

# Commentary

QJM

## Burning mouth syndrome (stomatodynia)

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### Introduction

A recent paper by a research group from the University of Kentucky has shed new light on the pathophysiology of burning mouth syndrome (BMS), an enigmatic disorder causing chronic pain of the intra-oral soft tissues.<sup>1</sup> The researchers used functional magnetic resonance imaging (fMRI) to show that patients with BMS have a specific qualitative and quantitative pattern of brain activation, leading to a net brain hypo-activity. Their findings suggest that BMS patients may have impaired brain network dynamics essential for descending inhibition, leading to diminished inhibitory control of sensory experience; as a consequence they may experience intra-oral proprioception as burning pain.<sup>1</sup> These results may have significant clinical relevance; the pathophysiology of BMS has been ill-understood, causing difficulties in providing effective therapies. But what exactly is BMS?

### Definition

BMS is synonymous with stomatodynia, oral dysaesthesia, glossodynia, glossopyrosis, and stomatopyrosis. The International Association for the Study of Pain and International Headache Society defines it as a 'distinctive nosological entity', including 'all forms of burning sensation in the mouth, including

complaints described as stinging sensation or pain, in association with an oral mucosa that appears clinically normal in the absence of local or systemic diseases or alterations'.<sup>2–5</sup> Many systemic and local disorders can cause a burning sensation localized at the oral mucosa, but 'true' idiopathic BMS is defined as a burning pain in the tongue or other oral mucosal membrane in absence of clinical and laboratory abnormalities.<sup>2–6</sup> In brief, the term is applied to those patients with chronic oral pain or burning sensation of the mouth which appears to be medically unexplainable, due to the absence of obvious visible lesions or relevant systemic disorders.<sup>6</sup>

The pain of BMS is usually moderate to intense, and as in other chronic pain syndromes, associated with disruption of patients' normal social relationships.<sup>7,8</sup> Two recent reviews, based on different selected populations and inclusion criteria, have reported that BMS prevalence might range from 0.7% to 4.6%,<sup>9</sup> suggesting that there might be millions of people with this condition, leading to a significant social and economic burden. However, epidemiological data of BMS should be read with caution. Strict diagnostic criteria have been rarely adopted and, given the high number of different local and systemic disorders potentially causing burning sensation of the mouth, this may have led to an overestimation of the prevalence of BMS.

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## Patient characteristics

BMS appears to be more prevalent in middle-aged and older women (mean age 50–60 years), with a female-to-male ratio varying from 3:1 to 16:1.<sup>9–11</sup> Its pathogenetic mechanisms and aetiological factors are largely unknown. Some researchers have suggested that the disorder may be a manifestation of somatization,<sup>10,12–14</sup> while others have reported it to be more closely related to neuropathic pain than to somatoform chronic pain syndromes.<sup>15–18</sup> The majority of studies have revealed a variety of psychosocial features and personality disorders in BMS patients, such as alexithymic traits, cancerphobia, somatization, obsession-compulsion, personal sensitivity, hostility, psychoticism, and social isolation,<sup>7–13,19–21</sup> as well as significantly higher adverse early life experiences and higher mean score for anxiety and depression, compared with appropriate controls.<sup>19–21</sup> However, as with other chronic pain syndromes, these findings do not distinguish between cause and effect.

## Possible mechanisms

Neurophysiological and imaging studies have suggested that a dysfunction of the nigrostriatal dopaminergic pathway may play a role in the pathophysiology of BMS.<sup>15–17</sup> It has also been suggested that BMS may represent a form of oral pain phantom due to damage of taste pathways (e.g. chorda tympani nerve) interacting with tongue somatosensory system, and that particularly intense symptoms occur in genetically predisposed individuals defined as ‘supertasters’.<sup>22</sup> More recently, a study of a small group of patients with BMS found a lower density of epithelial nerve fibres and axonal degeneration on biopsy in the anterior two-thirds of the tongue,<sup>18</sup> suggesting that BMS is caused by a trigeminal small-fibre sensory neuropathy. Overall, these findings seem to highlight a peripheral and/or central neuropathic mechanism,<sup>1</sup> but are unlikely to clarify the nature of the syndrome definitively. Similar neurotransmitter changes are seen in psychiatric conditions such as major depression,<sup>23</sup> and dopaminergic functioning in both the nigrostriatal and mesolimbic dopamine pathways has been shown to be enhanced by the placebo response, indicating that the psychological status of belief and positive expectation can strongly influence dopamine functioning in both the dorsal and ventral striatum.<sup>24,25</sup>

The question of psychological vs. organic pathogenesis has been disputed in many chronic pain disorders, including BMS. With the benefit of

molecular and imaging techniques, however, a growing body of evidence suggests that abnormalities of central and/or peripheral nervous system are present in patients with chronic symptoms that were traditionally classified as functional, psychosomatic, or medically unexplained. Therefore, while the cause and pathogenesis of BMS still remain unknown, the question whether BMS should be considered a neuropathic disease or a somatoform pain disorder is losing relevance, as psychological changes and physical symptoms are likely to be considered expressions of the same pathological CNS abnormality.<sup>6</sup> The results of Albuquerque *et al.* seem to support this concept, as patterns of brain activation similar to those found in BMS patients are also implicated in the processing of anxiety and other levels of psychological distress.<sup>1</sup> Other aspects of this research will need clarification in future studies. For example, >50% of patients studied by Albuquerque *et al.* had pain level at the lower value to define pain as cause of significant decrements in quality of life,<sup>26</sup> and it is not known if this may account for specific patterns of fMRI. The study was also mainly aimed at observing changes in brain activity patterns in patients with BMS, and did not attempt to investigate their aetiology. Even if distinct central nervous system changes, including reduced activation, usually occur as a consequence of ongoing pain (central sensitization), it has also been suggested that a loss of function in descending inhibitory serotonergic and noradrenergic pathways can cause, or at least contribute to, chronic pain (explaining the efficacy of serotonin and noradrenalin re-uptake-blocking antidepressants in some neuropathic pain syndromes).<sup>27,28</sup> Future studies should clarify whether cortical dysfunction is directly responsible for some types of chronic (facial) pain, as the findings of Albuquerque *et al.* and others seem to suggest.<sup>28</sup>

## Treatments

In the past two decades, a variety of different therapies for BMS have been proposed, including benzodiazepines, tricyclic antidepressants, gabapentin, trazodone, selective serotonin reuptake inhibitors (SSRIs), amisulpride, topical capsaicin, alpha-lipoic acid, and cognitive behavioural therapy.<sup>4,7,29</sup> Variable, unpredictable and often discouraging outcomes have been reported, leading to the impression that BMS therapy is always difficult, often unsuccessful and rarely completely effective.<sup>6,7</sup> The low methodological quality of many relevant studies has led some authors to conclude that, to date, there is little research evidence to

provide clear, conclusive demonstration of any effective intervention and treatment for BMS sufferers.<sup>4,29</sup> Nevertheless, even if most available studies represent the weakest form of evidence, they can be considered relevant, as high-quality research evidence is unavailable.<sup>30</sup>

Clearly, further high-quality studies are warranted to provide evidence-based support for the use of these treatments. Recently, a multi-centre, randomized, double-blind study found that topical administration of clonazepam improved symptoms in two-thirds of one group with BMS,<sup>31</sup> confirming the results reported by previous open-label trials.<sup>32,33</sup>

This is a step in the right direction, but few consistent data from trials support any particular intervention. BMS remains a fascinating if poorly understood condition, characterized by varying definitions, multiple proposed causes, and largely anecdotal treatment evidence. Though it seems likely that both neuropathy and psychology play important roles in BMS, further well-planned studies on both aetiopathogenesis and therapeutic interventions are needed.

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