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FORENSIC AND ETHICAL PARTICULAR ISSUES IN THE CASE OF IDIOPATHIC BURNING MOUTH SYNDROME (BMS)

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Abstract: Burning mouth syndrome (BMS) is a chronic clinical condition, characterized clinically by the persistent sensation of pain perceived in the form of burning or stinging in the oral mucosa, which does not yield to the usual local or systemic therapies, without being accompanied by BMS normal clinical or biological results. It is a little-known disease outside oral pathology, so it is frequently underdiagnosed, late-diagnosed therapies are often inadequate and sometimes can be a cause of iatrogenicity and polypragmasia. In our article, we want to expose a series of ethical and medico-legal aspects about burning mouth syndrome that will facilitate the understanding of the sources of diagnostic errors and possible malpractice in addressing this condition. It is our belief that as this pathology is better known and understood, including from an ethical and forensic perspective, therapeutic goals can be achieved more easily, within the current knowledge of the disease.

Keywords: idiopathic burning mouth syndrome (BMS), ethical and medico-legal issues, misdiagnosis and late diagnosis, oral pathology.

INTRODUCTION

First described in the 19th century, burning mouth syndrome (BMS) was characterized in the early 20th century by Butlin and Oppenheim as glossodynia [1], the tongue being the main location site for the pain sensations in most patients. In the years that followed, burning mouth syndrome was referred to as glossopyrosis, oral dysesthesia, tongue pain, stomatodynia, orodynia, and stomatopyrosis [2].

The International Association for the Study of Pain defines BMS (1994) as "burning pain of the tongue and/or other oral mucous membranes in the absence of clinical signs or laboratory findings" [3,4]. It was first categorized as a distinct disease in 2004 by the International Headache Society, which defined primary BMS as "an intraoral burning sensation for which no medical or dental cause can be found" [5].

According to the International Classification of Orofacial Pain, starting with the year 2020, "burning mouth syndrome (BMS) is defined as idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 hours per day and more than 3 months, without any identifiable causative lesions" [6].

Lamey and Lewis (1989) categorized burning mouth syndrome into three categories based on fluctuations in pain severity over a 24-hour period:

- type 1 typically has no symptoms on waking and progressively worsens throughout the day with variable nighttime symptoms. It may be related to nutritional deficiency or endocrine conditions such as diabetes mellitus.

- type 2 is associated with chronic anxiety and displays symptoms throughout the day.

- type 3 displays intermittent daytime symptoms and may have periods without any symptoms. Food allergy is thought to be a potential underlying mechanism (Table 1) [7].

Scala *et al.* (2003) proposed five clinical criteria to diagnose burning mouth syndrome: 1) Deep and bilateral burning pain is reported daily; 2) Burning

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pain lasts for at least four to six months; 3) Constant or increasing severity throughout the day; 4) No worsening but improvement in eating and drinking, and 5) No sleep interference [10].

Depending on the aetiology, BMS can be classified into two forms:

- primary form (essential/idiopathic), in which local/systemic organic causes cannot be identified, but which may involve peripheral and central neuropathological pathways;

- secondary form, determined by local, systemic or psychological factors [10,11].

The prevalence of BMS varies significantly in studies, especially due to variations in selection criteria and definitions over time, age variations in patient groups, and the fact that patients with burning sensations were more frequently included in studies rather than patients with idiopathic BMS. In the general population, depending on which studies are cited, a prevalence ranging between 1% and 15% has been reported [12]. Lipton *et al*. reported a prevalence of 0.7% in the general population, based on the analysis of responses from 45,000 self-administered questionnaires in the United States [13]. A Brazilian study conducted on a group of almost 300 patients who addressed oral pathology departments reported a prevalence of BMS of about 1% [14]. A cross-sectional study in which 1,000 randomized patients were selected from Swedish Public Health Service registries reported an incidence of BMS of approx. 3.7%. A Finnish study reported a 15% incidence of BMS symptoms in the adult population, but about half of the respondents had oral lesions [15]. The prevalence of pain syndrome in the Oral Pathology service of the Faculty of Dental Medicine - "Carol Davila" University of Medicine and Pharmacy of Bucharest is 16.23% [11].

BMS has a different distribution depending on gender and age. Women are 2.5 to 7 times more frequently diagnosed with BMS than men, and in some studies, the proportion can reach up to 1:30. Among women diagnosed with BMS, up to 90% are in perimenopause or menopause [14].

In the literature, it is considered that the onset interval of BMS can vary between 27 and 87 years, with an average age of 61 years [9,15].

These data from the literature, although providing a variable rate of BMS prevalence that necessitates further studies, provide an additional argument that BMS is a frequently underdiagnosed public health problem.

The aetiology and pathogenesis of BMS syndrome are still insufficiently known. Based on the definition provided by the International Society for the Study of Headache, which assumes that BMS is idiopathic in nature, attempts are being made to identify factors with a possible etiopathological role associated with BMS.

A frequently cited cause in the aetiology of BMS is oral infections caused by various microorganisms, such as Candida albicans, Enterobacter, Klebsiella, Fusobacterium and Staphylococcus aureus; however, no significantly higher prevalence of oral microbial load was identified in patients with BMS *versus* control [16]. Helicobacter pylori was isolated by oral mucosal biopsies and molecular biology techniques in 86% of cases and in some studies, the prevalence of H. pylori infections is double in patients with BMS *versus* control [17]. Several studies discuss the possibility that at least some cases of BMS are due to chronic infections with viruses such as herpes simplex 1 [18], varicella-zoster virus [19], human papilloma virus [20]. Recently, persistent oral burning sensations have also been described in patients infected with the SARS-CoV-2 virus who did not require ventilatory support [21-23].

Studies in the last decade have also focused on dysfunctions observed in the central nervous system, especially maladaptive activation patterns in the anterior cingulate cortex, bilateral precuneus, hippocampus and thalamus, as well as impairments in the functionality of the dopaminergic system involved in pain modulation [24-26].

More and more research confirms the involvement of the endocannabinoid (eCB) system in peripheral pain control, given that activation of CB1 and CB2 receptors reduces nociceptive stimulus signaling and local perception of nociceptive stimuli is influenced by endocannabinoids such as AEA and 2-AG [27-29]. In a recent study, plasma levels of palmitoylethanolamide (PEA), but not oleoylethanolamide (OEA), anandamide (AEA) or 2-arachidonoyl-glycerol (2-AG), were significantly elevated in patients with BMS, when compared to plasma from healthy, individuals. Plasma

Table 1. Classification of BMS subtypes [8]

Type 1	Daily pain, not present upon awakening, worsens as the day progresses	Non-psychiatric
Type 2	Constant pain	Psychiatric, chronic anxiety
Type 3	Intermittent pain in unusual sites (floor of mouth)	Allergic contact stomatitis due to preserving agents and additives

PEA, OAS and AEA levels correlated with depressive symptomatology [30].

Along with the eCB system, neurotrophic factors (NTFs) appear to be involved in both BMS and mood disorders, such as anxiety and depression [31,32]. For example, artemin, a member of the glial cell line-derived neurotrophic factor, is increased in the tongue mucosa of BMS patients [33].

A significant number of studies highlight the association between psychiatric pathologies and mood disorders in glossodynia [34], most often attributed to complex mechanisms involving altered signaling and processing of nociceptive stimuli and impairment of psychological functions [35]. Given that BMS has been associated since the 19th century with various psychiatric manifestations (most commonly with anxiety and depressive disorders), the causal relationship between the two conditions remains a topic open to debate. On the one hand, there is the opinion that BMS is a somatoform disorder, the condition being considered to be predominantly psychiatric, emphasizing for example the subjective overlap between the onset of BMS symptoms and impaired emotional state. BMS symptoms are considered by most patients to be a major cause of the significant decline in quality of life and the leading cause of the apparent onset of psychiatric suffering. A counterargument, in this case, is that patients with BMS have a higher degree of neuroticism and have a latent predisposition to affective disorders (in many cases psychiatric pathology is absent or is not subsequently recognized by the patient). There is a number of studies that highlight persistent organic lesions (local, central and systemic nervous system) in patients with BMS, which appear to be involved in the aetiology of this disease.

Antidepressant medication is commonly used in moderate or resistant cases to local therapy and is considered a valid option in the treatment of burning mouth syndrome (BMS). The effects of antidepressants (tricyclic, SSRI - serotonin reuptake inhibitors, SNRI - serotonin-noradrenaline reabsorption inhibitors, clonazepam) are manifested both by reducing the perception of pain intensity and in worsening the anxiety-depressive symptoms, the therapeutic effects being confirmed by numerous studies [36, 37]. Multimodal antidepressants (such as vortioxetine) used in the case of glossodynia have had positive effects on symptoms and are a safe and effective alternative, especially in patients with other pain syndromes or psychiatric comorbidities [38, 39].

The differential diagnosis of odynophagia involves the differentiation of local manifestations of systemic diseases or other localization and loco-regional pathologies. From the first category, we can mention herpes simplex virus infection, HIV/AIDS infection, gastroesophageal reflux disease, scleroderma, Sjogren's syndrome, neuropathies, diabetes, vitamin deficiencies, multiple sclerosis, fibromyalgia, anaemias, dehydration, severe dyselectrolyemia, anticholinergic drugs, pemphigus, neoplastic and paraneoplastic syndromes, smoking, chronic alcohol consumption, drug addiction etc. [7].

At the loco-regional level, the differential diagnosis is made especially with idiopathic orofacial pain (AOFI) which includes, according to the new classifications the following pathologies: atypical facial pain, stomatodynia, atypical toothache, arthromyalgia of the temporomandibular joint and some pain of the masticatory muscles. Regardless of the type of idiopathic orofacial algae, they have some features in common with glossodynia, especially similarities related to the clinical aspects of the painful syndrome, triggers and pathophysiological mechanisms, diagnostic methodology, diagnostic investigations and therapeutic recommendations (Table 2).

Therapeutic strategies include benzodiazepines (clonazepam), tricyclic antidepressants (amitriptyline), anticonvulsants (gabapentin), selective serotonin receptor inhibitors (paroxetine and sertraline), topical/systemic capsaicin, alpha-lipoic acid, 15% benzidamine hydrochloride, hormone replacement therapy, administration of vitamin and/or zinc supplements, iron and psychocognitive therapy (Table 3) [41].

In the case of idiopathic BMS, the therapeutic principles aim at a triple purpose: the improvement of the symptomatology, the correction of the biological and/or morphological anomalies and psycho-emotional therapy [11].

MATERIALS AND METHODS

The conceptualization of a synthetic literature review from databases such as PubMed, Cochrane, and Google Academic highlights the absence of a systematic approach in the literature dedicated to ethical and medico-legal aspects of BMS. However, even in these conditions, we find a number of disparate references in articles on pain therapy and the quality of life of patients with refractory to therapy BMS.

Our methodology was based on Grant and Booth's typology of reviews [43]. Our search was performed in medical databases (PubMed, Cochrane),

using the following search terms: burning mouth syndrome, glossodynia combined with medico-legal, legal, ethical. The search covered the 1990-2021 period and was limited to the English, French and Italian languages.

RESULTS AND DISCUSSIONS

A first step in the discussion of BMS is the terminology used and the need for disambiguation, given that it has been frequently inaccurate, confusing, controversial, subjective or sometimes derogatory to the patient.

As early as the first half of the 19th century, the origin of BMS was considered to be predominantly, if not exclusively, of a psychological nature ("psychism"), the causes ranging from "suggestion" and "imagination" to "cancerophobia" (incidentally frequently encountered today); to these are added other diagnoses from that time – "hypochondria", "hysteria", "neurasthenia" or "neuropathy" - these being conceptualized in neurotic syndromes - disorders of the intellect with a sensitive and motor component (Dechambre, Duval, and Lereboullet, 1885) [44].

Other causes considered probable for BMS, which directly influenced the name and taxonomy of BMS, mentioned until the '60s of the last century are local organic lesions (stomatitis, ulcers, "lingual varicose veins", herpes lesions, oral syphilis), oral manifestations of systemic pathologies (such as gout, vitamin deficiencies - scurvy, beriberi, pellagra etc., deficiency anaemias), manifestations of dysfunctions

Table 2. Differential diagnosis of BMS - systemic and local causes of a burning sensation in the oral cavity [40]

Oral mucosal conditions	**Systemic factors**
- Erythema/erosion of whatever cause	- Diabetes
- Atrophic tongue	- Decreased levels of vit. B_1, B_2, B_{12}, folate, iron, zinc
- Candidiasis	- Allergic reaction to food or dental materials
- Geographic tongue	- Lichenoid tissue reactions
- Lichen planus	- Autoimmune conditions
- Pemphigoid, pemphigus	- Hormonal disturbances
	- Parkinson disease
Parafunctional habits	**Drugs**
- Cheek sucking	- Paroxetine
- Tongue thrusting	- Angiotensin-converting enzyme inhibitors
Trauma	**Local nerve damage**
- Mechanical	- Chemotherapy-associated neuropathy
- Chemical	- Local physical irritation
- Thermal	
Xerostomia and altered salivary quality	**Various peripheral or central neuropathies**
- Radiotherapy	
- Chemotherapy	
- Other drugs	
- Sjögren's syndrome	

Table 3. Most widely used therapeutic options described in the literature [42]

Topical Treatments	Oral Treatments
- 0.025% capsaicin cream	- α-Lipoic acid, 600–800 mg/d
- Tabasco diluted 1:8–1:1 in water	- Clonazepam, 0.5–2 mg/d
- 2% lidocaine gel	- Paroxetine, 10–30 mg/d
- Clonazepam, 0.5-1 mg up to 3 times/d	- Sertraline, 50 mg/d
- Doxepine, 10mg/ml aqueous solution	- Amitriptyline, 5–100 mg/d
- Sucralfate	- Duloxetine, 30–60 mg/d
- Artificial saliva	- Amisulpiride 10–150 mg/d
- Sialogogue spray with 1% malic acid	- Gabapentin, 300–900 mg/d
- Saliva substitutes (carboxymethycellulose and mucin)	- Pregabalin, 25–300 mg/d
	- Capsaicin, 0.25% capsules
	- Pilocarpine, 5–30 mg/d

of the central nervous system (neurosyphilis, post-meningitis, various neuropathies), neuropathies of the peripheral nerves (especially branches of the cranial nerve V), reflex pain triggered by gastroesophageal pathologies and chronic constipation etc.

Under these conditions, names, definitions, diagnostic criteria, therapeutic approaches, etc. have been very varied over time, often there are conceptual conflicts reflected in the name BMS, a situation that has continued to influence and shape the perception of physicians to date.

Keeping the historical line, we mention that the poor understanding of the causes of BMS and the fact that it was considered predominantly a manifestation in the psychic sphere, especially affecting postmenopausal women, led to the application in the past of some treatment lines that in many situations proved ineffective and a cause of iatrogenicity. We mention a series of historical therapeutic attitudes, practically without therapeutic value in BMS, which today would represent rather the cause of malpractice:

- moral treatment, proposed in the early 1800s is the current equivalent of psychotherapy, although with a more pronounced coercive valence (aimed to change by suggestion the "disturbed imagination" of the patient);

- use of sedatives such as valerian, bromide, belladonna extract, chloral, laudanum sometimes with positive effects but with an increased risk of abuse and addiction;

- painkiller medication - aconite (neurotoxic in higher doses), antipyrine or exalgin (potentially neurotoxic);

- anti-arthritic medication (as it was called at the time) aimed at administering "therapeutic" doses of quinine, arsenic or alkaline salts;

- hydrotherapy, a common medical practice at the time for patients with gout, was recommended both externally and through the internal use of alkaline mineral waters with a high content of magnesium and iodine salts;

- topical treatments - local applications or the use of solutions containing glycerin, menthol, cocaine (frequently used at that time as an anaesthetic), silver nitrate, and various "emollients" (based on oats, opium etc.);

- cauterizations (thermal, electrical, chemical) - but frequently used on small mucosal surfaces, especially for the persistent placebo effect;

- surgical treatments - frequently criticized for their intrusiveness and predisposition to complications - involved lingual nerve sectioning or infiltration of the sphenopalatine ganglion with a solution of phenol and cocaine;

- other treatments, including the administration of mercury salts (used at the time in the treatment of syphilis), various diets to combat some relatively common nutritional deficiencies (especially B cxx vitamins, animal proteins), laxatives for the treatment of constipation, basic antacids for treatment of reflux disease, galvanic therapy, homoeopathic remedies, cod liver oil, hypnosis sessions, use of artisanal / master preparations ("elixirs").

Currently, although the risk of iatrogenicity is much lower, a major problem has remained the misdiagnosis and late diagnosis of BMS. In a study conducted in 2005, Mignogna *et al*. establishes in a large group of patients that the time elapsed between the apparent onset of symptoms until the definite diagnosis of BMS is on average 15.6 months (with an interval between 2 months and 48 months) for men and 36.8 months for women (interval between one month and 348 months). During this time, the average number of specialists consulted in this issue was 3.2 for female patients and 2.5 for men. The most common misdiagnosis in this study was no diagnosis, nonspecific stomatitis, oral candidiasis, depressive disorder, allergic reactions to prosthetic materials, hypovitaminosis, xerostomia, trigeminal nerve neuralgia, viral hepatitis, gastroesophageal reflux disease, bruising, intolerance [45]. Other studies with smaller patient groups confirm the problem of late diagnosis and a large number of inaccurate diagnoses, as well as the longer duration of diagnosis among women [46, 47]. One solution would be to increase awareness among dentists and other medical specialities, as well as intensify efforts to educate patients with persistent (neuropathic) pain syndromes.

The reverse of a late or erroneous diagnosis of BMS, although less common in medical practice, involves the identification of primary causes with very low frequency ("black swans") that require a complex multidisciplinary differential diagnosis. The most common occult causes in which persistent sensations of oral burning with similar BMS characteristics are: progressive neuropathic pain from neoplasms, benign tumours (schwannomas) [48], autoimmune pathologies (Sjogren lupus, pernicious anaemia, etc.), giant cell arteritis, post-stroke etc. [49].

In the absence of a correct and complete diagnosis, patients with BMS face a delay in the administration of a specific treatment, being exposed

to a set of pharmacological therapies with a more or less therapeutic impact that can generate polypragmasia, detrimental drug interactions and finally iatrogenicity. The association of BMS with a series of psychiatric pathologies involves the use by patients, both before and after the diagnosis of BMS, of a large number of drugs and supplements with the antidepressant role (selective serotonin reuptake inhibitors (SSRIs) - fluoxetine, citalopram, escitalopram, sertraline, paroxetine, clomipramine, serotonin-norepinephrine reuptake inhibitors (SNRIs) - venlafaxine, duloxetine; milnacipran, trazodone, amitriptyline), anxiolytic (benzodiazepines - especially clonazepam topical and systemic, bromazepam, prazepam), antipsychotic and antiparkinsonian (olanzapine, aripiprazole, pramipexole, levodopa), anticonvulsant (pregabalin, gabapentin), hypnotic (melatonin), sedative (Hypericum perforatum extract) etc. [50].

In addition to psychiatric medication, patients with ABM often suffer from other comorbidities, such as cardiovascular disease (frequently hypertension, ischemic heart disease, peripheral circulatory disorders), metabolic (obesity, dyslipidemia, diabetes), various types of chronic pain etc.

Examples of iatrogenic BMS described in the literature are burning mouth syndrome induced by angiotensin-converting enzyme inhibitors (captopril, enalapril, lisinopril, eprosartan and candesartan) [51], antidepressant-induced burning mouth syndrome (fluoxetine) [52]; cases in which symptoms similar to those in BMS have been reported have involved drugs such as efavirenz (anti-HIV medication), clonazepam, hormone replacement therapy, SSRI antidepressants such as fluoxetine, sertraline and venlafaxine etc. [53].

A recent trend in the therapy of neuropathic pain syndromes is the use of various cannabis products, topical or systemic. The main arguments for BMS would be the encouraging results obtained in other pain syndromes [54], the imbalances observed in the endocannabinoid system in patients with persistent BMS, and a possible improvement in anxiety-depressive symptoms. Although there is only one published study [55], small and without evaluating the placebo effect, we consider that from the local perspective this approach is risky and creates opportunities for addiction and legal conflicts.

Another possible source of malpractice in BMS management is the failure to notice deterioration in the patient's condition. Considering that in primary BMS the pain is nociplastic and no macroscopic lesions are highlighted, the periodic evaluations are performed based on the detailed anamnesis and by using standardized tests, scales and scores. In patients with multiple comorbidities, especially those with psychiatric disorders, there is a risk of ignoring or failing to understand the worsening of symptoms if the examination is incomplete, superficial or incorrectly performed.

In particular, the failure to understand and treat the psychiatric aspects related to BMS can be dramatic, both in terms of deteriorating quality of life and, in extreme cases, increasing the risk of suicide. Although a rare event in patients with BMS resistant to therapy, the literature describes several cases in which persistence and worsening of symptoms have been considered to have played a decisive role in suicidal behaviour [56,57].

The aspects mentioned above oblige the attending physician to make efforts to avoid the failure to understand and conceive strategies for quality of life improvement in BMS patients. Patients with resistant BMS frequently associate comorbidities, including psychiatric, sometimes adherence to the therapeutic plan is reduced, may be demanding and inconsistent, may associate some cognitive deficits and have a lower socio-professional status. It is estimated that about one-third of BMS cases have a good response to treatment, another third satisfactory/partial and in about one-third of cases, the therapies do not control the symptoms. Especially in the latter case, it is very important to recognize the therapeutic failure and to have honest and direct communication with the patient. A central objective of communication strategies is to understand and dispel the patient's fears related to serious pathology and /or cancer and to identify by mutual agreement the strategies of accepting the symptoms and improving the quality of life.

The patient with idiopathic BMS requires a synchronized multidisciplinary approach, ideally performed in a university clinic or centre of excellence, with specialists who know the particularities of this disease. An essential role is played by mental health professionals (psychiatrist, psychologist, psychotherapist), both in adjusting pharmacological therapy and psychotherapy and in maintaining a fruitful and direct channel of communication [58].

An ethical issue of interest in BMS is the use of fMRI in the study of lesions of the pathways and centres of the central nervous system. In the literature, we have identified nine studies published from 2006 to date that have used patients diagnosed with BMS [59]. The techniques currently used by fMRI - both acquisition and advanced processing of neuroradiological data - allow

sophisticated reconstructions of the brain pathways and capture some complex processes of reaction to stimuli and thinking ("brain fingerprinting"). There is a real concern that such yields can capture profound and involuntary aspects of the mind-brain relationship and affect "cognitive intimacy". The risk is even higher as this data in electronic format can be shared by accident or accessed illegally [60,61].

In conclusion, burning mouth syndrome remains a little-known pathology outside of oral pathology and dental practice. Prolonged medical trajectory (months to years), consultation of a large number of specialities before receiving a firm diagnosis, the need for interdisciplinary consultation in patients with BMS, psychological exhaustion of patients seeking a therapeutic solution, additional costs for the medical system and patients, diagnostic failure in many situations, significant and long-term decrease in the quality of life of patients and relatives, decreased productivity in the professional field, altered relationships in family life, etc. are just some of the aspects commonly encountered in this pathology. We believe that these problems can be prevented if awareness campaigns are conducted periodically for medical specialities with increased addressability for patients with BMS, such as psychiatry, neurology, otolaryngology, gastroenterology, and dermatology.

The main forensic aspects of BMS refer especially to the late and frequently erroneous diagnosis, which contributes to the recommendation of inadequate therapeutic solutions and in some cases is generating iatrogenicity. Poor cooperation between medical specialities in the case of the complex patient with BMS is often one of the reasons for polypragmasia and avoidable complications.

Failure to recognize the psychiatric dimension of the patient with BMS, both independent of oral pathology and secondary to BMS manifestations, significantly decreases the chances of therapeutic success and in some cases contributes to increased suicide risk. The quality of communication, tact, empathy, and specialization of medical actors in the particularities of BMS are essential keys to a successful therapeutic alliance.

The risk of abuse of psychotropic drugs or supplements unapproved and unauthorized on the domestic market is another facet of medical-related concerns in BMS.

The research ethics in BMS presents a series of particularities, from the representation of gender (considering that BMS is generally much more common in women) to the realization of informed consent that takes into account the particularities of this pathology (nociplastic pain, psychiatric dimension, suicide risk assessment etc.), concern for maintaining the quality of life during research, maintaining cognitive intimacy when using advanced methods of neuroimaging.

Considering the poor representation in the specialized literature of the systematized research regarding the medico-legal and ethical aspects of BMS and by extension to the orofacial (nociplastic) pain syndromes, we consider that more research in this direction is needed.

Conflict of interest

The authors declare that they have no conflict of interest.

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