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Pain Part 8: Burning Mouth Syndrome

Abstract: Burning mouth syndrome (BMS) is a rare but impactful condition affecting mainly post-menopausal women resulting in constant pain and significant difficulty with eating, drinking and daily function. The aetiology of BMS remains an enigma. Recent evidence suggests it likely to be neuropathic in origin, the cause of which remains unknown. There is no cure for this condition and the unfortunate patients remain managed on a variety of neuropathic pain medication, salivary substitutes and other non-medical interventions that help the patient 'get through the day'. Some simple strategies can assist both clinician and patient to manage this debilitating condition.
CPD/Clinical Relevance: The dental team will recognize patients presenting with burning mouth syndrome. They are difficult patients to manage and are often referred to secondary care and, ultimately, depend on their general medical practitioners for pain management.
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Burning mouth syndrome (BMS) is a chronic and intractable pain condition, which predominantly affects post-menopausal women in their 5th to 7th decade. The International Association for the Study of Pain (IASP)[1] has identified BMS as a 'distinctive neuropathic entity' characterized by bilateral burning oral mucosal pain, usually affecting the anterior two-thirds of the tongue, that may comply with the anatomy of peripheral nerves. There is a lack of any visible signs of mucosal pathology and the symptoms usually last for more than 6 months.[2] The International Headache Society (IHS)[3] defines BMS as 'an intra-oral burning sensation for which no medical or dental cause can be found'. The IHS diagnostic criteria state the need for constant pain, normal appearance of the oral mucosa and exclusion of any local/systemic diseases. The pain intensity ranges from moderate to severe throughout the day, may vary during the day, and may last several years.[4,5]

Traditionally, BMS was thought to be purely psychogenic,[6] especially owing to the absence of any visible clinical pathology. Although there is likely to be a psychological component to the condition, in common with most chronic pain conditions,[4,7–9] increasing evidence indicates that the aetiology of BMS is likely to be more complex. Possible peripheral neuropathic involvement has been suggested,[10–16] and upstream effects of any peripheral changes within the central nervous system are likely.[16–19, 74]

A recent review article on BMS[19] summarizes that neurophysiologic, psychophysical, neuropathological and functional imaging studies may have elucidated multiple neuropathic mechanisms, mostly subclinical, acting at different levels of the neuroaxis and contributing to the pathophysiology of primary BMS.

Some authors conclude that the clinical diagnosis of primary BMS may encompass three distinct, subclinical neuropathic pain states that may overlap in individual patients.[18–22]

1. Subgroup 1 (50–65%) is characterized by peripheral small diameter fibre neuropathy of intra-oral mucosa;
2. Subgroup 2 (20–25%) consists of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be dissected with careful neurophysiologic examination but is clinically indistinguishable from the other two subgroups;
3. Subgroup 3 (20–40%) fits the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia.

The neurogenic factors acting in these subgroups differ, and will require different treatment strategies. In the future, with proper use of diagnostic tests, BMS patients may benefit from interventions

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specifically targeted at the underlying pathophysiological mechanisms.

Despite such ongoing research, central and peripheral pain mechanisms in BMS are still not understood in their entirety. Questions remain regarding the possibility of a dominating nervous system driving the condition or a more complex network of central, peripheral and psychological aspects impacting on a susceptible patient, with a possible genetic involvement.

Clinical features

Eliciting a good clinical history from the patient is essential in diagnosing burning mouth syndrome. Most patients report an increase in pain intensity from morning to night, similar to other neuropathic pain conditions. Most patients report a decreased pain with eating, oral dryness that waxes and wanes with the burning, and the frequent presence of taste disturbances.[8]

Essentially, clinical examination confirms that there is no mucosal abnormality detected (Figure 1), however, some patients may present with concomitant conditions, for example erythema migrans (geographic tongue) or lichen planus unrelated to their burning symptoms. In over 50% of patients with burning mouth syndrome, the onset of pain is spontaneous, with no identifiable precipitating factor. Thirty per cent of patients cite onset caused by dental procedure, recent illness or medication course (including antibiotic therapy). Regardless of the nature of pain onset, once the oral burning starts it often persists for many years.[4,23] Extra-oral sites are not affected, however, other mucosal sites may be concomitantly affected such as vulvodynia.

In many patients with neuropathic pain, pain is absent during sleep but occurs at a mild to moderate level in the morning. Again, similar to other neuropathic pain conditions, the pain increases throughout the day, with maximum intensity late in the day.[4] The

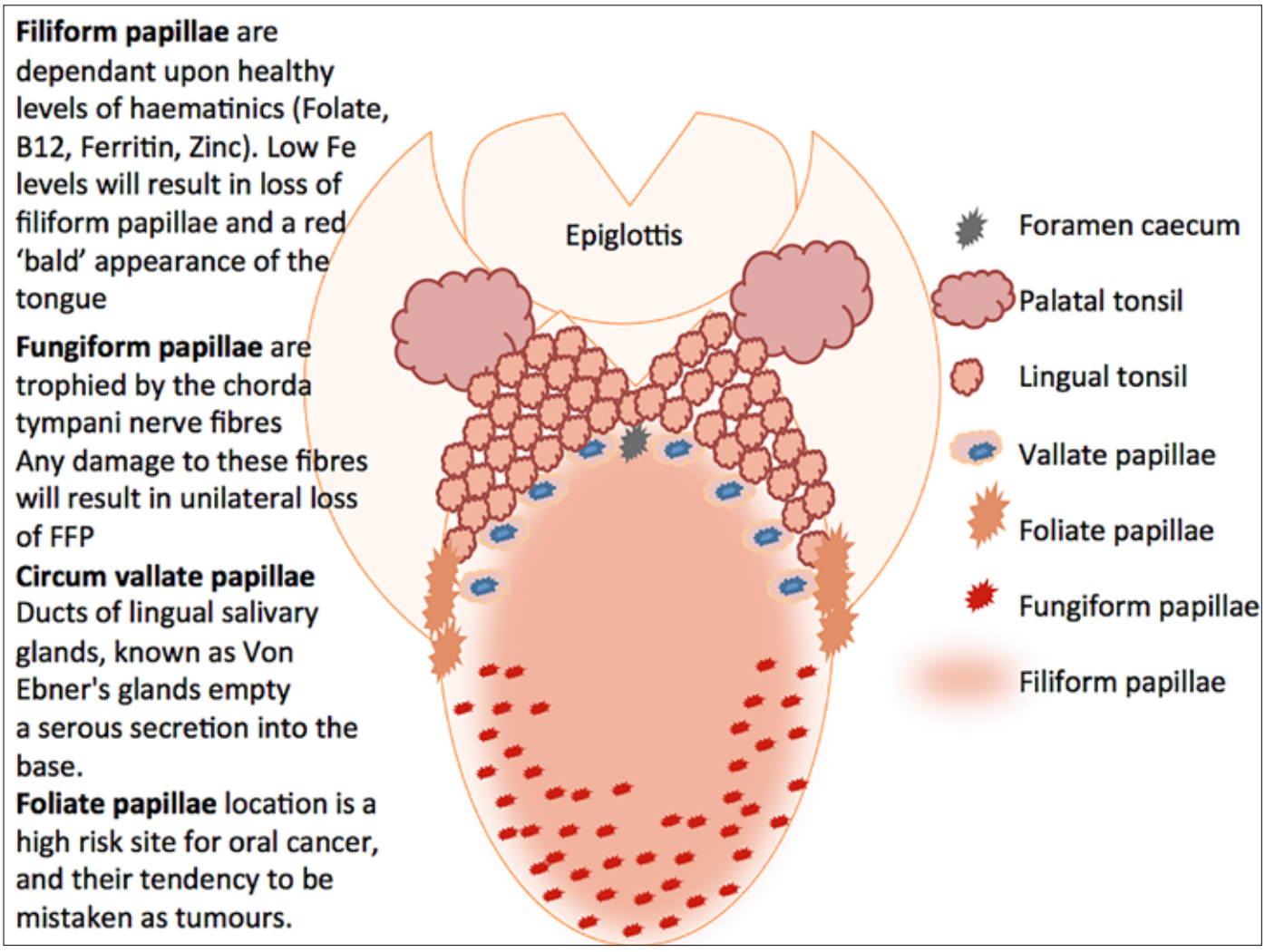

Figure 1. Normal lingual anatomy.

pain is moderate to severe and may prevent onset of sleep and may alter mood changes, including irritability, anxiety and depression.[4]

There is a scarcity of evidence on the natural course of burning mouth syndrome, with no identified factors indicative of recovery. Spontaneous partial recovery within six to seven years after onset has been reported in up to two-thirds of patients, with recovery often preceded by a change from constant to episodic burning.[5]

Most studies have found that oral burning is frequently accompanied by other symptoms, including dry mouth and altered taste.[4] Alterations in taste occur in as many as two-thirds of patients and often include complaints of persistent tastes (bitter, metallic or both) or changes in the intensity of taste perception. Dysgeusic tastes accompanying oral burning are often reduced by stimulation with food.[4,5] In contrast, application of a topical anaesthetic may increase oral burning while decreasing dysgeusic tastes.

Epidemiology

Epidemiological data available on BMS is very limited. The lack of strict diagnostic criteria has lead to the publication of many studies reporting on the symptom of oral burning rather than the syndrome specifically (Table 1).[19] As a result, the quoted prevalence of BMS within the general population varies from 0.7% to 15%.[24]

The prevalence of BMS increases with age, predominantly affecting women, with a female to male ratio of 3:1, varying between 0.6% in 30–39-year-old women, increasing to 12.2% by their seventh decade.[9]

Aetiology

The precise aetiology of BMS is unclear. Several studies have suggested various local, systemic and psychological precipitating factors, however, there is a lack of general agreement due to poor quality prospective studies and case reports. As stated by a Cochrane review, it is important to diagnose BMS only on exclusion of any such aetiological factors.[2] These factors include the following.

Oral candidiasis

Candidal infections have been shown to induce a burning sensation.[4] There is a lack of consensus, however, due to the fact that treatment of the candidal infection has failed to relieve burning symptoms.[19]

Xerostomia (Dry Mouth)

Prevalence of xerostomia in BMS patients varies, ranging from 34%[25] to over 60%.[8] Some studies have failed to show a difference in saliva production compared with controls.[26] Drug-induced xerostomia is known to be a cause of dry mouth. Reduced saliva production in BMS patients taking antidepressants would be an understandable finding. In addition, BMS patients are known to have higher anxiety and depression scores, increasing the chances of a dry mouth,[22] however, xerostomia itself has not been shown to be a cause of BMS.

Nutritional neuropathy

Grushka[4] investigated the role of deficiencies of iron, folate, serum ferritin and vitamin B12 in 72 age- and sex-matched BMS patients with 43 controls and showed no significant differences between both groups. Some studies, however, report significant lower levels of vitamin B12 in BMS patients.[27,28,29] There have also been suggestions of deficiencies of vitamins B1, B2 and B6 causing BMS.[28,31,32,33] More recently, deficiency in zinc levels have been demonstrated in BMS patients with replacement therapy causing a decrease in pain, although not curing it completely.[34]

Dysgeusia

Femiano *et al* reported up to

Condition	Characteristic Pattern	Management
Mucosal disease (eg lichen planus, candidiasis)	Variable pattern Sensitivity with eating	Establish diagnosis and treat mucosal condition
Menopause	Onset associated with climacteric symptoms	Hormone replacement therapy (if otherwise indicated)
Nutritional deficiency (eg vitamins B1, B2 or B6, zinc, others)	More than one oral site usually affected. Possibly mucosal changes	Oral supplementation
Dry mouth (eg in Sjögren's syndrome or subsequent to chemotherapy or radiation therapy); altered salivary content	Alteration of taste Sensitivity with eating	High fluid intake Sialagogue
Cranial nerve injury	Variable pattern Usually bilateral Decreased discomfort with eating	Central pain control: benzodiazepine, tricyclic antidepressant, gabapentin (*Neurontin*) Local desensitization: topical capsaicin
Medication effect	Onset related to time of prescription	If possible, change medication

Table 1. Possible causes and management of oral burning symptoms.[8]

two thirds of BMS patients with complaints of taste disturbances, especially persistent bitter and/or metallic tastes.[35] Significantly different taste acuity in BMS patients has also been shown.[24,36]

Mechanical factors

Poorly fitting prostheses causing local irritation and microtrauma have been suggested as a cause for BMS-like symptoms.[37] Conversely, it has been shown that denture replacement did not always relieve the symptoms, as is the case with supposedly allergic reactions to acrylic dentures.[27,38]

Parafunctional habits

Parafunctional activity is commonly seen in patients with increased levels of anxiety. There have been suggestions of such habits predisposing to BMS, but there have not been any controlled studies to support this.[19]

Endocrine disorders

Certain systemic conditions have been implicated with BMS. Diabetes mellitus has been linked to BMS, possibly due to reports of glossodynia in diabetics and also the risk of peripheral neuropathies, such as burning feet.[39,40] Some studies suggest that it is poorly controlled diabetes that can lead to BMS[40,41] and better glycaemic control can improve symptoms.[42] Hypothyroidism has also been implicated in predisposing patients to BMS.[43]

With BMS being more common in post-menopausal women, a decrease in oestrogen levels has been a suggested cause for burning mouth symptoms.[44,45,46] This has not been confirmed, however, due to the lack of improvement following oestrogen replacement therapies.[47]Salivary cortisol levels have been investigated in BMS patients. Although they followed the same circadian cycle, salivary levels were generally higher in BMS than controls.[48] Chronic anxiety in BMS has also been related to a dysregulation in the production of adrenal steroids.[49]

Psychological disorders

BMS is stated to be 'conceptualized as a psychogenic physical continuum'[8] and over 50% of patients have been associated with psychological factors.[7] Bergdahl *et al* demonstrated a significantly higher score on the somatic anxiety, muscular tension and psychoasthenia scales in the BMS cohort and lower socialization scores, compared to controls.[20] Conversely, studies, such as Carlson *et al*, have shown there to be no significant prevalence of psychiatric symptoms in BMS patients.[50] It is important to note that patients with chronic pain commonly have psychologic dysfunction and this may be a result of the ongoing pain, or a predisposing factor to the syndrome itself. It would therefore be sensible to identify those patients with underlying psychological disorders as those at risk of developing a chronic pain condition.[8]

Helicobacter pylori (H. pylori) and gastrointestinal disease

Recent studies have suggested a correlation between the presence of *H. pylori* and burning sensations within the oral cavity.[51] When tested for this bacterium, higher levels were found in BMS patients compared to controls.[51,52] In 2006, Brailo *et al* found 51.3% of BMS patients had gastritis and 12.3% showed evidence of *H. pylori*.[53] In addition, BMS patients were found to be 3.2 times more likely to suffer from gastrointestinal disease.[54] When all factors possibly contributing to BMS were analysed, gastrointestinal problems were most common in BMS patients.[55]

Autoimmune

The role of various cytokines in BMS have been suggested in the past. Simčić *et al* found salivary interleukins 2 and 6 (IL-2 and IL-6) to be elevated in correlation to the severity of the symptoms of BMS.[56] Conversely, other studies have demonstrated a significant decrease in IL-2 and IL-6 which was negatively correlated to chronic pain levels.[57] More recently, no difference was found in salivary interleukin levels in BMS patients.[58]

Contact hypersensitivity

Studies using patch testing on BMS patients have shown contact allergy not to play a significant role in its aetiology.[59] Levels of IgE have also been investigated with no evidence to support its role.[60] In addition, contact dermatitis has not been shown in BMS patients.[30,61]

Exclusion of other causes of peripheral neuropathy

Various secondary causes for peripheral neuropathies have been implicated and it is important to exclude these when diagnosing BMS. These causes include:

- Diabetic peripheral neuropathy;
- Inherited neuropathies;
- Idiopathic small fibre sensory neuropathy;
- Peripheral neuropathies associated with connective tissue disease;
- Acquired amyloid polyneuropathy;
- Neuropathy with renal failure;
- Hereditary sensory autonomic neuropathy;
- Sarcoid polyneuropathy;
- Arsenic neuropathy;
- Fabry's disease;
- Coeliac's disease;
- HIV-related neuropathy;
- Paraneoplastic sensory neuropathy;
- Post-traumatic peripheral sensory neuropathy;
- Post-herpetic neuropathy; and
- Demyelination in multiple sclerosis.

Based on the evidence discussed, albeit controversial, it is vital to employ strict criteria to ensure BMS is correctly diagnosed as a diagnosis of exclusion.

Diagnostic screening, therefore, should include exclusion of: nutritional neuropathies (serum Fe, Ferritin, Vitamins B1, B6, B12, Folate and Zinc), blood dyscrasias (FBC, WBC, RBC, MCV, ESR), liver disease (LFTs), renal disease (renal function test), candidal infection (candida count), diabetes (fasting blood glucose or HbA1C), hormone imbalance (FSH, oestradiol, TSH, FT3, FT4) and, if the clinical history indicates, gastrointestinal disease (antibodies to *H. pylori*), allergy (serum total IgE, patch test for dental materials) and xerostomia (salivary flow rate). This would ensure BMS is diagnosed correctly, as a diagnosis of exclusion (Table 2).

Pathogenesis

BMS was originally thought to be purely psychogenic in origin, however, growing evidence suggests

Nutritional Neuropathy	Blood Dyscrasia	Liver Disease	Renal Disease	Candidal Infection	Diabetes	Hormone Imbalance
Iron	FBC	LFTs	RFT	Candida	Fasting	TSH
Ferritin	WBC			count	blood	FSH
Vit B1	RBC			(Swab+	glucose/	FT3
Vit B6	MCV			Saliva)	HbA1C	FT4
Vit B12	ESR					Oestradiol
Folate						
Zinc						

If indicated by clinical history:

Gastrointestinal Disease	Allergy	Xerostomia
Antibodies to *H. pylori*	Serum IgE levels	Salivary flow rate
	Dental materials patch test	

Table 2. Screening tests required to diagnose BMS: a diagnosis of exclusion.

that it is in fact a much more complex condition involving multiple factors. Studies are now beginning to show BMS to be neuropathic in origin,[10-16] with one study demonstrating a significantly lower density of epithelial nerve fibres in oral mucosa of BMS patients with morphological differences in the nerve fibres themselves[13] and a significantly lower number of fibres penetrating the epithelium in oral mucosa of BMS patients.[11] More specifically, some peripheral pain receptors have been shown to be upregulated after analysis of tongue biopsies of patients suffering from BMS in comparison to controls.[11,12] These changes in the peripheral nervous system suggest BMS to be (at least in part) a small fibre trigeminal neuropathic condition.

Upstream effects of any peripheral change are expected within the central nervous system[62] and evidence is beginning to indicate a role for the central nervous system in BMS.[16,17,18, 74] There is evidence to suggest irreversible neuropathic degeneration both peripherally and centrally.[49] This study demonstrated a different response to the blockade of peripheral sensory input causing attenuation of pain in one subgroup, the alleviation of pain in another and no change at all in the third group, illustrating the complex relationship between peripheral and central nervous systems. Grushka found that the tolerance of pain in BMS patients was significantly reduced.[4] The question still remains as to whether this is due to changes within the peripheral or central nervous system or, more likely, a combination of both.

A psychological element to chronic pain conditions is often reported.[7,8,20,50,63] Behavioural studies rely on patient questionnaires to complete the understanding of this debilitating condition and to help suggest appropriate multidisciplinary management of these patients.

Peripheral nervous system

Investigating peripheral pain mechanisms not only advances our understanding of BMS, but is also essential for the development of new therapeutic drugs. The majority of the orofacial tissues are supplied by the trigeminal nerve and BMS has been shown to involve trigeminal neuropathies.[11,12,13] The trigeminal primary afferent nerve fibres (A delta and C fibres) tend to be the non-specialized peripheral nerve endings that act as nociceptors and are responsible for eliciting pain.[64] Once these nerve endings are activated, action potentials are conducted to the sensory cortex. Activation of these peripheral nerves involves several factors and chemicals. Chemical mediators released as a result of tissue damage, such as prostaglandins, can excite the peripheral nerves and translate as pain and damage to adjacent tissues due to an inflammatory response, releasing substances such as 5-hydroxytyramine (5-HT) and cytokines which again activate these nerve endings.[65] With neuropathic pain, such as BMS, damage to or pathology of the peripheral nerve endings themselves can lead to an increase in excitability and aberrant firing, causing chronic pain conditions.[66] A wide range of mediators and receptors have been suggested to be involved in neuropathic pain, such as calcitonin gene-related peptide (CGRP), somatostatin, nerve growth factors and substance P.[65] In addition, voltage-gated sodium (Na_v) channels are known to play a key role in the elicitation of action potentials in neurons, including nociceptors.[67] Our study demonstrated voltage-gated sodium channel Nav1.7 to be maintained in BMS and upregulated in pulpitis, indicating further that BMS is likely to be neuropathic in origin rather than inflammatory.[10]

Expression of various receptors has been shown on afferent nerve endings including purinergic, serotonergic, opiate, cholinergic, anandamide, bradykinin, histamine, prostaglandin, adrenoreceptors, transient vanilloid receptor V1, ionotropic glutamate receptors, neurokinin receptors, acid-sensitive receptors and gamma-aminobutyric acid (GABA) receptors.[11,65,68] We have shown purinergic receptor P2X3 to be significantly upregulated in BMS.[12] Further research will help to determine which specific receptors are involved

in BMS, working towards identifying a therapeutic goal.

Following investigation of the peripheral nervous system in BMS, the question still remains as to whether this is purely a peripherally driven condition. A growing body of evidence is beginning to indicate a role for the central nervous system in BMS and, being a chronic pain condition, central changes would be expected.[16,17,18,74]

Medications	Examples of Specific Agents	Common Dosage Range	Prescription
Tricyclic antidepressants	Amitriptyline Nortriptyline	10 to 150 mg per day	10 mg at bedtime; increase dosage by 10 mg every 4 to 7 days until oral burning is relieved or side-effects occur Maintain 40 mg nocte 3 months
Benzodiazepines	Clonazepam	0.25 to 2 mg per day	0.25 mg at bedtime; increase dosage by 0.25 mg every 4 to 7 days until oral burning is relieved or side-effects occur; as dosage increases, medication is taken as full dose or in three divided doses
	Chlordiazepoxide	10 to 30 mg per day	5 mg at bedtime; increase dosage by 5 mg every 4 to 7 days until oral burning is relieved or side-effects occur; as dosage increases, medication is taken in three divided doses
Anticonvulsants	Gabapentin	300 to 1,600 mg per day	100 mg at bedtime; increase dosage by 100 mg every 4 to 7 days until oral burning is relieved or side-effects occur; as dosage increases, medication is taken in three divided doses
Capsaicin	Hot pepper and water	Variable (see next column)	Rinse mouth with 1 teaspoon of a 1:2 dilution (or higher) of hot pepper and water; increase strength of capsaicin as tolerated to a maximum of 1:1 dilution
Topical Clonazepam		300 µg tablet crushed	Applied to affected area 5 mins then rinsed out not swallowed

Table 3. Medical management of burning mouth syndrome.

Central nervous system

Pain is a complex, multi-dimensional experience produced by nerve impulses being generated within the brain, for example, following stimulation of peripheral pain receptors.[69] The pathways involved in translating this peripheral input as pain was previously known as the 'pain neuromatrix'.[62]

Initially, the 'pain neuromatrix' was first described by Melzack in 1999.[69] It was thought that the huge network of neurons within the brain contributes to the many 'pain centres' and collectively was known as the 'pain neuromatrix'. Typically, this includes the thalamus, sensorimotor cortex, insular cortex, frontal cortex, premotor cortex and anterior cingulate cortex.[62] This 'pain neuromatrix' was thought to be genetically determined within each individual and refined by various sensory inputs over time.[69]

Neuro-imaging studies have furthered our understanding of the central representation of pain; both in experimental and clinical pain, and central changes within the 'pain neuromatrix' can now be investigated. The use of these various imaging techniques have demonstrated the complexity of subjective pain perception and suggested a more individualized 'cerebral pain signature' rather than a rigid neuromatrix.[70,71] The previously named 'pain centre' is also seen as a grossly simplified term for the complex interactions involved in pain perception.[72]

Novel functional neuro-imaging techniques are providing us with a unique method of evaluating pain mechanisms in real time, whilst patients can report the quality and quantity of the pain that they are experiencing.[73] Cerebral activation has been assessed in BMS patients following thermal stimulation of the trigeminal system[16,18] and, more recently, a decrease in grey matter volume has been reported in BMS patients at rest.[74] Our group is currently using functional magnetic

resonance imaging to analyse the central representation of BMS and help to localize areas of the brain involved in chronic orofacial pain.

Psychometry

Patients with chronic pain commonly have psychological dysfunction and this may be a result of the ongoing chronicity of pain or an underlying risk factor for developing the pain condition itself.[8] BMS is a chronic pain condition and we can expect these patients to have a psychological aspect to their condition. Studies have reported over 50% of BMS patients to be associated with a range of psychological factors[7] and show a significantly higher score on the somatic anxiety, muscular tension and psychoasthenia scales and a lower score on the socialization scale.[9]

Current management

Currently, there are multiple treatment modalities for the management of BMS, all of which are unsatisfactory (Table 3). Cognitive behavioural therapy (CBT) is at present the only evidence-based treatment for BMS and this is still not always available for patients in some hospitals.

Medical treatment of burning mouth syndrome is similar to the medical management of other neuropathic pain conditions (Table 3).[76] Studies generally support the use of low dosages of clonazepam (*Klonopin*), chlordiazepoxide (*Librium*), tricyclic antidepressants (eg nortryptyline and amitriptyline) and also supports the utility of a low dosage of gabapentin (*Neurontin*).[75,78] Studies have not shown any benefit from treatment with selective serotonin re-uptake inhibitors or other serotoninergic antidepressants (eg trazodone [*Desyrel*]).[79]

Although benzodiazepines may be thought to exert their effect on oral burning by acting as a sedative-hypnotic, this possibility appears to be unlikely because the maximal effect of clonazepam is usually observed at lower dosages.[75] The beneficial effects of tricyclic antidepressants in decreasing chronic pain indicate that, in low dosages, these agents may act as analgesics.[23]

Topical capsaicin has been used as a desensitizing agent in patients with burning mouth syndrome.[80] However, capsaicin may not be palatable or useful in many patients.[80]

Conclusion

There is no doubt that current research is beginning to unravel the mystery of BMS, previously thought to be purely psychogenic in origin, and prove that it is a complex condition involving the peripheral nervous system, the central nervous system, psychometrics and perhaps a genetic involvement. The importance of a correct diagnosis in the first instance is key to preventing patients from being labelled with this debilitating condition, which is still not completely understood and currently difficult to manage. Referral of these patients to specialist pain centres will ensure correct diagnoses are made and optimum management is provided involving a multidisciplinary team.

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