ABSTRACT: Burning Mouth Syndrome (BMS) is a chronic pain syndrome that mainly affects middle-aged/old women with hormonal changes or psychological disorders. This condition is probably of multifactorial origin, often idiopathic, and its etiopathogenesis remains largely enigmatic. The present paper discusses several aspects of BMS, updates current knowledge, and provides guidelines for patient management. There is no consensus on the diagnosis and classification of BMS. The etiopathogenesis seems to be complex and in a large number of patients probably involves interactions among local, systemic, and/or psychogenic factors. In the remaining cases, new interesting associations have recently emerged between BMS and either peripheral nerve damage or dopaminergic system disorders, emphasizing the neuropathic background in BMS. Based on these recent data, we have introduced the concepts of “primary” (idiopathic) and “secondary” (resulting from identified precipitating factors) BMS, since this allows for a more systematic approach to patient management. The latter starts with a differential diagnosis based on the exclusion of both other orofacial chronic pain conditions and painful oral diseases exhibiting mucosal lesions. However, the occurrence of overlapping/overwhelming oral mucosal pathologies, such as infections, may cause difficulties in the diagnosis (“complicated BMS”). BMS treatment is still unsatisfactory, and there is no definitive cure. As a result, a multidisciplinary approach is required to bring the condition under better control. Importantly, BMS patients should be offered regular follow-up during the symptomatic periods and psychological support for alleviating the psychogenic component of the pain. More research is necessary to confirm the association between BMS and systemic disorders, as well as to investigate possible pathogenic mechanisms involving potential nerve damage. If this goal is to be achieved, a uniform definition of BMS and strict criteria for its classification are mandatory.

Key words. Burning mouth syndrome, stomatodynia, oral dysesthesia, neuropathic pain, pain management.

(I) Introduction

Burning Mouth Syndrome (BMS) is a chronic pain syndrome that mainly affects middle-aged/old women with hormonal changes or psychological disorders (Gorsky et al., 1987, 1991; Grushka, 1987). This condition is probably of multifactorial origin, often idiopathic, and its etiopathogenesis remains largely obscure. BMS represents a disorder with a very poor prognosis in terms of quality of life, and the patient’s lifestyle may worsen when psychological dysfunctions occur (Lamey and Lamb, 1988; Bergdahl et al., 1995b; Jerlang, 1997). As a result, BMS subjects continue to be high consumers of healthcare resources (Yontchev and Carlsson, 1992; Haberland et al., 1999).

Despite the fact that a voluminous amount has been published in this field, a universally accepted definition of this syndrome is still lacking. Various synonyms—such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral dysesthesia—have been interchangeably adopted to emphasize the quality and/or the location of pain in the oral cavity. In this syndrome, however, pain represents the main symptom within a variety of chronic oral complaints. Thus, BMS appears to be the most appropriate terminology (van der Waal, 1990), and only this term will be used in the present dissertation.

In the last decade, the International Association for the Study of Pain (IASP) has identified BMS as a "distinctive nosological entity" characterized by "unremitting oral burning or similar pain in the absence of detectable oral mucosa changes" (Merskey and Bogduk, 1994). The state of knowledge on BMS was presented at the 3rd World Workshop of Oral Medicine (Grushka and Epstein, 1998), and, very recently, different selective review papers focusing on specific BMS issues have been published (Fraikin et al., 1999; Marbach, 1999; Muzyka and De Rossi, 1999; Rhodus et al., 2000; Botha et al., 2001; Zakrzewska et al., 2001). Despite this large body of knowledge, some issues on BMS are still debated, and they present a challenge for both researchers and clinicians. What generates a major dilemma is that BMS is defined by symptoms that can potentially arise from numerous different local/systemic pathologies, some of which can be clearly identified and managed, and others that elude diagnosis and, thus, hamper management. Very recently, several authors (Grinspan et al., 1995; Zakrzewska, 1995; Bergdahl and Bergdahl, 1999; Sardella and Carrassi, 2001; Zakrzewska et al., 2001) have focused their efforts on establishing whether BMS should be considered as a distinct "syndrome", or if it mostly represents a "symptom disruption" for a large number of conditions arising from a wide array of pathologies (hormonal changes, nutritional deficiency, etc.). They have proposed the lack of local/systemic factors as inclu-
(II) Epidemiology

BMS is a disorder typically observed in middle-aged and elderly subjects with an age range from 38 to 78 years (Basker et al., 1978; Lamey and Lamb, 1988; Tammiala-Salonen et al., 1993; Bergdahl and Bergdahl, 1999). Occurrence below the age of 30 is rare (van der Waal, 1990), and the female-to-male ratio is 2.76 (Bergdahl and Bergdahl, 1999). Occurrence below the age of 30 may be one symptom within the clinical spectrum of BMS prevalence appears to be widely inaccurately estimated. At least, there was an over-diagnosis of BMS patients in the investigated populations. Previous studies, in fact, reported various and extremely large ranges of BMS prevalence, from 0.7% to 4.6% (Grushka and Sessle, 1991; Lipton et al., 1993; Hakeberg et al., 1997; Bergdahl and Bergdahl, 1999) or more (Tammiala-Salonen et al., 1993). This variability was likely due to the various criteria used for BMS diagnosis. For instance, when BMS was identified only on the basis of a prolonged burning sensation of the oral mucosa, a prevalence of 14.8% was estimated (Tammiala-Salonen et al., 1993). However, when diagnosis was arrived at by the use of more correct criteria (Bergdahl and Anneroth, 1993), BMS prevalence fell to 0.7%. At present, we have significant reasons to believe that this syndrome is more widespread than is estimated around the world. To appreciate the potential distribution of BMS in a population, one should note that a representative survey in subjects reporting orofacial pain in the United States estimated that about 1.3 million American adults were potentially affected with BMS (Lipton et al., 1993). Major demographic data, however, are limited to studies from Northern Europe (Tammiala-Salonen et al., 1993; Thorstensson and Hugoson, 1996; Hakeberg et al., 1997; Clifford et al., 1998; Bergdahl and Bergdahl, 1999), North America (Lipton et al., 1993; Riley et al., 1998; Haberland et al., 1999), South America (Grinspan et al., 1995), and South Africa (Maresky et al., 1993).

In conclusion, the use of an appropriate and consistent classification system based on a universally accepted definition of BMS and strict diagnostic criteria is mandatory, if the prevalence of this syndrome is to be accurately estimated.

(III) Clinical Features

The term "BMS" clinically describes a "variety of chronic oral symptoms (Table 1) that often increase in intensity at the end of each day, and that seldom interfere with sleep" (Grushka, 1987; Gorsky et al., 1991). Accordingly, two specific clinical features define this syndrome: (1) a "symptomatic triad", which includes unrelenting oral mucosal pain, dysgeusia, and xerostomia; and (2) "no signs" of lesion(s) or other detectable change(s) in the oral mucosa, even in the painful area(s). Full-blown syndrome is commonly observed in specific subgroups of patients, such as peri-/post-menopausal women (Basker et al., 1978; Zachariasen, 1993; Ben Aryeh et al., 1996). In the remaining cases, "oligosymptomatic" (pain and dysgeusia or pain and xerostomia) or "monosymptomatic" (pain only) forms of BMS are the most frequent presentations.

More recently, increasing attention has been given to the altered perception of sensory/chemosensory functions as well as to the changes in the psychological profile of many BMS patients. As a result, both disturbances should be included in the clinical spectrum of BMS.

(A) Pain

Oral pain represents the cardinal symptom of BMS. The type of pain experienced by BMS patients is a prolonged "burning" sensation of the oral mucosa, similar in intensity to, but different in quality from, that associated with toothache (Grushka et al., 1987a). However, scalding, tingling, or numb feelings of the oral mucosa have also been reported (van der Waal, 1990). The onset of oral pain is generally spontaneous and without any recognizable precipitating factors (Grushka, 1987; Tammiala-Salonen et al., 1993). However, some individuals with BMS relate the onset of pain to previous events such as dental procedures (particularly dental extractions) or other diseases (Grushka, 1987;}

| TABLE 1 |
| Main Symptoms in Patients with Burning Mouth Syndrome |

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Type(s) of Complaint(s)</th>
</tr>
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<tbody>
<tr>
<td>Oral mucosal pain*</td>
<td>Burning, Scalding, Tingling, Numb feeling</td>
</tr>
<tr>
<td>(main complaint)</td>
<td>Persistent taste</td>
</tr>
<tr>
<td>Dysgeusia*</td>
<td>Altered taste perception</td>
</tr>
<tr>
<td>Xerostomia*</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Others</td>
<td>Thirst, Headache, TMJ pain, Tendon pain</td>
</tr>
<tr>
<td></td>
<td>Tenderness/pain in masticatory, neck, shoulder, and suprahyoid muscles</td>
</tr>
</tbody>
</table>

* BMS symptomatic triad; TMJ = temporomandibular joint.
Tammiala-Salonen et al., 1993). Spontaneous remission of pain in BMS subjects has not been definitely demonstrated, although a few studies report relief without intervention (Mott et al., 1993).

To fulfill the diagnostic criteria for BMS (Bergdahl and Anneroth, 1993; Merskey and Bogduk, 1994), pain episodes must occur continuously for at least 4-6 months. They may last for 12 years or more (van der Waal, 1990), with an average duration of 3.4 years (Browning et al., 1987). Pain levels may vary from mild to severe (Grushka et al., 1987a; Bergdahl et al., 1995; Carlson et al., 2000; Pokupec-Gruden et al., 2000), but moderate pain is the most frequent presentation (Barker et al., 1978; Jerlang, 1997). The mean severity of BMS pain has been assessed at about 5-8 cm (or 50-80 mm) on a 10-cm (100-mm) Visual Analogue Scale (VAS) (Lamey and Lamb, 1988; Carlson et al., 2000), where “0 cm (or 0 mm)” represents “no pain” and “10 cm (or 100 mm)” corresponds to “the worst possible pain”.

The location of pain is not pathognomonic, and patients with BMS may complain of burning sensations in many different sites, including extra-oral mucosa such as in the anogenital region (van der Waal, 1990). Oral pain is invariably bilateral, and more than one oral site may be affected (van der Waal, 1990). The sites of predilection for pain are the tongue (especially the tip or anterior two-thirds) (Grushka, 1987), the lower lip, and the hard palate (Dutree-Meulenberg et al., 1992; Tammiala-Salonen and Söderling, 1993; Eli et al., 1994; Grinspan et al., 1995; Svensson and Kaaber, 1995). The upper lip and mandibular-alveolar region may also be affected, whereas the buccal mucosa and the floor of the mouth are rarely involved (van der Waal, 1990). As far as pain locations are concerned, some BMS subjects may experience other separate types of pain in association with oral burning. BMS patients, in fact, may suffer from headache and pain in temporomandibular joint areas (Bergdahl et al., 1994), as well as tenderness/pain in masticatory, neck, shoulder, and suprhyoid muscles (Svensson and Kaaber, 1995). However, evidence of cause/effect relationships between oral symptoms and head and neck pain has not yet been provided.

More than one clinical oral-pain pattern may occur in association with local, systemic, and/or psychogenic disorders (Lamey and Lamb, 1988). On the basis of these patterns, it has been suggested that BMS patients may be classified into three types (Lamey and Lewis, 1989). Type 1 BMS is characterized by a pain-free waking, with burning sensation developing in the late morning, gradually increasing in severity during the day, and reaching its peak intensity by evening (Grushka, 1987; Grinspan et al., 1995). This type is linked to systemic disorders such as nutritional deficiency, diabetes, etc. (Lamey and Lamb, 1988). Type 2 consists of continuous symptoms throughout the day, which, once started, often make falling asleep at night difficult for many individuals (Grushka, 1987; Eli et al., 1994). This subgroup of patients often reports mood changes, alterations in eating habits, and a decreased desire to socialize, which seem to be due to an altered sleep pattern (Grushka, 1987; Grinspan et al., 1995). Common clinical findings in these subjects include parotid gland hypofunction related to the use of anti-depressant drugs (Lamey et al., 2001). Finally, Type 3 BMS is characterized by intermittent symptoms with pain-free periods during the day. Frequently, these patients show anxiety and allergic reactions, particularly to food additives (Lamey et al., 1994). Overall, this sub-classification is not universally considered essential for BMS patient management. However, it suggests the value of investigating possible local/systemic factors which ultimately lead to the neuropathic disturbance(s).

(B) Dysgeusia

In almost 70% of BMS patients, persistent taste disorders (dysgeusia) are also evident (Main and Basker, 1983; Grushka, 1987; Lamely and Lamb, 1988; Eli et al., 1994; Svensson and Kaaber, 1995). The dysgeusia taste is most commonly bitter, metallic, or both (Ship et al., 1995). Different alterations in taste perception appear at either threshold or suprathreshold levels (Grushka, 1987; Grushka and Sessle, 1988). In fact, at threshold concentrations, subjects with BMS may perceive sweet solutions as significantly less intense, whereas the capacity to taste both sweet and sour may increase at suprathreshold concentrations. Disorders in the sense of taste may be a sign of a disturbance of sensory modalities at the level of small-diameter afferent fibers (Ship et al., 1995).

(C) Xerostomia

Approximately 46-67% of BMS patients complain of dry mouth (xerostomia) (Gorsky et al., 1987; Grushka, 1987; Bergdahl and Bergdahl, 1999). In these individuals, the feeling of oral mucosal dryness generally reflects a subjective sensation (Bergdahl and Bergdahl, 1999), rather than one objective symptom of salivary gland dysfunction. Subjective xerostomia in BMS patients appears to be related to psychological problems such as depression (Bergdahl et al., 1997). Strongest evidence, however, suggests that either feeling or evidence of dry mouth in these subjects is more likely due to idiosyncratic side-effects from an extensive abuse of anticholinergics, such as psychotropic drugs/medications (Glass, 1989; Bergdahl and Bergdahl, 2000; Culhane and Hodle, 2001) or antihistamines, and diuretics (Astor et al., 1999).

In a variable number of BMS patients complaining of xerostomia, clear alterations in saliva quantity and/or quality may be detected (Hugoson and Thorstensson, 1991; Bergdahl and Bergdahl, 1999). A reduction in salivary flow rate (hyposalivation) is a common finding (Grushka et al., 1987b; Lamely and Lamb, 1988; Maresky et al., 1993; Johansson et al., 1994), whereas changes in salivary composition may vary. Protein (Ben Aryeh et al., 1996), potassium, and phosphate concentrations (Glick et al., 1976), in fact, have been found to be significantly higher in unstimulated saliva of some BMS subjects, whereas other patients have shown a decrease in total salivary protein concentrations (Basker et al., 1978; Tammiala-Salonen and Söderling, 1993). These findings suggest variability in salivary gland function disorders in some BMS subjects. As a result, a variable number of these patients may suffer from lack of lubrication and become more prone to develop infections, because of reduced local host defenses (Jensen and Barkvoll, 1998; Chen and Samaranayake, 2000).

(D) Sensory anomalies

The frequent occurrence of dysgeusia in BMS subjects has led to the assessment of sensory and chemosensory functions in these patients. The perception of touch and temperature as well as the pain tolerance are normal in several intra-oral and facial areas of some BMS subjects (Lamey et al., 1996), the only exception being a significantly reduced perception of pain tolerance following heat stimuli at the tip of the tongue (Grushka et al., 1987b). More recently, however, sensory anomalies and significantly increased pain thresholds have been shown through the use of more sensitive methods, such as the argon laser stimulation (Svensson et al., 1993) and objective electrophysiological examination of the trigeminal-facial system (Jaaskelainen et al., 1997; Gao et al., 2000). These findings suggest a possible change...
in the peripheral and/or central nervous system in BMS patients (Svensson et al., 1993; Jaaskelainen et al., 1997).

(E) ORAL FINDINGS

For the diagnostic criteria for BMS to be fulfilled (Bergdahl and Anneroth, 1993; Merskey and Bugduk, 1994), the clinical evaluation of the oral mucosa must show complete absence of lesion(s) or other change(s), even in the painful areas (main finding).

BMS patients may show oral signs related to other associated pathological conditions, such as salivary gland dysfunction and/or masticatory system disorders (Bergdahl et al., 1994). Some patients may exhibit parafunctional habits such as lip and cheek biting, bruxism, tooth grinding and clenching, and, finally, tongue thrusting (Paterson et al., 1995), whereas others may reveal parafunctional activity of lip pressure, lip licking, lip sucking, and mouth breathing (Lamney and Lamb, 1994). A great many BMS subjects are denture-wearers (Gorsky et al., 1987; Grushka, 1987; Eli et al., 1994). Common findings in this subgroup of patients include decreased daily usage of dentures, reduced tongue space, incorrect placement of occlusal table, and increased vertical dimension (Svensson and Kaaber, 1995). In these individuals, a correlation between denture design errors and either local physical trauma or parafunctional habits has also been suggested (Basker et al., 1978; Main and Basker, 1983; Gorsky et al., 1987; Lamney and Lamb, 1988).

(F) PSYCHOLOGICAL PROFILE

A strong psychological component in BMS has been clearly identified in the last decade (Maresky et al., 1993; Bergdahl et al., 1994, 1995a,b; Eli et al., 1994; Lamey et al., 1994; Rojo et al., 1994; Bergdahl, 1995; Grinspan et al., 1995; Svensson and Kaaber, 1995; Van Houdenhove and Joostens, 1995; Humphris et al., 1996; Jerlang, 1997; Bergdahl and Bergdahl, 1999). It has been suggested that somatic complaints from unfavorable life experiences associated with chronic pain may influence both individual personality and mood changes (Jerlang, 1997). Many BMS patients, in fact, report one or more adverse life events in their clinical/social history, such as difficult infancy, inadequate parenting, poor adaptation to school and/or work, family or marital strife, and financial problems (Jerlang, 1997).

Alterations in personality traits in BMS patients are comparable with those observed in groups of subjects with other chronic pain pathologies (Grushka et al., 1987a), such as atypical facial pain, atypical odontalgia, and some forms of masticatory muscle and temporomandibular joint (TMJ) disorders (Woda and Pionchon, 1999). Mood changes consist of different grades of anxiety and depression (Demange et al., 1996; Trikkas et al., 1996; Jerlang, 1997; Bogetto et al., 1998; Carlson et al., 2000; Nicholson et al., 2000; Pokupe-Gruden et al., 2000), which often result in an extremely poor quality of life. Other disruptions include decreased aptitude to socialization, dizziness, psychasthenia, excessive concern about health, too many sad thoughts, and reluctance to take the initiative (Bergdahl et al., 1995b). All these psychological disorders seem to be independent of symptom intensity (Bergdahl and Bergdahl, 1999), but appear to be mostly related to the prolonged period of pain and a long history of unsuccessful treatment (Bergdahl et al., 1995b).

The hypochondria and other phobias that may be associated with BMS subjects represent a bad prognostic index. In particular, these patients may experience higher levels of pain, anxiety, and depression, especially when oral cancerophobia occurs (Grushka et al., 1987a; Lamney and Lamb, 1988; Jerlang, 1997). This concern may be particularly evident in those patients whose family history is positive for head and neck cancer.

(IV) ETIOPATHOGENESIS AND CLASSIFICATION

The etiopathogenesis of BMS is still unclear, and the issue has generated considerable controversy in the literature. The most debated aspect is whether BMS should be definitively consid-
tered either as a "distinctive nosological entity" or as a "symptom disruption" which has its origin in different pathologies (Grinspan et al., 1995; Zakrzewska, 1995; Bergdahl and Bergdahl, 1999; Woda and Pionchon, 1999; Sardella and Carrassi, 2001; Zakrzewska et al., 2001). The crux of the problem is that BMS may represent a complex of multiple diseases with overlapping symptoms. Consequently, dealing with a syndrome which is poorly defined by symptom(s) without regard to etiology actually causes more problems relative to diagnosis and management.

A recent trend in the field of pain has been to attempt an accurate definition of different poorly understood pain conditions and to standardize a classification scheme which could be of value for improving both clinical/laboratory research and patient management (Woda and Pionchon, 1999). In this context, it has been noted that specific chronic pain conditions, such as BMS, "atypical facial pain" and "atypical odontalgia", some "masticatory muscle disorders", and "temporomandibular joint disorders" show common clinical features (Table 2), such as similar pain patterns in the absence of clear etiologic evidence, and they are equally difficult to manage. As a result, it has been proposed that all these chronic pain disorders should be included in a unified concept of idiopathic orofacial pain (Woda and Pionchon, 1999, 2000).

According to this concept, the pain or burning of the oral mucosa caused by a known pathologic process should be considered only as one symptom of this pathology, whereas the pain that cannot be attributed to any local or systemic cause may be classified as "true BMS" (or "stomatodynia").

The inclusion of stomatodynia (BMS) in the above new classification is very cogent, but it would assume that little is known about the mechanisms capable of generating oral mucosal burning or pain-like symptoms. Thus, if all BMS patients are grouped into this proposed orofacial pain category, effective therapies for managing the local or systemic etiologic factors underlying this syndrome might be lost. The clinical features of BMS underscore that the same specific symptomatic pattern (pain, dysgeusia, and/or xerostomia) in the absence of mucosal lesions exists in BMS patients with identified etiologies as well as in idiopathic cases. Thus, the above proposed BMS classification is likely to result in the exclusion of many patients, since recent pivotal studies, utilizing sophisticated diagnostic techniques, have drawn attention to the neuropathic background in BMS (Jaaskelainen et al., 1997, 2001; Gao et al., 2000; Fosse et al., 2002).

From another point of view, clinical-epidemiological evidence reveals local/systemic factors in the majority of patients suffering from BMS symptoms (Bergdahl and Anneroth, 1993; Ship et al., 1995; Zakrzewska, 1995; Cibirka et al., 1997; Muzyka and De Rossi, 1999). Elimination/treatment of these factors has been shown to result in clinical improvement (Basker et al., 1978; Main and Basker, 1983; Lamey et al., 1986; Gorsky et al., 1991; Forabosco et al., 1992). In this context, therapeutic failures might be explained by an underlying irreversible neuropathic damage or disorder (Jaaskelainen et al., 2001) which can result in the persistence of BMS even after removal of precipitating factor(s). Therefore, it seems more appropriate to classify this larger subgroup of patients as affected with "secondary" BMS due to local/systemic factor(s). It then follows that a smaller subgroup of BMS patients remains in whom it is not possible to identify clear etiologic factor(s) and who are, therefore, particularly difficult to manage. Accordingly, BMS can be considered a "specific spectrum" of chronic oral symptoms (Table 1, Fig. 1c), which has its origin in the activation of neuropathic mechanism(s) (Fig. 1b) from either unknown factor(s) ("Primary BMS") or a wide array of pathologies ("Secondary BMS") (Fig. 1a). In both subgroups, the etiologic role of psychogenic factors is still unclear (Figs. 1a, 1d).

(A) LOCAL FACTORS

Many local conditions (infections, allergic reactions, galvanism,
geographic tongue, dental treatment, etc.) have been proposed in the etiopathogenesis of BMS (Bergdahl and Anneroth, 1993; Ship et al., 1995; Zakrzewska, 1995; Cibirka et al., 1997; Muzyka and De Rossi, 1999). As far as local factors are concerned, however, there is strong evidence only for local nerve trauma, oral parafunctional habits, and salivary gland dysfunction.

The frequent observation of taste changes and/or sensory/chemosensory dysfunctions in BMS patients has suggested that this syndrome could reflect a neuropathic disorder (Itkin, 1968; Grushka and Sessle, 1991). In particular, a peripheral nerve injury has been hypothesized (Grushka and Epstein, 1998), since the oral burning and the associated symptoms show a pattern similar to that observed in some inflammatory neural conditions (neuritis) or regional nerve trauma (neuroma). In addition, some patients with dysgeusia exhibit a loss of inhibitory interactions between the central projection areas of the chorda tympani or glossopharyngeal taste nerves following peripheral injury to either nerve (Levigne and Paterson, 1989; De Rossi, 1999). As far as local factors are concerned, however, there is strong evidence only for local nerve trauma, oral parafunctional habits, and salivary gland dysfunction.

Several studies report that parafunctional habits are observed in patients with BMS (Lamey and Lamb, 1988; Paterson et al., 1995). This parafunctional activity (tongue thrusting, bruxism, clenching) is significantly related to anxiety, and the activity most related to a high anxiety score seems to be tooth clenching (Paterson et al., 1995). Parafunctional activity appears to be influenced by various exogenous factors, such as stressful life events, alcohol abuse, some personality characteristics, and psychiatric or neurological pathologies (Levigne and Montplaisir, 1995). The parafunction (especially night bruxism) is probably the result of an interaction between the limbic system and the motor system, but the dopaminergic system might also be involved (Kydd and Daly, 1985; Okeson et al., 1994; Gomez et al., 1999). Since several studies have provided evidence for some neurological alterations in BMS, it is conceivable that the parafunctional habits might result in neuropathic changes that ultimately lead to BMS symptoms.

Salivary gland dysfunction might play a role in the onset of this syndrome. For instance, radiation therapy, some systemic diseases, and a variety of pharmacologic agents (Niedermeier et al., 2000), known to be capable of inducing a decrease in salivary flow rate (Glass, 1989; Astor et al., 1999), have reportedly been associated with increased incidence of BMS (Main and Basker, 1983; Jensen and Barkvoll, 1998). As previously mentioned, BMS subjects may exhibit salivary gland dysfunction (Lamey and Lamb, 1988; Maresky et al., 1993). It has been suggested that, in some cases, BMS results from either a reduction in salivary output (volume) (Grushka, 1987; Lamey and Lamb, 1988; Gorsky et al., 1991) or a decrease in the salivary components (glycoproteins) required for lubricating and protecting the oral mucosa (Grushka and Sessle, 1991; Jensen and Barkvoll, 1998).

(B) SYSTEMIC FACTORS

Several systemic factors may influence the prevalence, development, and severity of BMS symptoms (Bergdahl and Anneroth, 1993; Ship et al., 1995; Zakrzewska, 1995; Cibirka et al., 1997; Muzyka and De Rossi, 1999). The most significant systemic predisposing conditions for BMS are menopausal disorders, diabetes, and nutritional deficiencies.

There is a striking association between BMS and peri-/postmenopausal stages. Approximately 90% of women who attend healthcare clinics for their BMS symptoms are peri-/postmenopausal women (Main and Basker, 1983; Gorsky et al., 1987; Lamey and Lamb, 1988; Maresky et al., 1993; Zachariasen, 1993). They report pain onset ranging from 3 years before to 12 years after menopause (Grushka, 1987). Likewise, from 18% to 33% of menopausal women exhibit BMS symptoms (Wardrop et al., 1989; Ben Aryeh et al., 1996). In an attempt to understand a possible explanation for this association, investigators have assessed several features of menopause in BMS women. Within this group, the duration and the type (e.g., natural, surgical, etc.) of menopause as well as the treatment-related features do not appear to play a pivotal role in either BMS development or severity (Grushka, 1987). The most credited theory regards menopausal hormonal changes as a "master player" in BMS onset (Forabosco et al., 1992), although estrogen replacement therapy (ERT) does not relieve pain in many cases (Basker et al., 1978; Wardrop et al., 1989). The variable response to ERT treatment may be due to either the presence/absence of the expression of nuclear estrogen receptors in oral mucosa (Forabosco et al., 1992) or the possible activation of reversible/irreversible neuropathic mechanism(s).

The association between BMS and nutritional deficiencies has also been examined (Jacobs and Cavill, 1968; Brooke and Seganski, 1977; Lamey and Lamb, 1988). Occasionally, BMS patients exhibit low levels of blood serum vitamins B1, B2 (Hugoson and Thorstensson, 1991), and B6 (Dutree-Meulenberg et al., 1992), but a decrease in serum vitamin B12 (Vucicevic-Boras et al., 2001) is the most common finding in this subgroup of patients (Faccini, 1968; Main and Basker, 1983; Field et al., 1995). Vitamin B complex replacement therapy, however, often proves ineffective for pain relief (Hugoson and Thorstensson, 1991; Dutree-Meulenberg et al., 1992). Other minor findings of nutritional deficiency in BMS subjects may include low levels of blood serum folic acid and iron (Dutree-Meulenberg et al., 1992), suggesting a possible role of some type of anemia in the pathogenesis of this syndrome (Faccini, 1968; Jacobs and Cavill, 1968; Brooke and Seganski, 1977; Main and Basker, 1983; Schmitt et al., 1988; Lamey and Lewis, 1989).

The correlation between diabetes mellitus and BMS is still controversial. It has been suggested that type II diabetes mellitus plays a role in BMS development (Brody et al., 1971; Lamey and Lamb, 1988), and a link between the type of insulin used for the diabetes treatment and BMS has also been proposed (Basker et al., 1978). In contrast, other studies (Mott et al., 1993) report a lack of association between these two conditions (Lamey and Lewis, 1989; Lamey and Lamb, 1994). A possible explanation for this controversy may be that these diabetic patients were erroneously classified as BMS. In fact, at the time of the above studies, a lack of strict criteria for BMS diagnosis could have affected the selection of the patients. For instance, burning oral complaints in diabetic subjects, who are more prone to oral infections, are probably caused by oral candidiasis (Tourne and Fricton, 1992). However, the lack of data cannot exclude the possibility that the alteration of pain thresholds in this BMS subgroup is related to the neuropathy (Carrington et al., 2001), which is a common, though usually late, complication in type II diabetes mellitus.

(C) PSYCHOGENIC FACTORS

The long-held view, based on little or tenuous evidence, that BMS is due to psychogenic/psychosomatic factors (Gorsky et al., 1991; Maresky et al., 1993; Bergdahl et al., 1994, 1995a,b; Lamey et al., 1994; Rojo et al., 1994; Bergdahl, 1995; Grinspan et al., 1995; Van Houdenhove and Joostens, 1995; Humphris et al., 1996) has generally not been supported by scientific evidence, and the
Taste changes and/or sensory/chemosensory dysfunctions have been observed in many BMS patients, suggesting a neuropathic basis for this syndrome. It has been documented, in fact, that BMS patients may show: (1) abnormal perception of intensities in the pre-pain range and disturbances in the perception of non-nociceptive and nociceptive thermal stimuli (Svensson et al., 1993), (2) raised trigeminal nerve sensitivity and alterations in neuronal transmission (Gao et al., 2000), and (3) disturbances of the mucosal neurovascular microcirculatory system (Heckmann et al., 2001). These findings suggest peripheral alterations in the function of the sensory trigeminal nervous system in BMS. In further support of these preliminary results, it should be noted that electrophysiological examination reveals an abnormal blink reflex (BR) in BMS subjects (Jaaskelainen et al., 1997). This reflex is under dopaminergic inhibitory control through the basal ganglia connection with the facial motor nuclei (Evinger et al., 1993; Jaaskelainen et al., 2001), and an abnormal blink reflex is also a common finding in extra-pyramidal disorders such as Parkinson’s disease (Kimura, 1973) and facial dyskinesias (Berardelli et al., 1985). In these conditions, the abnormal reflex is thought to be due to a deficient dopaminergic striatal influence on the brainstem nuclei (Evinger et al., 1993). These considerations, together with the very recent evidence of a decreased dopaminergic inhibition in BMS subjects by Fluordopa-Pet scans (Jaaskelainen et al., 2001), lead one to suggest that BMS is a disorder of the nigrostriatal dopaminergic system, which would primarily affect the regulation of nociception of the trigeminal system, and thus cause a loss of sensory inhibition. A more recent study (Forssell et al., 2002) provides further support for the hypothesis that a neuropathic dysfunction is involved in BMS etiopathogenesis. These investigators used quantitative sensory testing (QST) in addition to the BR recordings in a large group of BMS patients. This study is very important, because it is the first attempt to evaluate the peripheral and central neural pathways of the trigeminal system in a large group of BMS patients. There was considerable heterogeneity in the findings, with some patients showing signs of large-fiber neuropathy, others of small-fiber neuropathy, and about one-fifth of the patients showing signs of increased excitability of the trigeminal system (Table 3). In most patients, however, a link between the electrophysiological signs of sensory disturbance and an anatomical alteration was not possible and, furthermore, was not strictly confined to the site of the pain. Overall, the authors inter-

Table 3: Neurological Alterations Detected via Electrophysiological Tests in Patients with Burning Mouth Syndrome

<table>
<thead>
<tr>
<th>Neurological Alteration</th>
<th>Electrophysiological Findings</th>
<th>Reported Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal neuropathy</td>
<td>Brainstem pathology or peripheral trigeminal neuropathy. In most of the cases, the BR abnormalities may represent sub-clinical changes in the trigeminal system</td>
<td>10/52 cases (19%)</td>
</tr>
<tr>
<td>Increased excitability of the trigeminal nervous system</td>
<td>Increased excitability of the BR in the form of a deficient habituation of the R2 component of the BR</td>
<td>11/52 cases (21%), with two patients also showing signs of warm allodynia</td>
</tr>
<tr>
<td>Pure thin-fiber dysfunction</td>
<td>Abnormality of one or more sensory thresholds, indicating thin-fiber dysfunction</td>
<td>35/46 cases (76%) with QST, with 33 patients also showing signs of hypoesthesia</td>
</tr>
</tbody>
</table>

* Reprinted with permission from Forssell et al. (2002).

pret their findings as suggestive of a generalized, possibly multi-
level abnormality in the processing of somatosensory informa-
tion in BMS, with electrophysiological evidence pointing to a
peripheral neurogenic mechanism in the majority of patients.

(V) Considerations of Diagnostic Criteria

Diagnosis of BMS may be complex for three main reasons: (1)
BMS is positively defined only by symptom(s) without regard
to signs or etiologies; (2) the symptomatic triad rarely occurs
simultaneously in one patient; and (3) overlapping or over-
whelming stomatitis may confuse the clinical presentation. As
a result, clinicians can arrive at a diagnosis of BMS by match-
ing specific details of the main complaint with clinical oral
findings that exclude oral mucosal changes, the only exception
being the presence of stomatitis, which requires proper and
prompt management. The search for identifiable causative fac-
tors represents a next stage in BMS patient management, and it
is essential for choice of the most appropriate therapy.

(A) Inclusion Diagnostic Criteria

The first step in an initial diagnosis of BMS consists of a careful
analysis of the symptom pattern experienced by each patient.
The identification of full-blown forms of BMS is not problemat-
ic, whereas the detection of either “oligosymptomatic” or “mono-
symptomatic” variants is more complex. In any case, specific
details of the main complaint (pain) represent the principal
“inclusion symptom criteria” for BMS. These details include
daily bilateral oral burning (or pain-like sensation) and pain that:
(1) is experienced deep within the oral mucosa,
(2) is unremitting for at least 4-6 months,
(3) is continuous throughout all or almost all the day,
(4) seldom interferes with sleep, and
(5) never worsens, but may be relieved, by eating and drinking.

Further support may come from the identification of the
other common complaints in BMS, which may be considered
additional “inclusion symptomatic criteria”, such as:
(6) the occurrence of other oral symptoms, such as dysgeusia
and/or xerostomia,
(7) the presence of sensory/chemo-sensory anomalies, and
(8) the presence of mood changes and/or specific disrup-
tion(s) in patient personality traits.

The pain pattern, which fulfills the inclusion symptomatic
criteria for BMS, must be compared with the oral mucosal sta-
tus of patients. Here, the oral examination plays a critical role
for the correct initial diagnosis of BMS. Patients with unremit-
ting oral burning who exhibit one or more well-defined signs
of oral mucosal disease(s), such as white spot/lesion, erythe-
ma, atrophy, erosion, ulcer, or other miscellaneous lesions,
should be initially diagnosed as affected with stomatitis. In
subjects without signs of oral mucosal disease(s), an initial
diagnosis of BMS can be entertained.

(B) Oral Complications

Possible oral complications in BMS may cause further prob-
lems with regard to diagnosis and management. Salivary
gland dysfunction and diabetes often make subjects more

<table>
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<th>TABLE 4</th>
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<tr>
<td>Micro-organism(s)</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Candida speciesa</td>
</tr>
<tr>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Enterobacterb</td>
</tr>
<tr>
<td>Fusospirochetal bacteria b</td>
</tr>
<tr>
<td>Helicobacter pylori b</td>
</tr>
<tr>
<td>Klebsiellad</td>
</tr>
<tr>
<td>a Fungi.</td>
</tr>
<tr>
<td>b Bacteria.</td>
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</tbody>
</table>

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<tr>
<th>TABLE 5</th>
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<tbody>
<tr>
<td>Principal Hypersensitivity Reactions Reported in Subjects with Burning Mouth Syndrome</td>
</tr>
<tr>
<td>Contact Sensitivity due to Dental Materials</td>
</tr>
<tr>
<td>Allergens</td>
</tr>
<tr>
<td>Benzoyl peroxidea</td>
</tr>
<tr>
<td>Cobalt chloridea</td>
</tr>
<tr>
<td>Mercuryb</td>
</tr>
<tr>
<td>Methyl-methacrylate monomer,b</td>
</tr>
<tr>
<td>Nickel sulfate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Petrolatum cadmium sulphate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>a Denture-base materials.</td>
</tr>
<tr>
<td>b Denture-filling materials.</td>
</tr>
<tr>
<td>c Ointment or cream preservatives.</td>
</tr>
<tr>
<td>d Food.</td>
</tr>
</tbody>
</table>
prone to developing overlapping oral mucosal infections (Table 4), which may complicate the presentation of BMS. Furthermore, hypersensitive reactions (Table 5) to denture-base/dental-filling materials and food allergens in BMS subjects are more frequent than expected (Type 3 BMS) (Lamey et al., 1994), but do not seem to have any influence on the outcome of the syndrome (Virgili et al., 1996). In fact, the replacement of dental-filling materials (Bergdahl et al., 1994) may relieve the burning symptom in very few cases, whereas the removal of the denture (Purello-D’Ambrosio et al., 2000) or diet modification (avoiding food allergens) (Whitley et al., 1991) often led to the clearing up of oral symptoms in a few days. The reported efficacy of denture removal in the relief of the oral complaint may be more likely due to the elimination of denture design errors or parafunctional habits (Paterson et al., 1995). Further complications in BMS may also result from inadequate oral hygiene due to oral pain in these patients (Perno, 2001). Thus, when mucosal erythema, ulcerative/erosive lesions, and atrophy, as well as gingivitis and periodontitis, are observed in BMS patients (Maresky et al., 1993), they should be considered as part of the clinical spectrum of a “complicated BMS”.

![Figure 2. Algorithm for the differential diagnosis of Burning Mouth Syndrome (BMS). (I) Algorithm for BMS diagnosis. (a) Anamnesis: BMS pain is invariably bilateral and often relieved by eating and drinking; in contrast, the pain associated with inflammatory/immunomedi- ated oral lesions may be unilateral and typically aggravated by food. (b) Oral mucosal examination plays a key role; lack of oral mucosal lesions points to BMS diagnosis, whereas changes in the oral mucosa suggest other disease(s) or complicated BMS. (c) Initial diagnosis: A correct anamnesis associated with a careful oral examination may be sufficient for arriving at an initial diagnosis of BMS; both intra- and extra-oral pain levels are measured through a linear Visual Analogue Scale (VAS). (d) Microbiological tests: The microbiological analysis of the oral mucosal areas where the pain is localized may be effective for excluding possible bacterial or fungal invasions. Epicutaneous patch tests are strongly recommended in patients with type 3 BMS. (II) Management of possible oral complication. Patients with oral mucosal lesions must be evaluated for their condition(s). In the case of a painful white lesion removable with a spatula, a microbiological oral culture of a smear sample should be performed to exclude candidiasis or possible bacterial infections. Patients must be administered with topical/systemic antifungal or antibiotic therapy, if fungal or bacterial infections, respectively, are diagnosed. Subjects with painful erythematous lesions may require epicutaneous patch tests for possible allergy. When hypersensitive reactions to denture components are found, removal of the denture may lead to the clearing up of oral symptoms in a few days. Dental examination is performed to exclude the presence of acute gingivitis, periodontitis, and/or other painful oral conditions. Appropriate oral hygiene interventions and dental treatments may contribute to relieving suffering of patients. Erosive-ulcerative lesions, which do not disappear after 2 weeks, must be considered for a peri-lesional biopsy. When inflammatory/immunomedi- ated diseases are diagnosed, appropriate treatment management should be provided. Persistence of the pain after proper treatments of such conditions is necessary for a diagnosis of complicated BMS.]
**Patient Management**

Owing to the large variety of associated factors, the protocol for BMS management is complex. An effective approach for these patients should be based on a strict collaboration among different oral medicine specialists. To begin with, it is very important that each patient be interviewed in an appropriately supportive manner, so that the investigator can become familiar with the subject (personal/familiar/social/medical history) as well as evaluate the organic component of his/her pain. Patient management involves a differential diagnosis for BMS (Fig. 2) and the discrimination between "Primary BMS" and "Secondary BMS" based on the identification of possible etiologic factors for the syndrome (Fig. 3). Patients with Secondary BMS can fall into specific sub-categories according to the identified disorder(s) ("patient stratification"), and, subsequently, they undergo appropriate therapy based on identified etiologies. The remaining cases (Primary BMS) will undergo proper pain control. This systematic approach to BMS has been reported to make patient management more predictable and effective (Scala et al., 2003).

**Differential diagnosis for BMS**

A correct clinical history associated with a careful examination
Both pain intensity and evolution can be recorded and monitored. Objective assessment of the pain should also be performed. The suspicion of BMS symptoms can be reinforced by detection of other symptoms commonly associated with BMS, such as dry mouth, taste changes, and sensory anomalies. Further aid may come from the identification of possible extenuating factors, such as xerostomia-inducing drugs. Patients who fulfill the inclusion criteria for BMS (Fig. 2, part Ib) should be additionally evaluated for the potential psychogenic component of their pain, with the use of psychometric instruments (Carlson et al., 2000), such as the McGill Pain Questionnaire (MPQ) (Melzack, 1987) and/or the Multidimensional Pain Inventory (MPI) (Kerns et al., 1985). An objective assessment of the pain should also be performed. Both pain intensity and evolution can be recorded and monitored via VAS.

Examination of the oral mucosa in these patients is crucial (Fig. 2, part Ib). BMS, in fact, must be differentiated from oral mucosal lesions (Bergdahl and Anneroth, 1993; Ship et al., 1995) that are accompanied by oral burning or pain-like symptoms, such as traumatic lesions, specific infections (e.g., candidiasis), and chronic erosive/ulcerative stomatitis (aphthous stomatitis, erosive lichen planus, pemphigoid, pemphigus, etc.). Neoplastic lesions must be excluded as well. The lack of oral mucosal pathology should lead one toward the diagnosis of BMS (Fig. 2, part Ic).

Disorders that can potentially arise from local conditions such as xerostomia should be explored. Xerostomia can alter the oral microflora, resulting in, for example, an increase in the number of Candida species or other microbes (also without clear clinical manifestations) (Osaki et al., 2000). Therefore, oral swabs for fungal/bacterial microbiological culture are indeed recommended, even if the painful areas of the oral mucosa have a normal appearance (Fig. 2, part Id). Allergy may also occur with or without oral manifestations (erythema). Thus, epicutaneous patch tests for both dental material and food allergens are particularly indicated in those subjects whose medical history reveals evidence of hypersensitivity.

In patients with oral mucosal lesions, one may be dealing with either a complicated BMS or other pathologies (Fig. 2, part II). Persistence of pain after proper treatment of these mucosal lesions is a "must" if the condition is to be considered a complicated BMS.

### TABLE 6

<table>
<thead>
<tr>
<th>Psychometric Test</th>
<th>Indication(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Anxiety and Depression Scale (HAD)</td>
<td>Anxiety and depression</td>
<td>Paterson et al., 1995</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Anxiety (HAM-A)</td>
<td>Anxiety</td>
<td>Maina et al., 2002</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression (HAM-D)</td>
<td>Depression</td>
<td>Maina et al., 2002</td>
</tr>
<tr>
<td>Karolinska Scales of Personality (KSP)</td>
<td>Alterations of personality traits</td>
<td>Bergdahl, 1995</td>
</tr>
<tr>
<td>Psychological Functioning Scale (PFS)</td>
<td>Psychological functioning disability</td>
<td>Bergdahl, 1995</td>
</tr>
<tr>
<td>Quality of Life Scale (QLS)</td>
<td>Quality of life</td>
<td>Bergdahl et al., 1995b</td>
</tr>
</tbody>
</table>

The procedure for differentiating "primary" from "secondary" BMS includes clinical/laboratory tests that are specifically meant to identify local/systemic factors associated with the syndrome (Fig. 3a). The evaluation of patients' masticatory systems includes clinical assessment of the occlusal table of natural teeth, denture design, temporomandibular joint status, and masticatory muscles (McNeill, 1997; Palla, 2001). Specific functional/parafunctional habits and salivary changes should be carefully recorded. Salivary flow rates below 0.1 mL/min for unstimulated whole saliva or 0.7 mL/min for stimulated whole saliva would suggest a condition of hyposalivation (Navazesh, 1993). Specific alterations in salivary composition can be detected by sialochemistry (Tammila-Salonen and Söderling, 1993). The objective evaluation of taste disturbances can be obtained by the whole-mouth test of gustatory function (Ahne et al., 2000). This test is based on the identification of the four basic tastes, with a maximum score of 24. Appropriate laboratory tests should be carried out if Secondary BMS due to systemic factors is suspected. Nutritional deficiency, diabetes mellitus, and menopausal disorders are diagnosed through hematological assessment of nutritional status, blood glucose, and estrogen/progesterone concentrations, respectively. If the clinical/laboratory examination unveils one or more of these local/systemic factors, such a patient should be considered as affected with Secondary BMS, whereas a lack of these factors points to a final diagnosis of Primary BMS (Fig. 3b). The pres-
TABLE 7
Drugs/Medications for Pain Control in Patients with Burning Mouth Syndrome

<table>
<thead>
<tr>
<th>Medication</th>
<th>Topical Administration</th>
<th>Systemic Administration</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin(^a)</td>
<td>3-4 times/day</td>
<td>Chlordiazepoxide(^c)</td>
<td>Epstein and Marcoe, 1994</td>
</tr>
<tr>
<td>Clonazepam(^b)</td>
<td>0.5 mg/day</td>
<td>Clonazepam(^c)</td>
<td>Woda et al., 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diazepam(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amisulpride(^d)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paroxetine(^e)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertraline(^e)*</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cream.  
\(^b\) Tablet.  
\(^c\) Benzodiazepines (GABA-receptor agonist).  
\(^d\) Tricyclic antidepressants (*selective serotonin re-uptake inhibitors).

ence of underlying psychological disorders can be revealed (Fig. 3c) by appropriate structured interviews and/or psychometric instruments (Table 6). The results of these tests may highlight both the nature and entity of the patients' psychogenic pain component.

(C) TREATMENT MANAGEMENT

Although a large variety of drugs, medications, and miscellaneous treatments has been proposed in BMS (Huang et al., 1996), the treatment management of this syndrome is still not satisfactory, and there is no definitive cure (Botha et al., 2001; Zakrzewska et al., 2001). BMS patients have shown a good response to long-term therapy with systemic regimens of antidepressants (Maina et al., 2002) and anxiolytics (Grushka et al., 1998). In addition, some patients undergoing topical capsaicin administration have experienced a partial or even complete remission of their pain (Epstein and Marcoe, 1994). However, the proposed pharmacological protocols have not consistently proved to be predictable and effective in all BMS subjects. The lack of strict criteria for the selection of the groups of patients can, in many cases, probably affect the response rate to the treatment. Accordingly, the different factor(s) associated with Secondary BMS and the type(s) of psychological disorder(s) detected in these patients deserve major emphasis at the time of treatment.

(a) Information for patients and psychological support

Initially, it is important to provide patients with information on the nature of their condition and give reassurance, since BMS subjects are likely to have consulted numerous specialists who stated that the mucosa was healthy and may thus be convinced that their problems are imaginary (Lamey, 1998). Patients must be made aware, instead, that their pain is "real", the syndrome is common in middle-aged/elderly individuals, and is often linked to some identified conditions. They must also be informed that the oral pain is not related to any form of cancer, that the treatment will be prolonged, and that not all the symptoms will definitely disappear. Precautionary measures, such as abstaining from smoking and specific food allergens, should also be suggested. Drugs able to induce either BMS (Savino and Haushalter, 1992; Culhane and Hodle, 2001) or xerostomia (Lamey et al., 2001) should be avoided as well. Some explanatory leaflets or booklets may be helpful for this purpose (van der Ploeg et al., 1987). When evidence of a psychogenic pain component is detected, specialists should also provide patients with adequate psychological support. This preliminary counseling, in fact, can have a great impact on the patients' attitude and may often result in long-term beneficial effects (Bergdahl et al., 1995a).

(b) Causative therapy in "Secondary BMS"

Subjects with Secondary BMS should initially be treated for the precipitating factors of this disorder. Depending on the type of salivary dysfunction, xerostomia is controlled with seven-day periods of saliva substitutes or saliva-stimulating agents (Jensen and Barkvoll, 1998; Niedermeier et al., 2000). Saliva substitutes have some properties similar to those of the salivary glycoproteins (Johansson et al., 1994). Active stimulation of salivation may be obtained by means of chewing gums or sweets (containing sorbitol, not sucrose), whereas passive stimulation is achieved through specific cholinergic drugs (sialagogues), such as pilocarpine (Gorsky et al., 1991; Astor et al., 1999; Niedermeier et al., 2000). Pyridostigmine is of greater benefit, since it is longer-acting and associated with fewer side-effects. Parafuncional habits are treated by a biofeedback technique (Carlsson et al., 1975; Turk et al., 1996; Greco et al., 1997; Glaros et al., 1998, 2000) and/or proper bite (McNeill, 1997; Palla, 2001). Muscular tensions/pain and temporomandibular joint mobilization are managed by means of physical relaxation training and physical therapy, respectively (McNeill, 1997; Marcus et al., 1998; Palla, 2001). Peri-/post-menopausal women with BMS should be referred to gynecologists. Proper administration of conjugated estrogens and medroxyprogesterone acetate, in fact, may relieve oral symptoms in this subgroup of BMS patients (Forabosco et al., 1992). Vitamin B complex replacement therapy (pyridoxine, riboflavin, thiamine, etc.) may yield a good response (Lamey et al., 1986) in very few cases of patients with nutritional deficiency (Hugoson and Thorstensson, 1991).

As mentioned previously, the different types of responses to etiology-directed therapy in "Secondary BMS" might be related to the type(s) of neuropathic change(s) underlying the syndrome. In non-responder cases, local and/or systemic pre-disposing factors may have caused an irreversible neuropathic damage/disorder(s), and thus patients should be additionally
treated with a therapy targeted to the neuropathic damage. Recently, a three- to four-week regimen of alpha-lipoic acid (ALA) has been claimed to provide a slight to decisive pain reduction in BMS patients (Femiano et al., 2000; Femiano and Scully, 2002). Based on the currently reported efficacy of ALA in neuronal damage (Tirosh et al., 1999), especially in diabetic neuropathy (Reljanovic et al., 1999; Ziegler et al., 1999), this drug might be particularly indicated in BMS subjects who show lack of response to etiology-directed therapy. Further investigation, however, is indeed mandatory for better definition of the role of this drug in BMS.

(c) Supportive care in "Primary BMS": the control of pain and associated symptoms

An effective approach to treatment management of patients with Primary BMS should take into account that its etiology is unknown. It is thus inappropriate to conceive a definitive therapy for this condition; rather, one should consider "supportive care in BMS" (Scala et al., 2003). The purpose of supportive care is to reduce the suffering of the patients, to bring their condition under better control and improve the quality of life. Given the chronic nature of this painful syndrome, the treatment procedures must particularly address the management of the main symptom (pain), which should be monitored through a VAS (Woda et al., 1998; Maina et al., 2002).

Many pharmacological agents, administered topically or systemically, have been proposed to overcome the pain in BMS (Table 7). Low doses of capsaicin, applied 3 or 4 times topically on the area(s) where the pain is localized, appear to be quickly effective in alleviating the pain in BMS subjects (Epstein and Marcoe, 1994; Lauritano et al., 1998; Scala et al., 2003). However, there is a limited number of trials for corroborating its role in BMS pain control, probably because long treatment periods with topical capsaicin are thought to result in depletion of substance P (by causing C-fiber degeneration) (Simone and Ochoa, 1991), with consequent loss of pharmacological effects. Consequently, administration of capsaicin for seven-day periods, interspersed by periods of no treatment and the removal of capsaicin after each application, is recommended. Owing to its action (desensitization) on the C-nociceptor (Lynn, 1990), topical capsaicin may be indicated in pain control of BMS subjects with organic pain. Based on the reported new evidence of changes in peripheral autonomous innervation in BMS (Jaaskelainen et al., 1997), topical administration of other drugs has recently been considered. In particular, daily topical use of clonazepam (¼ or ½ tablet applied 3 times each day for sucking) has shown partial to complete pain relief in most patients with idiopathic BMS (Woda et al., 1998), suggesting a possible local effect of this drug on gamma-amoно-butyric-acid receptors (gaba-receptors) within the oral mucosa. However, in this group of patients, the presence of high blood levels of clonazepam might also indicate a systemic effect of this medication in pain relief. Thus, the efficacy of clonazepam administration should be better documented and confirmed.

Patients with a stronger psychogenic component may be unresponsive to these medications. In these cases, the most effective pain management is the systemic administration of mood-altering drugs (Gorsky et al., 1991). Long-term treatment with benzodiazepine-class drugs (anxiolytics) may be clinically useful in BMS subjects (Bessho et al., 1998; Grushka et al., 1998). However, because of their target (central and peripheral gaba-receptors), benzodiazepines may be of special benefit in BMS patients with anxiety. Other mood-altering drugs in BMS include anti-depressants. Low doses of tricyclic anti-depressants are characterized by an analgesic action, independent of their anti-depressive effect (Tourne and Frichton, 1992; Mott et al., 1993). Sertraline (Van Houdenhove and Joostens, 1995), paroxetine, and amisulpride are reported to be well-tolerated and effective after a four- to eight-week administration in BMS subjects (Maina et al., 2002). Analgesic doses of anti-depressants should be adjusted according to the individual response and may be particularly indicated in BMS patients with minor depression. Treatment with anti-depressive doses is indicated in individuals with abnormal personality profiles, but it should be undertaken in consultation with psychiatrists.

Patients who do not respond to any of the above treatments (resistant BMS) should undergo "cognitive" (Bergdahl et al., 1995a) or "cognitive/behavior" (Humphris et al., 1996) therapies by qualified psychotherapists, since they probably have, in their BMS spectrum, a strong and complex psychogenic component of the pain. The purpose of psychodynamic therapy is to allow each patient to understand the causes of his/her symptoms. In this approach, patients are encouraged to explore the possibility that their symptoms may serve as a form of defense against overwhelming emotional distress. Successful treatment of BMS patients with combined psychotherapy and psycho-pharmacotherapy has also been reported (Van Houdenhove and Joostens, 1995).

(d) Follow-up

Because of the debilitative nature of this syndrome, as well as the frequently observed involvement of psychological disorders, BMS patients, particularly those resistant to treatment, should be offered regular follow-up from two to four times a month during the symptomatic period. Each evaluation should include an analysis of pain levels, personality, psychological functioning, and quality of life. A personal interpretation of the evolving nature of the syndrome should be included in a patient diary.

(VII) Conclusions

Burning Mouth Syndrome remains a fascinating, though poorly understood, condition in the field of oral medicine. New evidence for the neuropathic basis of this syndrome is emerging. As a result, a subgroup of BMS cases may fall into the category of nigrostriatal dopaminergic disorder. In the remaining group of patients, in whom there are clear precipitating local factors, BMS might be considered as a consequence of selective damage (trauma/chemo-mechanical irritation) to the nerve fibers of the trigeminal nervous system. In these cases, however, it is not unlikely that a central nervous system disorder could be a key factor in the persistence of the syndrome.

Our opinion is that two new criteria may be useful in the management of BMS: (1) the occurrence of a "complicated BMS", and (2) the distinction between "Primary BMS" and "Secondary BMS". Based on these distinctions, a caring supportive attitude, a correct patient stratification, and an appropriate multidisciplinary approach will be the gold standards for a rational and beneficial application of current knowledge.

Research in this area, undertaken according to a variety of approaches, is needed. In-depth studies for a clear definition of the associations between BMS and systemic disorders based on a uniform definition, strict diagnostic criteria, and proper patient selection are also essential. In addition, evidence
involving the peripheral and/or central nervous system in BMS should be better documented and confirmed.

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