Original Article

JOMP
Journal of Oral Medicine and Pain

pISSN 2288-9272 eISSN 2383-8493
J Oral Med Pain 2016;41(1):21-25
http://dx.doi.org/10.14476/jomp.2016.41.1.21

# Retrospective Review of Effectiveness of Various Pharmacological Agents in Treating Burning Mouth Syndrome

Yeong-Gwan Im[1], Byung-Gook Kim[2], Jae-Hyung Kim[2]

[1]Department of Oral Medicine, Chonnam National University Dental Hospital, Gwangju, Korea
[2]Department of Oral Medicine, School of Dentistry, Chonnam National University, Gwangju, Korea

**Received** February 26, 2016
**Revised** March 17, 2016
**Accepted** March 17, 2016

**Correspondence to:**
Jae-Hyung Kim
Department of Oral Medicine, School of Dentistry, Chonnam National University, 33 Yongbong-ro, Buk-gu, Gwangju 61186, Korea
Tel: +82-62-530-5844
Fax: +82-62-530-5679
E-mail: tmjkim@chonnam.ac.kr

**Purpose:** Burning mouth syndrome (BMS) is a chronic pain condition involving the oral and perioral regions, often characterized by a burning sensation and pain in elderly patients. In this study, we investigated the effectiveness of pharmacological agents for the treatment of BMS patients through a retrospective chart review.

**Methods:** We enrolled 61 BMS subjects (57 females, 4 males; 66.4±10.9 years of age) from among consecutive patients treated pharmacologically from January 2014 to June 2015 at Chonnam National University Dental Hospital. Patients with secondary BMS associated with local factors were excluded. The treatment period, number of pharmacological agents tried, and effectiveness of the drugs administered to each subject were analyzed.

**Results:** The mean treatment period for the management of BMS was 2.5 months. More than three agents were tried to control BMS symptoms in 17 subjects (27.9%); two agents were used in 10 subjects (16.4%), and a single agent in 24 subjects (39.3%). Clonazepam was prescribed most frequently and was effective at relieving symptoms in 30 of 39 subjects (76.9%). Paroxetine was moderately effective, relieving symptoms in 7 of 17 subjects (41.2%). Some of the subjects benefited from tricyclic antidepressants, gabapentin, and lipoic acid. A topical local anesthetic used to supplement other systemic agents had ameliorating effects in four of six subjects.

**Conclusions:** Within the study limitations, clonazepam was the most effective drug and antidepressants were efficacious in some subjects for relieving the symptoms of BMS. These pharmacological agents could be considered as first-line drugs for the management of BMS.

**Key Words:** Antidepressive agents; Burning mouth syndrome; Clonazepam; Drug therapy; Effectiveness

## INTRODUCTION

Burning mouth syndrome (BMS) is a chronic pain condition characterized by burning pain and dysesthesia, primarily in the lips and tongue. It affects predominantly menopausal women. The prevalence is 1.6% for men and 5.5% for women.[1)] The pathophysiology of BMS is still poorly understood. There is no specific laboratory test capable of providing a definitive diagnosis. According to the International Headache Society, diagnostic criteria for BMS include: (1) pain in the mouth presenting daily and persisting for most of the day, (2) oral mucosa of normal appearance, and (3) no associated local or systemic disease.[2)]

Management of BMS is complex. Primary and secondary BMS should be discriminated based on possible etiologic factors. In subjects with secondary BMS, causative factors are controlled or eliminated initially. Because the etiology of patients with primary BMS is unknown, those patients are provided with supportive care, consisting mainly of cognitive behavioral therapy and pharmacological therapy.[3)]

The most common medications in pharmacological therapy include tricyclic antidepressants, clonazepam, trazodone, serotonin-noradrenaline reuptake inhibitors (duloxetine), sodium channel blocking agents, antipsychotics (olanzapine, amisulpride), anticonvulsants (gabapentin, pregabalin), and alpha-lipoic acid.[4]

The treatment of BMS is difficult and the result is often frustrating. One study reported that complete spontaneous remission was seen in 3% of patients within 5 years of onset, and that fewer than 30% of patients improved moderately with different treatment modalities.[5] Another study reported similar results: symptoms remitted spontaneously in 3 of 91 patients within 5 years of treatment and 42% of patients improved significantly.[6]

In this study, we investigated the effectiveness of various pharmacological agents in reducing the symptoms of BMS subjects through a retrospective chart review. We report the treatment outcome of clinical cases managed with pharmacological agents.

## MATERIALS AND METHODS

The subjects were selected from among consecutive BMS patients treated pharmacologically from January 2014 to June 2015 at Chonnam National University Dental Hospital (Gwangju, Korea). All subjects had been assessed, diagnosed, and managed by a single orofacial pain specialist. Medical and dental histories had been taken and any organic problems that could cause secondary BMS had been identified by clinical examinations. Subjects having local factors associated with BMS were excluded from the study.

The subjects were managed with pharmacological therapy and counseling. Clonazepam, paroxetine, amitriptyline, nortriptyline, imipramine, buspirone, gabapentin, and lipoic acid were used for systemic administration; nystatin and lidocaine were applied locally to oral mucosa.

The principles for the pharmacological therapy were as follows:

(1) A single agent was prescribed at a time for systemic administration: no combined therapy of two or more agents was used.

(2) Each agent was tried for around 2 weeks to evaluate its pharmacological effectiveness and the subject was switched to another drug if there was little or no effect on BMS symptoms.

(3) Daily dosage of each agent was maintained at low to medium, and was not escalated to a maximum dose to avoid drug adverse effects and also to increase patient compliance.

(4) Local or topical agents were used, if necessary, to control local irritating factors along with a main, systemically administered agent.

The effectiveness of a pharmacological agent was determined by comparing the symptom severity before and after treatment with the agent. Drug effectiveness was described, using a 3-point ordinal scale, as “little or none”, “moderate”, or “high”. A pharmacological agent was rated “highly effective” when symptoms were completely resolved or significantly improved. An agent was judged as “moderately effective” when symptoms were reduced to around half. If the effect was negligible or absent, then the “little or none” classification was used. The total treatment period, number of pharmacological agents systemically administered per subject, and the effectiveness of the agents were analyzed.

## RESULTS

Sixty-one subjects were enrolled according to the selection criteria. They consisted of 57 females and 4 males with a mean age of 66.4 years (range, 42-86 years). Most subjects had one or more medical diseases or conditions identified by history taking (Table 1). The mean duration of

**Table 1.** Medical diseases and conditions of the burning mouth syndrome subjects[a]

| Medical disease | No. of subjects |
|---|---|
| Hypertension | 19 |
| Mental disorder | 14 |
| Cardiovascular disease | 12 |
| Musculoskeletal disease | 12 |
| Diabetes mellitus | 11 |
| Gastrointestinal disease | 9 |
| Neurological disorder | 8 |
| Thyroid disease | 6 |
| Respiratory disease | 5 |
| Kidney disease | 4 |
| Hematologic disease | 1 |

Subjects may have had two or more comorbid disorders.
[a]Identified by history taking.

the BMS symptoms was 15.6 months (range, 1 month-10 years). The symptoms were severe in 42, moderate in 16, and mild in 3 of the 61 total subjects.

The mean total treatment period was 2.5 months and the maximum treatment period was 9.6 months. During the treatment period, more than three agents were tried in 17 subjects (27.9%); two agents were tried in 10 subjects (16.4%), and a single agent was tried in 24 subjects (39.3%) (Table 2). Among the systemically administered agents, clonazepam was prescribed most frequently and was effective at relieving symptoms in 30 of 39 subjects (76.9%). Paroxetine was tried in 17 subjects and relieved symptoms in 7 subjects (41.2%) of them. Amitriptyline showed moderate-to-high effectiveness in 2 of 11 subjects (18.2%). Other tricyclic antidepressants, including nortriptyline and imipramine, were not notably effective in the few subjects in whom they were tried. Gabapentin was effective in two of four subjects. Lipoic acid was highly effective in one subject, and moderately effective in two of nine subjects.

**Table 2.** The number of pharmacological agents systemically administered to subjects

| No. of tried agents | No. of subjects |
|---|---|
| 7 | 1 |
| 6 | 0 |
| 5 | 3 |
| 4 | 4 |
| 3 | 9 |
| 2 | 10 |
| 1 | 24 |

The pharmacological agents were administered one by one, with no combination use of two or more agents.

Buspirone was tried in only one subject and showed high effectiveness. Although nystatin was applied locally and was used to supplement systemically administered agents, it was effective in relieving symptoms in 15 of 25 subjects (60.0%). A topical local anesthetic (2% lidocaine) ameliorated symptoms in four of six subjects (Table 3).

## DISCUSSION

The management of BMS is complex and difficult for several reasons. In most BMS patients, causative factors are unknown; thus, definitive treatments to remove or modify the etiology are typically not possible. There is no single therapy or pharmacological agent that is effective for all BMS patients. One strategy in pharmacological therapy is to try each agent in order of effectiveness until achieving a therapeutic response. In this study, we had many pharmacological agents to choose from for the treatment of our subjects. When there was little or no effect after administering one agent, it was replaced with another agent.

We found that clonazepam had moderate-to-high effectiveness in most of the subjects studied. Clonazepam and diazepam are benzodiazepine class tranquilizers. Both diazepam and clonazepam are useful for the management of BMS.[7] Clonazepam is more effective in relieving symptoms in older patients and those with severe pain.[8] Topical administration of clonazepam also improves BMS symptoms in some patients.[9] A recent review of 12 randomized controlled trials on BMS patients suggested that clonazepam, alpha-lipoic acid, and capsaicin showed greater reduction

**Table 3.** Effectiveness of all of the pharmacological agents tried

| Pharmacological agent | | Drug effectiveness | | | |
|---|---|---|---|---|---|
| Generic name (proprietary name) | Dosage (mg/day) | Little or none | Moderate | High | Total |
| Clonazepam (Rivotril) 0.5 mg | 1-1.5 | 9 | 16 | 14 | 39 |
| Paroxetine (Seroxat) 20 mg | 10-20 | 10 | 4 | 3 | 17 |
| Amitriptyline (Etravil) 10 mg | 10 | 9 | 1 | 1 | 11 |
| Nortriptyline (Sensival) 10 mg | 10 | 3 | 0 | 0 | 3 |
| Imipramine (Imipramin) 25 mg | 17.5 | 3 | 1 | 0 | 4 |
| Gabapentin (Neurontin) 100 mg/300 mg | 300-600 | 2 | 1 | 1 | 4 |
| Lipoic acid (Thioctacid HR) 600 mg | 600 | 6 | 2 | 1 | 9 |
| Buspirone (Buspar) 5 mg | 2.5-5 | 0 | 0 | 1 | 1 |
| Nystatin (PMS Nystatin) 100 kIU/mL | Topical, twice a day (auxiliary) | 10 | 8 | 7 | 25 |
| Lidocaine HCl (Lidocaine Viscous) 2% | Topical, as needed (auxiliary) | 2 | 4 | 0 | 6 |

Values are presented as number of subjects.

in symptoms.[10] In the present study, antidepressants, gabapentin, and alpha-lipoic acid were also effective in relieving BMS in some subjects. Paroxetine, an antidepressant of the selective serotonin reuptake inhibitor class, was effective in 40% of the subjects. One study reported that paroxetine reduced pain in about 80% of patients after 12 weeks of treatment.[11] Paroxetine and amisulpride are equally effective for pain reduction in short-term treatment.[12] Results pertaining to the therapeutic effect of alpha-lipoic acid are mixed and inconclusive. Some studies[13,14] reported improvement, while others[15-17] failed to demonstrate effectiveness over placebo.

The effectiveness of many pharmacological agents, including pregabalin,[18] topiramate,[19] duloxetine,[20] pramipexol,[21] and olanzapine,[22,23] has been reported in isolated cases or case series. In the present study, we reported the effectiveness of new pharmacologic agents that had not been discussed previously in the literature. Buspirone is an anxiolytic psychotropic drug primarily used to treat generalized anxiety disorder.[24] It is a selective 5-$HT_{1A}$ partial agonist,[25,26] and acts as an antagonist at the dopamine $D_3$ receptors and $D_4$ receptors.[27]

We tried buspirone in one subject and found it was highly effective. Tricyclic antidepressants are among the first-line treatments clinically recommended against neuropathic pain. The delta-opioid receptor of the endogenous opioid system is preferentially involved in the anti-nociceptive effect of antidepressants.[28,29] Imipramine is a tricyclic antidepressant that is mainly used in the treatment of major depression and enuresis. It can also be useful for the treatment of neuropathic pain. However, a recent review found little evidence to support the use of imipramine to treat neuropathic pain.[30] In this study, one out of four subjects benefited from imipramine therapy, which equates to moderate effectiveness.

This study had several limitations. Firstly, medical conditions were not thoroughly evaluated by consultation or laboratory tests in those subjects with systemic disorders that can cause secondary BMS. Secondly, the primary outcome measure or drug effectiveness was described using a simple 3-point ordinal scale. This scale may not have been sensitive enough to discriminate subtle changes. Symptom severity and symptomatic relief in BMS subjects are most commonly reported using a visual analog scale.[31] Thirdly, some agents were tried in only a few subjects; thus, it was hard to draw conclusions regarding the effectiveness of those agents. Fourthly, the order of drug administration was not controlled. Fifthly, there was no control group for comparison of the effectiveness of each pharmacologic agent. The placebo effect should be considered in the evaluation of any pharmacological therapy. Treatment with placebo can produce a response rate of 72%, as large as that of active drugs.[32] Finally, the treatment period of some of the agents was shorter than is generally recommended. Thus, the possibility cannot be excluded that a therapeutic response was not obtained due to the shortness of the treatment period.

Notwithstanding these limitations, the major findings of this study correspond well with those of previous studies. Additionally, this study showed the effectiveness of two new pharmacologic agents that had not been reported in the literature before. In conclusion, clonazepam and antidepressants were effective in relieving BMS symptoms and these agents could be considered as first-line drugs for the management of BMS.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med 1999;28:350-354.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24(Suppl 1):9-160.
3. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14:275-291.
4. Clark G, Dionne R. Orofacial pain: a guide to medications and management. Chichester: John Wiley & Sons; 2012. pp. 240-243.
5. Sardella A, Lodi G, Demarosi F, Bez C, Cassano S, Carrassi A. Burning mouth syndrome: a retrospective study investigating spontaneous remission and response to treatments. Oral Dis 2006;12:152-155.
6. Rodríguez-de Rivera-Campillo E, López-López J. Evaluation of the response to treatment and clinical evolution in patients with burning mouth syndrome. Med Oral Patol Oral Cir Bucal 2013;18:e403-e410.
7. Barker KE, Batstone MD, Savage NW. Comparison of treatment

modalities in burning mouth syndrome. Aust Dent J 2009;54: 300-305.
8. Min BK, Jung JK, Choi JK. Clinical features affecting the efficacy of systemic clonazepam for management of burning mouth syndrome. J Oral Med Pain 2012;37:161-167.
9. Gremeau-Richard C, Woda A, Navez ML, et al. Topical clonazepam in stomatodynia: a randomised placebo-controlled study. Pain 2004;108:51-57.
10. de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, de Oliveira Soares AC, Pinto LP, de Lisboa Lopes Costa A. Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature. J Oral Pathol Med 2012;41: 281-287.
11. Yamazaki Y, Hata H, Kitamori S, Onodera M, Kitagawa Y. An open-label, noncomparative, dose escalation pilot study of the effect of paroxetine in treatment of burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:e6-e11.
12. Maina G, Vitalucci A, Gandolfo S, Bogetto F. Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: a single-blind study. J Clin Psychiatry 2002;63:38-43.
13. Femiano F, Scully C. Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. J Oral Pathol Med 2002;31:267-269.
14. Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, Llamas-Martínez S, Esparza-Gómez G. Alpha lipoic acid efficacy in burning mouth syndrome: a controlled clinical trial. Med Oral Patol Oral Cir Bucal 2015;20:e435-e440.
15. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. J Oral Rehabil 2009;36:52-57.
16. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. Eur J Pain 2009;13:492-496.
17. Cavalcanti DR, da Silveira FR. Alpha lipoic acid in burning mouth syndrome: a randomized double-blind placebo-controlled trial. J Oral Pathol Med 2009;38:254-261.
18. Ito M, Tokura T, Yoshida K, et al. Five patients with burning mouth syndrome in whom an antidepressant (serotonin-noradrenaline reuptake inhibitor) was not effective, but pregabalin markedly relieved pain. Clin Neuropharmacol 2015;38:158-161.
19. Siniscalchi A, Gallelli L, Marigliano NM, Orlando P, De Sarro G. Use of topiramate for glossodynia. Pain Med 2007;8:531-534.
20. Kim YD, Lee JH, Shim JH. Duloxetine in the treatment of burning mouth syndrome refractory to conventional treatment: a case report. J Int Med Res 2014;42:879-883.
21. Stuginski-Barbosa J, Rodrigues GG, Bigal ME, Speciali JG. Burning mouth syndrome responsive to pramipexol. J Headache Pain 2008;9:43-45.
22. Gick CL, Mirowski GW, Kennedy JS, Bymaster FP. Treatment of glossodynia with olanzapine. J Am Acad Dermatol 2004;51:463-465.
23. Ueda N, Kodama Y, Hori H, et al. Two cases of burning mouth syndrome treated with olanzapine. Psychiatry Clin Neurosci 2008;62:359-361.
24. Apter JT, Allen LA. Buspirone: future directions. J Clin Psychopharmacol 1999;19:86-93.
25. Wong H, Dockens RC, Pajor L, et al. 6-Hydroxybuspirone is a major active metabolite of buspirone: assessment of pharmacokinetics and 5-hydroxytryptamine1A receptor occupancy in rats. Drug Metab Dispos 2007;35:1387-1392.
26. Loane C, Politis M. Buspirone: what is it all about? Brain Res 2012;1461:111-118.
27. Bergman J, Roof RA, Furman CA, et al. Modification of cocaine self-administration by buspirone (buspar®): potential involvement of D3 and D4 dopamine receptors. Int J Neuropsychopharmacol 2013;16:445-458.
28. Gray AM, Spencer PS, Sewell RD. The involvement of the opioidergic system in the antinociceptive mechanism of action of antidepressant compounds. Br J Pharmacol 1998;124:669-674.
29. Benbouzid M, Gavériaux-Ruff C, Yalcin I, et al. Delta-opioid receptors are critical for tricyclic antidepressant treatment of neuropathic allodynia. Biol Psychiatry 2008;63:633-636.
30. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev 2014;5:CD010769.
31. Ni Riordain R, McCreary C. Patient-reported outcome measures in burning mouth syndrome: a review of the literature. Oral Dis 2013;19:230-235.
32. Kuten-Shorrer M, Kelley JM, Sonis ST, Treister NS. Placebo effect in burning mouth syndrome: a systematic review. Oral Dis 2014; 20:e1-e6.