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An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives

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Summary

Burning mouth syndrome (BMS) is a chronic orofacial pain disorder of unknown cause. It is more common in peri- and postmenopausal women, and sex hormone dysregulation is believed to be an important causative factor. Psychosocial events often trigger or exacerbate symptoms, and persons with BMS appear to be predisposed toward anxiety and depression. Atrophy of small nerve fibers in the tongue epithelium has been reported, and potential neuropathic mechanisms for BMS are now widely investigated. Historically, BMS was thought to comprise endocrinological, psychosocial, and neuropathic components. Neuroprotective steroids and glial cell line–derived neurotrophic factor family ligands may have pivotal roles in the peripheral mechanisms associated with atrophy of small nerve fibers. Denervation of chorda tympani nerve fibers that innervate fungiform buds leads to alternative trigeminal innervation, which results in dysgeusia and burning pain when eating hot foods. With regard to the central mechanism of BMS, depletion of neuroprotective steroids alters the brain network related mood and pain modulation. Peripheral mechanistic studies support the use of topical clonazepam and capsaicin for the management of BMS, and some evidence supports the use of cognitive behavioral therapy. Hormone replacement therapy may address the causes of BMS, although adverse effects prevent its use as a first-line treatment. Selective serotonin

reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) may have important benefits, and well-designed controlled studies are expected. Other treatment options to be investigated include brain stimulation and TSPO (translocator protein 18 KDa) ligands.

Introduction

Burning mouth symptoms that occurred as secondary phenomena attributable to local conditions[1–9] were previously referred to as "secondary" burning mouth syndrome (BMS),[10] but BMS now refers only to burning symptoms not attributable to local or systemic causes.[11] After excluding such conditions, some common characteristics of BMS are important. Burning sensations are usually bilateral, and intensity fluctuates.[2] The most common site is the tip of the tongue, but pain is often noted at the lateral border of the tongue, lips, and hard palate.[12] Affected persons often complain of dysgeusia,[13] which may be accompanied by subjective xerostomia.[14] Peri- and postmenopausal women are predisposed to the condition. Some patients exhibit depressive symptoms and anxiety[15–18] and may express concern regarding the presence of a malignant condition.[10,16] Psychosocial stressors can trigger or worsen pain,[15,19] while eating and drinking usually alleviate pain.[10,20] These manifestations are characteristic features of BMS and should not be excluded as secondary signs or symptoms of primary disease. Agreement on these clinical features yields important clues in understanding the underlying pathophysiology of BMS.

Despite considerable knowledge regarding these common manifestations, BMS remains an idiopathic orofacial pain condition and one of the most frequently studied oral pathologies in pain research. Although a neuropathic etiology is

suspected by some researchers,[21] traditional chronic pain classifications do not include BMS in the neuropathic pain group.[22,23] This review surveys the literature regarding the pathophysiology of BMS and examines the condition from neuropathic, endocrinological and psychological perspectives.

1. Etiological perspectives

Although BMS remains an idiopathic pain condition, some findings are frequently observed in BMS patients. BMS has long been thought to be associated with psychosocial distress and to be induced by mental disorders like depression and anxiety.[17,24] The higher incidence of BMS in postmenopausal women led to a diagnosis of climacteric disorder.[25–27] This consensus increased the research focus on psychological stress, and many studies attempted to identify relationships between psychosocial,[28,29] endocrinological,[30,31] and immunological[32,33] factors believed to be associated with mental stress. Nevertheless, the cause of BMS remained elusive. In the late 1980s, studies began to report neurophysiological and electrophysiological data of BMS patients and yielded new important neurological insights.[34–36] Numerous pathological and imaging studies followed and led to the hypothesis that BMS could be a neuropathic pain condition.[37–39] Accumulating evidence suggests that the cause of BMS involves psychosocial, endocrinological, and neuropathic components.[37–40] Studies have examined its etiology and pathophysiology by analyzing clinical data or by using animal models that mimic characteristic findings. To clarify the signs and symptoms of BMS, this review will examine these three pathophysiological components and their possible relationships.

1) Neuropathic component

In 2005, Lauria et al. observed that small nerve fibers in the tongue epithelium were atrophied in BMS patients.[37] They also found a decrease in the number of nerve fibers innervating taste buds. These observations suggested that BMS patients could have peripheral neuropathy. Peripheral nerve atrophy specifically occurred in small-diameter fibers in the epithelium of BMS patients; subepithelial nerve fibers were less often affected.[40,41]

BMS patients frequently complain of dysgeusia and phantom taste.[42–44] Dysgeusia is defined as persistent alteration of taste in the presence of taste stimulation. Phantom taste is defined as an abnormal taste occurring in the absence of stimulation.[45] Studies reported that the ratio of taste detection threshold and tingling sensation was significantly altered in BMS patients[46] and that this alteration depended on the duration of symptoms.[47] These abnormal taste sensations are common symptoms of BMS and are believed to be involved in the etiology of BMS. The most common phantom tastes reported in BMS patients are “bitter” and “metallic” tastes.[48,49] Phantom taste likely results from disinhibition of the glossopharyngeal nerve after damage to the chorda tympani nerve.[47,48] The morphological studies discussed above reported decreases in the density of myelinated and unmyelinated thin fibers in the tongue epithelium of BMS patients.[37,40,50] These small-diameter fibers, which are normally observed in taste buds and receive impulses from taste cells, are absent in the taste buds of BMS patients; only fibers very close to taste buds surrounding papillae remain.[51] Grushka et al. reported that the density of fungiform papillae was greater in BMS patients than in controls and suggested that this high density of fungiform papillae could be a risk factor of BMS.[52] These findings are of concern, as they suggest that dysgeusia/phantom taste may be a kind of

neuropathic symptom caused by deafferentation of the chorda tympani nerve.[47,48] The challenge then remain to explain the trigger or cause of such a deafferentation in the absence of macro-trauma to the nerve.

Studies of the interaction of pain and taste have yielded a number of important insights. First, trigeminal and gustatory nerve fibers may interact by a peripheral mechanism. The anterior two thirds of the tongue is innervated by chorda tympani nerve fibers of the lingual nerve. This is the area most commonly affected by BMS, and it has a large number of taste buds in fungiform papillae.[53,54] These papillae and taste buds innervated by chorda tympani nerve fibers survive even after denervation of the chorda tympani nerve.[55] When this occurs, substance P (sP) and calcitonin gene–related peptide (CGRP)–containing nerve fibers are important in nerve fiber survival.[56] After chorda tympani nerve injury in the middle ear, surviving taste buds in fungiform papillae in the territory of the chorda tympani nerve disappeared after application of capsaicin, which depletes sP and CGRP.[56] Furthermore, fungiform papillae are innervated by fibers expressing $P2X_2$ and $P2X_3$ receptors and those expressing transient receptor potential vanilloid 1 (TRPV1). Most $P2X_2$ and $P2X_3$ immunoreactivity was abolished after transection of the chorda tympani nerve, although TRPV1 immunoreactivity remained unchanged.[57] These findings indicate that most fungiform papillae nerve fibers expressing $P2X_2$ and $P2X_3$ receptors are derived from the chorda tympani nerve, whereas TRPV1-immunoreactive fibers derive from the trigeminal nerve.[57] These findings in animals suggest that purinergic fibers are involved in conducting taste signals and that TRPV1-positive fibers that conduct hot “taste” and nociceptive signals take over after denervation of these purinergic fibers. Previous studies reported increased expression of TRPV1,[40] nerve growth factor (NGF),[40] and P2X receptors[41] in

damaged small nerve fibers from BMS patients. Further, changes were noted in the expression of endocannabinoid receptors cannabinoid (CB)1 and CB2, which modulate TRPV1 activation.[58] CB2 but not CB1 is important in anti-nociception in the trigeminal system.[59] In BMS patients, CB1 is suppressed, while TRPV1 and CB2 expression is high.[58] Taken together, these findings suggest an accelerated role of TRPV1 receptors in BMS. Patients often complain of hypersensitivity to capsaicin but not to taste stimuli. Capsaicin causes a bitter taste, and some salts, like $CuSO_4$, $ZnSO_4$, and $FeSO_4$, mediate metallic taste via TRPV1.[60] These findings could possibly explain the peripheral mechanism of pain–taste interaction. Thus, in summary denervation of the chorda tympani nerve fibers that innervate fungiform buds may lead to alternative trigeminal innervation, which subsequently could result in dysgeusia and pain when eating hot food.

Second, central involvement was reported in the pain–taste interaction. There are two pathways that conduct nociceptive signals to the brain stem through trigeminal afferents. First, trigeminal afferents travel along the trigeminal spinal tract and reach the trigeminal spinal nuclei, and second, a certain portion of trigeminal afferents reach the nucleus tractus solitarii (NTS) directly. [53,54,61] Trigeminal afferents have interconnections with chorda tympani nerve fibers at both sites. Although chorda tympani nerve fibers reach the NTS and connect with trigeminal sensory subnuclei via interneurons,[53,62] it is reported that subnucleus caudalis neurons receiving nociceptive thermal inputs do not receive any gustatory controls.[63] Contrarily, evidence indicates that the chorda tympani, glossopharyngeal, and trigeminal nerves control their functions mutually and that impulses from these nerve fibers help modulate interrelated nerve activity in the NTS.[53,54,64] Morphological studies have revealed that there are many NTS neurons projecting to the parabrachial nucleus

(PBN) and few neurons projecting to the thalamus.[61,65] Further, ascending projections from the PBN terminate in the central amygdaloid nucleus and thus nociceptive information from the NTS is mainly transmitted to the medial pain system, but not to the lateral pain system.[61,66] BMS patients report that pain is alleviated by eating non-hot food and drinking.[20] Hirsch reported that topical sucralose alleviated pain in BMS.[67] Schöbel reported a sweet taste and chorda tympani nerve block alter capsaicin-induced lingual pain in adults and that oral capsaicin suppressed central taste transmission.[68] Dental deafferentation may also lead to a taste deficit.[69] Lehman et al. studied the effect of nerve blocks on gustatory function[70] and found diminished taste sensation in bilateral glossopharyngeal nerve territory after a lingual nerve block. However, the taste sensitivity of the left (contralateral) glossopharyngeal nerve increased after right chorda tympani nerve block.[70] Further, they reported evidence of an obvious acceleration in contralateral taste sensation not only in the chorda tympani nerve but also in the glossopharyngeal nerve territory after unilateral chorda tympani nerve block.[45] This acceleration was also observed in the bilateral glossopharyngeal nerve territory after bilateral chorda tympani nerve block.[45] These local anesthetic studies of the lingual and chorda tympani nerves suggest the possibility of central modulation rather than peripheral interaction of these nerves.[45,70] A functional MRI (fMRI) study showed evidence of inhibition of brain activation in pain-related regions during a cold pressor test after administration of glucose[71]. These results suggest that taste impairment disinhibits taste analgesia. Damage to the chorda tympani nerve may block its inhibitory action on the trigeminal nerve and disinhibitory action on the glossopharyngeal nerve, which are seen not only at the medullary level but probably at higher levels, as well. Taken together, the evidence indicates that small fibers in the tongue epithelium atrophy in BMS and that impulses

from these afferents decrease. Under such conditions, mutual sensory modulation by these nerves changes at the NTS. Further, deafferentation–hyperactivity of the somatosensory regions of the trigeminal system might develop after loss of pain inhibition, due to taste fiber damage of the chorda tympani nerve.[20,46,72,73]

BMS patients often complain of pain when eating hot or spicy foods.[74] Quantitative sensory testing (QST) studies of the pain threshold of BMS patients have yielded inconsistent findings. Some studies observed increased sensitivity in warm and cold detection,[75] increased thermal pain sensitivity (warm[76] and cold[75] allodynia), and heat hyperalgesia,[34,77] while others reported less sensitive changes in warm[36,78] and cold[78,79] detection in the affected area in BMS patients. While changes in pain and detection thresholds to warm and cold stimuli have been inconsistent, BMS patients clearly have decreased pain tolerance to noxious heat stimulation[34,77] and topical capsaicin.[36,75] Ito reported prolonged pain perception not only to painful heat but to cold and mechanical stimulation, as well.[77] Our study revealed accumulated pain response was increased, although pain threshold was not decreased in BMS patients.[80] These findings suggest that once persons with BMS perceive pain, tolerability is reduced.[34] An electrophysiological study reported that habituation of the blink reflex can be suppressed in 20–36% of BMS patients.[35] These psychophysical and electrophysiological studies revealed abnormal responses that suggest temporal summation induced by central sensitization. Electrophysiological data revealed an exaggerated response in the trigeminofacial systems and trigeminal brainstem complex in patients with primary BMS.[81] BMS patients had an abnormal pain/detection threshold ratio in the extraterritorial region of the trigeminal system.[36] Local anesthetic block relieved pain in some BMS patients;[82] however, somatosensory blockade of trigeminal inputs aggravated pain in some patients.[82,83]

Gremeau-Richard observed comorbid mental distress in patients for whom lingual nerve block and topical clonazepam were ineffective.[82] These findings cannot be explained only by a peripheral mechanism.

2) Endocrinological component

What causes deafferentation of thin nerve fibers? In 2009, Woda et al.[27] proposed that reduced synthesis of ovarian steroids after menopause induces deficiency or dysfunction in adrenal steroids, which abolishes the neuroprotective effects of steroids on neural tissues.[27] Because BMS is an idiopathic condition, there are no animal models that clearly explain how depletion of gonadal steroids might result in morphological changes in somatosensory and gustatory fibers in the tongue. However, researchers have used animal models that mimic some major symptoms of BMS to study its pathophysiology. Ovariectomized animals are often used.[84] One study reported that the number of vaginal nerve fibers decreased after ovariectomy.[84] Ovariectomy induces thinning of tongue epithelium,[85,86] especially the keratinized layer,[86] and BMS patients also exhibit specific changes in the keratinized layer. In BMS patients, keratin 16, which is present in hyperproliferative epithelial cells, is abundant in spinous keratinocytes, which means keratinocytes are activated after possible epithelial damage.[87] Ovariectomy leads to upregulation of glial cell line–derived neurotrophic factor (GDNF) family ligands and their receptors.[88] mRNA expression of the GDNF family member artemin was increased in epithelial cells scraped from the tongues of BMS patients.[89] Animal models associated with increased artemin expression showed a fluorescent signal localized to basal epithelial cells and in heavily keratinized filiform papillae.[90] These results suggest that gonadal hormones are necessary for maintaining tongue epithelium thickness and that

artemin is important in keratinization. Further, artemin overexpression indicates overall atrophy of the lingual nerve, as compared with wild-type animals.[89,90] Interestingly, this atrophy was mainly observed in thinner fibers, and particularly in unmyelinated fibers, which corresponds to findings from BMS patients.[23,37,28] These animals showed hyper-innervation of artemin receptor (GFRα3)-positive fibers (some of which contained TRPV1) in the epithelial layer, and fungiform papillae. The densities of these fibers were much higher in transgenic mice that overexpress artemin than in wild-type mice,[90] and in rats treated with the artemin inducer 2,4,6-trinitrobenzenesulfonicacid (TNBS) than in vehicle-treated rats.[89] These findings resemble those seen in BMS patients, namely, elevated TRPV1 expression in atrophied small-nerve fibers.[40]

Many BMS patients complain of xerostomia, the subjective sensation of dry mouth.[13,91–94] Xerostomia is usually associated with decreased salivary flow rate,[95] although it is not always caused by hyposalivation.[96] It is generally accepted that hyposalivation leads to various oral complaints[97] and aggravates oral burning symptoms. Mental stress[98–100] and menopause[101,102] suppress salivary secretion, especially unstimulated flow rate. Some studies indicated that unstimulated salivary flow rate was significantly lower in BMS patients than in controls, despite the absence of a significant difference in stimulated flow rate.[103,104] Minor salivary glands are important in oral tissue lubrication,[105] and oral dryness in resting state is considerable because of decreased secretion by minor salivary glands.[106] Minor salivary glands may be more easily affected by denervation of the chorda tympani nerve because they are located in the lamina propria and purely parasympathetically innervated. Latent oral dryness keeps the oral mucous intact but may result in latent inflammation and subclinical changes in the tongue. Nakaya et al. reported that experimentally

drying the tongue increased nocifensive behavior against mechanical stimuli in rats without any inflammatory changes in the tongue epithelium and increased phosphorylation of extracellular signal-regulated kinase (ERK), a MAP kinase in trigeminal spinal subnucleus caudalis neurons, after noxious stimulation of the tongue.[107] Agha-Hosseini et al. reported that the severity of dry mouth was inversely correlated with whole salivary 17β-estradiol concentration[108] and positively correlated with whole salivary cortisol concentration.[109] Some studies reported elevation of levels of pro-inflammatory cytokines in saliva including IL-2,[33] IL-6 [33,110,111] and TNF-α,[111] and decrease in the level of anti-inflammatory cytokine IL-10 [110] in BMS patients when compared to controls. Authors have suggested that preclinical level of inflammation may be involved in the pathogenesis of BMS,[33] although other studies have described no significant changes of these cytokine levels in saliva.[112–114] Taken together, it is hypothesized that the lack of neuroprotective steroids leads to hypofunction of minor salivary glands that contributes in inducing oral dryness and preclinical inflammation of oral mucosa, and these peripheral changes may be involved in generating burning mouth symptoms.

Sex hormones are synthesized in gonadal organs and in the central and peripheral nervous systems.[115,116] In neural cells, these steroids are synthesized from cholesterol in the mitochondria and modulate transcription of DNA and subsequent protein synthesis in the nucleus.[117] These steroids are neuroprotective and are deeply involved in the synthesis of neurotransmitters that generate pain-related behaviors.[116] They modulate the function of various neurotransmitter receptors and exert neuroprotective effects.[118] Progesterone mediated a significantly better recovery from mechanical allodynia as compared with vehicle-treated rats when administered immediately after neuropathic surgery to the sciatic nerve.[119] GDNF and

its family modulate the effect of neuroprotective steroids.[120] Shinoda et al. noted increased mRNA expression of artemin in the epithelium of the tongue surface in BMS patients.[89] Further, they reported that induction of artemin in the rat tongue epithelium induced pain-related behavior to heat pain and increased TRPV1-positive afferents in tongue epithelium.[89] Boucher et al. reported that oral pain–related behavior was induced by ovariectomy but not by chorda tympani nerve transection in rats.[121] They also observed c-*fos*–like immunoreactivity both in the trigeminal subnucleus caudalis neurons and in neurons in the rostral NTS. This expression was significantly stronger in ovariectomized rats.[121] These results show that the deficit of gonadal steroids, namely neuroprotective steroids, directly or indirectly generates pain-related behaviors through the peripheral and the central mechanisms.

There is increasing evidence, including the findings of brain imaging studies, to explain the behavioral findings observed in neurophysiological and electrophysiological studies of BMS patients. fMRI studies revealed that noxious heat stimulation applied at the perioral region evoked greater activity in the anterior cingulate, motor, prefrontal, and insula cortices in BMS patients than in controls,[122,123] although perceived painful sensation was similar in BMS patients and controls. Further, ongoing noxious heat stimulation at the lower lip induced temporal summation of the brain activity in these areas in BMS patients.[124] Contrarily, it is reported that repetition of noxious stimulation with an appropriate interval induces pain habituation in healthy persons,[125,126] which is likely caused by C-fiber fatigue.[127,128] In our study, repeated thermal stimulation of the lower lip resulted in temporal suppression of brain activity, mainly in the cingulate cortices, without showing perceived pain habituation in BMS patients as compared with controls.[123] Thus, BMS brain more easily shows temporal summation to ongoing painful

stimulation and lack of pain inhibition against repeated noxious stimuli when compared with controls. These abnormal responses in brain areas associated with pain modulation may explain the findings of previous studies that BMS patients complained of reduction of pain tolerance[34,80,129] without showing reduction of pain threshold.[34,80,130] Voxel-based morphometry studies showed significant changes in grey matter volume in the medial prefrontal cortex,[131,132] hippocampus,[131] anterior and posterior cingulate cortices,[132] motor cortex,[132] and insula/frontal operculum.[132] Wada et al. studied the macroscopic fiber pathway of 83 brain regions from 60-axis diffusion tensor data by using 83 × 83 probability tractography and reported that the bilateral rostral anterior cingulate cortex, right medial orbitofrontal cortex, and left pars orbitalis had significant roles in local network metrics in the BMS brain.[133] Analysis of the BMS brain network showed that the anterior cingulate cortex and medial/orbital area of the prefrontal cortex had strong connectivity with the medial ascending pain pathway.[133] Further, Khan et al. reported significantly stronger connectivity between the medial prefrontal cortex and hippocampus in the afternoon than in the morning, and this difference was positively correlated with the degree of anxiety and depression.[134] As we learned before, denervation of the chorda tympani nerve leads to predominance of trigeminal inputs in the oral mucous membrane. Then a portion of nociceptive inputs via trigeminal afferents reach the NTS and lack of gustatory control again disinhibits trigeminal impulses here. Potentiated nociceptive signals ascend to the amygdala via the PBN and activate the medial pain system.[61,65,135] Jaaskelainen and colleagues hypothesized that impairment of the striatal dopamine loop may create a deficiency in inhibitory pain modulation in persons with chronic neuropathic orofacial pain.[136] The limited number of neurotransmitter positron emission tomography studies reported that fluorodopa uptake in the striatum was lower in BMS

patients than in controls.[38,39,137] These studies revealed a decline in striatal endogenous dopamine levels in BMS patients and a resulting defect in dopamine-mediated top-down pain modulation. Hagenberg et al. reported a decrease in D2 receptor coupling, which led to a decrease in D1/D2 ratio in the striatum of BMS patients.[39] Clinical reports support this intracranial dopaminergic dysregulation, and some researchers reported comorbidity with Parkinson disease[138–141] and, more recently, with restless legs syndrome (RLS).[138,142–146] In addition, some studies reported that the D2 agonist pramipexole alleviated burning mouth symptoms.[144,147] Some researchers have hypothesized that there is an overlap in the diagnoses of BMS and RLS.[142,143,147] In healthy persons, the motor cortex sends impulses to the striatum and receives feedback from the thalamus.[148] In RLS, the motor cortex is hyperexcitable,[149] as it is in BMS patients.[122,123] Nigrostriatal dopaminergic fibers have a crucial role in the onset of Parkinson disease and RLS.[137] Some of these fibers contain somatosensory fibers, and lesions in this pathway reveal deafferentation, which induces trigeminal pain.[150,151] In summary, BMS patients may perceive burning pain largely by central mechanisms based on the impaired pain modulation. Dysregulation of dopaminergic system at the basal ganglia may be involved in top-down control [136] from the motor cortex. Imaging studies of BMS patients show that the function of the brain areas that form the salience network is impaired.[152] These experimental findings indicate that the pain modulation system (motor cortex–basal ganglia–thalamus, anterior cingulate cortex–prefrontal cortex–insula cortex–hippocampus) is overused, even in the resting state, and easily overwhelmed in the BMS brain.

3) Psychological component

Researchers who studied character profiles of BMS patients have reported a high tendency towards neuroticism as shown in previous reports and these patients might have a personality trait making them cautious in starting new things.[153] They have suggested some personality traits are associated with depression.[153] Recent systematic review has reported the importance of anxiety and depression in comorbidity with BMS, although it did not found any differences in roles of these mood disorders from that in other chronic pain conditions.[18] To investigate the psychological involvement in BMS, we have to learn mood change after menopause and in the chronic pain conditions, first. It is well known that dysregulation of sex hormones—neuroprotective steroids leads to psychological distress.[154,155] Neuroprotective steroids, especially progesterone metabolites, modulate gamma-aminobutyric acid $(GABA)_A$ receptors.[156] Substantial evidence suggests that some neuroprotective steroids are associated with mood disorders via $GABA_A$ receptors.[157] Allopregnanolone exerts an anxiolytic effect by inducing positive allosteric modulation of the $GABA_A$ receptor and negative modulation of hypothalamic-pituitary-adrenal (HPA) axis activity.[155] Estradiol facilitates serotonergic neurotransmission in brain areas associated with affect and inhibits monoamine oxidases in ovariectomized animals.[158] Progesterone and estrogen regulate the endogenous anxiolytic effects of serotonin and allopregnanolone.[155] Allopregnanolone synthesis in the brain was affected by social isolation only when female mice had undergone ovariectomy,[159] which indicates that circulating gonadal steroids have a role in the biosyntheses of neuroprotective steroids in the brain. Therefore, after menopause the risks of anxiety and depression increase because of reduced serotonergic neurotransmission, reduced GABAergic inhibition and less

efficient HPA axis activity.[155] Furthermore, mental stress induces downregulation of the hypothalamic-pituitary-gonadal (HPG) and HPA axes by modulating the $GABA_A$ receptor,[160] thereby reducing sex hormone levels.[161] This modulation of the HPG axis is exerted by tonic GABAergic inhibition of gonadotropin-releasing hormone via extrasynaptic δ subunits.[160] In chronic mentally stress, especially post-traumatic stress disorder, the $GABA_A$ receptor configuration changes. Expressions of the α4, α5, and δ subunits significantly increase, and α1 and α2 subunit expression markedly decreases.[162] The α4, α5, and δ subunits are highly sensitive to neuroprotective steroids.[162] In women with BMS, there may be a decrease of neuroprotective steroids after menopause, and lack of neuroprotective steroid coupling to these subunits may lead to a lack of chloride influx that mediates GABAergic inhibition. Interestingly, benzodiazepines have been long used to treat mood disorders; the anxiolytic and sedative actions result from binding of α1 and α2 subunits,[163] whereas α4, α5 subunits have low sensitivity to benzodiazepines.[162] Two studies reported insufficient effectiveness of benzodiazepines, including clonazepam, for chronic anxiety in persons with BMS.[82,164] Gremeau-Richard et al. in a post-hoc analysis classified BMS in relation to response to topical clonazepam and lingual nerve block as peripherally affected cases (representing involvement of peripheral $GABA_A$ receptors), centrally affected cases (representing an unknown central mechanism), and combined peripherally and centrally affected cases. In the centrally affected group, anxiety and depression were more frequently observed,[82,165] which suggests that the insufficient effectiveness of clonazepam was due to lack of coupling to its receptors in the periphery and brain. Grushka et al.[166] reported that the longer patients had BMS, the less effective clonazepam was in alleviating pain, which might reflect changes in $GABA_A$ receptor configuration. It is known that reduced synthesis of allopregnanolone

in the hippocampus, amygdala and medial prefrontal cortex results in depression[167] and anxiety[168] and these brain areas are reported to indicate altered brain connectivity in BMS patients.[133,134]In summary, these findings suggest the role of neuroprotective steroids on mood in BMS patients and their effect on $GABA_A$ receptors. Figure 1 summarizes the possible pathophysiological mechanisms underlying BMS.

2. Management perspectives

The natural course and remission rate of BMS are unclear. Spontaneous remission within 5 years of onset was reported in only 3% of patients.[169] Longitudinal follow-up studies of BMS patients are expected to answer questions regarding specific temporal changes in manifestations and clarify the time course and prognosis of BMS. The etiology of BMS is not known and no curative treatment has been reported. Treatments found to be beneficial in meta-analyses include topical and systemic clonazepam[170,171] and cognitive behavioral therapy.[172] The details of these treatments have been reported elsewhere,[173,174] and this review article will discuss treatment options from an etiological perspective.

Peri- and postmenopausal women are predisposed to BMS;[25–27] thus, some clinicians recommend hormone replacement therapy (HRT) to such patients.[102,175] As described above, sex hormones are likely involved in the etiology of BMS; therefore, HRT could be the best treatment to address the cause of BMS. Unfortunately, few studies have investigated HRT for BMS. Using conjugated estrogens plus additional application of medroxyprogesterone acetate, Forabosco et al. examined the effect of HRT on oral symptoms.[175] Although the details of the treatment protocol were not described, HRT relieved xerostomia, burning discomfort and dysgeusia. In addition,

the authors used exfoliative cytology to study the ratio of collected cells originating from various layers of the oral mucous epithelium and reported that HRT increased the thickness of mature mucosal epithelium.[175] A cross-sectional study of the effect of HRT on oral symptoms found that oral pain and dry mouth were significantly less prevalent in patients receiving HRT than in those not receiving HRT.[92] The findings of these studies suggest that HRT is effective. However, HRT may increase the risk of thrombogenicity, and expert recommendations exclude elderly patients and those with a history of diabetes, coronary artery disease, stroke, or long-term menopause from the indications for HRT.[176] Another concern is that the effectiveness of HRT is not dose dependent. In an animal model, Li et al. reported that the number of vaginal nerve fibers was lower after ovariectomy and that estrogen replacement therapy restored fiber density; however, the treatment effect was not dose dependent.[84] Studies of the effects of neuroprotective steroids on nocifensive behaviors of animals after nerve injury showed significant recovery from neuropathic pain.[116,177–179] However, animals that received progesterone at a different schedule and duration showed no or insufficient recovery from neuropathic pain.[119] These findings from animal studies suggest that any management protocol involving gonadal steroids will not be straightforward. Although HRT appears promising, it may present safety concerns for subgroups such as elderly patients and women with a long menopause, both of which have an increased risk of BMS. These challenges complicate HRT for BMS patients.

From an endocrinological perspective, translocator protein 18KDa (TSPO) ligands are another candidate in BMS treatment. TSPO translocates cholesterol into mitochondria and exerts neurosteroidergic effects by synthesizing neuroprotective

steroids.[162] The TSPO ligand etifoxine is now used clinically to treat anxiety[180] and has been reported to reduce neuropathic pain.[181–183]

BMS has historically been regarded as a stress-related—a so-called psychogenic or functional—pain condition.[15–18,24] However, to our surprise few randomized controlled trials (RCTs) have examined the effect of antidepressants and anxiolytics other than clonazepam on BMS symptoms.[171] Fluoxetine was not superior to placebo in the management of pain and depression symptoms,[184] while trazodone showed moderate effectiveness.[185] Although some evidence from open-label studies supports the effectiveness of commonly used antidepressants for pain remission in BMS patients,[77,186–190] further study is required for a definitive conclusion. These drugs do not necessarily exert pain-relieving effects through their psychogenic mechanisms in chronic pain conditions. As mentioned above, SSRIs and SNRIs have neurosteroidergic effects at low, non-serotonergic, doses in the brain[162] and facilitate biosynthesis of neurosteroids.[191] These drugs are expected to be further investigated in controlled studies. Thus, current use of these drugs is primarily based on anecdotal clinical experience and is not supported by unambiguous evidence.[192] Clonazepam has been administered as a systemic,[193] topical,[165,194,195] and combined systemic/topical agent.[196] Topical clonazepam is a hypothesized etiology-based modality and has limited side effects.[165] This systemic and topical effect of clonazepam is believed to be exerted through its agonistic action on $GABA_A$ receptors.[165,171,197] There are a couple of studies that topical application of GABA analogs reduces experimental burning pain.[198,199] However, as described above, changes in the extrasynaptic $GABA_A$ receptor configuration have been noted, specifically downregulation of the α2 subunit (that is sensitive to benzodiazepines), and upregulation of the α4 and α5 subunits (that are insensitive to

benzodiazepines),[162] which complicates the working mechanism of clonazepam in BMS patients. Although a meta-analysis of clonazepam revealed good pain relief in BMS patients, only two of the included studies excluded secondary BMS.[171] Further RCT studies of the effects of clonazepam should include patients with strictly diagnosed primary BMS.

A recent network meta-analysis of pharmacological management of BMS pain indicated that capsaicin had beneficial effects.[200] Topical capsaicin is indeed an etiological treatment option.[201,202] As described above, in the epithelium of BMS patients, TRPV1 channels are overexpressed in remaining fibers after denervation of thin fibers.[40,58] Capsaicin induces depletion of substance P- and Ca^{2+}-dependent desensitization of TRPV1 channels, which leads to analgesia.[203] A double-blind crossover study revealed that a 0.025% capsaicin oral rinse significantly reduced pain.[202] When applied topically, capsaicin is generally safe.[204] However, topical application of capsaicin in the oral cavity often leads to intolerable adverse effects, including gastric pain, dysgeusia and severe burning pain in the oral mucosa.[202] Capsaicin has gastroprotective effects;[205] thus, gastric pain may be a sign of hypersensitivity to capsaicin. Capsaicin-induced analgesia requires activation of TRPV1 channels, which results in an extreme burning sensation and dysgeusia.[60,202] Further, some patients were reported to experience persistent burning pain even after repeated application of capsaicin.[202] This persistent burning sensation after capsaicin application is likely attributable to the fact that, even after desensitization, TRPV1 channels have further activation capacity.[203] These characteristic features of capsaicin must be further studied before topical capsaicin can be regarded as a first line-treatment for BMS.

Patients with Parkinson disease complain of persistent pain,[206] and BMS prevalence is high among this patient group.[140] Dopamine is deeply involved in pain modulation, although it has been suggested that pain in Parkinson disease was mainly due to muscular and structural abnormalities.[207] Some reports as mentioned previously suggest a dopaminergic mechanism in BMS etiology,[38,39,137,207–209] and converging evidence shows that neuroprotective steroids are involved in dopaminergic pain modulation.[210,211] A case series including five BMS patients with restless leg syndrome reported successful pain relief by L-Dopa.[143] The D2 agonist pramipexol relieved BMS symptoms.[144] These findings suggest that dopamine agonists have potential in BMS management. However, reports on the effects of L-Dopa are conflicting. One patient complained of burning mouth symptoms after taking daily L-Dopa, which completely disappeared after cessation of the drug.[139] Olanzapine, a dopamine blocker, alleviated BMS symptoms in two patients.[189] Because of the potential adverse effects of these drugs, including tardive dystonia,[212] they should be prescribed with caution.

Interventions that facilitate inhibitory pain pathways are now being utilized. Brain stimulation is applied by using two modalities: repetitive transcranial magnetic stimulation (rTMS)[213–215] and transcranial direct current stimulation (tDCS).[216] rTMS targets the primary motor cortex (M1),[215] secondary somatosensory cortex (S2),[215] and dorsolateral prefrontal cortex (dlPFC).[217] The mechanism of pain reduction is believed to be mediated by direct or indirect activation of functional connectivity between PFC and the limbic system,[215] which is involved in pain inhibition and emotional function (mood and affect).[134] tDCS has recently been used to manage orofacial pain, but its therapeutic effectiveness for chronic temporomandibular disorders is unclear.[218,219] These modalities are new, and well-designed RCTs are

needed in order to determine their effectiveness. Cognitive behavioral therapy (CBT) has also been used[220] and facilitated the pain modulation system of the brain in chronic pain patients.[221,222] CBT can be used with or without medication, as it has few serious complications.[223]

Conclusions

BMS is characterized by burning pain sensation, dysgeusia, xerostomia, and psychosocial distress. All these manifestations may be associated with menopause, which leads to neuroprotective steroid deficiency and subsequent atrophy of small-nerve fibers in the oral mucous membrane and central nervous system dysfunction resulting in alterations to the brain network. Therefore, modulation of pain and mood is impaired in the brain. These findings suggest that BMS could be a neuropathic condition; however, our hypothesis suggests that there may be atrophy of the gustatory and parasympathetic nerve fibers but not to the somatosensory nerve fibers, which may induce alteration in pain tolerance but not in pain threshold. Thus, the mechanism of neuropathic pain in BMS may not be due to the direct damage to the somatosensory nervous system but may be due to the dysfunction in the somatosensory nervous system and the brain network.

One of the most critical but postponed problems is that the prevalence of BMS is 0.7–3.7% in the adult population.[224] Because all mature women experience menopause, the cause of BMS cannot be fully explained by hormone dysregulation; something else must trigger BMS symptoms. In addition, we need further data on neuroprotective steroids, which are the target of current research.

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Figure Legends

Fig. 1 Putative pathophysiology of BMS

Menopause induces decreases in gonadal and adrenal steroids. A deficit of neuroprotective steroids following gonadal hypofunction is believed to induce atrophic changes in thin fibers in the epithelial layer of the oral mucosa. The atrophied fibers that innervate taste buds are mainly chorda tympani nerve fibers with $P2X_2$ and $P2X_3$ receptors and conduct taste information. In contrast, the remaining fibers in the subepithelial layer are trigeminal nerve fibers with rich TRPV1 channels. This "alternative" innervation results in the predominance of the trigeminal nerve and acceleration of TRPV1 channel function, which induce dysgeusia and hypersensitivity to capsaicin and hot foods. However, somatosensory fibers are not damaged, and quantitative sensory testing shows no significant changes in somatosensory and pain detection thresholds. Decreased inputs from chorda tympani nerve fibers lead to disinhibition of trigeminal impulses at the NTS and alter the mutual sensory control between the trigeminal, the chorda tympani and the glossopharyngeal nerves. Lack of neuroprotective steroids leads to mood changes by inhibiting serotonin synthesis and GABAergic modulation. Chronic mental distress induces changes in $GABA_A$ receptor configuration that reveals a decrease in α1, α2, and δ2 subunit expression, which are the target of benzodiazepines. Contrarily, expressions of the α4, α5, and δ subunits

that have a high sensitivity to neuroprotective steroids but almost no sensitivity to benzodiazepines increase. These changes may be involved in psychological distress and in generating burning pain. This mental distress and persistent pain suppress the function of the pain modulation system of the BMS brain. Furthermore, dysregulation of the dopaminergic system in the basal ganglia may be involved in disordered top-down pain modulation.