

Should be cited as: Psychiatr. Pol. 2013; 47(6): 973–988

PL ISSN 0033-2674

www.psychiatriapolska.pl

## Burning mouth syndrome: pathogenic and therapeutic concepts

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### Summary

Burning mouth syndrome (BMS) is a chronic pain condition characterized by pain, burning sensations and dryness within an oral mucosa, without any clinical changes of the latter. It occurs approximately seven times more frequently in women, mostly in perimenopausal age. The psychiatric aspect of BMS is significant: the most frequent co-morbidities are depression and anxiety disorders, and a number of psychotropic drugs play an essential role in its treatment. In the present review, the most important pathogenic and treatment concepts of BMS have been discussed. The BMS may be similar to neuropathic pain and has some related pathogenic elements with fibromyalgia and the restless leg syndrome. In primary BMS, the features of presynaptic dysfunction of dopaminergic neurons and deficiency of endogenous dopamine levels have been demonstrated. Other neurotransmitters such as serotonin, noradrenaline, histamine as well as hormonal and inflammatory factors may also play a role in the pathogenesis of BMS. In the pharmacological treatment of BMS a variety of drugs have been used including benzodiazepines, anticonvulsants, antidepressants and atypical antipsychotic drugs. In the final part of the paper, the possibility of using atypical antipsychotic drug, olanzapine, in the treatment of BMS has been discussed. In the context of the recent studies on this topic, a case of female patient with the BMS lasting more than ten years has been mentioned, in whom the treatment with olanzapine brought about a rapid and significant reduction of symptoms. The probable mechanism of the therapeutic effect of olanzapine in BMS can include its effect on dopaminergic receptors and probably also on histaminergic, noradrenergic and serotonergic ones.

**Key words:** burning mouth syndrome, dopaminergic system, olanzapine

Burning mouth syndrome (BMS) is a chronic pain syndrome which affects oral mucous membrane. It is characterized by burning sensations, pain, pinching or numbness within oral mucosa, accompanied by dryness, paresthesia, dysgeusia or hypersensitivity to some foods [1]. BMS is also called stomatodynia or glossodynia and most frequently affects the anterior two third of the tongue, hard palate, lower lip and floor of the mouth. The complaints generally include bilateral, of moderate intensity and last for at least 4-6 months, without any clinical signs of mucosal pathology [2]. Depending on the adopted criteria, the prevalence of BMS ranges from 0.5% to 15% and the value of 15% applies to women. The illness affects women seven times more frequently than men, mainly middle-aged and older (fifth-seventh decade of the life) females, in peri- and postmenopausal age [3].

The psychiatric aspect of BMS is very important. A relationship has been found between BMS and depression, increased anxiety, hypochondria, cancerphobia and emotional instability [4, 5]. The most common diagnosis associated with BMS is depression, anxiety disorders being on the second place [6] and sleep disorders are also frequent [7]. These conditions may be possible triggering factors of the BMS symptoms, but, on the other hand, chronic symptoms of BMS can possibly lead to the appearance of depression and anxiety. Furthermore, BMS symptoms can be somatic forms of anxiety or depression [8]. In a Polish study published in 2004, it has been demonstrated that frequency of co-morbid depressive and anxiety disorders was more than a half of patients with BMS [9]. In that study, Polish term “zespół piekących ust” was used which, in opinion of the authors of this paper, inaccurately reflects the nature of the disorder. In the present article, the term “zespół pieczenia w jamie ustnej” has been proposed.

We can distinguish primary and secondary BMS depending on different aetiological factors. Secondary BMS is related to the diseases of oral mucosa (local factors) or systemic illnesses (systemic factors) including diabetes, hypothyroidism, nutrition deficiency (iron, vitamin B12s or the folic acid deficiency anemia), fungal and bacterial infections, perimenopausal hormonal disorders, the use of drugs causing xerostomia, allergic reactions or mechanical irritation by prosthetic restorations [10, 11]. The diagnosis of primary or idiopathic BMS is based on excluding local or systemic aetiology, on the basis of carefully collected medical history and after conducting appropriate laboratory tests.

### **The pathogenetic concepts of burning mouth syndrome**

The pathogenesis of BMS is not fully understood. A lot of data relate to dopaminergic dysfunction, there are also some indications for contribution of other neurotransmitters including norepinephrine, serotonin, histamine, glutamic acid and also inflammatory and hormonal factors.

In recent years many pieces of evidence have been gathered indicating that BMS may show similarities to neuropathic pain. Over 25 years ago, Grushka et al. [12] demonstrated that patients with BMS were characterized by a reduced tolerance for thermal stimuli, experiencing a feeling of pain on the tip of the tongue. Forssell et al. [13] examined a large group of patients with BMS, carrying out quantitative sensory tests (QST) and analyzing the blink reflex (BR), searching for the central or peripheral cause of BMS connected with the function of trigeminal nerve. Seventy-six percent of patients with BMS demonstrated taste and temperature disorders within the tongue, the most of them presented symptoms of sensory neuropathy of the thin nerve fibers, some of them displayed large-fiber neuropathy of the trigeminal nerve and about one-fifth of the patients showed increased excitability of the trigeminal nerve, manifested as a lack of habituation of R2 component of the blink reflex. In the Lauria et al. [14] study, significantly reduced density of the nerve fibers within the epithelium were demonstrated as well as diffused morphological changes within epithelial and subpapillary nerve fibers, reflecting axonal injury. A neuropathy of tympanic cord can be also one of the

aetiological factors of BMS. An injury of the nerve, even unilateral, causes characteristic sensations of burning, tingling and taste disorders on both sides of the tongue [15]. In spite of above evidences for neuropathic aetiology, the localization of the symptoms is not compatible with classical neuroanatomical boundaries and primary BMS does not meet diagnostic criteria of the definition of neuropathic pain [16].

The most of the data on central dysfunction of neurotransmission in BMS concern dopaminergic system. The basal ganglia, in particular nigrostriatal pathway, is one of the most important neurotransmitter systems involved in arising and control of pain and its dysfunction can lead to the BMS [17]. Disturbances in the analysis of impulses on presynaptic and synaptic level of the nigrostriatal system lead to the dysfunction of control of experiencing pain at the central level. Therefore, degenerative conditions, i.e. Parkinson's disease, in which a dysfunction of the nigrostriatal system occurs, present with typical pain symptoms, not compatible with peripheral innervations [18]. One of the best documented disorder co-occurring with BMS is lack of habituation of the blink reflex revealed in electrophysiological examination [19, 20]. Similar results were obtained in patients with Parkinson's disease [21].

Using the positron emission tomography (PET), Jääskeläinen et al. [22] demonstrated that patients with BMS, similarly as patients with Parkinson's disease, show decreased striatal reuptake of labelled fluorodopa. A possible cause may be an impairment of dopamine reuptake by presynaptic terminals of nigrostriatal system. This findings support the hypothesis about nociceptive pathway from the substantia nigra to the striatum. Hagelberg et al. [23] found that dopaminergic dysfunction of striatal neurons in BMS pertains mainly to its presynaptic part. The PET studies with labelled raclopride in BMS patients revealed an increased availability of striatal dopamine D2 receptors. This could indicate a decreased synaptic dopamine levels and, consequently, reduced control of pain [23, 24].

Clifford et al. [25] showed that BMS occurs in 24% of patients with Parkinson's disease. However, the authors suggest that the mechanism of pain in BMS may be different from pains of central origin in Parkinson's disease which favorably respond to dopaminergic treatment. Coon and Laughlin [26] described a case report of 65-year old woman with Parkinson's disease with appearance of BMS symptoms after discontinuing pramipexole and starting treatment with carbidopa/levodopa. The symptoms aggravated with increasing doses of the drug and prescribed clonazepam brought no relief. Discontinuation of carbidopa/levodopa treatment and resuming pramipexole – the dopamine receptor agonist with high affinity to D2 receptors, led to complete resolution of symptoms.

Besides BMS and Parkinson's disease, disturbances in dopaminergic neurotransmission has been found in fibromyalgia and restless legs syndrome (RLS). Wood et al. [27] demonstrated in PET studies that patients with fibromyalgia, similarly as patients with BMS, show presynaptic dysfunction of dopaminergic neurons in central nervous system. In RLS, similarly to BMS, PET findings revealed dysfunction of D2 receptors in basal ganglia and increased availability of D2 receptors which may reflect their higher density and endogenous dopamine deficiency. Paulus i Trenkwalder [28] observed an improvement in RLS after small doses of dopamine and subsequent de-

terioration during long-term treatment. Based on the analogy to RLS we can presume that pathogenesis of BMS is mostly related to dopamine D2 autoreceptors.

A significant role of dopaminergic system in pain reaction is supported by data of its cooperation with opioid system. After a noxious stimulus, an endogenous opioids are released as first, in the brain regions rich in dopamine (nucleus accumbens). The research show that administration of endogenous opioids and opioid  $\mu$ -receptor agonists, results in dopamine release within 10-30 minutes. This suggests that both systems can cooperate in pain processing, with opioid system acting as first, and after prolonged pain stimulation dopaminergic system is activated. Conversely, physiological or pharmacological decrease in dopamine levels enhances sensitivity to pain stimuli [29].

Besides dopamine, norepinephrine and serotonin are the most important neurotransmitters influencing pain perception in the descending inhibitory spinal projections. Noradrenergic neurons of the locus coeruleus inhibit neurotransmitters release from the primary afferent neurons directly through alpha 2 receptors. Serotonergic neurons of nucleus raphe magnus inhibit primary afferent neurons through postsynaptic serotonin receptors 5HT1B/D. The role of descending projections is to inhibit perception from properly functioning organs and dysfunction of this process corresponds with chronic pain sensations in the presence of adequate physiological stimuli [30].

Inflammatory and hormonal factors also play an important role in the pathogenesis of BMS. Boras et al. (2010) demonstrated significantly decreased serum neurokinin A levels which may reflect a central deficiency in dopaminergic system [31]. The salivary levels of substance P, neurokinin A and calcitonin gene-related peptide (CGRP) have been increased, although not being statistically significant, which may reflect a peripheral neurogenic inflammation. In contrast, Zidverc-Trajkovic et al. (2009) reported a decreased salivary CGRP levels in patients with BMS, as a consequence of trigeminal nerve degeneration [32].

Guimaraes et al. [33] demonstrated that gene polymorphism of proinflammatory 1-beta interleukin affecting the perception of pain is probably related to predisposition to BMS. Guarneri et al. [34] proposed that the characteristic features of BMS i.e. altered pain perception, disturbances of conducting nerve impulses, increased excitability of nerve fibres, disorders of processing stimuli by the trigeminal nerve system result from inflammatory reaction within the nervous system. Amenabar et al. [35] in BMS patients demonstrated hormonal changes such as increased salivary cortisol levels and its positive correlation with increased anxiety level. Particularly frequent BMS manifestations occurring in women in perimenopausal age also suggest a contribution of hormonal factors. Perhaps it is a result of reduction in number of estrogen receptors on the mucous surface. However, there was no improvement after hormonal replacement therapy [36].

Glutamate system also contributes to the pathophysiology of nociceptive processing. In 2012, Japanese researchers presented a new experimental animal model of inflammatory tongue pain based on glutamatergic conception [37]. According to this theory, injection into the anterior two-third of the tongue substance, which induces mechanical allodynia and heat hyperalgesia, leads to subsequent activation of metabotropic glutamate receptor 5 (mGlu5R) and concomitant influence on phosphorylation

of extracellular signal-regulated kinase (ERK) in trigeminal subnucleus caudalis and upper cervical spinal cord C1-C2.

There are many other systems involved in the control of pain sensation including nicotinic, opioid or cannabinoid receptors. Histamine is another neurotransmitter exerting significant influence on pain perception. Blockers of histamine receptors, both H1 and H2, applied in large doses, show analgesic effect [38].

Frequent BMS comorbidity with depression and anxiety disorders may point to partially common pathogenic mechanisms. Similar neuronal circuits are connected with depression, anxiety and pain perception [39, 40] and certain brain areas are common for depression and pain, e.g. cingulate gyrus [41].

### **Therapeutic concepts for the burning mouth syndrome (BMS).**

Due to its considerable prevalence and long-lasting symptoms, and taking into consideration the concomitant diagnostic and therapeutic difficulties, finding an effective method of treating BMS is becoming ever more significant. Currently, the diagnostic process of BMS is based primarily on the exclusion of other conditions, and treatment is frequently symptomatic, with the objective being the reduction of pain, while assessments of the results of BMS treatment are based on the subjective reports of patients concerning their individual experience of pain.

The basic recommendation for patients complaining of a burning sensation in the oral cavity is to commence activities aimed at identifying and subsequently eliminating factors causing and/or maintaining the unpleasant sensation (e.g. alcohol, spices, sour-tasting drinks, mechanical irritations, sensitivity to artificial dentures, etc.). Such a course of action, directly addressing causal factors, is effective in the case of secondary BMS.

The concept of BMS concerning disturbances in the reception of peripheral stimuli from mucous membrane receptors in the oral cavity has led to the elaboration of therapeutic proposals that include the application of various substances locally: directly to the tongue or by washing the oral cavity. Since depression and anxiety are factors connected with an intensification of the perception of pain symptoms, it has been proposed that sedatives and antidepressants, as well as psychotherapy, should all be used in the treatment of BMS. Concepts of dopaminergic dysfunction justify treatments with drugs influencing dopaminergic transmission.

Tab. 1 – *next page* contains a list of therapeutic interventions that have been mentioned in publications [according to ref. 42], modified.

Numerous data on the treatment of BMS is related to the application of alpha-lipoic acid (ALA). ALA is a compound with an antioxidant action, which increases the concentration of intracellular glutathione, thereby leading to the activation of reconstructive processes in nerves and the stimulation of production of the nerve growth factor. It has been used successfully for quite some time in the treatment of peripheral neuropathy and diabetes [43]. A number of open and controlled studies have been conducted concerning the application of ALA in the treatment of BMS, with positive results being achieved in the majority of cases [44-48]. Favourable results have also been obtained

for the joint application of ALA and cognitive-behavioural psychotherapy [49], and the joint application of ALA and gabapentin [50].

Table 1. Selected therapeutic interventions in BMS according to [42], modified

<p><b>Topical treatment</b></p> <ul style="list-style-type: none"> <li>• Clonazepam – anxiolytic drug</li> <li>• Lidocaine – anaesthetic drug</li> <li>• Capsaicin – atypical analgesic drug</li> <li>• Doxepin (cream) – tricyclic antidepressant</li> <li>• Bensidamine – non-steroidal antiinflammatory drug</li> <li>• Lactopeoxidase – antibacterial drug</li> <li>• Sulphacrate – protective agent for mucous membrane</li> </ul> <p><b>Oral administration</b></p> <ul style="list-style-type: none"> <li>• Alpha-lipoic acid – antioxidant</li> <li>• Capsaicin – atypical analgesic drug</li> <li>• Clonazepam, chlordiazepoxide - benzodiazepines</li> <li>• Gabapentin, pregabalin, topiramate – anticonvulsant drugs</li> <li>• Amitriptyline, imipramine, nortriptyline, dezipramine – tricyclic antidepressants</li> <li>• Paroxetine, sertraline – selective serotonin reuptake inhibitors</li> <li>• Trazodone - serotonin antagonist and reuptake inhibitor</li> <li>• Milnacipran, duloxetine – selective serotonin and norepinephine reuptake inhibitors</li> <li>• Amisulpride, olanzapine – atypical antipsychotic drugs</li> <li>• Pramipeksol – dopamine D2 receptor agonist</li> <li>• Lafutidine – histamine receptor antagonist</li> <li>• Hypericin</li> <li>• Pilocarpine, sialor, cevimiline, betanechol - stimulants of saliva secretion</li> <li>• Proton pump inhibitors</li> </ul> <p><b>Other methods</b></p> <ul style="list-style-type: none"> <li>• Cognitive-behavioral therapy</li> <li>• Group therapy</li> <li>• Electroconvulsive therapy</li> <li>• Acupuncture</li> <li>• Laser therapy</li> <li>• Tongue protector (shield)</li> <li>• Biofeedback</li> </ul>
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Another substance used in the treatment of BMS is capsaicin, a compound present in chilli peppers. It binds with the vanilloid receptor TRPV1, leading to inactivation of the neuronal reaction to burning sensation (chilli pepper in the mouth). Long-lasting exposure „exhausts” TRPV1 in peripheral tissues, which results in the long-term de-

sensitisation of nociceptors and the reduction of BMS symptoms [51, 52]. Capsaicin has been used successfully in BMS when applied as topical [53] and oral treatment [54]. The most frequent side-effects were abdominal pains. Patients still experienced an improvement as regards BMS symptoms even 2 months after discontinuation of capsaicin treatment due to these side-effects. In comparative studies, capsaicin administered either topically or orally showed similar efficacy.

Among psychotropic drugs, clonazepam (anticonvulsant and anxiolytic drug) has been used most frequently to treat BMS [55]. It has been applied as topical or oral treatment or as a combination of both methods. In a study assessing the effectiveness of the local application of clonazepam, a considerable improvement was achieved after 6 months of BMS treatment, although not in all patients [56]. Equally effective was oral application of clonazepam, in a dose of 0.25-0.75 mg/d, although side-effects (e.g. dizziness, somnolence) were reported as the reason for discontinuing treatment [57,58]. It should also be kept in mind that elderly patients may experience drug-related withdrawal symptoms, addiction, or excitation.

Another drug used in peripheral neuralgia and neuropathy is gabapentin, and this has led to a proposal of its application in the treatment of BMS. The effectiveness of the drug was not proven during an open 6-week study [59], however, in a randomised study conducted in 2011, a positive effect of gabapentin in a dose of 300 mg/d, applied jointly with alpha-lipoic acid (ALA), 600 mg/d, was observed [40].

Treating BMS with antidepressants has also been reported. In an open study that included 71 persons, paroxetine in doses up to 30 mg/d brought about an improvement in approximately 70% of patients (the improvement depended on the dose) [60]. In the treatment of BMS patients with a different antidepressant, trazodone, using randomized design, the effectiveness of this drug in comparison with the control group was not established [61]. Milnacipran administered to 12 BMS patients over a period of 12 weeks in doses of 60 mg brought about a significant reduction of depression symptoms measured on the Hamilton scale, but did not significantly reduce BMS symptoms [62]. In another case, BMS was treated using duloxetine [63] in a dose of 60 mg/d, with complete disappearance of symptom.

A role of the D2 receptor in the pathogenesis of BMS may be supported by the favourable effects of treatment with amisulpride, which has a selective affinity to D2 and D3 dopaminergic receptors, in a dose of 50 mg/d, with relieving of symptoms after 8 weeks of treatment and maintaining the effect after 24 weeks of continued treatment [64]. Further evidence for this has been provided by the clinical effectiveness of pramipexole, a drug stimulating D2 receptors [65]. Another atypical antipsychotic drug, olanzapine, will be discussed later in greater detail.

In the treatment of BMS, other methods have also been described. In 2013, Sardella et al.[66] reported on the results of treatment of 10 persons with BMS using acupuncture; the efficacy of this method was not observed. Neither was that of laser treatment - although the concentration of pro-inflammatory cytokines in saliva was significantly reduced. [67]. A decrease in the intensity of pain perception was achieved by application a tongue protector (shield), which was used by BMS patients for 15 minutes per day

over a period of 8 weeks. There is also case report of using electroconvulsive therapy in treatment-resistant BMS [68].

Cognitive-behavioural psychotherapy, conducted over a dozen or so weeks, resulted in the reduction of pain, with the effect being maintained after 6 months [69]. In a randomised study aimed at determining the effectiveness of group psychotherapy in reducing BMS symptoms, psychotherapy scored more than 70%, in comparison with a 40% improvement in the control group [70]. The authors suggest that the effectiveness of psychotherapy may point to a psychogenic component of the disorder, which would be consistent with the results of research indicating a high level of stress, anxiety and depression symptoms in BMS patients.

In a review of research concerning BMS treatment, conducted in 2001 [71] and published by the Cochrane Library in 2004, [72] only 6 studies were found in electronic databases and seminar proceedings that satisfied such criteria as: randomised controlled trials (RCT) and controlled clinical trials in a sample with placebo or another drug, confirmed BMS diagnosis, and confirmed effect of treatment as a reduction of experienced symptoms. In these trials, antidepressants (clomipramine vs. mianserin, trazodone), cognitive-behavioural therapy, lipoic acid, hormone replacement therapy, and an analgesic drug, benzydamine, were used. A reduction of symptoms was found only after the application of psychotherapy and ALA. The authors emphasized that this may result from methodological imperfections of the review and from the fact that only small groups were studied, and not from actual inefficacy of the methods of treatment.

In 2012, Brazilian authors presented a summary of results of randomised BMS trials, conducted in accordance with the rules of research set forward in the Cochrane Reviewers' Handbook. Based on PubMed and Scopus, 495 articles on the treatment of BMS in years 2001-2011 were identified. Only 12 RCT trials were admitted to the final analysis. According to the RCT review, treating BMS with topical and oral administration of ALA, topical and oral administration of capsaicin, and topical administration of clonazepam reduced BMS symptoms to the greatest degree [73].

BMS runs a chronic course, with periods of exacerbations. Usually, the treatment does not result in sustained remission, for example, in a group of 91 patients who underwent follow-up examinations, only 3 were in remission at 18 months after the commencement of treatment, while 42% assessed their improvement as considerable; the majority had been treated topically with clonazepam [74]. In another study assessing the effectiveness of BMS treatment over a period of about 6 years, out of 43 patients, as many as 23 stated that they felt no improvement, while 13 were in permanent remission, although 9 of the latter had not been undergoing any BMS-related treatment (spontaneous remissions) [75]. Spontaneous remissions were observed in the group of BMS patients following an analysis of 48 patients on average 56 months after treatment, but this group also contained 26 patients (49%) who reported continued presence of symptoms [76].

There have been several reports in the literature on the efficacy of olanzapine in the treatment of BMS. The first report appeared in 2004 and described a 73 year-old man who did not meet criteria for depressive episode or anxiety disorder, and who

had symptoms of glossodynia for approximately 6 months. Due to severe intensity of symptoms, a loss of appetite and body mass, by approximately 20 kg had occurred. Because of dysphoria and anxiety connected with intense pain symptoms, the patient was treated with olanzapine, in doses of 5 mg/day, which brought about the disappearance of all symptoms within 3 days [77]. In 2008, Japanese researchers described the case of two patients diagnosed with BMS, who had been treated with olanzapine [78]. A 54 year-old woman, with a 6-month history of BMS and cancerophobia, and a 51 year-old man without any accompanying mental disturbances, who had initially been unsuccessfully treated with milnacipran and paroxetine, respectively, received olanzapine in doses of 2.5 mg/day, increased to 5 mg/day in the next week. In both cases, the symptoms disappeared nearly completely, and the quality of their lives improved. Following the discontinuation of olanzapine treatment, the female patient experienced a sudden recurrence of symptoms, and when the drug was re-administered, all symptoms disappeared completely. In the Poznań centre, we described a case of a 64 year-old woman with diagnosed burning mouth syndrome, in which treatment with olanzapine brought about rapid and significant reduction of symptoms [79].

Analgesic action of olanzapine has been also observed in patients with fibromyalgia. Kiser et al. [80] described two cases of patients with fibromyalgia, in which the administration of olanzapine in doses of 5 mg/day and 10 mg/day brought about sudden and nearly complete disappearance of symptoms. This made possible to reduce in the first case previously used doses of baclofen and tramadol, while in the latter case to allow a discontinuation of oxycodone/acetaminophen. Due to an increase in body mass, in one of the patients olanzapine was changed to quetiapine: it turned out that quetiapine in doses of 100 mg/day did not have any analgesic effect, and for this reason, the patient decided to resume olanzapine treatment, with the rapid and nearly complete disappearance of symptoms.

In the context of the dopaminergic nigrostriatal system dysfunctions found in BMS, probably the main therapeutic mechanism of olanzapine results from its specific properties as atypical antipsychotic, including antagonistic action on both dopaminergic D2 receptors and serotonin 5HT<sub>2A</sub> receptors. The effect of olanzapine only by antagonism to D2 receptors in striatum could lead to inhibition of dopamine release, subsequent decrease of dopamine levels and exacerbation of pain symptoms. The critical mechanism of blocking 5HT<sub>2A</sub> receptors results in disinhibition of dopaminergic neuron and stimulation of dopamine release. This mechanism is known to be responsible for reduction of extrapyramidal symptoms and in BMS it can cause an alleviation of pain symptoms [81].

Serotonin receptors 5HT<sub>2A</sub> exert two critical effects on neurotransmission possibly modulating pain processing. Firstly, they stimulate cortical pyramidal neurons, enhancing glutamate release with increase of neuronal activity and pain perception. Secondly, stimulation of 5HT<sub>2A</sub> receptors located on dopaminergic neurons or GABAergic interneurons, which mediate between serotonergic and dopaminergic neurons, can inhibit dopaminergic neurotransmission and decreases dopamine release. Thus, a blockade of 5HT<sub>2A</sub> receptors can cause reduction in pain symptoms both through inhibition of activity of glutaminergic projections from cortical regions to striatum and through

reduction of inhibition of dopaminergic neurons directly or indirectly by attenuation of inhibitory effect of GABA on dopamine release. Gick et al. [77] have proposed that the pain-killing mechanism of olanzapine consists of its peripheral blockade of serotonin receptors or alpha-2-adrenergic receptors. It cannot be excluded that these additional mechanisms are synergistic with the two described above.

Specific therapeutic properties of olanzapine can, however result from additional receptor mechanisms, because quetiapine, being also atypical antipsychotic, has no anti-nociceptive effect. Apart from the effect on dopaminergic transmission, another potential analgesic mechanism of olanzapine could be connected with its strong blockade of the H1 histamine receptor and the interaction between histamine and opioid receptors [38, 82].

Olanzapine also influences the muscarinic M1 receptor, which is a frequent cause of undesirable anticholinergic side-effects, among other dryness in the oral cavity. In spite of these actions, which could potentially intensify the symptoms of BMS, olanzapine brings about a considerable and rapid improvement. This may point, on the one hand, to a specific pathogenic mechanism of BMS, and, on the other hand, to exceptional therapeutic properties of olanzapine in this illness.

It is important to keep in mind the possible adverse effects of olanzapine, including weight gain and metabolic disorders and also consider, especially in older people, to give smaller doses of the drug with regular monitoring blood pressure in patients over 65 years, due to infrequent cases of orthostatic hypotension.

#### **Синдром жжения в ротовой полости – патогенетические и терапевтические концепции**

##### **Содержанке**

Синдром жжения в ротовой полости (BMS – burning mouth syndrome) это хронический синдром боли характеризующийся чувством болезненности, жжения и сухости слизистой оболочки ротовой полости, не связанный с её патологией. ВМ появляется в 7 раз чаще у женщин, г.о. в периоде перед мензисом. Существенным является психиатрический аспект синдрома: эта болезнь часто сосуществует с депрессией и фобийными нарушениями, а ряд психотропных препаратов играет существенную роль в ее лечении. В представленном обзоре обсуждены более важные патогенетические концепции синдрома и более частые способы лечения этой болезни. Синдром BMS может быть подобный до нейропатической боли, а его определенные патогенетические элементы фибромиалгии и синдрома беспокойных ног. При первичном ВМ отмечены черты пресимпатической дисфункции допаминэргических нейронов в радиусе поперечно полосатых структур и уменьшение эндогенной концентрации допамина. В патогенезе синдрома принимают участие также иные нейротрансмиттеры (серотонин, норадреналин, гистамин), гормональные факторы и воспалительные факторы. При фармакологическом лечении этого синдрома применяются, м.п. производные бензоидина антиконвульсивные лекарства, противодепрессивные и атипичные антипсихотические препараты. В последней части работы обсуждена возможность применения атипичного лекарства оланзепина. В контексте последних работ на эту тему, приведено собственное наблюдение пациентки с продолжающимся несколько лет синдромом жжения в ротовой полости, у которой лечение оланзепином принесло быстрое, значительное уменьшение утяжеления симптомов. Правдоподобный механизм терапевтического действия оланзепина при BMS опирается на его влияние на допаминэргические гистаминовые рецепторы, а также дополнительно на норадренэргические и серотонинэргические рецепторы.

**Ключевые слова:** синдром жжения в ротовой полости, допаминэргическая система, оланзепин

## Burning Mouth Syndrome (BMS) – Konzepte zur Pathogenese und Therapie

### Zusammenfassung

Das Zungen- und Mundschleimhautbrennen (BMS - Burning Mouth Syndrome) ist ein chronisches Schmerzsyndrom. Es charakterisiert sich mit dem Empfinden von Schmerz, Mundbrennen und Mundtrockenheit und ist nicht mit seiner Pathologie verbunden. Das BMS tritt 7 mal häufiger bei Frauen im perioklimakterischen Alter auf. Das Wichtigste ist der psychiatrische Aspekt von BMS: die Krankheit ist oft mit der Depression und Angststörungen komorbid, und in ihrer Behandlung spielt eine Reihe von psychotropen Mitteln eine signifikante Rolle. Im vorliegenden Review bespricht man die wichtigsten pathogenetischen Konzepte zum BMS und seine häufigste Behandlungsweise. Das BMS kann dem neuropathischen Schmerz ähnlich sein, und seine gewissen pathogenetischen Bestandteile sind ähnlich wie Fibromyalgie oder das Restless-Legs-Syndrom. Im primären BMS wurden die Eigenschaften der präsynaptischen Dysfunktion der dopaminergen Neurone im Striatum und die Senkung der Konzentration der endogenen Dopamin nachgewiesen. An der Pathogenese von BMS nehmen auch andere Neurotransmitter (Serotonin, Noradrenalin, Histamin), hormonelle und entzündliche Faktoren teil. In der pharmakologischen Behandlung wurden u.a. die Derivate von Benzodiazepin, Antikonvulsiva, Antidepressiva und atypische Antipsychotika eingesetzt. Im letzten Teil der Arbeit wurde die Möglichkeit der Anwendung beim BMS eines atypischen Antipsychotikums besprochen – Olanzapin. Im Hinblick auf die letzten Arbeiten zu diesem Thema wurde auch der Fall einer Patientin dargelegt, die einige Jahre am Mundbrennen litt und bei der die Behandlung mit Olanzapin schnelle, signifikante Senkung der Intensität der Symptome bewirkte. Der wahrscheinliche Mechanismus der therapeutischen Wirkung von Olanzapin im BMS stützt sich auf seinem Einfluss auf die Dopamin - Rezeptoren und Histamin - Rezeptoren und zusätzlich noch auf die noradrenergen und Serotonin - Rezeptoren.

**Schlüsselwörter:** Mouth Syndrome, dopaminerges System, Olanzapin

### Le syndrome de la bouche brûlante (ou la stomatodynie – angl. burning mouth syndrome = BMS) – conceptions de sa pathogénie et thérapie

#### Résumé

Le syndrome de la bouche brûlante est le syndrome de la douleur chronique caractérisée par des sensations continues des brûlures et de la sécheresse des muqueuses buccales, non lié avec ses pathologies. Ce syndrome est 7 fois plus fréquent chez les femmes, surtout dans la période de ménopause. Dans la cas de ce syndrome l'aspect psychiatrique est signifiant : cette maladie coexiste souvent avec la dépression et les troubles anxieux ; plusieurs psychotropes jouent le rôle important dans sa thérapie. Cette revue de littérature présente les conceptions les plus importantes de la pathogénie de ce syndrome et les thérapies les plus souvent appliquées. Ce syndrome ressemble parfois à la douleur neuropathique, parfois à la fibromyalgie, parfois au syndrome des jambes sans repos. Dans le cas du syndrome primaire on note les dysfonctions pré synaptiques des neurones dopaminergiques et la diminution de la concentration de la dopamine endogène. Dans la pathogénie de ce syndrome les autres neurotransmetteurs / sérotonine, noradrénaline, histamine/ et les facteurs hormonales et inflammatoires jouent aussi leur rôle. Dans la pharmacothérapie de la stomatodynie on use les benzodiazépines, anticonvulsifs, antidépresseurs, antipsychotiques atypiques. A la fin du travail on décrit la possibilité de la thérapie d'olanzapine. Les auteurs présentent aussi le cas particulier de leur propre pratique thérapeutique – histoire d'une femme souffrant plusieurs années du syndrome de la bouche brûlante qui, après la thérapie d'olanzapine, obtient rapidement la réduction importante des symptômes. Le mécanisme probable de l'activité thérapeutique d'olanzapine base sur son effet sur les récepteurs dopaminergiques et de histamine ainsi que sur les récepteurs noradrénergiques et sérotoninergiques.

**Mots clés :** syndrome de la bouche brûlante, système dopaminergique, olanzapine

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