

# Effectiveness of Pregabalin for Treatment of Burning Mouth Syndrome

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Treatment of burning mouth syndrome (BMS) is challenging because there is no consensus regarding pharmacological or nonpharmacological therapies. The use of anticonvulsants is controversial. We present nine patients BMS who respond to pregabalin. They were diagnosed secondary BMS except two. Etiologic regulations were made firstly in patients with secondary BMS but symptoms did not decrease. We preferred pregabalin in all patients and got good results. Furthermore the addition of pregabalin to the treatment of two patients who did not respond adequately to duloxetine provided good results. We are only aware that pregabalin may reduce symptoms as a result of case reports. We believe that the diagnosis of pathologic etiology with appropriate diagnostic tests will result in better outcomes in treatment.

**KEY WORDS:** Burning mouth syndrome; Anticonvulsants; Pregabalin.

## INTRODUCTION

Burning mouth syndrome (BMS) is classified in 'painful cranial neuropathies and other facial pains' section (part 3) in the International Classification of Headache Disorders III-beta (ICHD-III-beta). In this classification it is defined as "an intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours/day over more than 3 months, without clinically evident causative lesions."<sup>1</sup> It has numerous different definitions belonging to several organizations such as the American Academy of Orofacial Pain, The International Association for the Study of Pain. In 2003, Scala *et al.*<sup>2</sup> have suggested the definitions 'primary (essential or idiopathic—there is no underlying cause) and secondary BMS (resulting from local or systemic precipitating factor)'. This classification was probably more pragmatic approach.<sup>2</sup> This chronic idiopathic pain condition affects to range from 0.7% up to 15% of the population. It is more common in female than male

and occurs in the fifth-seventh decade of life in general.<sup>2,3</sup> We present nine patients who were diagnosed with BMS and successfully treated with pregabalin.

## CASE

All patients who had complaint of dysesthesia or burning in the mouth were included from the outpatient clinic of Department of Neurology, Adnan Menderes University. The intensity, onset, duration, alleviating-aggravating factors of symptoms and medical history were evaluated. Thereafter intraoral-systemic exam and laboratory-imaging-electroencephalography (EEG) studies were performed. All patients fulfilled the International Headache Society diagnostic criteria (ICHD-III-beta version) for BMS (Table 1). Demographic data, predisposing factors or comorbidities, pain intensity according to numeric rating scale, treatment period and follow-up duration are summarized in Table 2. Seven patients were female, only two were male. There were hypertension, thyroid nodule, diabetes mellitus, sickle cell trait, hypertriglyceridemia, gastritis, migraine, tension type headache in their medical histories. The duration of symptoms was six months or longer in all patients. The complaints started in two patients after their teeth had been extracted. One patient with Parkinson disease was taking levodopa treatment.

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**Table 1.** Demographic data and clinical characteristics of patients with burning mouth syndrome

No.	Age (yr)	Sex	Comorbidity/ predisposition state	Affected region in the mouth	BDI scores	BAI scores	NRS baseline	NRS endpoint	Treatment period	Follow-up duration
1	49	M	Tooth extraction history	Hard palate mucosa	11	7	8	3	6 mo	6 mo
2	22	M	Migraine	Soft palate mucosa	8	7	7	2	6 mo	6 mo
3	60	F	Gastritis	Tongue	10	6	8	3	1 yr	1 yr
4	54	F	Diabetes mellitus Iron deficiency Thyroid nodule	Palate mucosa, dorsum lingua	15	15	9	1	2 yr	1 yr
5	61	F	Peripheral facial paralysis Vitamin B12 deficiency Hypertri glyceridemia	All of the oral mucosa, lingual margins	13	14	8	0	2 yr	1 yr
6	52	F	Diabetes mellitus Sickle cell trait Thyroid nodule Hypertri glyceridemia	Labial mucosa of the lips	16	7	9	2	2 yr	1 yr
7	93	F	Parkinson's disease Hypertension	All of the oral mucosa	12	15	7	1	3 yr	2 yr
8	70	F	Tooth extraction history Hypertension	Tongue, hard palate mucosa	12	5	8	0	1 yr	1 yr
9	55	F	Hypertension Thyroid nodule Tension type headache	Lower lip	13	6	8	2	3 yr	2 yr

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NRS, Numeric Rating Scale; M, male; F, female.

**Table 2.** International Headache Society diagnostic criteria for burning mouth syndrome

13.10 Burning mouth syndrome (BMS)
A. Oral pain fulfilling criteria B and C
B. Recurring daily for >2 hours per day for >3 months
C. Pain has both of the following characteristics:
1. Burning quality
2. Felt superficially in the oral mucosa
D. Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
E. Not better accounted for by another ICHD-III-beta diagnosis.

ICHD, International Classification of Headache Disorders.

Laboratory work-up including blood urea nitrogen, creatinine, electrolytes, alanine amino transferase, aspartat amino transferase, cholesterol, tryglicerids, complete blood cell count, iron, ferritin, vitamin B12, erythrocyte sedimentation rate, albumin, total protein, tri-iodothyronine, thyroxine and thyroid stimulating hormone was conducted. All parameters were normal in all patients (including those with thyroid nodules) except hemoglobin A1c levels. Blood glucose control (increased hemoglobin A1c levels) was unfavorable in two patients with diabetes mellitus. No pathology was detected in the EEG that was performed to exclude partial epilepsy and cranial magnetic resonance imaging had also no features. They

were diagnosed secondary BMS based on clinical and laboratory data except two patients.

## DISCUSSION

BMS is an enigmatic disease characterized by intraoral discomfort such as burning, tingling, tender, scalding and numbness that reported in different sites of oral cavity. Most commonly affected areas are anterior part, dorsum and lateral borders of tongue, anterior facet of hard palate and labial mucosa of the lips in the mouth respectively.<sup>3)</sup>

The pathogenesis of BMS is still unclear. For this reason, recently it is considered that BMS has multifactorial etiology with enigmatic pathophysiology. Several hypotheses have been put forward with the reason of many findings revealed in the literature; neuropathic mechanism, hormonal alterations, psychologic mechanism. These findings in the literature are as follows: Lower density of epithelial and subpapillary nerve fibers of tongue reflecting trigeminal small fiber sensory neuropathy and axonopathy; changes in saliva composition, mucosal blood flow and cell morphology; intensely decreasing of neurosteroids following falls of systemic steroids; damage to any special sensory nerve responsible for taste sensation (glossopharyngeal, vagus, chorda tympani, greater pet-

rosal nerve) and hence probably impairing central inhibitory activity on the trigeminal system; pathologic responses of blink reflexes again indicating subclinical trigeminal neuropathy; impairment in autonomic system findings which are similar to those found in Parkinson disease that exhibited by autonomic nervous function studies and reduction in dopamin levels in nigrostriatal neurons displayed by PET studies suggesting involvement of the central dopaminergic system; thalamic hypoactivation demonstrated by functional magnetic resonance imaging supporting that loss of central inhibitor mechanism, etc.<sup>3-8)</sup>

In conclusion, it appears that BMS implicate disturbance of the central and/or peripheral nervous system. Furthermore, psychological inconvenience and hormonal alterations may contribute to these neuronal changes. An increasing number of studies are on the way to establish the underlying pathological process/processes.

The diagnosis of primary BMS based on the exclusion of all possible systemic or local factors and is purely clinical. All possible causes of secondary BMS must be excluded.<sup>5,6)</sup> If an underlying cause is detected, it should be regulated or removed firstly according to determined pathology. Some of the local and systemic factors that may cause burning mouth are as follows: oral infections (bacterial, viral or fungal); mechanical and chemical irritations; thermal injury; hyposalivation; parafunctional habits; oral mucosal lesions; allergic contact stomatitis; nutritional deficiencies involving iron, zinc, folate and vitamin B1, B2, B6, B12; autoimmune, gastrointestinal and endocrine-hormonal deficiencies disorders (connective tissue disorders, diabetes, hypothyroidism); drug induced conditions that possibly causing hyposalivation/xerostomia as side effect (tricyclics, antipsychotics, antihypertensives such as angiotensin-converting enzyme inhibitors, opioids etc). A thorough evaluation is needed when BMS is suspected and the diagnosis of BMS remains a major challenge in general.<sup>3,5,6)</sup>

First of all, we organized underlying causes (disorder or deficiencies) that identified in the etiologic investigation. For example, iron and vitamin B12 deficiencies were replaced in the patient 4 and 5, respectively or uncontrolled glucose levels were detected in patient 4 and 6, so they were consulted to Department of Endocrinology and the treatments were rearranged. Although HbA1C levels were normal after three months, the complaints of the patients

continued. Also these patients (patient 4 and 6) were taking duloxetine treatment at 60 mg/day when they applied to our outpatient clinic. Levodopa which is known to cause hyposalivation/xerostomia side effect was stopped in patient 7 with Parkinson disease. Treatment of this patient was resumed with dopa agonist (pramipexol). Patient 1 and 8 were consulted to the department of dental surgery since the complaints did not resolve despite the completion of wound healing period of tooth extraction. However there was no additional recommendation. Mild mood disturbance scores which were assessed by the Beck Depression Inventory were detected in these patients who were thought to be secondary BMS. Also the anxiety scores which were assessed with the Beck Anxiety Inventory were found mild levels in three patients (patient 4, 5 and 7). Patient 9 was taking amlodipine for hypertension treatment and also had thyroid nodule but thyroid function tests were normal. Nonetheless, this patient was regarded as secondary BMS. In our series, the comorbidities were not considered as underlying cause in two patients (patient 2 and 3) so they were diagnosed as primary BMS.

Treatment of BMS is challenging because there is no consensus regarding pharmacological, nonpharmacological (cognitive behavioral therapy, complementary and alternative medicine, acupuncture, etc) and interventional therapies (lingual nerve block, topical anesthetic dyclonine). Clonazepam, topical benzydamine, systemic capsaicin, trazodone, amisulpride, paroxetine, sertraline, alpha lipoic acid (ALA) are studied in a few randomized controlled trial in the literature. Gabapentin, nortriptyline and pregabalin commonly used but there is no randomized controlled study except gabapentin. Nonetheless distinct recommendations are scarce and the optimal approach is not yet satisfactory in patients with BMS.<sup>6,7,9)</sup>

The pathophysiological evidence related to neuropathic mechanisms has increased recently. However, a consensus concerning treatment for BMS has not been attained. Furthermore the use of anticonvulsants is controversial in the literature. White *et al.*<sup>10)</sup> reported that gabapentin has favorable results in BMS patient, but Heckman *et al.*<sup>11)</sup> did not support their findings. In 2009, López *et al.*<sup>12)</sup> reported a case with BMS that improved with pregabalin treatment. Thereafter, in their randomized double blind placebo controlled study, López-D'alexandro and Escovich<sup>13)</sup> reported that the use of combination

ALA and gabapentin was useful than gabapentin alone or placebo and also gabapentin alone was beneficial than placebo. In another study related to anticonvulsants, Ito *et al.*<sup>9)</sup> proposed pregabalin may become treatment option for BMS patients who are not responsive to serotonin-norepinephrine reuptake inhibitors.

We administered immediately pregabalin treatment to two patients with primary BMS diagnosis whereas other seven patients diagnosed with secondary BMS received the same treatment after the etiologic evaluation or corrections. It is known that we usually treat comorbidities such as depression, anxiety, insomnia, cognition deficit besides the therapy of pain and neuropathies. Pregabalin has antiepileptic, analgesic and anxiolytic effects and also perfect effect at allodynia and hyperalgesia. Its action appears to be alpha 2-delta subunit of voltage dependent calcium channels widely distributed throughout the peripheral and central nervous system. It modulates the excessive release of excitatory neurotransmitters by reducing depolarization-induced calcium influx. It has highly predictable and linear pharmacokinetics, good bioavailability, dose-proportional plasma concentrations.<sup>14-16)</sup> For this reasons pregabalin was used as the first choice agent and also by considering the existence of both central and peripheral neuropathic mechanisms in BMS. Therefore pregabalin was initiated 2x50 mg/day. After one week the doses of pregabalin were increased to 2x150 mg/day. In three patients who did not respond adequately, it was increased to 2x225 mg/day (patient 4, 5, 6). Dizziness and impaired balance was observed in three patients, hypersomnia in one patient and constipation in two patients as a side effect. None of the patients terminated their treatment due to these side effects.

We considered two patients as primary BMS and the remaining as secondary. However there is still diagnostic dilemma to distinguish primary and secondary cases.<sup>17)</sup> This present report demonstrated that good results were obtained with pregabalin treatment in both primary and secondary types. There were no patients presenting with a new episode after pregabalin was discontinued. Topics such as drug choice, individualization of treatment, duration of treatment are not yet clear. We believe that further randomized controlled trials are needed to confirm the clinical algorithm.

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