

## Burning mouth syndrome as a manifestation of an unbalanced psycho-neuro-immuno-endocrine axis in mentally ill women with intestinal dysbiosis: A literature review

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### Abstract

**Background:** Burning mouth syndrome is currently defined as a type of chronic orofacial pain of unknown etiology; however, several publications describe this syndrome as a neurological disorder with multifactorial pathogenesis in which psychogenic, endocrine, and neuropathic factors are involved. The objective of this article is to propose an etiopathogenic model of BMS based on clinical and preclinical evidence published to date.

**Methods:** Through a systematic bibliographic search in 4 scientific databases: PubMed, Science Direct, Embase and the Cochrane library, of articles published in English in the last 20 years.

**Results:** We dare to propose BMS as a trigeminal small-fiber sensory neuropathy influenced by low-grade chronic systemic inflammation, in a scenario of intestinal dysbiosis or psychiatric disorders and exacerbated in peri or postmenopausal women, due to neuroprotective steroid deficiency and greater propensity to psychological disturbances.

**Conclusion:** It is necessary to develop lines of research linked to the taxonomic and functional characterization of the intestinal microbiome in patients with BMS and to compare it with that obtained in mentally ill patients without BMS against a control group, in order, to elucidate its pathogenesis and find new therapeutic targets that allow us to better manage the syndrome, with stable responses over time.

**Keywords:** Burning mouth syndrome; Psychoneuroimmunology; Anxiety; Depression; Women; Dysbiosis

### 1. Introduction

Burning mouth syndrome (BMS), also called scalded mouth, burning mouth, glossodynea, glossopyrosis, stomatodynea, stomatopyrosis or oral dysesthesia, is currently defined as a condition of chronic orofacial pain of unknown etiology, and interpreted as burning, itching or roughness usually referred to the lingual level in its anterior two thirds with bilateral distribution and variable intensity, with or without dysgeusia or xerostomia [1, 2]. Its diagnosis is made after ruling out local or systemic factors that can explain the burning symptomatology; whereby only the idiopathic forms of stomatodynea will be categorized as BMS [3, 4]. According to a recent systematic review, the prevalence of the syndrome in the general population is around 2% on average, reaching almost 8% in patients with underlying pathology and

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varying according to geographic region, sex and age. Europe is the continent that shows the highest rate followed by North America, significantly affecting women after 50 years of age in postmenopausal condition and with a predisposition to psychiatric disorders such as anxiety and depression [5-7].

In 2013, the syndrome was included in the third edition (beta version) of the International Classification of Headache Disorders (ICDH-III) [8]. According to this taxonomy, BMS is characterized as an intraoral burning or dysesthesia sensation that recurs daily for more than two hours a day and for more than three months in the absence of clinically evident causal injuries, without affecting food or liquid intake and without interfering with sleep (Table 1) [9]. Although this last symptom is discussed. The pathophysiology of BMS remains unclear, regarding this topic, several previous publications propose BMS as a neurological disorder with multifactorial pathogenesis [7] [10-13]. Based on this background, we wonder if BMS is a form of expression of the psycho-neuro-immuno-endocrine syndrome under intestinal dysbiosis. To answer the question asked a search was carried out with certain methodological criteria in prestigious scientific databases, in order, to obtain evidence that will allow us to better understand the pathogenesis of this syndrome.

Although the International Headache Society currently qualifies BMS as a form of painful cranial neuropathy clinically expressed as intraoral dysesthesia or burning sensation, supported to date by histological and neurophysiological findings, brain imaging and quantitative sensory test, its pathophysiology and higher incidence in women has not yet been explained [8]. This review aims to propose an etiopathogenic model that explains the semiogenesis of BMS in women and its co-morbid relationship with psychiatric disorders.

## 2. Material and methods

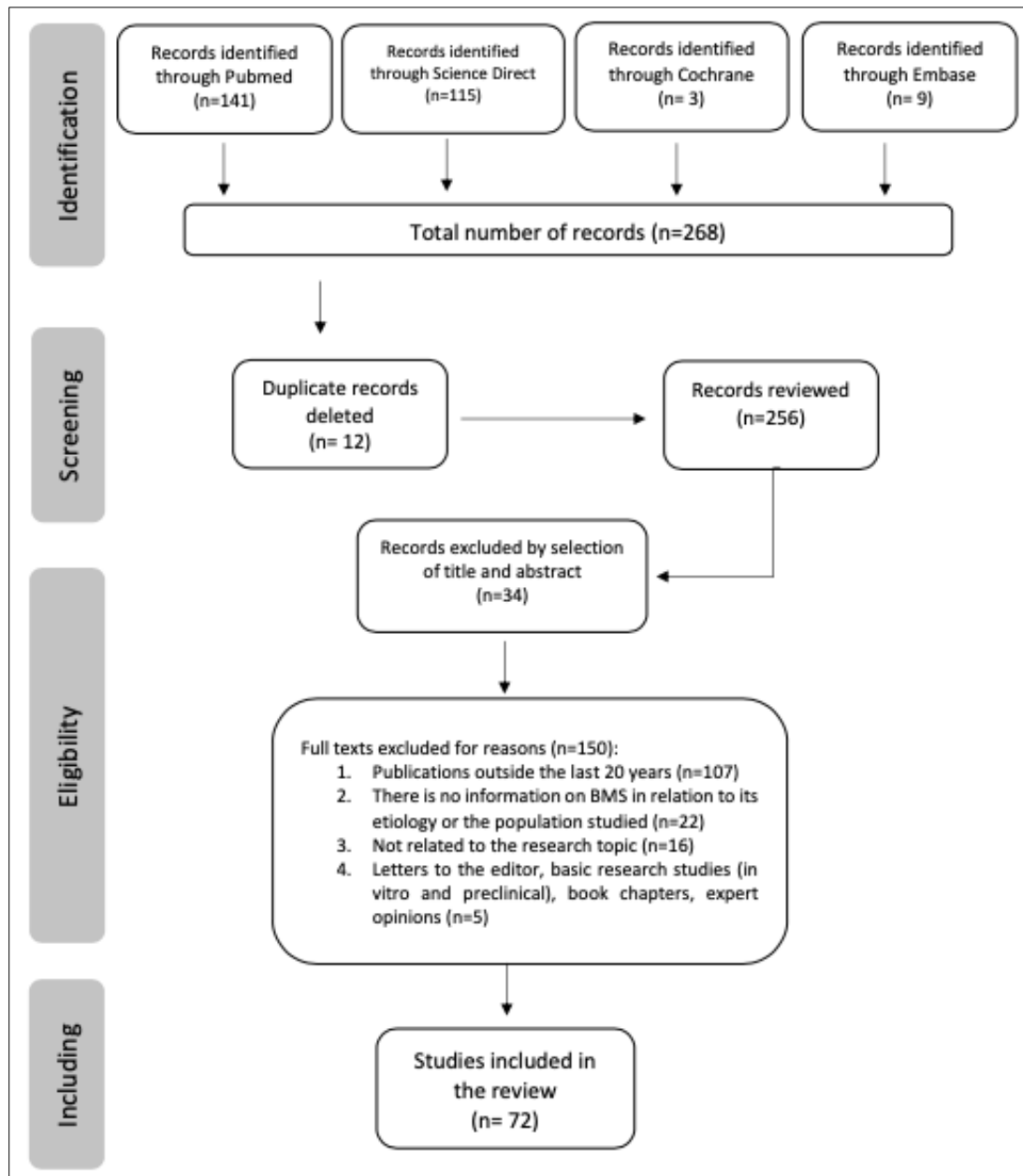
To answer the question asked and achieve the proposed objective, a literature review was carried out with electronic search in the scientific databases PubMed, Science Direct, Cochrane Library and Embase, of articles published from January 2001 to December 2021, using keywords validated by MeSH vocabulary: *Burning mouth syndrome* OR *neuropathic pain* OR *chronic pain* AND *psychoneuroimmunology* AND *psychiatric disorders* OR *anxiety* OR *depression* AND *menopause* AND *dysbiosis*.

The criteria used for the selection of articles were the following: Descriptive/observational clinical research (case reports; cross-sectional studies) and analytical (case controls and cohorts) studies, experimental studies (clinical trials), narrative reviews, systematic reviews, and preclinical studies, all published in the English language in full text or not. Publications of type letter to the editor and all those studies published in a language other than English were excluded. Figure 1 summarizes the publication search and selection process.

**Table 1** Diagnostic criteria for burning mouth syndrome from ICDH-3

<b>Diagnostic criteria</b>
Oral pain fullfiling criteria B and C
Recurring daily for >2 hours per day for >3 months
Pain has both of the following characteristics:
Burning quality
Felt superficially in the oral mucosa
Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
Not better accounted for by another ICHD-3 diagnosis

**Source:** Taken from the work of Galli and collaborators [7].



**Figure 1** Flowchart summarizing the bibliographic search and selection of articles

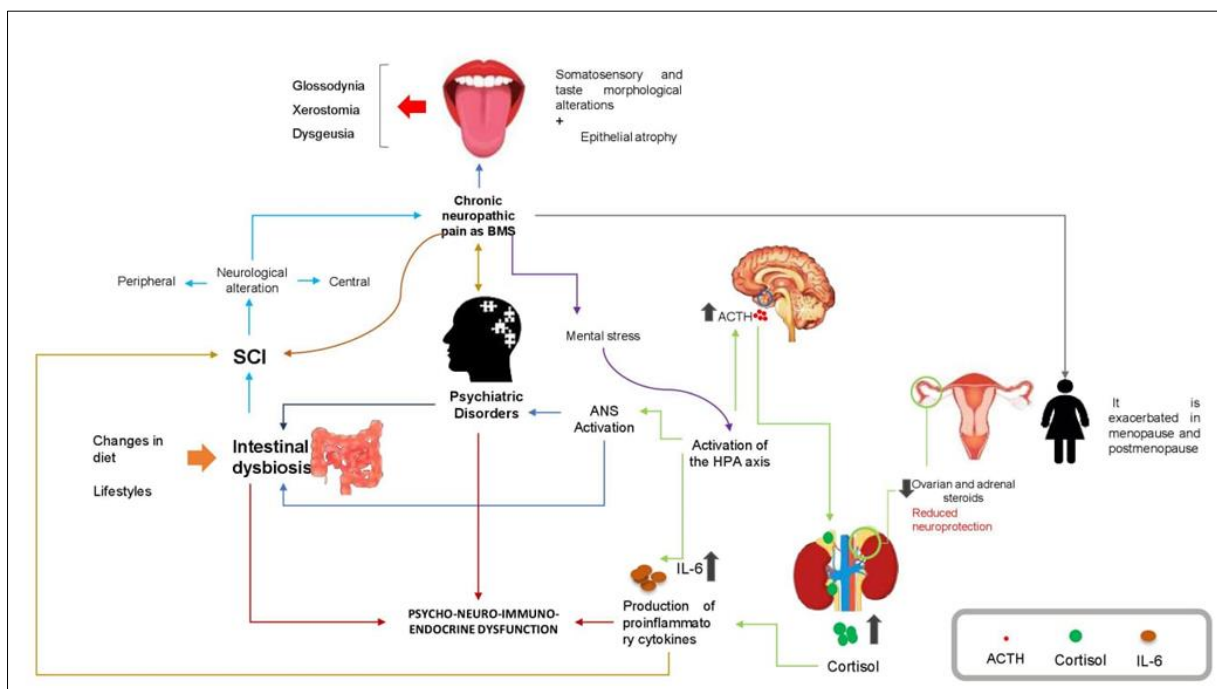
### 3. Results

#### 3.1. BMS as a manifestation of an unbalanced psycho-neuro-immuno-endocrine axis in mentally ill women with intestinal dysbiosis

Until now, the etiopathogenesis of BMS is unknown, however, based on a growing volume of preclinical and clinical evidence published in the last 20 years on the relationship between neuropathic pain (BMS is currently assumed to be a type of chronic neuropathic pain) with psychiatric disorders and exacerbated immuno-inflammatory responses, the latter linked to intestinal dysbiosis, we propose a model that would explain the etiopathogenesis of BMS in women with psychiatric disorders conditioned by intestinal dysbiosis.

Intestinal dysbiosis, favored mainly by dietary habits and lifestyle exacerbates the pro-inflammatory T response with depletion of regulatory T lymphocytes, leading to a state of low-grade chronic systemic inflammation (SCI). This condition promotes the development of neuropathic disorders due to dysfunction of the peripheral and central nervous systems a phenomenon that is exacerbated in peri and postmenopausal women due to the deficiency of neuroprotective

steroids. This peripheral and central neuropathy, clinically expressed with pain or oral dysesthesia, would lead the patient to a state of chronic stress causing dysfunction of the hypothalamus-pituitary-adrenal system (HPA) with the consequent activation of the autonomic nervous system (ANS), and evidence suggests that the activation of this system increases the risk of developing psychiatric disorders such as anxiety and depression which can exacerbate intestinal dysbiosis, feeding back the circuit (Figure 2). These psychiatric disorders have been shown to prevail in female patients in the postmenopausal stage due to the withdrawal of neuroprotective steroids [14-16]. Additionally, an association between dopamine deficiency and anxiety disorders has been reported [17]. Parallel to this, studies have shown that certain bacterial strains such as *Echerichia coli*, *Proteus vulgaris*, *Serratia marcescens*, *Bacillus subtilis* and *Bacillus mycoides* are capable of producing neurotransmitters such as dopamine and norepinephrine, although the underlying mechanism is unknown [18, 19]. Intestinal dysbiosis induced by environmental factors could cause a decrease in the abundance of dopamine-producing intestinal bacterial phyla and evidence suggests that dopaminergic deficits lead to poor top-down inhibitory control of the nociceptive process [11]. Indeed, a 50% prevalence of carrying low levels of synaptic dopamine in the striatum has been reported in patients with neuropathic orofacial pain, compared to the general population (27%) [20]. It is not known whether this dopaminergic deficit is congenital or acquired, what is known is that the vulnerability to unmodulated chronic pain is exacerbated in patients with psychiatric disorders such as depression, anxiety and type C personality disorders [21].



**Figure 2** Intestinal dysbiosis exacerbates the pro-inflammatory T response with depletion of regulatory T lymphocytes, generating low-grade chronic systemic inflammation (SCI) which leads to peripheral and central nervous system dysfunction a situation that is exacerbated in peri- and postmenopausal women due to the deficiency of neuroprotective steroids. Peripheral and central neuropathy can be expressed as BMS which would lead the patient to a state of chronic stress, generating dysfunction of the hypothalamus-pituitary-adrenal (HPA) system, the latter mediating immune alteration with an increase in pro-inflammatory cytokines such as IL-6, endocrine alteration with an increase in ACTH and cortisol, as well as activation of the autonomic nervous system (ANS), which promotes intestinal dysbiosis by altering colon motility and increases the risk of psychiatric disorders (anxiety and depression) that aggravate intestinal dysbiosis. Results in animal studies postulate intestinal dysbiosis as a promoter of neuropathic disorders [22].

The most relevant evidence that would support our hypothesis about the pathogenesis of BMS is detailed below:

- In 2016, the first meta-analysis that analyzed the association between psychopathological symptoms and BMS was published. Anxiety and depression were the most common and most frequently studied disorders among patients with BMS, the forest plot analysis determined that patients with BMS have between 1.6 and 4.3 times more risk of suffering from anxiety compared to people without BMS. Regarding depression, patients with BMS have between 1.7 and 5.8 times more risk of suffering from depression compared to patients without BMS [7].

- A retrospective cohort study published in 2020 and conducted in 1758 individuals with and without BMS showed that the overall incidence of depression and anxiety during the follow-up period was higher in patients with BMS, compared to subjects without BMS; after adjusting for age, location of residence, household income level and comorbidities, the BMS was shown to associate a 2- to 3-fold increased risk of depression and anxiety. Of the total number of participants, 61.8% were women and BMS patients older than 64 years were the age group that showed the highest average risk of psychiatric disorders such as depression and anxiety. [23].
- Evidence suggests that psychiatric disorders such as anxiety and depression associate changes in colon motility as a result of the involvement of the autonomic nervous system, a fact that would alter the composition and stability of the intestinal microbiome [24], translating into pro-inflammatory responses through translocation of some bacterial products such as LPS from the intestinal lumen; both psychiatric disorders and neuropathic pain have been shown to be associated with increased levels of pro-inflammatory cytokines [24-26]. Additionally, the mental stress generated by psychiatric disorders [17] would lead to a deficit in the levels of ovarian and adrenal steroids via modulation of GABA<sub>A</sub> receptors decreasing the level of sex hormones and their protective effect on neural tissues [27, 28], increasing the risk of neuropathies such as BMS.
- A study conducted in germ-free mice subjected to stress showed an excessive release of corticotropin-releasing hormone (ACTH) and cortisol [29]. Parallel to this, observational clinical studies have shown significantly higher levels of cortisol in patients with BMS [30]. Pascale et al., in their review of the relationship between psychiatric disorders and the intestinal microbiota, establish that altered levels of hormones linked to stress (ACTH and cortisol) alter the composition of the microbiome (dysbiosis) and bidirectional communication between the intestine and the brain, favoring the development of diseases such as metabolic disorders, psychiatric and neurodegenerative disease and autism [17].
- Psychiatric disorders have been shown to associate decreased levels of certain neurotransmitters such as serotonin and norepinephrine in depressive subjects, while subjects with anxiety show reduced levels of dopamine. Parallel to this, intestinal dysbiosis is related to reduced levels of dopamine, serotonin and short-chain fatty acids (SCFAs) [17]. Additionally, the alteration of another neurotransmitter such as gamma aminobutyric acid (GABA), known to be an inhibitor of the central nervous system (CNS) has been related to CNS diseases such as neuropathic and visceral pain, insomnia, depression, altered behavior. It has been reported that bacteria such as *E. coli* can degrade GABA into succinate; which is necessary for their growth; while other bacterial genera such as *Bifidobacterium* and *Lactobacillus* can synthesize the neurotransmitter GABA for physiological reasons [19]. A study in germ-free mice showed that GABA levels in the intestine and in the blood were lower compared to control mice [31]. Parallel to this, a study in a murine model suggested a relationship between bacterial GABAergic production and improved animal behavior. The experiment dealt with mice colonized by *Lactobacillus rhamnosus* JB-1, and these GABA-producing bacteria caused a decrease in depression and anxiety in mice, probably due to an inhibited brain-intestine communication via the vagus nerve [32].
- An estimated 20% of the US adult population suffers from chronic pain with a higher prevalence among older women [33, 34]. Zhou et al recently presented in their perspective review published in *Frontiers in Molecular Neuroscience*, clinical evidence to support their hypothesis about the impact of SCI on the genesis of chronic pain, as well as the pathological processes that cause SCI. Regarding the latter, psychiatric disorders such as depression are proposed as a cause of SCI and based on the evidence obtained by Zhou et al., SCI is postulated as a cause of chronic pain given the predominance of mRNA and protein level for pro-inflammatory cytokines such as IL-2; IL-1 and TNF in the serum of patients with chronic neuropathic pain, when compared with patients with non-painful neuropathic pain and healthy subjects [35]. Regarding the pathogenesis of the SCI and chronic pain association, now there are only two hypotheses. The first has to do with the disruption of the blood-brain barrier (BBB) in certain regions of CNS related to pain, and with neurovascular dysfunction associated with states of obesity and advanced age [36-39]. The second hypothesis proposes that the free nerve endings (nociceptors) and their body (DRG) lacking barriers such as the BBB; blood nerve barrier (BNB) and blood spinal cord barrier (BSCB) are directly exposed to circulating products and other danger signals, generating chronic pain responses. However, according to Zhou et al., it is not yet clear whether this repeated chronic stimulation in the SCI context is sufficient to excite nociceptors or sensory neurons [35].
- A volume of clinical evidence postulates BMS as a type of neuropathic pain mediated by peripheral and central mechanisms [40-43]. The former is associated with atrophy of predominantly unmyelinated nerve fibers in the oral mucosa [11, 40]. Regarding the central neurogenic mechanisms that would act in patients with BMS, the literature reports: a) deficient mutual modulatory activity at the level of the nucleus of the solitary tract (NTS)

between trigeminal, glossopharyngeal and chorda tympani afferents after injury to the latter, predominantly nerve conduction from trigeminal afferents (TRPV1+ fibers) which translates into dysgeusia and pain [44, 45] and b) presynaptic dysfunction in the nigrostriatal dopaminergic system with a decrease in endogenous dopamine in the putamen; which would lead to a poor top-down inhibitory control of nociceptive processing [11, 43]. In fact, imaging studies of patients with BMS show that the pain modulation system (motor cortex, basal ganglia, thalamus, anterior cingulate cortex, prefrontal cortex, insular cortex, hippocampus) is overused, even in resting states, with a tendency to be easily overloaded [11].

- In 2009, it was proposed that the reduction of ovarian steroids after menopause generates adrenal steroid deficiency, affecting the integrity of the neural tissue given the neuroprotective effect of these hormones [46]. Based on clinical and pre-clinical evidence, this biological response that occurs in postmenopausal women would generate a positive regulation in the ligands and receptors of the glial cell line-derived neurotrophic factor (GDNF) family, thus inducing pain responses by increasing TRPV1-positive inputs [47, 48]. Additionally; preclinical evidence suggests that ovarian steroid deficiency thins the oral mucosal epithelium and keratin layer [11, 49]. This fact would activate the keratinocytes because of the epithelial damage, promoting the release of inflammatory mediators such as IL-2 and IL-6, indeed increases in these cytokines have been reported in the saliva of patients with BMS [11, 50].

In view of what is mentioned in point 8, what is the relationship between menopause and psychiatric disorders? It has been postulated that after menopause, the risks of developing anxiety and depression increase, given the lower production of ovarian steroids, which translates into lower serotonergic neurotransmission, reduction of the GABAergic system and dysfunction of the HPA system. At the same time, states of anxiety and depression generate emotional stress, a situation that feeds back into the process, since mental stress once again deregulates both the HPO (hypothalamus, pituitary, ovary) and HPA axes, modulating GABA<sub>A</sub> receptors and reducing levels of sex hormones [11, 28, 51, 52].

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#### 4. Discussion

The precise etiology underlying psychiatric disorders such as anxiety and depression is still not entirely clear. The literature relates these disorders to various neurobiological mechanisms such as deficiency of some neurotransmitters; alterations in the ANS and in the intestine-brain communication linked to intestinal dysbiosis; mechanisms that were reviewed in the results segment. BMS shares neurobiological characteristics with both psychiatric disorders, which are summarized in Table 2. In fact, it has been reported that psychological disturbances are present in more than 50% of BMS cases, with anxiety and depression being the protagonists [53]. However, BMS has also been linked to other psychiatric disorders such as personality disorders [7, 21, 54].

Based on the evidence available until now, BMS is understood as a type of chronic orofacial pain of a neurogenic nature perceived in the absence of any detectable organic cause of the oral mucosa and linked to a psycho-neuro-endocrine alteration [11]; apparently precipitated by a qualitative-quantitative imbalance in the intestinal microbiome [17, 22, 55]. This review offers the evidence that supports our hypothesis regarding the etiopathogenesis of the syndrome, which is summarized in Figure 2.

The gathered background allows BMS to be proposed as a prevalent oral neuropathy in psychiatric women and linked to an alteration in the psycho-neuro-immuno-endocrine axis in which the intestinal microbiome would be a key player in the pathogenesis of this syndrome. Indeed, studies sustain that intestinal dysbiosis would cause immune deregulation with high levels of pro-inflammatory cytokines [17, 35], event that has been observed in murine models of neuropathic pain with intestinal dysbiosis [22]. This change in the immune profile with a predominance of pro-inflammatory cytokines would lead to a state of SCI probably resulting in a central neurogenic alteration (linked to the deficiency of certain neurotransmitters such as dopamine and serotonin, in addition to altered connectivity in brain regions related to the modulation of pain) [11, 35, 43], and peripheral (linked to a small fiber atrophic process) [11, 40]. Dopaminergic deficiency has been reported in BMS and anxiety disorder [11, 17, 43]. On the other hand, ANS dysfunction has been linked to neuropathic and psychiatric disorders [11, 17, 56]. Evidence sustains that both anxiety and depression lead to a state of emotional stress [17, 35] causing activation of the HPA axis with endocrine (increased secretion of ACTH and cortisol); immunological (increased production of IL-6) and neurological consequences with activation of the ANS, feeding back the process, since both autonomic dysfunction, increased cortisol and a pro-inflammatory immune phenotype have been associated with neuropathic pain and psychiatric disorders [11, 35, 55]. In fact, IL-6 a neurotrophic and pro-inflammatory cytokine has been shown, together with IL-2 to correlate with the severity of BMS [56]. Table 2 shows the neurobiological similarities found between BMS and psychiatric disorders.

**Table 2** Biological similarities between BMS and psychiatric disorders

<b>Biological characteristic</b>	<b>Psychiatric disorders (anxiety/depression)</b>	<b>Burning Mouth Syndrome (BMS)</b>
Alteration in neurotransmitter levels	Serotonin and dopamine deficiency [17].	Alteration in the dopaminergic system [11, 43, 57]. Increase in saliva of neurotransmitters linked to painful behaviors such as substance P and neurokinin A [58].
Endocrine alterations	Decreased ovarian and adrenal steroids with less neuroprotection. This results in deficient serotonergic and GABAergic neurotransmission, in addition to dysfunction in the HPA axis [11, 15].	High prevalence of BMS in peri and postmenopausal women [11, 53]. Postmenopausal is associated with deficiency of ovarian and adrenal steroids; resulting in less neuroprotection [11]. This would generate morphological changes in somatosensory and taste fibers of the tongue with epithelial atrophy and predominance of trigeminal afferents [11, 40].
Immunological alterations	Increased production of IL-6 given the deregulation of the HPA axis resulting from mental stress triggered by psychiatric pathologies [55].	Increased serum IL-6 levels have been reported in patients with BMS [56].
Neurological alterations	Animal studies show that reduced levels of allopregnanolone (neurosteroid secreted by glutamatergic neurons and responsible for promoting GABAergic neurotransmission) at the level of cortico-limbic structures (basolateral amygdala, olfactory bulb, hippocampus, and medial prefrontal cortex) induce behavioral dysfunctions such as aggression, fear, and anxiety [59-61].	Altered connectivity in limbic structures has been reported in patients with BMS [62].
Low-grade systemic chronic inflammation (SCI)	A meta-analysis of 50 studies showed that post-traumatic stress disorder is associated with high serum and plasma levels of IL-6, IL-1 $\beta$ , TNF- $\alpha$ e INF- $\gamma$ [63]. At the same time; a body of evidence has revealed that anxiety and depression are strongly associated with low-grade SCI [35].	A prospective study with a mean of 6.5 years of follow-up in an elderly population demonstrated that low-grade SCI precedes both the onset and progression of distal polyneuropathy [64]. The same group reported that higher levels of IL-6 and TNF- $\alpha$ are associated with the incidence of neuropathies.

A higher prevalence of BMS has been reported in peri- or postmenopausal women [11], probably associated with a drop in the levels of sex steroids, which have been attributed neuroprotective roles linked to promote serotonergic and GABAergic neurotransmission, protect the nigrostriatal dopaminergic system, and influence the physiology of the HPA axis [11, 15, 57]. Indeed, a volume of evidence from experimental animal studies confers an important role to GABAergic neurotransmission in modulating anxiety-related behaviors in the cerebral amygdala. For example, agonists of GABA receptors expressed in amygdala decrease levels of distress and anxiety in several animal species, while infusions of GABA antagonists show anxiogenic effects [65, 66]. Additionally, the GABAergic system would not be the only neurotransmitter involved in the modulation of anxiety responses with serotonin also playing a key role in this context [67, 68], as well as corticotropin-releasing hormone [69]. Parallel to this, it has been documented those psychiatric disorders such as anxiety and depression can alter the composition and abundance of the intestinal microbiome [17, 35] a situation that could mediate central and peripheral neurological alterations via SCI, although, Zhou et al., maintain that there is still no direct evidence that systemic signals from the SCI potentiate neuroinflammation to increase central

and peripheral arousal [35]. According to Karshikoff et al. (2016), systemic inflammation modulates brain circuits involved in descending pain inhibition, making the individual more sensitive to painful stimulus [70].

Regarding intestinal dysbiosis as a mediator of psychiatric disorders, a study demonstrated a significant increase in the abundance of Bacteroidetes and a marked decrease in the level of Firmicutes in a murine model of depressive state [17]. For their part, Burokas et al., reported in 2017 a decrease in Bifidobacterium and/or Lactobacillus levels in subjects suffering from depression [71]. Similarly, Sudo et al., demonstrated excessive release of ACTH and cortisol in mice under stress conditions, and that this response could be restored by colonization with *Bifidobacterium infantis* [29]. Other studies, also preclinical, have reported that low-dose administration of *Campylobacter jejuni* can induce anxiogenic effects in mice [72]. No studies on the association between BMS and intestinal dysbiosis were found.

Against this background, it is worthwhile to characterize the composition, abundance, diversity, and function of the intestinal microbiome in patients with BMS and to determine the level of similarity with that found in patients with psychiatric disorders significantly associated with BMS such as anxiety and depression [7, 23].

Based on all the above, we dare to propose BMS as a neuropathy of small trigeminal sensory fibers, influenced by low-grade SCI in a scenario of intestinal dysbiosis or psychiatric disorders and exacerbated in peri or postmenopausal women due to deficiency of neuroprotective steroids and increased propensity for psychological disturbances.

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## 5. Conclusion

Following the evidence obtained in the last 20 years, we propose an etiopathogenic model of BMS in which psychiatric disorders and intestinal dysbiosis play key roles. Indeed, clinical evidence suggests that psychiatric disorders such as anxiety and depression may precede BMS or appear during its evolution; pre-clinical evidence proposes intestinal dysbiosis as a mediator of central and peripheral neurological alterations that underlies neuropathic and psychiatric disorders, leading to a state of chronic mental stress that promotes endocrine, immunological, and neurological alterations, feeding back the psycho-neuro-immuno-endocrine imbalance. Based on this, it is necessary to develop lines of research linked to the taxonomic and functional characterization of the intestinal microbiome in patients with BMS and to compare it with that obtained in psychiatric patients without BMS, to elucidate its pathogenesis and find new therapeutic targets that will allow us to do better management of the syndrome with stable responses over time.

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## Compliance with ethical standards

### *Acknowledgments*

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### *Disclosure of conflict of interest*

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### *Statement of ethical approval*

The present study did not require an evaluation by an ethics committee, since as it is a systematic review, it uses secondary data sources.

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