Burning Mouth Syndrome: a review

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INVITED REVIEW

Burning mouth syndrome: a review

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Abstract

Burning mouth syndrome (BMS) is characterised by chronic daily intraoral burning or dysaesthetic sensations, often combined with taste alterations and dry mouth, which cannot be explained by any clinically evident oral or systemic pathology. Around 1%–3.7% of the population suffer from the condition, with highest prevalence figures in menopausal and post-menopausal women up to 12%–18%, and BMS can have a significant impact on quality of life. BMS still seems to be poorly understood in terms of aetiology, although there is growing evidence from multiple lines of research that neuropathic changes at different levels of the neuraxis are critically involved in its pathogenesis. With accurate neurophysiological, psychophysical, neuropathological and neuroimaging methods, clinically homogenous BMS can be subdivided into three major types of neuropathic pain, that may coexist. According to some preliminary evidence, efficacy of different treatments may depend on the neurophysiological subtype of BMS. However, as these subtypes cannot be distinguished with standard clinical examination and detailed diagnostic methods are not routinely applied in the clinic nor in the treatment trials, management of BMS remains challenging, with little high quality evidence available. This review aims to address the current evidence and understanding in relation to aetiology, diagnosis and management of BMS.

Introduction

Burning mouth syndrome (BMS) is defined as 'an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 h per day over more than 3 months, without evident causative lesions on clinical examination and investigation'[1,2], this has previously been referred to as primary BMS[3]. There are, however, various definitions reported throughout the literature[4,5]. Epidemiological studies have indicated that 0.7%–18%, or even up to 40% of the population are affected by BMS[6–10]. This huge range of prevalence in the literature is partly due to the various definitions of BMS being applied. Especially in older studies, primary BMS has not been separated from secondary oral burning sensations due to local or systemic causes[4,11]. Well-conducted studies with currently accepted diagnostic criteria show clearly lower prevalence around 1.0%–3.7%[4,12]. In general, questionnaire based (self-report) studies report higher prevalence figures than more meticulous clinical studies that in turn also differ depending on the clinical profile and catch-up area of the hospital[3]. Menopausal and post-menopausal women are most commonly affected, with reported female to male ratios varying between 2:1 and 20:1[4,6,9,13]. The aetiology of BMS is still poorly understood, although in the majority (around 90%) of the patients, either peripheral and/or central neuropathic alterations can be found with more detailed and accurate diagnostic methods[4,14–16]. However, in the standard clinical setting, BMS is likely to appear more complex and multifactorial, which can make management challenging. This is further compounded by the fact that many studies in the area use small patient groups and are limited in design and diagnostic

methodology. This paper aims to describe the current understanding regarding the aetiology, diagnosis and management of (primary) BMS.

Aetiology and pathophysiology

The aetiology of BMS is complex and is likely to be multifactorial. However, the current concept underpinning its aetiology[4,14,17], is that the peripheral and central nervous system are likely to both be critically involved in the pathophysiology of BMS[4,11,14,15,18–20]. It may, therefore, be regarded as a neuropathic pain condition. Accordingly, International Headache Society lists it under the heading "Painful lesions of cranial nerves and other facial pain" in the latest version of the International Classification of Headache Disorders[1]. Over the last two decades, studies on over 250 BMS patients, utilising adequate diagnostic criteria of BMS and accurate, quantitative psychophysical and neurophysiological methods, have been able to confirm definite deficits, i.e. loss of function signs, in the trigeminal somatosensory system in the majority (around 75%) of BMS patients[18,21–28]. Loss of function signs are unanimously considered crucial biomarkers of an underlying neuropathic pain condition, as they confirm and quantitate the causal neural pathway damage. In these studies, thermal quantitative sensory testing (QST) has indicated damage to the small fibre tracts: loss of function (hypoesthesia) in the innocuous thermal modalities of cooling and warming and, to a lesser extent, in heat pain perception. These loss of function signs are similar to those in clinically evident trigeminal and other neuropathic pain conditions[27,29–32]. They have later been confirmed in several smaller neuropathological studies on tongue mucosal biopsies of BMS patients to be due to neuropathic damage and loss of the intraepithelial small nerve fibres of the tongue, compatible with focal small fibre neuropathy of the intraoral mucosa[19,26,32,33]. This intraoral, focal, small fibre neuropathy may represent one form of the non-length dependent small fibre neuropathies[34] that may be very difficult to recognise and diagnose in the clinic. However, part of the QST and biopsy findings seem to be due to major, but subclinical trigeminal neuropathic pain as also the sub-epithelial large fibres have shown damage in some of the patients[19]. Supporting this are brainstem reflex recordings indicating peripheral trigeminal neuropathy or brainstem level pathology in the trigeminal system in approximately 20% of BMS patients[18,22,28]. Both of the small fibre and large fibre subtypes of BMS fit to the concept of neuropathic pain due to peripheral neuropathy. The frequently reported taste alterations, in up to two-thirds of BMS patients, are most likely caused by peripheral neuropathy; either due to damage of the third trigeminal division, its lingual branch or chorda tympani fibres, or due to the intraoral small fibre neuropathy affecting the small myelinated Aδ taste afferents in addition to somatosensory small fibres[4,18,19,26,32,33,35–37]. Psychophysical investigation with electrogustatometry has confirmed the subjective taste alterations quantitatively in BMS[36]. Taste alterations have raised a hypothesis of an aetiological role of dysfunction of the chorda tympani, as well as other nerves carrying taste, such as the glossopharyngeal, vagus and greater petrosal nerves, in BMS pain as in normal physiological conditions taste afferents exert inhibition of the somatosensory pain system. This hypothesis therefore suggests that pain in BMS arises as a disinhibition phenomenon after damage to the nerves associated with taste[37]. This may be the case, but in the majority of patients it is unlikely to be due to an isolated chorda tympani neuropathy or damage to only taste afferents but rather part of a more widespread small fibre neuropathy involving both the small somatosensory and taste afferents of the intraoral mucosa[4,11,28]. Preferential damage to the small Aδ fibres has been associated with central neuropathic pain as the Aδ cool fibres in normal conditions inhibit the slow C fibre pain system[39], and Aδ cool fibres have been shown to be more affected than the C fibres in BMS patients[26,28]. Thus, an imbalance in Aδ and C fibre signalling might be responsible for burning neuropathic pain[39,40] in BMS patients[4,14,15].

In addition to signs of peripheral neuropathy, approximately 35%–50% of the patients show signs indicating a major role for central nervous system alterations in their BMS pain[4,14,17,21,33,41,42], closely resembling other central pain conditions[38]. These patients may also show hypoesthesia in thermal QST, but normal peripheral innervation and, additionally, demonstrate neurophysiological signs of deficient descending inhibition of the trigeminal brainstem complex (for more detailed reviews c.f. [4,15]). According to one study[21], peripheral lidocaine block may be used to differentiate the peripheral and central subgroups of BMS; only the peripheral type benefits from local anaesthesia, while the central type may even get worse. In individual patients, peripheral and central features may co-exist; i.e. BMS patients may have a peripheral neuropathic pain condition with signs of deficient top-down inhibitory control; a similar neurophysiological profile can be identified in patients with clinically obvious trigeminal neuropathic pain[11,30]. BMS patients with

predominantly a more centrally driven pain also demonstrate the highest incidence of comorbid psychiatric disorders, depression and anxiety[21,43]. These psychiatric disorders are associated with low brain dopamine tone, as are Type C personality disorders which have been associated with BMS in valid, structured psychiatric investigations[43].

Neurophysiological findings indicating a deficient inhibition of the trigeminal brainstem complex in BMS[22] similar to Parkinson's disease with striatal dopamine depletion led on to a series of positron emission tomography studies examining the brain's dopamine system function in BMS and neuropathic pain[41,42,44,45]. These studies showed similar alterations in the striatal dopamine function of BMS patients as in early Parkinson's disease, a brain dopamine deficit disorder that has been related both to central neuropathic pain and an increased incidence of BMS[4,14,41,46]. Furthermore, there is recent evidence that a single nucleotide polymorphism of the dopamine D2 receptor gene, DRD2 C> T957, that regulates the striatal synaptic dopamine concentration is associated with pain experience in orofacial neuropathic pain[28,47]. TT homozygote genotype associates to the lowest striatal dopamine tone and leads to the most severe pain ratings and highest scores of pain interference in daily life in BMS patients[28,47]. Thus, deficient top-down inhibitory control via the nigrostriatal dopamine system seems to form one part of the puzzle of the aetiology and pathophysiology of BMS, either alone or in combination with peripheral neuropathic involvement.

In addition, in functional and structural neuroimaging studies, patients with BMS have shown neuroplastic changes in regions and networks of the brain associated with somatosensory functions, pain perception and control[48–51], similar to those found in other chronic neuropathic pain conditions[52].

To summarise, BMS patients with clinically similar presentations can be subdivided into three distinct neuropathic pain subgroups when accurate diagnostics is applied: (1) subclinical neuropathic pain after damage to the trigeminal nerve or its lower divisions or the trigeminal brainstem complex; (2) pain associated with focal small fibre neuropathy of the tongue and intraoral mucosa; and (3) central pain with signs of deficient top-down inhibitory control of the trigeminal brainstem complex via the brain dopamine-opioid circuit. Importantly, it seems that the efficacy of different treatments may differ between these aetiological subgroups. Table 1 presents the findings in accurate diagnostic investigations according to the specific subtype of BMS with reference to optimally tailored treatment options that should be systematically assessed in future RCTs.

Endocrinology studies in BMS have largely been restricted to use of animal models and findings are conflicting. When all studies are examined in combination, however, it has been hypothesised that related to the onset of menopause there is a decrease in gonadal steroids necessary for the synthesis of neuroprotective steroids such as allopregnanolone and dehydroepiandrosterone. In the context of stress reaction and hypothalamus-pituitary-adrenal axis

Table 1 Three BMS subtypes in advanced diagnostic testing, with treatment options.

BMS/ Peripheral 1 Small fibre neuropathy (SFN)	BMS/ Peripheral 2 Trigeminal neuropathic pain	BMS/ Central pain Psychiatric comorbidity
Normal brainstem reflexes and ENMG (normal large fibre function)	Deficits in brainstem reflex recordings and ENMG	Abnormal habituation of blink reflex
Thermal sensory loss in QST	Thermal sensory loss in QST	Central reorganisation in neuroimaging Dopamine deficit in PET
Reduced ENFD in oral mucosa	Reduced ENFD in oral mucosa	Normal ENFD QST may be abnormal
Local anaesthesia effective	Local anaesthesia effective	Local anaesthesia not effective
Topical clonazepam Neuropathic modulatory agents for example: anticonvulsants, antidepressants Topical capsaicin? HRT/DHEA?	Neuropathic modulatory agents for example: anticonvulsants, antidepressants Topical capsaicin? Topical clonazepam? HRT/DHEA?	Dopaminergic drugs Tricyclic antidepressants NSRI/SSRI? HRT/DHEA?
Therapeutic brain stimulation?	Therapeutic brain stimulation	Therapeutic brain stimulation
Aetiology of SFN –> specifically targeted interventions	Cognitive behavioral therapy	Cognitive behavioral therapy

ENMG, electroneuromyography; ENFD, epithelial nerve fibre density; QST, quantitative sensory testing; NSRI, noradrenaline reuptake inhibitors; SSRI, serotonin reuptake inhibitors; HRT, hormone replacement therapy; DHEA, dehydroepiandrosterone.

Table 2 Causes of intraoral burning to exclude in patients presenting with intraoral burning symptoms.

Cause of intraoral burning	Investigation required
Candidiasis	Intraoral swab for *C. Albicans* or smear for fungal hyphae
Lichen Planus	Incisional biopsy
Hyposalivation	Salivary gland function and salivary flow studies
Contact mucosal reactivity	Incisional biopsy
Medication induced: Angiotensin-converting enzyme inhibitorsAngiotensin receptor blockers	Full medical history
Anaemia	Full blood count
Deficiencies of vitamin B12 or folic acid	Vitamin B12 and folate levels
Sjorgen's syndrome	Autoantibodies, labial gland biopsy
Diabetes	Fasting blood glucose and/or HbA1c
Hypothyroidism	Thyroid panel

dysfunction this decrease leads to poor neuronal repair and increased neurodegeneration, preferentially of the most vulnerable small myelinated Aδ nerve fibres and dopaminergic neurons that seem to be critical components in the pathogenesis of BMS[4]. Menopause and stress related steroid dysregulation can also lead to a decrease in minor salivary gland function, which contributes to the symptoms of xerostomia often reported in BMS, along with preclinical inflammation of oral mucosa which in turn may generate the sensation of oral burning[17]. Other neuroendocrine changes have also been reported, with BMS patients having lower plasma adrenaline levels[53] and alterations in cortisol levels[54].

Psychological factors also play an important part in BMS, as in all chronic pain conditions, with anxiety and depression being frequently reported in questionnaire studies on patients with BMS[21,55,56]. When assessing the reports on psychiatric morbidity in BMS, it should be noticed that most of these studies have adopted patient questionnaires that are not valid tools for psychiatric diagnostics. Nevertheless, one appropriate study applying current diagnostic criteria for BMS and well-validated structured psychiatric interviews (SCID axis I and II) for both state and lifetime trait diagnoses reported increased incidence of depression and anxiety as well as type C personality disorders in BMS[43]. These conditions were not, however, found aetiological causes but instead, comorbid disorders in BMS that may share central hypo-dopamine dysfunction as a common vulnerability factor[4,43]. Although the very skewed sex distribution of BMS with up to 20:1 female to male preponderance[4] makes comparisons between genders ambiguous, female patients with BMS have been reported more likely to have psychogenic disturbances than male patients[57]. BMS has also been suggested to have a biopsychosocial and somatisation component, as the onset of the burning symptoms of BMS may sometimes be triggered by an acutely stressful life event, and this can contribute to maintenance of symptoms if it is not addressed in the patient's management plan[58]. In addition, as in other chronic pain conditions, psychosocial stressors with consequent alterations in the plasma steroid profile may make existing BMS symptoms worse[4,17].

As in other chronic pain conditions, patients with BMS have also been found to have poor quality sleep compared to control patients[59–61], and sleep disorders may also increase the risk of developing BMS[62]. However, the reports on sleep disturbances in BMS patients are conflicting with some studies reporting high incidence of sleep difficulties, and others that up to 70% of the patients have normal sleep quality[4]. Some studies have reported a subgroup of BMS patients with a so called night benefit phenomenon; i.e., the pain does not disturb sleep and is significantly better in the morning, getting worse during the day[58]. Regarding the dopamine hypothesis of BMS it is interesting that Parkinson's disease patients show similar night benefit in their symptoms because more dopamine is released during the night[15]. The effect of sleep in BMS may also be linked to the presence of psychological factors, and therefore sleep disturbance may simply be linked to associated psychiatric disorders via shared vulnerability to BMS pain and depression or anxiety[43]. Emerging research in circadian clock dysfunction may also contribute to pathophysiology of BMS, particularly given that pain perception, depression, anxiety and sleep disorders are all linked with circadian disturbances, and are also closely linked to BMS[63]. To conclude, based on current evidence, no causal relationships can be established between sleep quality and BMS pain, although disturbed sleep occurs in a subgroup of BMS patients, possibly as a parallel phenomenon to psychiatric morbidity[43].

Presentation and diagnosis

Intraoral burning pain is the presenting complaint of patients with BMS, this is frequently accompanied by complaints of dysgeusia and xerostomia. The onset of symptoms is typically spontaneous, however, in some cases can occur after a precipitating event. The symptoms are typically bilateral and

localised to the anterior two thirds of the tongue, but any part of the oral mucosa including the lips, palate, gingiva, buccal mucosa and oropharynx can be affected. In addition, pain symptoms of BMS typically range in intensity from moderate to severe, and have a negative impact on quality of life[28,59,60,64]. Pain intensity typically fluctuates with patients often waking with little to no pain, and as the day progresses the pain intensity increases; however sleep may not be disturbed by the pain[11,59,60].

Examination of the oral mucosa is unremarkable in patients with BMS and diagnosis is one of exclusion, the aim being to exclude any organic causes of secondary intraoral burning pain, and therefore ensure a correct diagnosis of BMS. Common causes of intraoral burning pain are summarised in Table 2, and as such for a diagnosis of BMS to be made the causes listed must be excluded. Previously, patients who complained of intraoral burning and had an underlying cause identified were diagnosed as having secondary BMS. However, with the introduction of the International Classification of Orofacial Pain 2019[2] these patients are now placed within the domain of oral mucosal pain with a known local or systemic cause. Difficulty occurs when a patient presents with an underlying cause of the intraoral burning pain, and once the underlying factors have been addressed the intraoral burning remains. In these patients it has been suggested that the diagnosis of BMS can be made as it is possible for BMS and underlying secondary burning mouth symptoms to co-exist[65]. Regarding the recent findings of neuropathic aetiology in the majority of BMS patients, it is important to perform a proper neurological examination, testing somatosensory and taste functions within the trigeminal distributions and intraorally. Especially in the rare cases of unilateral BMS symptoms, an underlying neuropathic aetiology should be carefully searched. Nevertheless, the clinical neurological examination will mostly remain normal or equivocal even in BMS patients with an underlying neuropathic condition as the diagnostic accuracy of clinical sensory testing is rather poor even in evident trigeminal neuropathies[16,29,66]. Thus, if available, neurophysiological and psychophysical testing is highly recommended to diagnose and classify BMS patients correctly, especially in order to guide the treatment trials (Table 1).

Management

An integral part of management of BMS is ensuring a correct and timely diagnosis as per the previous section. Delayed or incorrect diagnosis increases the risk for chronic and more severe pain as well as the incidence of psychiatric comorbidity[67,68]. Once it has been established that the patient has no underlying factors causing the burning symptoms, or any underlying factors have been corrected with no improvement of symptoms, then the treatment for BMS should be started. Management of the condition can be challenging, with little high quality evidence base to follow[4]. A recent Cochrane systematic review found there to be low level evidence for treatment, and the only management strategies showing low-quality evidence of long term benefit were: topical capsaicin, topical benzodiazepines and cognitive behavioural therapy[69]. The most commonly used clinical and research management strategies are summarised below.

Topical therapies investigated for BMS include: clonazepam, capsaicin and laser therapy. There is better evidence for the first two options that can be particularly useful for patients who are unable to, or do not wish to take systemic medications. Topical clonazepam, a benzodiazepine, reduces symptoms associated with BMS [4,20,70,71]. It is taken by holding the medication in the mouth for 3 min and spitting it out. However, it may have the side effects of xerostomia and fatigue. In addition, the symptoms may return on cessation of the medication, therefore the patient may need to take it long term, causing potential issues with dependence as there may be slight systemic absorption of the drug even with this local application method. Topical capsaicin, a compound found in chilli peppers, may be effective in management of BMS symptoms[71] by desensitising pain receptors. It does however, cause an initial increase in the burning sensation immediately after application which the patient should be warned about, and can also cause dyspepsia, meaning that caution should be taken when prescribing this for patients with pre-existing gastrointestinal disorders[71]. Low level laser therapy has also been suggested to be effective in patients with BMS[72], working by increasing serotonins, and certain endorphins, as well as depolarising C-fibres, however, this therapy may not be widely available and further research is required to provide more robust evidence of its effectiveness. Topical local anaesthetic agents may also provide relief, although only temporarily[71].

Systemic medications include: clonazepam, gabapentin, pregabalin and amitriptyline. Clonazepam can be taken systemically for BMS where appropriate, or used in a combined topical/systemic route, whereby the patient holds the medication in the mouth to

achieve a topical effect, before swallowing it. Preliminary evidence shows that systemic clonazepam is effective in pain reduction in BMS, however its use should be limited to short-term treatment because of the serious adverse effects of benzodiazepines in long-term use including cognitive impairment and dependence[4]. Further studies are needed to fully evaluate its safety for long-term use in BMS[73,74]. Gabapentin and pregabalin, which are anticonvulsant medications used to treat neuropathic pain, are increasingly being used in clinical practice for the management of chronic orofacial pain conditions, although there is very scarce evidence from properly conducted RCTs for their efficacy in BMS[71]. Amitriptyline is a tricyclic antidepressant which is also commonly used in the management of neuropathic pain, and it has been used in patients with BMS with some success although evidence for its efficacy is scarce[4,69]. Other antidepressants, such as specific serotonin and serotonin-noradrenalin reuptake inhibitors have shown contradictory evidence for efficacy in a few single trials, requiring further properly controlled randomised trials applying current diagnostic criteria[4,69]. In line with findings of deficient dopaminergic tone in a subgroup of BMS patients, there is some preliminary evidence that dopaminergic drugs, such as dopamine D2 receptor agonist pramipexol, may be beneficial for BMS pain[75,76]. Management of BMS with systemic medications may be needed in patients where topical therapy is unsuccessful, however, the prescribing clinician should bear in mind the potential side effects of these medications as well as their potential to induce dependence. Some of the medications can cause xerostomia, which in turn can contribute to further intraoral pain if used in the long-term.

Other systemic treatments for BMS include alphalipoic acid (ALA) that is a mitochondrial coenzyme with some antioxidant and neuroprotective properties; it is sold in health food shops. The evidence for efficacy of ALA in BMS is scarce, and results of the RCTs performed so far contradictory and thus, it has not been recommended for the treatment of BMS in some of the recent comprehensive reviews[4,69]. According to conclusions of one review, though[71], ALA may induce pain reduction when taken alone or with gabapentin in BMS; its benefit is a low side effect profile.

As mentioned previously, BMS has a biopsychosocial component, nearly half of the patients showing significant psychiatric comorbidity, which should not be forgotten in patient management. Patients often rely on a biomedical explanation for their pain and suffering, and when an organic cause is not found it can lead to symptom maintenance[58]. It is therefore important to remember to reassure BMS patients regarding their diagnosis, and to incorporate psychological management into their treatment plan along with other treatments[4]. This should include a psychological evaluation, and where appropriate referral to a clinical psychologist or a psychiatrist. Psychological management strategies in clinical practice include use of cognitive behavioural therapy, as well as other psychological interventions[4,77]. Although there is low-level evidence that cognitive behavioural therapy reduces the symptoms of BMS, further research is needed also in this area[69].

Due to the possible, previously mentioned, endocrine aetiology linked to the menopause it has been suggested that hormone replacement therapy (HRT) may be of benefit to BMS patients who present at or after menopause. There is, however, only low level evidence for its use, and a major concern is of safety, particularly as the patients who would require it for BMS are likely to be elderly and the use of HRT may then be contraindicated[17]. Along the same lines, and additionally based on anecdotal finding of decreased morning salivary dehydroepiandrosterone (DHEA) concentration in BMS[78], neuroprotective steroids such as DHEA have been suggested to be worth investigating further with properly conducted randomised controlled trials (RCT) in early BMS[4].

As a novel option, therapeutic brain stimulation with repetitive transcranial magnetic stimulation (rTMS) has emerged as an effective treatment for neuropathic pain[79], thus offering a promising treatment option also for BMS pain[25,80]. rTMS exerts its effects via induction of neural plasticity and release of endogenous dopamine and opioids[47,79]. Some preliminary evidence suggests that high-frequency rTMS given to the right parieto-opercular region[25] or the left dorsolateral prefrontal cortex[80] may be highly effective in reducing BMS pain and its interference in daily activities, but further controlled trials are required to confirm its role in the long-term treatment of BMS.

Management of BMS is challenging for the clinician, and the evidence base for management remains poor, with only a limited number of RCTs with a low risk of bias applying appropriate diagnostic criteria for BMS, with large enough study groups available. Medications which can prove to be successful with some patients, will not be successful with others. In the light of recent pathophysiological evidence this heterogeneity is likely to depend on the specific subtype of BMS (Table 1), which cannot be

defined in clinical examination. Currently in the clinic, patients often need to be trialled on a range of different management strategies until a successful approach is found. If a more systematic approach with accurate and sensitive diagnostics tools is applied in the clinic and especially in future RCTs, taking into account the specific subtype of BMS as suggested in Table 1, the efficacy of tailored treatments may be rationally assessed and overall benefit for the patients will finally increase. Recent systematic and comprehensive reviews have highlighted the importance for high quality RCTs in order to fully assess the best management strategies for BMS patients[4,69,81].

Future directions

Given the impact BMS can have on patients, and the sparsity of high level evidence on management, further research is needed in the area. A major barrier in clinical research concerns the differing definitions used for what BMS is, meaning that patients who do not have true BMS may be included in clinical trials for aetiology, pathophysiology and treatment of BMS[4,5,11]. Therefore, development and use of specific research diagnostic criteria are currently under development, and further research is needed for ensuring that only patients who fit the clinical criteria for true primary BMS are included. These research diagnostic criteria should be validated against specific diagnostic means such as neurophysiological and QST investigations as well as neuropathological examination or brain imaging data in order to be able to correctly sub-classify the different neuropathic profiles of patient with clinically similar representation of BMS[15,16]. With valid diagnostic criteria and diagnostic testing, further research can be carried out on the various management aspects to determine which treatments are most successful in the specific subtypes of BMS patients (Table 1). Future research should also focus on the aetiology of the small fibre neuropathy in BMS, as many of its causes may be treatable. Another research line with specific bearing to novel treatment options is the dysfunction of the central dopaminergic and serotoninergic system in BMS. Suitable and specific diagnostic tools for the dysfunction would allow specific treatments with dopaminergic medications and therapeutic brain stimulation for this BMS patient group. Regarding neuroendocrine alterations as a potential trigger of BMS, HRT and especially neuroprotective steroids such as DHEA seem to offer an interesting novel, may be even preventive treatment line for BMS, which should be addressed in RCTs with properly set diagnosis of early BMS in younger patients. There is also great need for further studies examining non-pharmacological approaches to management of BMS patients given the biopsychosocial component of the disorder, as well as the potential of therapeutic neuromodulation with rapidly evolving brain stimulation techniques.

Conclusion

In conclusion, in the majority (over 90%) of patients diagnosed with adequate diagnostic tools and proper criteria, BMS seems to be a neuropathic pain condition consisting of different, distinct peripheral and central subtypes when accurate neurophysiological and psychophysical diagnostics is applied. However, a small subgroup of BMS patients falls within normal limits of the so far applied diagnostic tests. They may either represent a separate disease entity and may fall within the remit of the recently defined IASP term of nociplastic pain[82], or just reflect the relative insensitivity of the currently available diagnostic tools. Due to insensitivity of clinical sensory testing, in routine clinical examination of BMS patients, the underlying neuropathic components cannot usually be detected. The first step in the diagnostic process is ensuring that all local and systemic organic causes of intraoral burning are excluded to guarantee an accurate clinical diagnosis of BMS. BMS has a large impact on quality of life of those who suffer from it. The current evidence base is often conflicting and of low level regarding management. In the future, detailed, advanced quantitative diagnostics will hopefully aid in assessing treatment efficacy and tailoring management in distinct sub-clusters of BMS patients.

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