



## ORIGINAL ARTICLE

# Burning mouth syndrome: clinical description, pathophysiological approach, and a new therapeutic option<sup>☆</sup>



A. Cárcamo Fonfría<sup>a,\*</sup>, L. Gómez-Vicente<sup>b</sup>, M.I. Pedraza<sup>c</sup>, M.L. Cuadrado-Pérez<sup>b</sup>,  
A.L. Guerrero Peral<sup>c</sup>, J. Porta-Etessam<sup>b</sup>

<sup>a</sup> Servicio de Neurología, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

<sup>b</sup> Servicio de Neurología, Hospital Universitario Clínico San Carlos, Madrid, Spain

<sup>c</sup> Servicio de Neurología, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

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## KEYWORDS

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## Abstract

**Introduction:** Burning mouth syndrome is defined as scorching sensation in the mouth in the absence of any local lesions or systemic disease that would explain that complaint. The condition responds poorly to commonly used treatments and it may become very disabling.

**Methods:** We prospectively analysed the clinical and demographic characteristics and response to treatment in 6 cases of burning mouth syndrome, diagnosed at 2 tertiary hospital headache units.

**Results:** Six female patients between the ages of 34 and 82 years reported symptoms compatible with burning mouth syndrome. In 5 of them, burning worsened at the end of the day; 4 reported symptom relief with tongue movements. Neurological examinations and laboratory findings were normal in all patients and their dental examinations revealed no buccal lesions. Each patient had previously received conventional treatments without amelioration. Pramipexol was initiated in doses between 0.36 mg and 1.05 mg per day, resulting in clear improvement of symptoms in all cases, a situation which continues after a 4-year follow up period.

**Conclusions:** Burning mouth syndrome is a condition of unknown aetiology that shares certain clinical patterns and treatment responses with restless leg syndrome. Dopamine agonists should be regarded as first line treatment for this entity.

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\* Corresponding author.

E-mail address: [albacarcamof@gmail.com](mailto:albacarcamof@gmail.com) (A. Cárcamo Fonfría).

**PALABRAS CLAVE**

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## Síndrome de boca ardiente: descripción clínica, planteamiento fisiopatológico y una nueva opción terapéutica

**Resumen**

**Introducción:** El síndrome de la boca ardiente se define como sensación de ardor intrabucal, en ausencia de lesiones locales o patología sistémica que lo justifique. Se trata de una entidad con pobre respuesta a los tratamientos comúnmente utilizados, que puede resultar muy discapacitante.

**Métodos:** Analizamos prospectivamente las características clínicas, demográficas y la respuesta a tratamiento de 6 casos de síndrome de la boca ardiente diagnosticados en las consultas de cefaleas de 2 hospitales de tercer nivel.

**Resultados:** Se trata de 6 pacientes de sexo femenino, con edades entre 34 y 82 años, que referían síntomas compatibles con síndrome de la boca ardiente. En 5 pacientes, las molestias empeoraban a última hora del día y 4 referían mejoría de los síntomas con los movimientos linguales. En todos los casos la exploración neurológica fue normal, los estudios analíticos no mostraron alteraciones que justificaran los síntomas y en el examen odontológico no se evidenciaron lesiones intrabucales. Todas las pacientes habían sido tratadas previamente con los tratamientos convencionales, sin mejoría. Se instauró pramipexol a dosis entre 0,36 mg y 1,05 mg al día, con lo que se consiguió mejoría evidente en todos los casos, que persiste tras una media de 4 años de seguimiento.

**Conclusiones:** El síndrome de la boca ardiente sigue siendo una entidad de etiología desconocida, que comparte ciertos patrones clínicos y respuesta al tratamiento con el síndrome de piernas inquietas. Los agonistas dopaminérgicos deberían considerarse como tratamiento de primera línea en esta entidad.

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**Introduction**

Burning mouth syndrome (BMS) or glossodynia is defined as intraoral burning or dysaesthetic sensation recurring daily during more than 2 hours over a period exceeding 3 months, without clinically evident causative lesions or any other possible causes.<sup>1</sup> It is a complex and probably underdiagnosed syndrome with no specific treatment. Patients with BMS frequently visit several specialists who may be unable to alleviate the condition or answer their questions. We present a series of patients with BMS who shared several clinical characteristics and displayed a similar response to treatment with a dopaminergic agonist.

**Patients and methods**

We prospectively analysed 6 patients with BMS who had been diagnosed with the disease at the headache units of 2 tertiary hospitals and describe their demographic and clinical characteristics and response to treatment. Case 1: 72-year-old woman with no relevant medical history. Over the course of several years, she had been experiencing an intraoral burning sensation which worsened in the evening. Pain affected the entire mouth, was severe in intensity, and caused discomfort. A neurological examination and a complete analysis (including ferritin, vitamin B<sub>12</sub>, and thyroid hormone measurements) yielded normal results. The

patient had previously visited several dentists who had not detected any significant alterations. Clonazepam mouthwash had failed to provide relief. Pramipexole dosed at 0.18 mg and administered in the afternoons and at night led to substantial improvement; the patient remained nearly asymptomatic 4 weeks after dose escalation. Case 2: 71-year-old woman with no relevant medical history. She was a frequent consumer of clebopride and simeticone. She reported an intraoral burning sensation that intensified over the course of the day. Pain affected the tongue in particular and subsided with tongue movement. Thorough neurological and maxillofacial examinations and a complete laboratory analysis revealed no abnormalities. Clonazepam and nystatin mouthwashes achieved no improvement. Our patient was treated with increasing doses of pramipexole. At 4 weeks (with doses of 0.18 mg in the afternoon and 0.36 mg at night), our patient experienced significant relief, which remains to date, after nearly 4 years of follow-up. Case 3: 37-year-old woman with a family history of glossodynia. Our patient had experienced symptoms compatible with BMS for several years. Symptoms fluctuated, with pain intensifying later in the day and subsiding while speaking or eating. A complete laboratory analysis and a neurological examination revealed no abnormal findings. A dentist's assessment had ruled out local lesions. Symptoms did not respond to clonazepam or amitriptyline. We initiated treatment with increasing doses of pramipexole until achieving significant improvement at 6 weeks from treatment onset (0.35 mg in the afternoon and 0.70 mg at

bedtime). Improvements remain after 3 years of follow-up. Case 4: 82-year-old woman with depression treated with duloxetine dosed at 30 mg. She reported a 4-year-history of fluctuating pain and burning sensations in the mouth area without any clear pattern of intensification in the evening. A brain MRI scan, an otorhinolaryngological examination, and a complete laboratory analysis all yielded normal results. She had previously received gabapentin dosed at 1800 mg per day and amitriptyline dosed at 25 mg per day, which achieved no response. Clonazepam mouth-wash yielded slight improvements. Pramipexole dosed at 0.18 mg every 8 hours improved symptoms considerably. Our patient has been in treatment for 3 years and is nearly asymptomatic to date. Case 5: 55-year-old woman with a history of anxiety and depression. In the preceding 6 months, she had been experiencing a fluctuating burning sensation in the anterior half of the tongue; symptoms intensified over the course of the day and improved with speaking and eating. A dentist reported no lesions affecting the oral mucosa; the neurological examination and complete analysis (including an autoimmune profile) yielded normal results. Lorazepam dosed at up to 2 mg per day had failed to lessen symptoms. We started treatment with pramipexole, which was initially poorly tolerated. Pramipexole dosed at 0.36 mg and administered in single night-time doses achieved nearly complete symptom resolution, which remains after 5 years of follow-up. Our patient reports symptom recurrence and difficulty initiating sleep whenever she forgets to take the medication. Case 6: 34-year-old woman with a history of anxiety, depression, subclinical hypothyroidism, mild tobacco use, and psoriasis, which was managed with topical treatment. In the previous 4 months she had experienced a fluctuating burning sensation in the anterior half of the tongue; symptoms worsened in the afternoon and at night and improved with speaking or moving the tongue. Pregabalin dosed at up to 150 mg per day had failed to achieve any improvements. A dentist found no lesions and the results from a buccal smear were normal. The neurological examination displayed no abnormalities; a complete blood count revealed increased levels of nuclear antibodies (1:640). We introduced pramipexole dosed at 0.18 mg after lunch and 0.36 mg after dinner, which initially led to substantial improvements. Over a 4-year follow-up period, we have had to increase the dose to 0.7 mg per day to manage symptoms, but were later able to decrease it to 0.36 mg per day. During this period, our patient underwent hemithyroidectomy to treat benign nodular hyperplasia. She was diagnosed with autoimmune overlap syndrome, with fluctuating autoantibody titres and no other associated symptoms.

## Discussion

BMS or glossodynia is characterised by a burning or dysaesthetic sensation in the tongue or the oral mucosa in the absence of evident causative lesions or any other local or systemic causes.<sup>1,2</sup> The course of this syndrome is chronic and symptom severity ranges from mild discomfort to complete dysfunction. BMS may have a negative impact on patients' quality of life.<sup>3</sup> Pain has a burning quality and

varying intensity, and it affects the surface of the oral mucosa and the anterior part of the tongue. It may also be accompanied by a sensation of dry mouth, dysaesthesia, and taste disorders. It mainly affects postmenopausal women and has been associated with different factors, including xerostomia, allergies to dental materials, oral candidiasis, periodontitis, mouth ulcers, nutritional deficiencies (iron; vitamins B<sub>1</sub>, B<sub>2</sub>, or B<sub>12</sub>; folic acid; zinc), diabetes, hormonal alterations, and various psychiatric disorders. A diagnosis of BMS entails first ruling out other potential causes of symptoms. Different classifications have been established based on pain patterns and symptom fluctuations throughout the day.<sup>4,5</sup> Type 1 (35%): characterised by progressively intense pain. Patients wake up pain-free before pain appears and then intensifies as the day progresses. It is rarely associated with psychological factors but frequently linked to such systemic alterations as nutritional deficiencies. Type 2 (55%): symptoms remain constant throughout the day. Patients have difficulty initiating sleep. This type is frequently associated with psychiatric disorders. Type 3 (10%): pain is intermittent and appears at atypical locations, with unusual features. It may result from contact with oral allergens.

The pathophysiology and aetiology of this entity are unknown.<sup>6–12</sup> Different pathophysiological mechanisms have been proposed, including alterations in dopaminergic neurotransmission at the level of the central nervous system. Increased excitability of the blink reflex (a brainstem reflex under dopaminergic inhibitory control) has been documented in some patients with BMS.<sup>8</sup> The dopaminergic function of the striatum has also been studied using positron emission tomography with 6-[<sup>18</sup>F]fluorodopa in patients with BMS.<sup>9</sup> In this study, presynaptic dopaminergic function in the putamen was clearly lower in these patients than in controls. This finding supports the hypothesis that patients with BMS exhibit increased blink reflex excitability due to poor dopaminergic inhibitory control. Studies in animal models suggest that striatal dopamine may inhibit pain modulation at the level of the central nervous system. Treatment with dopamine agonists may theoretically contribute to restoring striatal dopaminergic function, which is altered in these patients; this may explain symptom abatement. BMS has also been suggested to be a type of peripheral neuropathy of the cranial nerves.<sup>10</sup> This hypothesis is based on neurophysiological and neuropathological studies demonstrating loss of peripheral nerve fibres in the epithelium of the tongue,<sup>11</sup> which in turn explains the altered tongue sensitivity to temperature and pain in these patients and the increases in the taste threshold found by quantitative sensory testing.<sup>12</sup> These proposed mechanisms are similar to those explaining the pathophysiology of restless legs syndrome (RLS), which may be linked to alterations in the nigrostriatal dopaminergic system; according to recent studies, however, it may also involve sensory fibres at the peripheral level.<sup>13</sup> According to the diagnostic criteria for RLS, other body parts, such as the upper limbs, may also be affected. The literature describes the cases of 3 patients who reported abnormal sensation in the abdominal wall with features similar to those of RLS and were diagnosed with 'restless abdomen'.<sup>14</sup> Other reported cases involve a burning sensation similar to that of BMS in the anogenital or vulvar area (vulvostomatodynia)<sup>15</sup> and in the feet (burning

**Table 1** Characteristics shared by burning mouth syndrome and restless legs syndrome.

|                                                              |
|--------------------------------------------------------------|
| Sex: women > men                                             |
| Age: middle-aged to elderly                                  |
| Linked to iron deficiency                                    |
| Family history                                               |
| Burning pain, tingling; not precisely localised              |
| Worsens in the last hours of the day (BMS type 2)            |
| Improves with movement: upon eating (tongue), walking (legs) |
| Linked to dopaminergic dysfunction                           |

**Table 2** Treatments used for burning mouth syndrome.

|       | Clinical trials                                                                  | Case reports                                                                                                                 |
|-------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Local | Clonazepam                                                                       | 0.025% capsaicin<br>Sucralfate                                                                                               |
| Oral  | 0.025% capsaicin<br>amisulpride<br>Alpha-lipoic acid<br>Paroxetine<br>Sertraline | Amitriptyline<br>Nortriptyline<br>Levosulpiride<br>Gabapentin<br>Topiramate<br>Clonazepam<br>Chlordiazepoxide<br>Pramipexole |

feet).<sup>16</sup> The literature also describes 4 patients who met the criteria for both BMS and RLS and in whom both conditions responded well to levodopa.<sup>17</sup> Patients with BMS and RLS exhibit clearly overlapping clinical and epidemiological characteristics (Table 1). Both entities have a similar prevalence in the general population and are more frequent in perimenopausal women. The associated discomfort or pain is difficult to locate, intensifies as the day progresses, and interferes with sleep. Insomnia is frequent in patients with RLS and in those with BMS, especially type 2 according to the classification described above.<sup>4,5</sup> In RLS, symptoms frequently improve with leg movement and worsen with rest. In BMS, pain decreases with speaking, eating, or simply moving the tongue and lips repeatedly and/or compulsively. Management of these patients is difficult, and they often experience anxiety and depression. Multiple topical or oral treatments have been proposed, including clonazepam, capsaicin, amisulpride, alpha-lipoic acid, and SSRIs (Table 2). There is an earlier case of BMS showing good response to pramipexole.<sup>18</sup> In our case series, one of the patients was a frequent user of clobopride (a dopamine receptor D2 antagonist), 4 patients reported relief when moving the tongue, and 5 patients reported symptom exacerbation as the day progressed. These findings led us to consider the similarities between BMS and RLS. On this basis, and given that our patients' symptoms were refractory to traditional treatment, we decided to administer pramipexole, with good results. Although we cannot rule out the possibility of a placebo effect or spontaneous remission in our patients, these hypotheses seem unlikely since all patients had experienced symptoms for several months or even years and had tried different treatments without success. Furthermore, there is a temporal correlation between onset of treat-

ment with the dopaminergic agent and onset of symptom remission. In addition, symptoms reappeared in one of our patients when she forgot to take her medication. BMS is an entity of unknown aetiology that shares some clinical features and drug response patterns with RLS. We therefore feel that these 2 entities may have a pathophysiological mechanism in common. BMS may be severely disabling and standard treatment fails to achieve satisfactory symptom control. Although this is a small series of only 6 cases, we recommend dopaminergic agonists as a first-line treatment option for BMS.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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