Clinical Characteristics, Treatment Effectiveness, and Predictors of Response to Pharmacotherapeutic Interventions in Burning Mouth Syndrome: A Retrospective Analysis

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Aims: To identify the clinical characteristics of patients with primary and secondary burning mouth syndrome (BMS), to assess the effectiveness of pharmacotherapy in treating BMS, and to determine the clinical variables that may predict significant relief of clinical symptoms. **Methods:** A retrospective chart review of patients who underwent clinical management for BMS in the Massachusetts General Hospital between January 2011 and December 2016 was carried out. Information regarding demographics, diagnostics, and therapeutic characteristics was extracted and analyzed. **Results:** Of 112 BMS patients, 77 had primary BMS. Patients with primary and secondary BMS had similar clinical characteristics except when it came to the presence of at least one symptom of sensory discrepancy, which was more prevalent in primary BMS. Following pharmacologic intervention, 46.8% of the patients with primary BMS experienced significant relief in symptoms, and this therapy was associated with a lower level of pain, an onset of symptoms of less than 1 year, hyperlipidemia, absence of depression disorder, and nonconcurrent use of other neuropathic medications. In contrast, only 31.4% of patients with secondary BMS experienced significant relief in symptoms, and this was associated with the presence of anxiety disorder. Stepwise forward conditional logistic regression analysis suggested that nonconcurrent use of neuropathic medications was a predictor for significant relief of symptoms in patients with primary BMS. Likewise, the model suggested that presence of anxiety disorder was a predictor in patients with secondary BMS. **Conclusion:** The prevalence of an associated sensory discrepancy was higher in primary BMS. Pharmacologic intervention provided significant relief for approximately half of the patients with primary BMS and nearly one-third of the patients with secondary BMS. Concurrent use of neuropathic medications was a negative predictor, and presence of anxiety disorder a positive predictor, of therapeutic response among patients with primary BMS and secondary BMS, respectively. *J Oral Facial Pain Headache 2020;34:157–166. doi: 10.11607/ofph.2180*

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The third edition of the International Headache Society (IHS) Classification of Headache Disorders (ICHD-3) describes burning mouth syndrome (BMS) as an intraoral burning or dysesthetic sensation recurring daily for more than 2 hours per day for over more than 3 months without clinically evident causative lesions.[1] The prevalence of BMS in the general population ranges from 0.7% to 15%,[2,3] and the male-to-female ratio varies from 1:3 to 1:16. However, occurrence tends to increase with age in both men and women, and BMS is most prevalent in women in the fifth to seventh decade of life.[4–6]

Based on its etiology, BMS can be classified into primary and secondary subtypes. The diagnosis of primary BMS is based on the patient's history and pathognomonic features. The onset of symptoms is often spontaneous and in the absence of any objective abnormalities or clinical examination findings.[1,2,7] In secondary BMS, the manifestation of burning pain or dysesthesia occurs after a secondary illness, dental procedure, or medication.[2,7] The pathophysiology of BMS is poorly understood, and multiple theories have been postulated in an attempt to explain its occurrence. These include disinhibition of the chorda

tympani and lingual nerves, peripheral and central neuropathic changes, and alteration of the neuroendocrine system. However, none of these theories fully explain the diverse clinical manifestations of BMS.[2,7,8]

Clinically, BMS presents with a bilateral symmetric distribution and most frequently affects the anterior two-thirds of the tongue, followed by the dorsal and lateral borders of the tongue, the anterior aspect of the hard palate, and the mucosal surfaces of the labial and buccal mucosa. It may be localized to a single region in the oral cavity or widespread in distribution, involving multiple sites. The burning pain or dysesthesia is often associated with a subjective feeling of oral dryness (xerostomia) and/or taste disturbances (metallic taste or reduction in taste perception). The presentation of symptoms can be constant in nearly one-third of patients, with no intermittent relief.[2,3,5–7]

The management of BMS is difficult and often refractory to treatment. Prior to establishing a therapeutic strategy for management of its clinical symptoms, it is vital to differentiate BMS into primary and secondary subtypes, as in secondary BMS, the underlying local or systemic condition would also need to be addressed. There is evidence that behavioral interventions, low-level laser therapy, nutritional supplements, and topical and systemic pharmacotherapy may help in the management of pain and concomitant symptoms associated with BMS. However, none of these therapies have shown to have an out-and-out response. In addition, little is known regarding the clinical characteristics of patients with BMS that would predict a benefit from a particular therapeutic intervention.[2,7,9]

The aims of this investigation were to identify the clinical characteristics of patients with primary and secondary BMS, to assess the effectiveness of pharmacotherapy in treating BMS, and to distinguish the demographic, diagnostic, and therapeutic variables that may predict significant relief of clinical symptoms.

Materials and Methods

Patients, Study Design, and Clinical Setting

A retrospective chart review of patients who underwent clinical evaluation and management for BMS in the Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA, between January 2011 and December 2016, was carried out. Approval from the department research committee and Partners Institutional Review Board (IRB) was obtained (IRB# 2017P000641). This study was exempted from obtaining informed consent from the patients by the IRB.

All of the patients underwent a comprehensive clinical assessment comprised of a detailed history, thorough examination, and, if indicated, laboratory or imaging evaluation. ICHD-3 criteria for BMS were used to establish the diagnosis of primary BMS (ie, a positive history for presence of intraoral burning pain or dysesthetic sensation recurring daily for at least 2 hours per day over more than 3 months, without clinical evidence of any associated local or systemic pathology). Similarly, a diagnosis of secondary BMS was considered if there was a positive history for presence of intraoral burning pain or dysesthetic sensation that was recurring daily for at least 2 hours per day over a period of at least 3 months, with evidence that these symptoms had developed in temporal relation to the development of a localized or systemic condition. Localized oral pathologic conditions, such as oral lichen planus and oral candidiasis, were diagnosed by a dentist, and systemic conditions, such as Sjögren syndrome and human immunodeficiency virus infection, were diagnosed by a respective medical specialist.

All patients who met the criteria for primary or secondary BMS were included in the investigation. Patients with nonburning/extraoral pain or dysesthesia symptoms were excluded.

Clinical Information

The investigators de-identified the data of all patients. Medical charts were reviewed to extract information regarding: patient demographics; body mass index (BMI); pain characteristics such as location, frequency, pattern, duration, chronicity, and severity; presence of subjective dryness; taste alterations; alternate perception (ie, subjective feeling of intraoral paresthesia); prior or concurrent therapies (concurrent use of opioids or neuropathic and psychotropic medications); and history of chronic head, neck, and body pain disorders. Similarly, information on the presence of systemic conditions, including gastrointestinal disease, heart disease, hyperlipidemia, thyroid disorder, sleep disorder, osteoarthritis, diabetes mellitus, hypertension, respiratory disorder, depression disorder, anxiety disorder, and psychiatric disease, was noted.

Protocol for Therapeutic Modalities

The patients had received a variety of therapeutic pharmacologic modalities for the management of symptoms associated with BMS. These primarily consisted of clonazepam, tricyclic antidepressants, gabapentinoids, corticosteroids, capsaicin, and alpha-lipoic acid (ALA), either alone or as a combination modality. Clonazepam was prescribed as an oral rinse, topical dissolving tablet, lozenge, or systemic tablet formulation. Tricyclic antidepressants, gabapentinoids, and ALA were prescribed in capsule or tablet form. Capsaicin was prescribed in a gel formulation, and corticosteroids were prescribed in an oral solution preparation.

Topical clonazepam therapy entailed patients to swish for 3 minutes with the mouthrinse and then expectorate the solution. If lozenges or dissolving tablets were used, patients were instructed to suck on the medicine for 3 minutes and then expectorate the tablet and saliva. Systemic clonazepam therapy consisted of swallowing the oral rinse or the tablet without swishing or sucking on it. In instances where combination therapy was indicated, patients were advised to swallow the liquid solution or tablet following its topical utilization. Capsaicin was used in a gel formulation for topical therapy and was required to be applied and rubbed over the area of burning pain or dysesthesia. Topical corticosteroid therapy included use of dexamethasone elixir as a mouthwash that was instructed to be swished for 3 minutes, then expectorated. Patients were asked to not eat or drink anything for at least 30 minutes following application of any topical intervention.

Response to Therapeutic Modalities

At each clinical visit, patients recorded their pain score based on an 11-point Likert-type numeric verbal pain rating scale (VPS), on which 0 indicated no pain and 10 indicated worst-ever pain experience. Patients reporting at least 75% improvement in pain score were considered to have had significant relief in symptoms. Patients failing to report for a follow-up visit after initiation of a therapeutic modality were considered to have had nonsignificant relief in symptoms for the purpose of the analysis. Furthermore, records from visits to other medical providers were correlated to reduce the risk of recall and reporting bias.

Statistical Analysis

The statistical analysis was performed using SPSS version 22.0 software (IBM). Chi-square and *t* tests were used for analyses between independent and dependent variables, respectively; however, if assumptions for chi-square test were not met, Fisher exact test was used. Statistical associations with a *P* value of < .15 were used to run a forward stepwise logistic regression analysis for the patients reporting significant relief in symptoms. A *P* value of < .05 was considered statistically significant.

Results

A total of 151 charts were identified and reviewed, and 112 patients met the criteria for the present investigation. The 39 patients were excluded for nonburning pain or dysesthetic sensation (n = 36) and extraoral symptoms of burning pain (n = 3).

Of the 112 patients, 81 (72.3%) were women. The mean age of the sample was 60.49 ± 11.58 years, and mean BMI was 24.14 ± 4.09. Burning pain was reported by 82.1% of the patients. Likewise, 17.9% reported burning dysesthesia. The mean intensity of pain in the patient population at the time of initial presentation was 6.51 ± 2.1 on the numeric VPS. The pain score was reported to be 6.16 ± 1.99 in patients with primary BMS and 7.21 ± 2.20 in those with secondary BMS. Approximately 64% of patients with BMS reported spontaneous onset of symptoms. The location of pain was bilateral in 90.2% of the patients, and the tip of the tongue was the most common site of complaint (66.1%), followed by the anterior dorsal two-thirds of the tongue (55.4%), anterior hard palate (36%), maxillary and mandibular labial mucosa (38.7%), ventrolateral margins of the tongue (33.9%), and buccal mucosa (14.4%). Moreover, the frequency of pain was constant in 70.6% of the patients, and 44.3% had a daily pattern associated with the severity of the symptomatology. The majority of these patients (94.1%) had worsening of symptoms with progression of the day, while the rest reported the opposite. In addition to the symptoms of pain or dysesthesia, 71.9% of patients reported xerostomia, 57.6% reported dysgeusia, and 22.7% reported altered perception. At least one sensory symptom was reported by 79.4% of the patients with primary BMS, compared to 55.9% of patients with secondary BMS. This difference was statistically significant *(P* < .05). These results are summarized in Table 1.

Information regarding concurrent use of opioids (9.2%), neuropathic medications (42.2%), and psychotropic agents (40.4%) among participants was recorded. Among neuropathic medications, benzodiazepines were the most common group of medications used by the patients. Chronic non–BMS-related orofacial pain was reported by a quarter of the patients, nearly one-sixth had chronic cervical pain, and almost one-third had chronic pain in other parts of the body. Patients with secondary BMS had a higher percentage of systemic medical conditions than patients with primary BMS. The most common medical disorders among patients with primary and secondary BMS were gastrointestinal disease (42.9% and 54.3%, respectively), hypertension (36.4% and 45.7%), hyperlipidemia (33.8% and 42.9%), and heart disease (10.4% and 37.1%). The difference in the prevalence of heart disease between the two populations was statistically significant. Similarly, 56.3% of the patients had at least one psychiatric condition, with anxiety disorder being the most prevalent (Table 2). The mean follow-up period for patients with primary BMS was 8.69 ± 8.93 months, and for secondary BMS was 26.33 ± 33.49 months.

After pharmacotherapeutic intervention, 46.8% of the patients with primary BMS felt significant relief in symptoms, compared to 31.4% with secondary BMS.

Table 1 Summary of Demographic and Diagnostic Characteristics of Patients with Primary and Secondary BMS

Demographic/clinical characteristics	Primary BMS (n = 77)	Secondary BMS (n = 35)	Total	*P*
Gender				
Female	56 (72.7)	25 (71.4)	81 (72.3)	.89
Male	21 (27.3)	10 (28.6)	31 (27.7)	
Age (y), mean + SD	59.99 ± 10.9	61.66 ± 13.14	60.49 ± 11.58	.50
BMI, mean ± SD	24.71 ± 4.01	23.12 ± 4.12	24.14 ± 4.09	.12
Burning symptoms				
Pain	65 (84.4)	27 (77.1)	92 (82.1)	.35
Dysesthesia	12 (15.6)	8 (22.9)	20 (17.9)	
Pain intensity, mean ± SD VPS	6.16 ± 1.99	7.21 ± 2.2	6.51 ± 2.1	.08
Onset				
Spontaneous	54 (70.1)	18 (51.4)	72 (64.3)	.06
Laterality of pain				
Bilateral	68 (88.3)	33 (94.3)	101 (90.2)	.50
Area of pain				
Tip of tongue	54 (70.1)	20 (57.1)	74 (66.1)	.18
Anterior dorsal two-thirds	42 (54.5)	20 (57.1)	62 (55.4)	.80
Anterior hard palate	27 (35.5)	13 (37.1)	40 (36)	.87
Maxillary and mandibular labial mucosa	31 (40.8)	12 (34.3)	43 (38.7)	.51
Ventrolateral margins of tongue	27 (35.1)	11 (31.4)	38 (33.9)	.71
Buccal mucosa	12 (15.8)	4 (11.4)	16 (14.4)	.77
Other areas	11 (14.5)	5 (14.3)	13 (11.7)	.99
Frequency of pain				
Constant	51 (69.9)	21 (72.4)	72 (70.6)	.80
Pattern of symptoms				
Present	34 (47.9)	9 (39.1)	51 (44.3)	.46
Chronicity				
< 1 y	31 (43.7)	13 (39.4)	44 (42.3)	.68
≥ 1 y	40 (56.3)	20 (60.6)	60 (57.7)	
Relief of symptoms in morning				
Present	34 (56.7)	7 (35)	41 (51.2)	.09
Absent	26 (43.3)	13 (65)	39 (48.8)	
Xerostomia	46 (69.7)	23 (76.7)	69 (71.9)	.48
Dysgeusia	41 (61.2)	16 (50.0)	57 (57.6)	.29
Alternate perceptions	18 (23.7)	7 (20.6)	25 (22.7)	.72
Sensory changes	54 (79.4)	19 (55.9)	73 (71.6)	.013

All data are reported as n (%) unless otherwise indicated.

Table 2 Summary of Medical History of Patients with Primary and Secondary BMS

Medical history	Primary BMS (n = 77)	Secondary BMS (n = 35)	Overall	*P*
Concurrent use of opioids	5 (6.6)	5 (15.2)	10 (9.2)	.15
Concurrent use of neuropathic medications	34 (44.7)	12 (36.4)	46 (42.2)	.42
Concurrent use of psychotropic medications	28 (36.8)	16 (48.5)	44 (40.4)	.26
Chronic headache disorder	17 (22.1)	11 (33.3)	28 (25.5)	.21
Chronic neck pain disorder	10 (13.0)	6 (18.2)	16 (14.5)	.48
Chronic pain disorder (other sites)	21 (27.3)	15 (45.5)	36 (32.7)	.06
Gastrointestinal disease	33 (42.9)	19 (54.3)	52 (46.6)	.26
Heart disease	8 (10.4)	13 (37.1)	21 (18.8)	.001
Hyperlipidemia	26 (33.8)	15 (42.9)	41 (36.6)	.36
Thyroid disease	12 (15.6)	5 (14.3)	17 (15.2)	.86
Sleep disorder	23 (29.9)	6 (17.1)	29 (25.9)	.15
Osteoarthritis	11 (14.3)	6 (17.1)	17 (15.2)	.70
Diabetes mellitus	6 (7.8)	4 (11.4)	10 (8.9)	.50
Hypertension	28 (36.4)	16 (45.7)	44 (39.3)	.35
Respiratory disorder	8 (10.4)	8 (22.9)	16 (14.3)	.08
Depression disorder	28 (36.4)	11 (32.4)	39 (35.1)	.68
Anxiety disorder	31 (40.3)	14 (41.2)	45 (40.5)	.93
Psychiatric illness	42 (54.5)	21 (60)	63 (56.3)	.59

All data are reported as n (%).

Among single pharmacologic interventions, topical clonazepam therapy (41.8%) and systemic clonazepam (38.8%) provided the most efficacious and significant relief in symptoms. However, overall combination therapy had the highest efficacy (43.1%).

There was no statistical association between dosage and therapeutic response for a given pharmacologic intervention. Similarly, there was no observable pattern regarding the choice of pharmacologic agent used to initiate the therapy. The dosage and frequency of topical clonazepam therapy varied from 0.5 mg/5 mL to 2.5 mg/5 mL up to three times a day. Similarly, for systemic clonazepam therapy, the dosage ranged from 0.25 mg to 1 mg up to three times a day. Gabapentin dosage ranged between 100 and 3,600 mg per day, in up to three divided doses. Pregabalin was prescribed up to 450 mg per day in three doses. Dexamethasone rinse was used in an elixir formulation at a concentration of 0.5 mg/5 mL three times a day. Amitriptyline and nortriptyline dosages ranged between 10 and 30 mg per day as a single dose at night. The dosage of ALA varied between 400 and 1,200 mg per day in two or three divided doses. Topical capsaicin gel was prescribed at a concentration of 0.025% and used by the patients three times a day. The most commonly used combinations in combination therapy were topical and systemic clonazepam therapy; topical clonazepam therapy and gabapentin; topical clonazepam therapy and ALA; systemic clonazepam therapy and ALA; and gabapentin and ALA.

The demographic, diagnostic, and therapeutic characteristics of patients with primary BMS were analyzed. Among the 77 patients with primary BMS, 56 (72.7%) were women. The mean age of this population was 59.99 ± 10.9 years, and the mean BMI was 24.71 ± 4.01. The majority of the patients had burning pain symptoms (84.4%). The intensity of pain at the time of first presentation to the clinic was statistically less in the patients who experienced significant relief in symptoms ($P < .05$). Similarly, there was a significant association between chronicity of symptoms and outcome following therapeutic intervention, in that the patients experiencing significant relief in symptoms were likely to be suffering from primary BMS for less than 1 year of chronicity ($P < .05$). No statistically significant association was established between therapeutic outcome and onset of symptoms, laterality of pain, location of pain, frequency of pain, pain pattern, or associated sensory dysfunction (Table 3). Concurrent use of neuropathic medications was significantly less in patients experiencing significant relief of symptoms from primary BMS. In addition, associations were found between therapeutic outcome and prevalence of hyperlipidemia and depression disorder (Table 4).

Among 35 patients with secondary BMS, 25 (71.4%) were women. The mean age of this group was 61.66 ± 13.1 years, and mean BMI was 23.12 ± 4.12. No significant associations were observed between therapeutic outcome and various demographic, diagnostic, and therapeutic characteristics, except for prevalence of anxiety disorders, which was reported to be higher in patients reporting significant relief in symptoms. These results are summarized in Tables 5 and 6. The most common cause of secondary BMS was hyposalivation or dry mouth associated with use of medication or systemic disorder (such as Sjögren syndrome) or postradiation therapy (48.5%). Other notable causes were lichenoid lesions associated with lichen planus, leukoplakia, autoimmune mucosal conditions, trauma, and infection-associated lesions.

Forward conditional logistic regression analysis was performed to determine the predictor variables for significant relief in symptoms among patients with primary and secondary BMS. Based on the logistic analysis, concurrent use of neuropathic medications was found to have a negative predictive effect in patients with primary BMS. Among patients with secondary BMS, presence of anxiety disorder was found to have a positive predictive effect (Table 7).

Discussion

The purpose of this investigation was to determine clinical characteristics, effectiveness of pharmacotherapeutic intervention, and predictors of significant response to pharmacotherapeutic modalities among patients with primary and secondary BMS.

In the present investigation, the male-to-female ratio of the patients with BMS was nearly 1:4. Furthermore, the mean age at the time of onset of symptoms was approximately 60 years. The majority of patients reported symptoms of constant burning pain that were spread bilaterally over the tip and anterior dorsal two-thirds of the tongue, maxillary and mandibular labial mucosa, and anterior hard palate. These epidemiologic and clinical charactertics are similar to those previously reported by other investigations.[2,6] More than two-thirds of the patients reported at least one symptom of associated sensory discrepancy. The prevalence of these symptoms was significantly higher in patients with primary BMS than in those with secondary BMS. The pathophysiology of primary BMS has been associated with peripheral and central neuropathies.[2,7] There have been reports indicating neurodegeneration of the chorda tympani nerve and alterations in chorda tympani and lingual nerve function,[10,11] altered sensory thresholds,[12] reduction in inhibition of the nigrostriatal dopaminergic system,[13,14] and variation in brain activity patterns.[15]

Table 3 Demographic and Diagnostic Characteristics and Therapeutic Outcomes of Patients with Primary BMS

Demographic/clinical characteristics	Significant relief (n = 36)	Nonsignificant relief (n = 41)	Total	*P*
Gender				
Female	26 (72.2)	30 (73.2)	56 (72.7)	.93
Male	10 (27.8)	11 (26.8)	21 (27.3)	
Age (y), mean ± SD	59.57 ± 11.65	60.36 ± 10.33	59.99 ± 10.9	.76
BMI, mean ± SD	23.93 ± 3.56	25.31 ± 4.30	24.71 ± 4.01	.26
Burning symptom				
Pain	30 (83.3)	35 (85.4)	65 (84.4)	.8
Dysesthesia	6 (16.7)	60 (14.6)	12 (15.6)	
Pain intensity, mean ± SD VPS	5.53 ± 1.80	6.79 ± 2.02	6.16 ± 1.99	.049
Onset				
Spontaneous	23 (69.7)	28 (68.3)	51 (68.9)	.90
Laterality of pain				
Bilateral	31 (86.1)	37 (90.2)	68 (88.3)	.73
Area of pain				
Tip of tongue	22 (61.1)	32 (78)	54 (70.1)	.11
Anterior dorsal two-thirds	16 (44.4)	26 (63.4)	42 (54.5)	.10
Anterior hard palate	11 (31.4)	16 (39)	27 (35.5)	.49
Maxillary and mandibular labial mucosa	13 (37.1)	18 (43.9)	31 (40.8)	.64
Ventrolateral margins of tongue	14 (38.9)	13 (31.7)	27 (35.1)	.63
Buccal mucosa	5 (14.3)	7 (17.1)	12 (15.8)	.74
Other areas	4 (11.4)	7 (17.1)	11 (14.5)	.53
Frequency of pain				
Constant	23 (69.7)	28 (70)	51 (69.9)	.98
Pattern of symptoms				
Present	14 (41.2)	20 (54.1)	34 (47.9)	.28
Chronicity				
< 1 y	20 (58.5)	11 (29.7)	31 (43.7)	.014
≥ 1 y	14 (41.2)	26 (70.3)	40 (56.3)	
Relief of symptoms in morning				
Present	12 (44.4)	22 (66.7)	34 (56.7)	.08
Xerostomia	22 (62.9)	24 (77.4)	46 (69.7)	.20
Dysgeusia	18 (56.2)	23 (65.7)	41 (61.2)	.43
Alternate perception	11 (30.6)	7 (17.5)	18 (23.7)	.18
Sensory changes	27 (77.1)	27 (81.8)	54 (79.4)	.63

All data are reported as n (%) unless otherwise indicated.

Table 4 Medical History and Therapeutic Outcomes of Patients with Primary BMS

Medical history	Significant relief (n = 36)	Nonsignificant relief (n = 41)	Total	*P*
Concurrent use of opioids	2 (5.7)	3 (7.3)	5 (6.6)	1.00
Concurrent use of neuropathic medications	9 (25.7)	25 (61)	34 (44.7)	.002
Concurrent use of psychotropic medications	13 (37.1)	15 (36.6)	28 (36.8)	.96
Chronic headache disorder	7 (19.4)	10 (24.4)	17 (22.1)	.78
Chronic neck pain disorder	6 (16.7)	4 (9.8)	10 (13.0)	.5
Chronic pain disorder (other sites)	10 (27.8)	11 (26.8)	21 (27.3)	.93
Gastrointestinal disease	12 (33.3)	21 (51.2)	33 (42.9)	.11
Heart disease	5 (13.9)	3 (7.3)	8 (10.4)	.46
Hyperlipidemia	18 (50)	8 (19.5)	26 (33.8)	.005
Thyroid disease	5 (13.9)	7 (17.1)	12 (15.6)	.7
Sleep disorder	8 (22.2)	15 (36.6)	23 (29.9)	.17
Osteoarthritis	8 (22.2)	3 (7.3)	11 (14.3)	.10
Diabetes mellitus	4 (11.1)	2 (4.9)	6 (7.8)	.41
Hypertension	12 (33.3)	16 (39)	28 (36.4)	.64
Respiratory disorder	3 (8.3)	5 (12.2)	8 (10.4)	.72
Depression disorder	8 (22.2)	20 (48.8)	28 (36.4)	.016
Anxiety disorder	15 (41.7)	16 (39)	31 (40.3)	.81
Psychiatric illness	19 (52.8)	23 (56.1)	42 (54.5)	.77

All data are reported as n (%).

Table 5 Demographic and Diagnostic Characteristics and Therapeutic Outcomes of Patients with Secondary BMS

Demographic/clinical characteristics	Significant relief (n = 11)	Nonsignificant relief (n = 24)	Total	*P*
Gender				
Female	8 (72.7)	17 (70.8)	25 (71.4)	.70
Male	3 (27.3)	7 (29.2)	10 (28.6)	
Age (y), mean ± SD	61.1 ± 8.69	61.9 ± 14.91	61.66 ± 13.1	.88
BMI, mean ± SD	23.25 ± 5.13	23.03 ± 3.49	23.12 ± 4.12	.90
Burning symptom				.23
Pain	7 (63.6)	20 (83.3)	27 (77.1)	
Dysesthesia	4 (36.4)	4 (16.7)	8 (22.9)	
Pain intensity, mean ± SD VPS	8.00 ± 1.77	6.64 ± 2.38	7.21 ± 2.2	.19
Onset	4 (36.4)	14 (58.3)	18 (51.4)	.29
Spontaneous				
Laterality of pain	11 (100)	11 (91.7)	33 (94.3)	1.00
Bilateral				
Area of pain				
Tip of tongue	6 (54.5)	14 (58.3)	20 (57.1)	.83
Anterior dorsal two-thirds	5 (45.5)	7 (29.2)	15 (57.1)	.34
Anterior hard palate	4 (36.4)	9 (37.5)	13 (37.1)	1.00
Maxillary and mandibular labial mucosa	5 (45.5)	7 (29.2)	12 (34.3)	.35
Ventrolateral margins of tongue	2 (18.2)	9 (37.5)	11 (31.4)	.44
Buccal mucosa	3 (27.3)	1 (4.2)	4 (11.4)	.08
Other areas	3 (27.3)	7 (29.2)	10 (28.6)	1.00
Frequency of pain	7 (87.5)	14 (66.7)	21 (72.4)	.38
Constant				
Pattern of symptoms	2 (28.6)	7 (43.8)	9 (39.1)	.66
Present				
Chronicity				
< 1 y	6 (54.5)	7 (31.8)	13 (39.4)	.21
≥ 1 y	5 (45.5)	15 (68.2)	20 (60.6)	
Relief of symptoms in morning				
Present	3 (42.9)	4 (30.8)	7 (35.0)	.65
Xerostomia	7 (77.8)	16 (76.2)	23 (76.7)	1.00
Dysgeusia	6 (60)	10 (45.5)	16 (50)	.70
Alternate perception	2 (20)	5 (20.3)	7 (20.6)	1.00
Sensory changes	6 (60)	13 (54.2)	19 (55.9)	1.00

All data are reported as n (%) unless otherwise indicated.

Table 6 Medical History and Therapeutic Outcomes of Patients with Secondary BMS

Medical history	Significant relief (n = 11)	Nonsignificant relief (n = 24)	Total	*P*
Concurrent use of opioids	1 (9.1)	4 (18.2)	5 (15.2)	.64
Concurrent use of neuropathic medications	5 (45.5)	7 (31.8)	12 (36.4)	.44
Concurrent use of psychotropic medications	5 (45.5)	11 (50)	16 (48.5)	.81
Chronic headache disorder	3 (30)	8 (34.8)	11 (33.3)	1.00
Chronic neck pain disorder	–	6 (26.1)	6 (18.2)	.15
Chronic pain disorder (other sites)	5 (50)	10 (43.5)	15 (45.5)	.73
Gastrointestinal disease	8 (72.7)	11 (45.8)	19 (54.3)	.17
Heart disease	4 (36.4)	9 (37.5)	13 (37.1)	1.00
Hyperlipidemia	7 (63.6)	8 (33.3)	15 (42.9)	.14
Thyroid disease	1 (9.1)	4 (16.7)	5 (14.3)	1.00
Sleep disorder	3 (27.3)	3 (12.5)	6 (17.1)	.35
Osteoarthritis	4 (36.4)	2 (8.3)	6 (17.1)	.06
Diabetes mellitus	1 (9.1)	3 (12.5)	4 (11.4)	1.00
Hypertension	6 (54.5)	10 (41.7)	16 (45.7)	.48
Respiratory disorder	3 (27.3)	5 (20.8)	8 (22.9)	.69
Depression disorder	4 (40)	7 (29.2)	11 (32.4)	.69
Anxiety disorder	8 (80)	6 (25)	14 (41.2)	.006
Psychiatric illness	9 (81.8)	12 (50)	21 (60)	.14

All data are reported as n (%). Variation in percentages is due to missing information.

Table 7 Results of Logistic Regression Analysis to Determine Predictor Variables for Significant Clinical Outcome Among Patients with Primary and Secondary BMS

						95% confidence limits 95%	
Variable	Individual characteristic	B	SE	Sig (*P*)	Exp (B)	Lower	Upper
Primary BMS	Concurrent use of neuropathic medication	−0.161	0.775	.04	0.20	0.04	0.91
Secondary BMS	Anxiety disorder	2.485	0.92	.007	12	1.98	72.89

B = regression coefficient; SE = standard error; Exp(B) = exponentiation of coefficient (odds ratio).

The varying site of neuropathic changes may explain the inconsistent pattern of presentation observed in the present investigation.

Following pharmacologic intervention, nearly half of the patients with primary BMS and about one-third of the patients with secondary BMS reported significant relief in symptoms at the final follow-up visit. On the contrary, in previous investigations, a successful outcome has been reported in up to 70% of patients.[16–18] This may be due to disparity in the operational definition for successful outcome. Multiple guidelines have been used, such as statistical relief in symptoms or pain associated with BMS, clinical relief in pain or symptom score by 2 or 3 points on an 11-point Likert-type scale, and subjective feeling of significant improvement in pain or symptoms. In the present investigation, a stringent criterion of at least 75% reduction in pain score was used for defining a successful outcome. Furthermore, patients who were lost to follow-up were considered to have had poor, nonsignificant relief in symptoms. The majority of investigations have been performed in patients with primary BMS, minimal or no underlying chronic medical conditions, and less chronicity of pain symptoms.[16,18,19] In the present investigation, more than half of the patients had symptoms present for more than 1 year, and nearly one-fifth had symptoms for at least 5 years. Furthermore, at least a quarter of the patients had a concurrent chronic pain disorder, gastrointestinal disorder, hypertension, or hyperlipidemia, and more than half had at least one psychiatric disorder. Presence of pain for a long period of time and presence of systemic medical disorders are associated with poor outcome of pharmacologic therapy, as indicated by these findings.

The relatively low success rate in patients with secondary BMS may be associated with the underlying pathophysiology of this disorder. In nearly half of the patients with secondary BMS, the speculated cause was hyposalivation secondary to use of systemic medications or underlying systemic disorder. In such cases, management of secondary BMS generally consists of treatment of the underlying condition. However, this may not be an easy task to accomplish due to the severity/extent of the underlying pathology or the irreplaceability of the responsible pharmacologic agent. The pharmacologic management of secondary BMS is similar to that of primary BMS. In the present investigation, no differences were observed between the effectiveness of individual pharmacologic agents for the management of primary and secondary BMS.

In the present study, topical or systemic use of clonazepam was the most efficacious therapeutic modality among the individual pharmacologic agents. Clonazepam is an antiepileptic medication that has an agonistic effect on peripheral and central gamma-aminobutyric acid (GABA) receptors. The analgesic effects of systemic clonazepam in BMS are likely to be associated with GABA receptor–associated serotonergic descending pain inhibition and suppression of spontaneous central neuronal hyperactivity.[20] On the contrary, it has been argued that clonazepam may exert its effect by acting as an anxiolytic.[19] Prior investigations have shown clonazepam to have a local therapeutic effect without any systemic absorption,[21] and this is effect is postulated to take place by disrupting local neural pain pathways. The effectiveness of topical and systemic clonazepam in the present investigation was further improved when used in combination together or with ALA or gabapentin. This is corroborated by previously reported findings.[18] Using multiple agents or routes of administration (in the case of clonazepam), different neuronal pain and sensory pathways can be influenced. Gabapentin has a central mechanism of action; however, unlike clonazepam, it binds to alpha 2-delta (α-2-δ) subunits of voltage-gated calcium ion channels and inhibits the release of excitatory neurotransmitters, such as substance P and calcitonin gene-related peptide, from the primary afferent nerve fibers in the pain pathway.[22] Similarly, ALA has been proposed to be an antioxidant and a neuroprotective agent.[23]

In previous investigations, authors have found associations between therapeutic response and age at time of onset, chronicity of symptoms,[16] and initial pain intensity.[19] In the present investigation, age was not found to be associated with therapeutic efficacy. Nonetheless, a significant association was found between therapeutic response among patients with primary BMS and chronicity of symptoms, severity of pain at the time of presentation, presence of hyperlipidemia, absence of depression disorder, and concurrent use of neuropathic medications. Hyperlipidemia

has been suggested to be a risk factor for peripheral neuropathy and small-fiber neuropathy.[24,25] The exact mechanism is unknown; however, it appears that intracellular oxidative stress, inflammatory lesions, ischemia, and dysregulation of local lipid metabolism may play roles.[25] In the present cohort, patients with primary BMS appeared to have significant relief of symptoms if they had hyperlipidemia. This may be because hypercholesterolemia-associated neuropathy is receptive to the pharmacotherapeutic modalities used in the present investigation. Nevertheless, the current study design is limited and cannot determine the exact nature of this relationship. Similarly, it is out of the scope of this study to determine whether the included patients had BMS secondary to hyperlipidemia. However, this association does necessitate further research.

Using multivariable analysis, the concurrent use of neuropathic medications in patients with primary BMS was found to be predictive of a negative outcome following pharmacotherapy. The most common concurrent neuropathic medications were benzodiazepines, which were being used as a sleep aid. Chronic use of benzodiazepines and anticonvulsants has shown to result in the development of tolerance to benzodiazepines and other neuropathic medications due to downregulation of benzodiazepine receptor binding and GABA receptor function.[26–28] This may result in minimal or no clinical relief at a given therapeutic dosage; ie, poor therapeutic response. Similarly, among patients with secondary BMS, statistically significant associations were found between therapeutic response and presence of anxiety disorder. This may have been possible due to the analgesic properties of anxiolytics. Nonbenzodiazepine anxiolytics, such as serotonin selective reuptake inhibitors, nonselective reuptake inhibitors, and tricyclic antidepressants, can provide relief in chronic pain disorders, including BMS, as a stand-alone or adjunctive therapy.[2,3,29,30]

A possible limitation of the present investigation was that it is a retrospective analysis. Because of this, it was not possible to account for all clinical variables, such as concurrent frequency, chronicity, and type of therapy, interval(s) between visits, treatment adherence or compliance, or duration of interaction between patients and clinicians. Moreover, retrospective studies are considered to be low-quality trials in the hierarchy of evidence due to lack of randomization and blindness and absence of a control arm. Altogether, this may result in a false-positive association or magnification of the positive responses. However, in the present investigation, patients failing to report for a follow-up visit after initiation of a therapeutic intervention were considered to have no relief in symptoms and included in the statistical analysis. Similarly, records from other medical providers were correlated to reduce the risk of recall and reporting bias.

Conclusions

Patients with primary and secondary BMS have similar clinical demographic, diagnostic, and therapeutic characteristics, except for the prevalence of at least one symptom of sensory discrepancy (dysgeusia, xerostomia, paresthesia), which was significantly higher in patients with primary BMS. Pharmacologic intervention provided significant relief in symptoms in approximately half of the patients with primary BMS and in nearly one-third of the patients with secondary BMS. Of the pharmacologic interventions, the most efficacious modality was combination therapy consisting of topical or systemic clonazepam and gabapentin or ALA. Concurrent use of neuropathic medications was a negative predictor of therapeutic response among patients with primary BMS, and presence of anxiety disorder was a positive predictor of response among patients with secondary BMS.

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