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Prospective, randomized, double-blind, clinical evaluation of *Aloe vera Barbadensis,* applied in combination with a tongue protector to treat burning mouth syndrome

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OBJECTIVES: The aim of this study was to evaluate the efficacy of aloe vera (AV) applied in combination with a tongue protector, comparing this with a placebo.
METHODS: A total of 75 patients with burning mouth syndrome (BMS) were divided into three groups randomly: Group I (tongue protector three times a day), Group II (tongue protector and 0.5 ml AV at 70% three times a day) and Group III (tongue protector and 0.5 ml placebo three times a day). Symptoms were evaluated by visual analogue scale (VAS), while patient psychological profiles were assessed using the Hospital Anxiety-Depression scale and their quality of life using the Oral Health Impact Profile 49 (OHIP-49). Treatment continued for 3 months.
RESULTS: Visual analogue scale pain values improved for all three study groups but without statistically significant differences between the groups ($P = 0.210$). Regarding quality of life, no significant differences were found between groups with the exception of the OHIP-49 score for handicap. The overall clinical improvement was greater for Group II, with a difference almost reaching significance.
CONCLUSIONS: The concomitant prescription of tongue protector and AV is effective for treating patients with BMS.

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Keywords: aloe vera; efficacy; pain; quality of life; topical treatment

Introduction

Burning mouth syndrome (BMS) is manifested as a subjective burning sensation of the tongue, lips or entire oral cavity, but does not manifest any objective lesions or laboratory test findings capable of accounting for the discomfort (1). BMS is more common among women in middle-aged to elderly age groups (2, 3) and prevalence is estimated to be 0.7–4.6% of the general population. The causes of BMS remain open to controversy. Its aetiological factors have been classified as local and systemic (3–9) BMS is considered to be idiopathic/primary when the cause is impossible to determine and secondary when it is possible to identify the syndrome's aetiological factors (1). Some researchers have claimed that it is related to neuropathic pain rather than to somatoform chronic pain syndromes (2, 4–6, 10–12).

To date, the treatment for BMS has been largely empirical and depends on the individual patient's condition and the physician's preference. No single effective treatment applicable to most patients with BMS has been found. Nevertheless, many treatments have been recommended for improving the symptoms of BMS, including sialogogues, topical anaesthetics in rinses, anxiolytic drugs, antidepressants, anticonvulsivants, alpha-lipoic acid and psychotherapy (13–22), although these have limited results. However, Heckmann et al. (23) have found that clonazepam appears to have a positive effect on pain in BMS patients.

Aloe vera (AV – *Aloe Barbadensis Miller*) is a member of the *Liliacea* family. It is widely used as a natural treatment and alternative therapy for various disorders and diseases. Clinical studies have confirmed the potential of topical AV in promoting the healing process in the treatment of burns, psoriasis and oral lichen planus (OLP) (24–28). Recently, various studies have reported that patients with OLP treated with topical applications of AV experienced some improvement. In effect, 81% of patients with OLP treated with AV were seen to improve, with 7% undergoing complete remission (24). Nevertheless, topical application of AV has not come into common use.

The hypothesis of this study is that the control of oral parafunctional habits together with the application of topical AV can protect the oral mucosa from repetitive trauma and decrease the oral discomfort associated with BMS. This study was designed to evaluate the efficacy of a tongue protector in combination with topical AV applied three

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times a day (0.5 ml) at a concentration of 70% for patients with BMS, comparing this treatment with a placebo.

Materials and methods

Participants

The study sample consisted of patients diagnosed with BMS who attended the Department of Oral Medicine (Faculty of Medicine and Dentistry, University of Murcia, Spain), during the period from October 2009 to July 2011. The study was performed following principles laid down by the Declaration of Helsinki and was approved by the Ethics Committee of the University of Murcia. All patients were volunteers, provided informed consent to take part and received no remuneration.

Inclusion criteria for participating in the study were as follows: a clinical history of continuous symptoms of oral burning or pain on a daily or almost daily basis, during all or part of the day for more than 6 months, without paroxysms, and independent of the nervous pathway; an absence of clinical abnormalities that might account for the symptoms; normal blood test findings (complete blood count, blood glucose, serum iron and transferrin levels, serum vitamin B12, and folate).

Patients with pain attributable to other conditions (angiotensin-converting-enzyme inhibitor use, candidiasis, lichenoid reactions, sores, tongue atrophy, etc.) were excluded, as were those presenting problems with dentures, biochemical anomalies (deficiencies in iron, Vitamin B12, folate, zinc, B complex vitamins, thyroid disease) and a history of hypersensitivity or allergy to the materials or drugs used in the study. Patients with known neurological disorders and those previously treated, even irregularly, with antidepressants, anticonvulsants, other psychotropic drugs, or psychological therapies were also excluded from the study. Patients occasionally using anxiolytics to induce sleep were accepted. Subjects with signs of lingual and labial parafunctional activity were also considered (tongue rubbing, lip or cheek nibbling). In addition, they were required to have received no treatment for BMS in the last 2 weeks in the case of topical treatments or in the last 4 weeks in the case of systemic therapies.

Study design

A randomized, double-blind and placebo-controlled study design was adopted with a duration of 12 weeks. The randomization sequence was generated by an operator external to the study, using the random number generator in Microsoft Excel. Both patients and researchers were blind to treatment assignment (placebo/AV).

Study products

The study used AV in a transparent gel in a 500 ml container with a transparent 5 ml syringe. The placebo consisted of a formulation identical to that of the study product but containing no AV. Both the study product and placebo were obtained from Laboratorios Ababo S.L., Cosmética Terapéutica Profesional, Murcia, Spain.

The products were coded by an operator external to the study in identical opaque containers: *Aloe barbadensis* gel [70% water, sorbitol, E-202 (potassium sorbate) and E-223 (sodium metabisulfite)] and placebo [water, sorbitol, E-202 (potassium sorbate) E-223 (sodium metabisulfite)] (24).

The tongue protector consisted of a transparent, low-density polyethylene sheath covering the tongue from the tip to the posterior third. These tongue protectors were single-use devices measuring 0.1 mm in thickness, with a standard size (67 mm in length and 66 mm wide) and were custom manufactured by the research team (14).

Each patient received an explanation regarding the possible aetiology and management strategies for BMS. All patients were instructed not to touch the tongue tip to the teeth or restorations and to avoid tongue thrusting, tongue or mucosal biting, clenching, lip pressure or sucking.

At the first visit, an oral examination and blood test were performed on each patient. At the second appointment, the selection criteria were confirmed, and the patients received the products with instructions for their correct use. In all cases, data were collected by a single researcher (D.M.P), blind to the group to which each patient belonged.

Patients were divided into three groups according to treatment. Group I used the protector alone, Group II the protector and AV, and Group III the tongue protector and the placebo. Each patient received a kit with the protectors, products and reminder points for treatment and instructions for their use. The protector was worn during the daytime for a period of 3 months. Use of the protector for 15 min/three times a day was recommended with the therapeutic aim of avoiding continuous rubbing against the teeth and/or dentures. Groups II and III applied the gels (0.5 ml) to the tongue and then spat them out before fitting the tongue protector. Patients were instructed to apply the medication by applying the gel directly to the sore areas using their fingertips or a cotton bud three times daily and were prohibited from using any other gel or mouthwash for the duration of the study.

The primary study endpoint was the visual analogue scale (VAS) for pain at the start and after 12 weeks of treatment. In this way, the difference between baseline and endpoint scores numerically expressed any symptomatic improvement.

Pain was scored with a VAS (0 = no pain, 10 = extreme pain). The subjects were asked to mark a vertical line through a 10-cm horizontal line to indicate their level of pain. The scores for pain were classified into slight (≤ 3.3), moderate (3.4–6.6) and severe (≥ 6.7).

The Spanish version of the Oral Health Impact Profile-49 (OHIP-49) was used to assess oral health, 29 each item being scored as follows: 0 = never; 1 = hardly ever; 2 = occasionally; 3 = fairly often; 4 = very often. The OHIP-49 is divided into seven different domains and the possible score range for each is as follows: 'functional limitation' (nine items), from 0 to 36; 'physical pain' (nine items), from 0 to 36; 'psychological discomfort' (five items), from 0 to 20; 'physical disability' (nine items), from 0 to 36; 'psychological disability' (six items), from 0 to 24; 'social disability' (five items), from 0 to 20; 'handicap' (six items), from 0 to 24; and finally, 'overall OHIP score' (49 items), from 0 to 196. In this way, higher scores indicate poorer states of oral health.

The Hospital Anxiety-Depression (HAD) scale was then used to evaluate patients' psychological profiles. This

instrument comprises two subscales relating to anxiety and depression (29). Each subscale contains seven items pertaining to mood disorder. For interpreting HAD scale scores, >10 indicates the probable presence of anxiety or depression, scores of 7 or less indicate no significant anxiety or depression, and scores of 8–10 are of borderline significance.

The third visit took place at 12 weeks. Compliance with treatment was assessed, the VAS for pain was applied, and OHIP-49. Global perceived effect (GPE) – adapted from Femiano et al. (20) – was scored by the patient (self-reported description) on a 5-point scale, ranging from: −1 = worse, 0 = no change, +1 = slight improvement, +2 = decided improvement, +3 = no burning anymore (resolution). At this appointment, subjects were also questioned about tolerability and possible adverse effects. At the start of the study and at the final appointment (day 0 and at 3 months), each patient's medication was weighed to observe the level of patient compliance. Compliance with the products was evaluated by the following nominal variables: good, adequate or insufficient.

Statistical analysis

The sample size was calculated according to previously published data (24) assuming an overall efficacy of 81% and 4% for administered AV and placebo, respectively. Data were analysed using the SPSS 12.0 statistics program (SPSS® Inc, Chicago, IL, USA). A descriptive study was made of each variable. The Kolmogorov–Smirnov normality test and Levene variance homogeneity test were applied and the data showed a skewed distribution, and so was analysed using a non-parametric ranking test. Associations between the different qualitative variables were studied using Pearson's chi-square test. The Kruskal–Wallis test (for more than two independent samples) was used for quantitative variables. Probability of <0.05 was accepted as significant.

Results

Ninety-three patients were selected consecutively to take part in the study of which 18 were excluded (10 did not meet the inclusion criteria and seven refused to participate, one patient for another reason) (Fig. 1). The 75 remaining patients were divided into groups randomly of who 71 followed treatment for the full 12 weeks, there being dropouts in Groups II and III as a consequence of irregular treatment compliance. No patients experienced any adverse effects resulting from treatment at any of the evaluation times.

The mean patient age was 59.7 ± 11.3, with ages ranging between 30 and 84. Table 1 shows the homogeneity of patient characteristics across the three groups regarding age, sex, psychological profile and duration of the syndrome's evolution. Table 2 shows results of the quality of life assessment by means of OHIP-49, in which it can be seen that the three study groups were homogenous. The VAS pain scores were classified into: Slight (≤ 3.3), Moderate (3.4–6.6) and Severe (≥ 6.7) and it can be seen that during the 3-month treatment period, the number of patients with severe BMS diminished but without statistically significant differences. (Table 3).

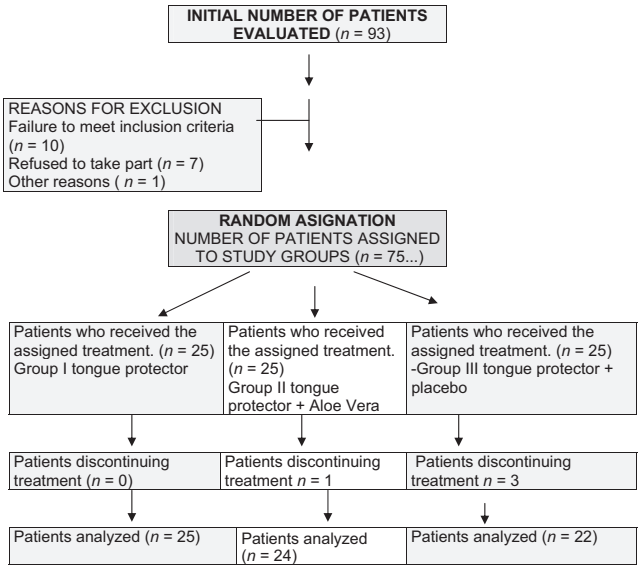

Figure 1 Patient flow diagram.

Table 1 Sample homogeneity at day 0 in terms of age and sex (Kruskal–Wallis H and Pearson's chi-squared tests) VAS for pain. HAD and evolution time

	Tongue protector (n = 25)	*Tongue protector + aloe vera* (n = 24)	*Tongue protector + placebo* (n = 22)	P-*value*
Age: median (range)	60 (37–84)	64.50 (30–75)	55.50 (40.79)	0.167
Sex				
Men: *n* (%)	2 (8)	2 (8.30)	4 (18.20)	0.284
Women: *n* (%)	23 (92)	22 (91.79)	18 (81.80)	
VAS (cm)	9 (5–10)	6 (1–10)	7.75 (4–10)	0.178
HAD				
Depression	9 (0–21)	8 (0–21)	6 (0–15)	0.225
Anxiety	12 (1–21)	11 (0–21)	8.50 (0–21)	0.427
Duration of burning pain (months)	6 (6–15)	7 (6–14)	6 (6–15)	0.150

HAD, hospital anxiety-depression; VAS, visual analogue scale.

The VAS scores for pain had decreased after 12 weeks although differences were not significant (Table 4). In group II, following treatment with AV, there was a tendency for 'slight intensity' VAS values to increase and 'severe intensity' to decrease.

Regarding the evolution of oral quality of life, assessed using the OHIP-49 prior to treatment and after 12 weeks, greater changes were found across the different domains for Group II. However, differences were not significant for any of the study groups except for the domain score relating to handicap (Table 5).

Group II presented the highest scores for the GPE at the end of the study, almost reaching statistical significance (Table 6).

Discussion

Considering the complexity of BMS pathogenesis (1, 3, 4, 19, 30), it is not surprising that there is no single treatment

Table 2 Sample homogeneity at day 0 regarding OHIP-49 (Kruskal–Wallis test)

OHIP-49: day 0	*Tongue protector* (n = 25) median (range)	*Tongue protector + aloe vera* (n = 24) median (range)	*Tongue protector + placebo* (n = 22) median (range)	P-*value*
Functional limitation	10 (0–22)	8.50 (0–36)	5.50 (0–21)	0.138
Physical pain	16 (4–32)	10 (3–36)	10.50 (2–18)	0.079
Psychological discomfort	10 (2–20)	8 (0–20)	8 (0–20)	0.716
Physical incapacity	7 (0–22)	8.50 (0–36)	7.50 (0–25)	0.689
Psychological incapacity	11 (0–24)	7 (0–24)	4.50 (0–24)	0.109
Social incapacity	0 (0–20)	4 (0–20)	0 (0–20)	0.107
Handicap	0 (0–20)	4 (0–20)	5 (0–20)	0.060
OHIP-49 total	52 (16–142)	47.50 (8–192)	38.50 (7–131)	0.273

OHIP, oral health impact profile.

Table 3 Evolution of pain VAS and HAD test during the 3-month study period (Kruskal–Wallis H test)

VAS (cm)	*Evolution (day 0 months)*	*Evolution (3 months)*	*Difference evolution (day 0–3 months)*
Tongue protector (n = 25)	9 (5–10)	5 (1–9)	3.5 (0 to 8)
Tongue protector + aloe vera (n = 24)	6 (1–10)	3.25 (0–10)	2.7 (−4 to 8)
Tongue protector + placebo (n = 22)	7.75 (4–10)	6 (0–10)	1 (−3 to 9)

HAD, hospital anxiety-depression; VAS, visual analogue scale. *P*-value = 0.210.

modality or medication effective for the majority of patients with BMS. However, clonazepam appears to have a positive effect on pain in patients with BMS (13, 19, 24). The results of this study show that the three study groups all underwent an improvement to BMS symptoms, reducing the number of severe cases. Patients with severe pain passed to moderate pain, undergoing clinical improvement but not a resolution of the problem. Because of the chronic nature (subjects experiencing pain for at least 6 months) and high prevalence of BMS, a large variety of treatments have been used in an attempt to alleviate the symptoms, but these do not always lead to satisfactory results (13–21).

In the present study, the primary measure was pain, which showed some decrease in all groups although without significant differences.

The majority of patients had severe burning sensations and had suffered from BMS over a long period, a fact that might explain the relationship between BMS and health-related quality of life (31, 32). In relation to quality of life, assessed by means of the OHIP-49, it was found that this improved for the three groups although there were no significant differences except for the score pertaining to handicap. According to Locker's model of oral health for conceptual domains in the hierarchy of social impact, discomfort or functional limitation caused by diseases leads to physical, psychological or social disability, which then cause handicaps (33).

Several studies have indicated psychogenic abnormalities as an important causative factor in patients with BMS. Specific psychogenic factors such as depression and anxiety have been reported to have a significant association with BMS (4, 8). In the present study, the groups were homogenous in terms of patients' psychological profiles. Patients scored an average of 11 for anxiety on the HAD scale, a score that indicates a trend towards anxiety or depression. The results of this study suggested a tendency for patients to suffer from anxiety rather than depression, which concur with other findings by Gremeau-Richard et al., 2010 (30).

Patients with BMS are generally prescribed protocols for chronic pain based on antidepressants, benzodiazepines (7, 8) and several other local and systemic therapies with varying results. In this context, the tongue protector used in our study offered protection and was tolerated satisfactorily by the patients, as it prevented direct friction or rubbing of the tongue mucosa against the teeth and/or dentures and isolated the tongue from changes in temperature and taste and salivary flow (increased), although its use could might have exerted some placebo effect (14). Another possibility is that its ability to reduce burning pain may be due to its capacity for altering cognitive processes, as it could act as a constant reminder to the individual to refrain from performing any parafunctional habit. Furthermore, when the tongue protector is worn, it is possible that this alters proprioceptive mechanisms.

Topical treatments of AV have been widely used for treating a variety of disorders as it can inhibit the

Table 4 Evolution of pain VAS for each group during the 3-month study period (Pearson's chi-squared test)

	VAS (day 0): n *(%)*			*VAS (3 months):* n *(%)*			
Group	*Slight ($\leq$3.3)*	*Moderate (3.4–6.6)*	*Severe ($\geq$6.7)*	*Slight ($\leq$3.3)*	*Moderate (3.4–6.6)*	*Severe ($\geq$6.7)*	P-*value*
Tongue protector (n = 25)	0 (0)	7 (28)	18 (72)	9 (36)	10 (40)	6 (24)	0.169
Tongue protector + aloe vera (n = 24)	2 (8.30)	11 (45.85)	11 (45.85)	12 (50)	7 (29.17)	5 (20.83)	0.236
Tongue protector + placebo (n = 22)	0 (0)	8 (36.37)	14 (63.63)	7 (31.81)	6 (27.29)	9 (40.90)	0.188

VAS, visual analogue scale.

Table 5 Evolution of OHIP-49 during 3-month study period (Kruskal–Wallis H test)

OHIP-49	*Tongue protector* (n = 25): median (range) *Evolution (day 0–3 months)*	*Tongue protector + aloe vera* (n = 24): median (range) *Evolution (day 0–3 months)*	*Tongue protector + placebo* (n = 22): median (range) *Evolution (day 0–3 months)*	P-*value*
Functional limitation	10 (0–22)–7 (0–17) = 0 (–2 to 19)	8.50 (0–36)–1.50 (0–18) = 3.50 (–2 to 32)	5.50 (0–21)–4.50 (0–16) = 0 (–12 to 15)	0.313
Physical pain	16 (4–32)–9 (0–28) = 0 (0 to 28)	10 (3–36)–4 (0–16) = 4.50 (–3 to 32)	10.50 (2–18)–5 (0–16) = 4.50 (–2 to 14)	0.283
Psychological discomfort	10 (2–20)–6 (0–20) = 0 (–2 to 18)	8 (0–20)–4.50 (0–12) = 4.50 (–4 to 12)	8 (0–20)–5 (0–16) = 3 (–6 to 16)	0.616
Physical incapacity	7 (0–22)–4 (0–22) = 0 (0 to 18)	8.50 (0–36)–3 (0–19) = 3.50 (–12 to 34)	7.50 (0–25)–3.50 (0–23) = 3 (–15 to 23)	0.674
Psychological incapacity	11 (0–24)–6 (0–20) = 0 (–1 to 24)	7 (0–24)–1 (0–13) = 5.50 (–3 to 23)	4.50 (0–24)–1.50 (0–19) = 1 (–12 to 18)	0.081
Social incapacity	0 (0–20)–0 (0–16) = 0 (–16 to 20)	4 (0–20)–0 (0–12) = 1.50 (–4 to 20)	0 (0–20)–0 (0–20) = 0 (–12 to 19)	0.219
Handicap	0 (0–20)–0 (0–20) = 0 (–10 to 16)	4 (0–20)–0.50 (0–12) = 2 (–10 to 18)	5 (0–20)–2.50 (0–15) =1.50 (–7 to 14)	0.053
OHIP-49 total	52 (16–142)–46 (4–104) = 6 (–20 to 123)	47.50 (8–192)–19.50 (0–84) = 25 (–3 to 177)	38.50 (7–131)–24.50 (0–117) = 14.50 (–47 to 81)	0.099

OHIP, oral health impact profile.

Table 6 Patient perception at end of study of benefits or otherwise produced by treatment (Pearson's chi-squared test)

Evaluation of treatment	*Tongue protector* (n = 25) n *(%)*	*Tongue protector + aloe vera* (n = 24) n *(%)*	*Tongue protector + placebo* (n = 22) n *(%)*	P-*value*
Benefit				
Extremely beneficial	0 (0)	6 (25)	4 (18.18)	0.057
Beneficial	1 (4)	5 (20.83)	3 (13.63)	
Slightly beneficial	7 (28)	2 (8.34)	2 (9.11)	
No change	9 (36)	5 (20.83)	4 (18.18)	
Deterioration	8 (32)	6 (25)	9 (40.90)	

inflammatory process through interference with the arachidonic acid pathway via cyclooxygenase. Recent data suggest that AV also has anti-inflammatory effects through the reduction of leucocyte adhesion and *TNF*-α levels (24). Nevertheless, there have been few studies to date on the application of AV to oral disease mucosa although it has been used to treat a range of other disorders such as skin burns, psoriasis and mucositis, although with varying results. Khorasani et al. (25) conducted a study of 30 second-degree burn patients with burns in two different body areas. One area was treated with topical silver sulfadiazine, while the other area was treated with AV. The authors demonstrated AV's efficacy for the treatment of second-degree burns.

However, the efficacy of AV in clinical studies remains controversial. Su et al. (27) conducted a double-blind study to determine whether AV is able to reduce the incidence, severity and duration of radiotherapy-induced mucositis in head and neck cancer patients. The authors reported no benefits arising from the addition of AV to oral care for the management of mucositis. Furthermore, the use of AV at the start of radiotherapy did not improve either the mucositis or the quality of life of the patients, compared to a placebo.

Choonhakarn et al. (24) carried out a double-blind study to explore the efficacy of AV gel in the management of OLP. In this study, AV was found to be more effective in application to OLP than a placebo. In effect, 81% of the patients with OLP treated with AV improved, with complete remission in 7%, while in the placebo series, only 4% of the patients improved, and complete remission was not achieved in any case.

It might be that parafunctional habits that endure for long periods result in neuropathic changes that ultimately lead to a chronic burning sensation (1). Therefore, treatment strategies might decrease the progression of an initial burning sensation to a chronic condition. The present study suggests that the prescription of a tongue protector and of topical AV 70% (0.5 ml three times daily for 12 weeks) combined with the control of oral parafunctional habits is an effective initial approach for the oral discomforts associated with BMS.

Nevertheless, the study did have some limitations. Patients taking antidepressants, anticonvulsivants, psychotropic drugs and psychological therapies were excluded and so it may be that the population studied was not entirely

representative of typical patients with BMS. In this way, excluding patients receiving psychotropic drugs may have increased the topical treatments' potential efficacy.

The protector was used to avoid direct friction but was applied for only 15 min, three times a day, so that the rest of the time (and particularly during the night) the patient was without the protector. The device was used as a protector rather than as a dental splint as proposed by Axell (34). A single standard size protector was used but in future research, it is hoped to individualize the tongue protector to each patient.

Topical medications for controlling discomfort caused by BMS include sialogogue, topical anaesthesia, oral rinse and capsaicin, proposed on the basis of the results of open studies or clinical experience (13, 35–37).

One single randomized, double-blind, placebo-controlled trial indicated that a topical 0.15% benzydamine solution used as a 15-ml mouthwash three times daily did not produce any improvement to the burning symptoms among patients with BMS (35).

Woda et al. (36) evaluated topical clonazepam in an open-label study of 25 patients, 80% of whom were receiving anti-depressive or anxiolytic therapy, which was not suspended during the study. The administered dose was 0.5–1 mg, two or three times a day. Six patients (24%) experienced no improvement, nine patients (36%) reported partial improvement and continued with the treatment and 10 patients (40%) reported complete remission of the symptoms.

In a randomized double-blind, multicentre parallel group study of topical clonazepam, Gremeau-Richard et al. (19) reported that it improved stomatodynia symptoms (of two-thirds of the study's subjects). However, the treatment was not effective for all subjects.

In an earlier study, Ko et al. (15) demonstrated the efficacy of a lubricant (glycerine-containing carboxymethylcellulose/corticosteroids) together with the control of oral parafunctional habits, suggesting that this combination is an effective initial approach for the oral discomforts associated with BMS.

Our results showed that the tongue protector and use of topical AV might be used as an 'alternative initial approach' to BMS management. In this way, neuropathy medications such as selective serotonin reuptake inhibitors or clonazepam could be reserved for patients with BMS who do not respond to a simple initial treatment protocol of this type (7, 16).

Recent neurophysiologic, psychophysical, neuropathological and functional imaging studies have elucidated that several neuropathic mechanisms, mostly subclinical, act at different levels of the neuraxis and contribute to the pathophysiology of primary BMS. Demonstration of loss of small diameter nerve fibres in the tongue epithelium explains thermal hypoesthesia and increase in taste detection thresholds found in quantitative sensory testing. As in neuropathic pain, decreased brain activation to heat stimuli has been demonstrated with fMRI in patients with BMS. However, it seems that the clinical diagnosis of primary BMS encompasses at least three distinct, subclinical neuropathic pain states that may overlap in individual patients. The first subgroup (50–65%) is characterized by peripheral small diameter fibre neuropathy of intraoral mucosa. The second subgroup (20–25%) consists of patients with subclinical lingual, mandibular or trigeminal system pathology that can be dissected with careful neurophysiologic examination but is clinically indistinguishable from the other two subgroups. The third subgroup (20–40%) fits the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia. The neurogenic factors acting in these subgroups differ and will require different treatment strategies (38).

In future research, it might prove worthwhile to classify patients as two types with two classes of response: those who show marked improvements and those who show little or no improvement. It could be that the first group of patients has 'peripheral' BMS and the second group 'central BMS', which does not respond to all topical applications.

We consider that further studies of a multicenter nature and involving larger patient series and longer periods of treatment are needed. It is essential to broaden our understanding of the physiopathological mechanisms of burning mouth in order to be able to select the best treatment and develop new therapies involving the different mechanisms influencing BMS.

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Conflict of interest

The authors declare that they have no conflict of interest.