Pharmacological treatment of burning mouth syndrome: A review and update

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ABSTRACT

Burning mouth syndrome (BMS) is defined as a burning sensation in the tongue or in any other region of the oral mucosa, in the absence of specific oral lesions. The present study reviews the pharmacological treatments used in the last 10 years to reduce the symptoms of BMS, and assesses the efficacy and safety of pharmacological interventions destined to alleviate the symptoms of BMS. To this effect, searches were made in the following databases: Micromedex®, Cochrane Database® and PubMed®, crossing the following key words: drug, treatment, clinical trial, pain management, and burning mouth syndrome. The searches were limited to articles published in the last 10 years in English or Spanish, and involving human subjects. The searches were conducted in November 2006. The literature contains clinical studies in which BMS has been treated with drugs belonging to different pharmacological groups: antidepressants, antipsychotics, antiepileptic drugs, analgesics and mucosal protectors, among others. Although effective therapies have been identified in concrete cases, a treatment modality offering efficacy in most cases of BMS remains to be established. It is essential to gain further insight to the physiopathological mechanisms of BMS, and to establish differential diagnostic criteria to develop drugs with improved efficacy and safety profiles in the treatment of BMS.

Key words: *Burning mouth syndrome, treatment, clinical trials, clinical cases, antidepressants, analgesics.*

RESUMEN

El Síndrome de Boca Ardiente (SBA) se define como una sensación de ardor o quemazón en la lengua o en cualquier otra localización de la mucosa oral en ausencia de lesiones bucales específicas. El presente artículo revisa los tratamientos farmacológicos utilizados en los últimos diez años para reducir la sintomatología del SBA y trata de objetivar la eficacia y seguridad de cualquier intervención farmacológica encaminada a aliviar los síntomas del SBA. Para ello se realizaron búsquedas en las bases de datos: Micromedex®, Cochrane Database® y Pubmed® cruzando las palabras: drug, treatment, clinical assay, pain management y burning mouth syndrome. Se establecieron como límites en la búsqueda los artículos publicados en los últimos 10 años, en inglés o español y los estudios realizados en humanos. Las búsquedas fueron realizadas en noviembre 2006. En la literatura encontramos estudios clínicos en los que el SBA se ha tratado con fármacos enmarcados en diferentes grupos farmacológicos: antidepresivos, antipsicóticos, antiepilépticos, analgésicos y protectores de la mucosa entre otros. Aunque se han encontrado tratamientos eficaces en casos particulares, se sigue buscando un tratamiento que resulte eficaz en la mayoría de los casos. Es indispensable profundizar en los mecanismos

fisiopatológicos del SBA y establecer criterios diagnósticos diferenciales para poder desarrollar fármacos con mejor perfil de eficacia y seguridad en el tratamiento del SBA.

Palabras clave: *Síndrome de boca ardiente, tratamiento, ensayos clínicos, casos clínicos, antidepresivos, analgésicos.*

INTRODUCTION

Burning mouth syndrome (BMS) is characterized by pain or burning sensation affecting an apparently healthy oral mucosa and that cannot be attributed to other disorders such as candidiasis or irritation caused by dentures. According to Bergdahl and Bergdahl (1), the syndrome affects 3.7% of the general population, and is more common in women (5.5%) - particularly after menopause - than in men (1.6%).

The etiopathogenesis of BMS is not known, though different psychological and biological factors have been implicated. In effect, the psychological component is important in patients with BMS. Problems such as depression and anxiety play an important role in modulating pain perception, and are able to increase or decrease nerve transmission from the peripheral pain receptors and thus modify individual perception of the pain. Consequently, treatment has been provided in the form of antidepressants among patients with BMS (2,3). On the other hand, the identification of sensory alterations in patients with BMS also suggests the existence of a biological basis related to alterations of both the central and peripheral nervous system (4). The peripheral alterations could be related to the density of the membrane receptors present in the oral mucosa, or to alterations in their reactive capacity - largely influenced by BMS risk factors such as stress, anxiety, the female sex, climacterium and old age (5). This theory is reinforced by the apparent topical action of clonazepam in the treatment of BMS (6,7). Gruskha and Bartoshuk suggested that BMS represents phantom pain caused by damage to the taste sensory system of susceptible individuals (8). Other authors have shown patients with BMS to suffer sensory alterations such as changes in heat tolerance, hypogeusia and dysgeusia, and increased excitability of the palpebral reflex, related to dysfunction of the dopaminergic system at central nervous system (CNS) level (4). Such dysfunction would comprise reduced dopaminergic inhibition and thus increased neuron excitability. Dysfunction of the dopaminergic system would justify systemic administration of the antiepileptic drugs gabapentin and clonazepam, which act upon the gabaergic system - enhancing its activity in an attempt to counter dysfunction of the dopaminergic system. On the other hand, it was seen that BMS shares a series of characteristics with other chronic pain syndromes. This led to the application of drugs such as capsaicin (9,10) and benzidamine (11), which had been shown to be of use in application to such chronic pain syndromes.

A possible relationship has also been postulated between estrogen hormone imbalances (seen in menopause) and onset of the sensory alterations characterizing BMS. This subject has generated debate, due to the divergent results reported by the different studies made to assess the effects of hormone replacement therapy (HRT)(12-14).

Lastly, mention should be made of alterations in vascularization as a possible cause of BMS (15).

At present there is no effective treatment applicable to most patients with BMS. The present study offers an exhaustive review of the pharmacological treatments used in BMS in the last 10 years.

In a first group, antidepressants were considered to be useful in view of the known psychogenic component present in most cases of BMS. The antidepressants tested to date for the treatment of BMS have been trazodone in a double blind study, and paroxetine together with sertraline and the antipsychotic agent amisulpiride, in another simple blind study.

Tammiala-Salonen et al. (16) evaluated trazodone in a randomized, double blind parallel group and placebo controlled trials with a duration of 8 weeks. During the first four days the patients received 100 mg of trazodone, followed by 100 mg every 12 hours. Of the 37 patients included in the study, 18 received trazodone and 19 placebo. Side effects of the medication led to the withdrawal of 7 patients in the treated group (39%) and two in the placebo group (11%). At the end of the study, 8 patients in the treated group (73%) reported improvement, two (18%) experienced no change, and one (9%) worsened. In the placebo group, 13 patients (76%) improved, and (24%) experienced no change. No differences in efficacy were observed between trazodone and placebo.

Maina et al. (17) compared the efficacy and tolerability of amisulpiride 50 mg/day, paroxetine 20 mg/day and sertraline 50 mg/day, in the treatment of BMS, in the context of a randomized, simple blind study with a duration of 8 weeks. Following clinical and psychological evaluation, the patients were randomized to three groups (27 patients received amisulpiride, 26 paroxetine and 23 sertraline). Before the end of the first week, 5 patients voluntarily abandoned the study due to a lack of efficacy or the appearance of adverse effects. None of these subjects belonged to the amisulpiride group. In addition, three patients failed to adhere to treatment as prescribed, and were removed from the study. The results showed an efficacy of about 70% after 8 weeks for the three types of treatment. The effect of amisulpiride manifested earlier, after a single week of therapy. There were no serious adverse effects in any of the three groups.

Antiepileptic drugs act in a way similar to gamma-aminobutyric acid (GABA), enhancing its inhibitory effects upon the CNS, with a reduction in neuron excitability and pain. Among the antiepileptic drugs that have been used to treat BMS, mention should be made of clonazepam, evaluated in a number of studies, and gabapentin - for which the literature yields a clinical case (18) and, very recently, an open-label study (19).

Heckmann et al. (19) conducted an open study of 15 patients treated with gabapentin. The starting dose was 300 mg/day, and was increased at a rate of 300 mg every 48 hours to a maximum of 2400 mg/day. Seven patients were treated during two weeks, 6 patients during four weeks and another two patients during 6 weeks. Although two patients (13%) reported a three-point reduction in pain, and another two patients (13%) reported a decrease in two points on the visual analog scale (VAS) for pain, the authors concluded that gabapentin exerts little or no effect upon BMS.

Grushka et al. (20) in turn tested clonazepam via the oral route in a group of 30 patients with BMS. The starting dose was 0.25 mg/day, and was increased at a rate of 0.25 mg/week, to a maximum of 3 mg/day, or until treatment response was elicited. The mean administered dose was 1.1 ± 0.65 mg/day. Three groups were established, based on the recorded response to treatment: 13 patients (43%) experienced at least slight improvement and continued with the treatment; 8 patients (27%) experienced improvement but abandoned the treatment because of adverse reactions; and 9 patients (30%) reported no benefit. In the first group, most patients (61%) responded to a dose of 0.75 mg/day or lower.

Woda et al. (6) evaluated topical clonazepam in an open-label study with 25 patients (80% of which were receiving antidepressive or anxiolytic therapy that was not suspended during the study). The patients were instructed to break up the clonazepam tablet and retain saliva in the mouth during three minutes, without swallowing - followed by expulsion. The administered dose was 0.5 to 1 mg, two or three times a day. Six patients (24%) experienced no improvement, 9 patients (36%) reported partial improvement but continued with the treatment, and 10 patients (40%) reported complete symptoms remission. In these subjects the treatment was discontinued after one to three months, without subsequent symptoms relapse. In the patients not using drugs with actions upon the CNS, the results were comparatively better - though the differences were not statistically significant.

Posteriorly, the same authors improved the previous study (6) and carried out a randomized, double blind parallel group and multicenter survey comparing topical clonazepam (1 mg three times a day) versus placebo (7). They included 24 patients with BMS in each group and evaluated pain with a VAS before the start of the study. The patients were previously trained to break up the clonazepam tablet in the mouth and retain the saliva in contact with the painful points during three minutes. The pain was re-evaluated 5 minutes after expelling the saliva with clonazepam. Initially, the treatment was planned to last 14 days, with administration three times a day - though measurements of clonazepam activity were also obtained after 6 months. Of the 22 patients who completed treatment with clonazepam, 9 (41%) reported the medication to be very effective - with a 4-7 point reduction on the VAS. Seven patients (32%) reported partial improvement (2-3 points), and 6 patients (27%) experienced no improvement (three of these actually worsened despite treatment). Thirteen patients were evaluated after 6 months of treatment with clonazepam: in 7 cases (54%) the treatment remained effective (with a pain score reduction of 2 or more points), while three patients (23%) recorded a pain reduction of under two points but claimed to feel better and wished to continue the treatment. Finally, three patients (23%) abandoned treatment due to a lack of efficacy or the appearance of drowsiness.

Analgesics have also been used to treat the symptoms of BMS. These drugs were selected in view of their usefulness in treating other chronic pain disorders (capsaicin) or other alterations of the oral mucosa involving pain (benzidamine hydrochloride).

Capsaicin 0.25% via the oral route was evaluated by Petruzzi et al. (9) in a randomized, triple blind and placebo controlled study. Two groups of 25 patients with BMS were established. In the treated group it was seen that of the 15 patients who initially presented VAS scores of 8-10, a full 14 (93%) showed improvement. In turn, of the 8 patients with VAS scores of 4-7, five (63%) improved after one month of treatment with oral capsaicin 0.25%. In the placebo group, of the 13 patients with VAS scores of 8-10, none improved. In turn, of the 7 patients with VAS scores of 4-7, only one showed improvement. In relation to adverse effects, progressive cases of gastric pain were documented in the treated group - totaling 8 cases (32%) after four weeks of treatment. This limits the use of capsaicin via the systemic route in prolonged treatments.

Likewise, the literature presents a case of BMS treated with topical capsaicin (19). This corresponded to a 59-year-old woman with a three-year history of BMS, and a VAS pain score of 10. The symptoms prevented her from eating, and she moreover wore dentures. Treatment for BMS with diluted Tabasco sauce was proposed: initially 1-2 drops in 60 ml of warm water, four times a day, followed by gradual dose escalation. After 6 weeks using a solution of 16 drops of Tabasco sauce in 60 ml of water, the patient reported pain relief. After 8 months, she claimed the pain intensity to have decreased 50%, and after 10 months using undiluted Tabasco sauce, she reported a 2-point pain score on a scale of 10 points (i.e., practically no pain).

Sardella et al. (11) carried out a randomized, double blind study to assess the efficacy and safety of benzidamine hydrochloride in the treatment of BMS. Three groups were established: the first received 15 ml of benzidamine hydrochloride 0.15% as a rinse for one minute, three times a day during four weeks; the second group received 15 ml of a placebo solution; and the third group received no treatment. In the treated group, 90% of the patients failed to improve, while 10% reported partial improvement. In the placebo group the corresponding percentages were 80% and 20%, respectively, while in the third group 90% of the patients failed to improve, and 10% actually worsened. The statistical analysis revealed no differences among these three groups.

Sucralfate was selected by Campisi et al. (21), on the grounds that it protects the digestive mucosa. The objective was to determine whether this protective effect could also be extended to the oral mucosa.

Table 1. Efficacy and safety of the drugs used to treat the symptoms of burning mouth syndrome (BMS).

AUTHOR	DRUG	HEALIN	IMPROVEMENT
Tammiala-Salonen et al. (16)	Trazodone [1]	0%	73%
Maina et al. (17)	Amisulpiride, Paroxetine, Sertraline	0%	70%
Heckmann et al. (19)	Gabapentin	0%	33%
Grushka et al. (20)	Systemic clonazepam [3]	0%	43%
Woda et al. (6)	Topical clonazepam [4]	40%	36%
Gremeau-Richard et al. (7)	Topical clonazepam	41%	32%
Petruzzi et al. (9)	Capsaicin [5]	0%	83%
Sardella et al. (11)	Benzidamine [6]	0%	10%
Campisi et al. (21)	Sucralfate	0%	36%
Femiano et al. (22)	Alpha-lipoic acid [7]	31%	50%

1- In the placebo group, 76% of the patients improved. Adverse reactions were
2- observed in 39% of the patients in the treated group and in 11% of the subjects
3- administered placebo.
4- Earlier effects were recorded for amisulpiride.
5- Adverse reactions were recorded in 27% of cases.
6- The healed cases did not suffer relapses.
7- Adverse reactions were recorded in 32% of cases.
8- In the placebo group, 20% of the patients experienced improvement.
9- After 6 months, 49% of the patients with initial improvement were seen to worsen.

The authors carried out a study to determine the efficacy of sucralfate in application to BMS, in two pharmaceutical forms. They established two groups of 7 patients each: the first group received a 20% suspension of sucralfate four times a day during three weeks, while the second group received chewable tablets containing 1 g of sucralfate, with the same dosing regimen as in the other group. After three weeks of treatment, and in the first group, three patients (42%) reported symptoms improvement; two patients (29%) experienced no improvement; and another two patients (29%) had worsened. In the second group, two patients (29%) improved; three patients (42%) showed no change; and two patients (29%) worsened.

Femiano et al. (22) evaluated alpha-lipoic acid (ALA) at a dose of 600 mg/day, in a parallel group and placebo controlled study. ALA was selected because of its neurological regenerative properties, demonstrated in the treatment of diabetic neuropathy - a disorder with features similar to BMS and involving chronic pain. In the treated group (n = 48), 5 patients (10%) experienced slight improvement, 19 patients (40%) reported clear improvement, and 15 patients (31%) showed resolution of their BMS. Eighty-one percent of the treated patients experienced some degree of improvement. In comparison, in the placebo group, only 6 patients (13%) experienced only mild improvement. After 6 months, 19 of the patients (49%) who had experienced improvement after two months of treatment with ALA worsened. The same authors have published other studies of ALA under different conditions (23-26).

DISCUSSION

A review has been made of the articles and clinical cases published in the literature between 1996 and 2006, describing different pharmacological options for the treatment of BMS. The data relating to the efficacy and safety of each of the drugs used in the different studies are summarized in Table 1.

Table 2. Data relating to the design of the studies published in the literature.

DRUG	SAMPLE [1]	DURATION	PLACEBO	MASKED [2]
Trazodone (16)	18 patients	8 weeks	Yes	Yes
Amisulpiride, Paroxetine, Sertraline (17)	27, 26, 23 patients	8 weeks	No	No [3]
Gabapentin (19)	15 patients	3.3 weeks	No	No
Systemic clonazepam (20)	30 patients	8 weeks	No	No
Topical clonazepam (Woda et al.) (6)	25 patients	4 weeks	No	No
Topical clonazepam (Gremeau-Richard) (7)	24 patients	2 weeks	Yes	Yes
Capsaicin (9)	25 patients	4 weeks	Yes	Yes [4]
Benzidamine (11)	10 patients	4 weeks	Yes	Yes
Sucralfate (21)	14 patients	3 weeks	No	No
Alpha-lipoic acid (22)	48 patients	8 weeks	Yes	No

1- Sample size in the trials versus placebo refers to the treatment group only.

2- Masking is assumed when the design is at least double blind.

3- Simple blind study.

4- Triple blind study

In view of the results obtained, it can be affirmed that capsaicin and clonazepam, administered systemically via the oral route, can be discarded because of their adverse reactions. Gabapentin has not shown efficacy. While alpha-lipoic acid appears useful, it loses efficacy over time. Benzidamine and trazodone have not been shown to be more effective than placebo in the treatment of BMS, and trazodone moreover generates an important number of adverse effects. With amisulpiride, paroxetine, sertraline and sucralfate, the patients reported improvement - though the study designs were deficient. Topical clonazepam presently seems to be the best option, with healing of almost half of all patients (40%).

However, the clinical trials conducted to date are not particularly robust. Most are open-label uncontrolled studies involving small patient samples, short periods of time, and in only half of the cases are treatments compared versus placebo (Table 2). Furthermore, expression of the results is heterogeneous. In this sense, it would be interesting to homogenize criteria for expressing the results obtained (27). Numerous etiological factors have been cited, including local problems such as salivary alterations, systemic disorders, and psychopathological alterations (27,28). The population most commonly expressing BMS, i.e., individuals with psychological or psychiatric problems and the polymedicated population, is often excluded from the trials (29).

Although effective therapies have been identified in concrete cases, a treatment modality offering efficacy in most cases of BMS remains to be established. It is essential to gain further insight to the physiopathological mechanisms of BMS, and to establish differential diagnostic criteria to develop drugs with improved efficacy and safety profiles in the treatment of BMS.

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