of their situation. Patient's assumptions, phobias, and anxiety need to be handled. Cautionary steps should also be taken (Patil *et al*, 2017), for example abstentions from smoking, unique food allergens and xerostomic medicines).Since BMS is a multifactorial illness, neither medication nor treatment can fully eradicate all symptoms. Across three fields, treatment of BMS, topical medicines, systemic medicines and comportemental therapy can be widely discusses (Aravindhan *et al*, 2014).

Systemic clonazepam appears to be the first-line therapy for BMS most commonly prescribed at present. Many patients have been relieved by the topical application of clonazepam, a Gamma Amino butyric acid receptor agonist (by sucking 1 mg tablet), 3 times a day for 14 days and have had some success (Aravindhan *et al*, 2014). Research was conducted by Heckmann (2012), that clonazepam is being revealedas an effectiveness in reducing pain experienced by BMS patients. Around the same time clonazepam has been well tolerated by all subjects and has no significant adverse effects, but few effects on the psychological state of the patient. Using clonazepam as topical treatment method showing a great reduction in pain scores. The action of this drug is attributed to peripheral nervous system dysfunction in patients with BMS and the involvement of peripheral tissue GABA receptors. Another combination by using Gabapentin and alpha lipoic acid has good result in 70% persons with BMS by Lopez-D'ales-sandro *et al* (2011). Combinations were showing different levels of action in the nociceptive system being useful treatment.

Lidocaine has been the most commonly-used local anesthetic agent, however due to its limited time of analgesic action, they have never been proven as an effective treatment. Aloe vera gel is found to be effective for a reduced burning and pain sensation of the tongue 3 times a day, combined with tongue-protector (Lo´pez-Jornet *et al*, 2012). Tricyclic antidepressants like the amitriptyline are useful for treating BMS (start dose 5-10 mg / day and eventually up to 50 mg / day). In patients with dry mouth, some writers reverse the medication as it can make the condition much worse. (Aravindhan *et al*, 2014). Femiano *et al* based on the possibility that BMS may be related to free toxic radicals, suggested in a series of studies that the use of lipoic acid as a successful alternative treatment for BMS. Alpha lipoic acid (ALA), is a potent antioxidant, with neuroprotective effects. Research showed that ALA used in combination with gabapentin is more efficacious than ALA or gabapentin alone because they target different nociceptive mechanisms (Nasri-Heir, 2015).

The drug of choice for treatment of burning mouth syndrome is systemic clonazepam for the first line. Followed by amytriptiline, alpha lipoic acid, vitamin B complex and gabapentin. Topical treatment used in burning mouth syndrome are lidocaine, followed by aloe vera, and benzydamine hydrochloride.

CONCLUSION

BMS is a multifactorial condition. The heterogeneity of this syndrome makes it difficult to conclude the best

therapy. The treatment outcomes of patients vary according to the prevailing clinical causes of human uncertainty such as neuropathy, central sensitization and psychiatric comorbidities. No single drug or teraphy procedure may cause all symptomps to be fully remission.

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