Efficacy of Moclobemide in Burning Mouth Syndrome: A Nonrandomized, Open-Label Study

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Aims: *To compare burning mouth syndrome (BMS) patients with age- and gender-matched controls for psychologic conditions, to analyze the effect of menstrual state on the intensity of burning, and to assess the efficacy of an antidepressant medication on the burning pain and psychologic status.* ***Methods:*** *Ninety-four patients with BMS and 94 matched control subjects participated in the study. Anxiety and depression were analyzed by means of the Spielberger State-Trait Anxiety Inventory and Zung Self-Rating Depression Scale, and the severity of the burning sensation was measured by means of a visual analog scale (VAS). In female BMS patients and controls, the menstrual state was noted (menstruating, menopausal, or postmenopausal). BMS patients were treated with the antidepressant moclobemide (150 mg 2 times daily) for 3 months. Thereafter, anxiety, depression, and burning pain intensity were reassessed. Patient-perceived satisfactory improvement for burning sensation was assessed using a 5-point categorical rating of change scale.* ***Results:*** *BMS patients had significantly higher anxiety and depression scores than controls (*$P < .05$*). After treatment, anxiety and depression scores as well as the VAS values for burning pain decreased significantly (*$P < .001$*). Thirty-seven patients reported good to very good improvement, and 44 reported satisfactory improvement. No adverse reactions were reported.* ***Conclusions:*** *The study confirmed earlier reports that BMS patients have higher anxiety and depression levels than controls. An antidepressant medication may be effective in alleviating the burning pain, at least in the short term.* J OROFAC PAIN 2008; 22:146–152

Key words: anxiety, burning mouth syndrome, depression, moclobemide, pain measurement, treatment

Burning mouth syndrome (BMS) is characterized by both positive sensory symptoms (burning pain, dysgeusia, and dysesthesia) and negative sensory symptoms (loss of taste) surrounding the oral cavity in sites that appear clinically normal.[1,2] Burning mouth complaints are reported more often in women, especially after menopause,[3] with a prevalence of 18% to 33%.[4] The presence of BMS is very uncommon before the age of 30 to 40 years.[1]

The cause of BMS and the underlying pathogenic mechanisms are still unknown. The etiology is presumed to be multifactorial, but it involves hormonal disturbances associated with menopause as well as an interaction between biologic (neurophysiologic) and psychologic factors.[1,4–16] Climacteric is a natural process that eventually occurs in all women. The period of hormonal transition is characterized by physical and emotional changes. Typical are vasomotor changes (hot flashes, profuse perspiration, palpita-

tions), psychologic symptoms (depression, tiredness, irritability, inability to cope, nervousness) and other complaints such as headaches, insomnia, and vaginal discomfort. Oral discomfort (burning and/or altered taste) is another complaint.[17] Several investigators have considered depression the most prevalent psychiatric disorder in patients with BMS,[2,10] although anxiety appears to play an important role as well.[5,8,16] Some studies have suggested that psychiatric disorders associated with BMS are best categorized as a mixture of anxiety and depressive disorder associated with social problems.[10] It has also been suggested that stressful life events and different degrees of mental disorders play an etiologic role.[2]

There is increasing evidence that a sensory neuropathy may underlie BMS symptoms. Quantitative assessment of the sensory and chemosensory functions in BMS patients have revealed that the sensory thresholds are different in these patients than in controls.[1,9,18–20] In addition, tongue biopsies have shown a lower density of epithelial nerve fibers in BMS patients than in controls.[1] These data generally support the view that BMS is a disorder of altered sensory processing which occurs following small-fiber neuropathic changes in the tongue.

Although the management of BMS is still not satisfactory,[1,21–26] the fact that BMS patients have higher scores of anxiety and depression indicate that BMS patients must be provided with psychologic treatment as needed.

The aim of the present study was to compare BMS patients with age- and gender-matched controls for psychologic conditions, to analyze the effect of menstruation state on the intensity of burning, and to assess the efficacy of an antidepressant medication on the burning pain and psychologic status.

Materials and Methods

Ninety-four patients with BMS were examined in the Department of Oral Diagnosis and Radiology, Faculty of Dentistry, Marmara University, Istanbul, Turkey. Inclusion criteria were *(1)* normal oral mucosa, *(2)* no medical or physical cause for BMS (diabetes mellitus, lichen planus, neuralgia, chronic pain conditions in other regions and geographic tongue), *(3)* normal hematologic and laboratory findings, and *(4)* presence of the burning sensation for at least 6 months.[5,25,26] Relief from the burning sensation during eating or drinking was not considered an exclusion criterion. An age- and gender-matched control group comprised 94 healthy individuals who attended the Department of Oral Diagnosis and Radiology. None of the control subjects had oral burning sensation.

The BMS and control patients were requested to sign a written informed consent statement. The study was carried out according to the recommendations of the Helsinki Declaration. The study protocol was approved by the local committee of research and ethics.

For all patients, medical histories were recorded in detail, thorough clinical oral examinations were performed by 2 dentists to confirm the absence of oral lesions, and laboratory investigations, including complete blood cell counts, fasting blood glucose levels, serum iron, total iron binding capacity, and levels of vitamin B_{12} and folic acid, were undertaken.

The study was divided into 2 parts. In the first part, BMS patients and controls were compared for differences in anxiety and depression and the effect of the menstrual state on the intensity of burning was also analyzed. In the second part, BMS patients were treated with an antidepressant, and its effect on the intensity of burning sensation as well as on anxiety and depression was analyzed.

Psychologic Evaluation

The levels of anxiety and depression were analyzed in BMS patients and controls by means of the Spielberger State-Trait Anxiety Inventory (SAI-TAI)[26] and Zung Self-Rating Depression Scale (ZDS).[27] The cutoff values of the tests for SAI and TAI for adults are 33.97 and 42.65, respectively. The answers given to each question in the ZDS were graded from 1 to 4. The following grading system was used to determine the severity of depression: less than 50: normal range, no psychopathology; 50 to 59: mild depression; 60 to 69: moderate depression; 70 or more: severe depression.

Menopausal State

Female BMS patients and controls were asked about symptoms of the climacteric and categorized as menstruating, menopausal, and postmenopausal.

BMS Treatment

BMS patients were treated by means of the antidepressant moclobemide (Aurorix [Roche]; 2 tablets of 150 mg per day for 3 months), which has been reported to be significantly more effective than placebo and as efficacious as tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) in a number of clinical studies.[28] Prior to

Table 1 Frequency of the Postmenopausal, Menopausal, and Menstruating States in the BMS Patients and Controls

	BMS		Control	
	n	%	n	%
Postmenopausal	21	26.2	21	26.2
Menopausal	26	32.5	28	35.0
Menstruating	33	41.3	31	38.8

Chi-square test = .137; *P* = .934.

Table 2 SAI-TAI and ZDS scores in the BMS Patients and Controls

	BMS		Control			
	Mean	SD	Mean	SD	*t*	*P**
SAI	40.19	9.92	30.47	4.58	8.624	.001
TAI	46.73	10.50	30.94	5.86	12.732	.001
ZDS	44.49	8.82	31.74	6.61	11.215	.001

*Student *t* test.

Table 3 Pre- and Post-treatment VAS, SAI-TAI, and ZDS Scores of the BMS Patients

	Before		After			
	Mean	SD	Mean	SD	*t**	*P**
VAS	3.38	0.90	1.78	0.76	13.686	.001
SAI	40.19	9.92	36.39	8.00	11.167	.001
TAI	46.73	10.50	41.72	8.58	14.094	.001
ZDS	44.49	8.82	40.39	7.23	11.233	.001

*Paired sample *t* test.

Table 4 Group Level Analysis of Mean Change in VAS Pain (in cm) at Follow-up for Categories of Patient-Perceived Change (n = 94)

	Absolute change*		Percent change†	
	Mean	SD	Mean	SD
Unchanged (n = 3)	–0.27	0.38	–8.47	11.07
Improved (unsatisfactory) (n = 10)	–1.00	0.00	–29.50	5.15
Satisfactorily improved (n = 44)	–2.07	0.33	–51.40	8.50
Improved (good to very good) (n = 37)	–2.73	0.61	–69.23	6.56
P	.001		.001	

*One-way ANOVA (F = 66.030, *P* = .001).
†One-way ANOVA (F = 144.817, *P* = .001).

Table 5 Comparison of VAS, SAI-TAI, and ZDS Scores of the BMS Patients in Relation to Menstrual State

	Postmenopausal		Menopausal		Menstruating			
	Mean	SD	Mean	SD	Mean	SD	*F*	*P*
VAS	3.24	0.77	3.81	0.98	3.24	0.87	3.615	.031*
SAI	42.47	9.27	40.77	12.34	37.70	8.59	1.556	.218
TAI	49.00	10.95	48.85	10.51	43.36	9.36	2.891	.062
ZDS	43.05	10.30	47.04	7.62	43.09	8.90	1.739	.183

*1-way ANOVA.

the first examination, patients were asked to rate the mean intensity of the burning sensation on a 10-cm visual analog scale (VAS) with the anchor points "no burning" and "most imaginable burning."[29–31] At the end of the treatment, patients, who were not blind to the first estimate, were reassessed for changes in the burning sensation as well as their psychologic condition. Patients were asked whether the burning pain was "worse," "unchanged," "improved (unsatisfactory)," "satisfactorily improved," or "improved (good to very good)." Patient-perceived satisfactory improvement was defined as the change in burning sensation on the VAS associated with satisfactory improvement at follow-up. Ratings of "satisfactorily improved" and "improved (good to very good)" were pooled to define satisfactorily improved patients. Patients were considered unimproved if they rated the pain as worsened, unchanged, or improved (unsatisfactory).[31]

Statistical Analysis

The differences in the SAI-TAI and ZDS scores between groups were analyzed by means of the Student *t* test. The treatment efficacy, ie, the post-treatment changes in the SAI-TAI, ZDS, and VAS scores, was analyzed using paired *t* tests.

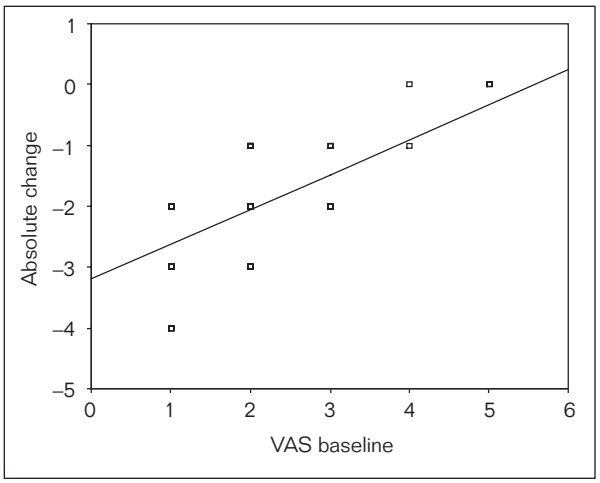

Fig 1 Relationship between the categorical rating scale and absolute VAS change in burning sensation.

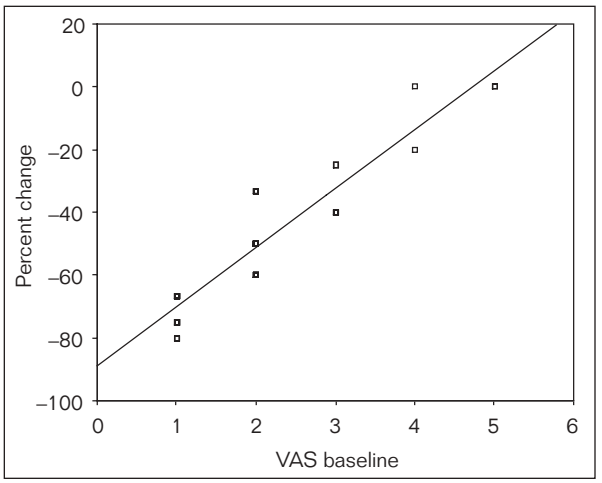

Fig 2 Relationship between the categorical rating scale and percent VAS change in burning sensation.

The method proposed by ten Klooster et al[31] was used to determine what would constitute a meaningful change in burning sensation. The categorical ratings—"worse," "unchanged," "improved (unsatisfactory)," "satisfactorily improved," "improved (good to very good)"—were associated with the absolute change in scores (VAS follow-up – VAS baseline) as well as the percent change in scores [absolute change/VAS baseline) × 100]. Differences among the 5 groups were analyzed by means of 1-way analyses of variance (ANOVAs) followed by post-hoc multiple comparisons. The association between the categorical ratings and the VAS absolute and percent changes in burning sensation was analyzed by means of Spearman rank correlation. Correlations ≥ .5 were considered indicative of the valid use of the rating scale.

Finally the age- and gender-matching between patients and controls was analyzed by means of the chi-square test. *P* values of less than .05 were interpreted as significant. Statistical analysis was performed by means of the Statistical Package for Social Sciences for Windows 10.0.

Results

The 2 groups did not differ significantly with respect to age or gender ($P > .05$). The mean ages of the BMS patients and controls were 50.84 ± 12.26 and 48.09 ± 11.92, respectively. Of the 94 BMS cases, 80 (85.1%) were female and 14 (14.9%) were male; of the 94 controls, 80 (85.1%) were female and 14 (14.9%) were male. There was also no significant difference in menopausal state between BMS patients and controls (chi-square test, $P > .05$; Table 1).

Psychologic Status

Table 2 summarizes the anxiety and depression scores for BMS and control patients. Subjects with BMS had significantly higher mean scores for anxiety and depression compared with controls ($P < .001$).

BMS Therapy

Burning Intensity. The mean intensity of the burning sensation decreased significantly ($P< .01$; Table 3). Thirty-seven patients reported good to very good improvement and 44 a satisfactory improvement, which corresponded, on average, to a relative improvement from baseline of 51.40 ± 8.50 and 69.23% ± 6.56%, respectively. Both the absolute and percent changes on the VAS were significantly different between the groups "unchanged," "improved (unsatisfactory)," "satisfactorily improved," and "improved (good to very good)" (ANOVA, $P < .001$; Table 4). The patient-perceived changes correlated significantly with the absolute and percent changes (Spearman's rho = 0.503 and 0.911, respectively; $P < .01$; Figs 1 and 2).

Patients with menopause had significantly higher mean VAS scores than postmenopausal and menstruating women ($P < .05$; Table 5). Of all female subjects, 41.3% were still menstruating, 32.5% stated that they were experiencing menopause, and 26.3% were postmenopausal (Table 1).

Psychologic Variables. The mean scores for anxiety and depression decreased significantly during treatment ($P < .001$; Table 3). However, the mean SAI-TAI values of the BMS patients were still higher than reported normal values.[26,27] In agreement with other studies,[23,32] higher scores for anxiety were observed in these patients. SAI-TAI and ZDS scores did not differ with statistical significance between postmenopausal, menopausal, and still-menstruating women (Table 5).

Moclobemide did not cause any adverse side effects over the short time period of this study.

Discussion

The results of the present study have shown higher anxiety and depression scores in BMS patients than in controls, thus confirming previous findings that these psychologic factors are often associated with BMS.[5,8,13,32] The fact that psychiatric/psychologic diagnosis is more common in BMS patients than controls does not, however, imply a causal relationship. Indeed, prolonged stress such as caused by the chronic burning sensation may affect and alter the patient's psychologic level of functioning.[32,33] In line with these considerations, it is interesting that the group of women in menopause reported, on average, a significantly higher intensity of burning sensation than the postmenopausal and menstruating patient groups. However, the groups did not differ with respect to anxiety or depression.

BMS treatment is still unsatisfactory, and there is no definitive cure.[34–36] Like many other chronic pain conditions, BMS is often treated by means of antidepressants. Both tricyclic and tetracyclic antidepressants have been used.[33] In this study, moclobemide was successful in reducing the burning sensation and also the SAI-TAI and ZDS scores in the short term. Indeed, 81 patients reported a satisfactory or good to very good improvement in the burning pain, and only 13 reported an unsatisfactory outcome. In a retrospective study on 150 consecutive BMS patients followed up for 1 month, 12.7% of the patients reported a profound relief, 23.9% a meaningful relief, and 54.9% a mild relief.[37] The most effective treatment modalities were habit awareness, followed by tricyclic antidepressants. Similarly, Grushka et al[3] observed that low doses of tricyclic antidepressants positively influence the burning pain, and Feinmann et al[38] prescribed tricyclic and tetracyclic antidepressant drugs because of the assumption that BMS was a primary psychogenic depressive disorder. Other drugs used in BMS therapy are clonazepam and capsaicin. A 4-week regimen with a local application of clonazepam (0.5 or 1 mg 2 or 3 times daily) to disrupt the neuropathologic mechanism underlying BMS reduced the burning pain intensity significantly from 6.2 ± 0.3 to 3.0 ± 0.5. Ten patients were totally cured, 9 patients had some improvement but were not considered cured since they did not wish to stop the treatment, and 6 had no benefit at all.[39] Systemic capsaicin was used in a triple-blind, placebo controlled, "intent-to-treat" study on 50 BMS patients. The VAS score decreased significantly in the experimental group (5.84 ± 1.17 versus 6.24 ± 0.96). However, the systemic use of capsaicin was associated with gastric pain, and the side effects seemed to increase with time.[40]

Moclobemide is a reversible inhibitor of monoamine oxidase type A, which was shown in a double-blind verum- and/or placebo-controlled study to exhibit comparable response rates to other antidepressants for major depression and other subtypes of depression.[41] Moclobemide is comparable to the SSRIs in both efficacy and tolerability.[42,43] It was well tolerated by patients in the present study, who did not report any adverse reactions.

It is difficult to compare the improvement rates of different studies because the initial intensity of the burning sensation differs among studies, and it is known that during post-treatment evaluation the recall of the initial pain intensity depends upon its pretreatment level. Patients with pretreatment pain of low intensity tend to recall it in an exaggerated manner.[44] This could alter the pain improvement evaluation. The initial mean intensity reported by the patients in the present sample was lower than that reported in studies by Woda et al[39] and Petruzzi et al.[40] In addition, different success criteria have been used. The results of the present study support the validity of the 5-point categorical rating scale to assess patient-perceived satisfactory improvement. Indeed, the categorical rating scale correlated adequately with the absolute changes on the VAS and were well correlated with the percent changes from baseline for the burning sensation as was shown in another study.[31] Thus, the rating scale allows for a clear distinction between satisfactorily and unsatisfactorily improved patients.

Two limitations of this investigation need to be noted. First, this study was performed without a placebo control; thus, the true therapeutic profile of moclobemide in the treatment of BMS could not be determined. Second, the efficacy and tolerability of moclobemide have been tested only in the short-term, but long-term studies are necessary to inves-

tigate whether it is effective and equally well-tolerated in the long run for the treatment of BMS.

In conclusion, the present study showed that anxiety and depression are dominant psychologic factors in BMS patients and that moclobemide may be effective in the treatment of BMS.

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