Burning Mouth Syndrome; Diagnosis and Management

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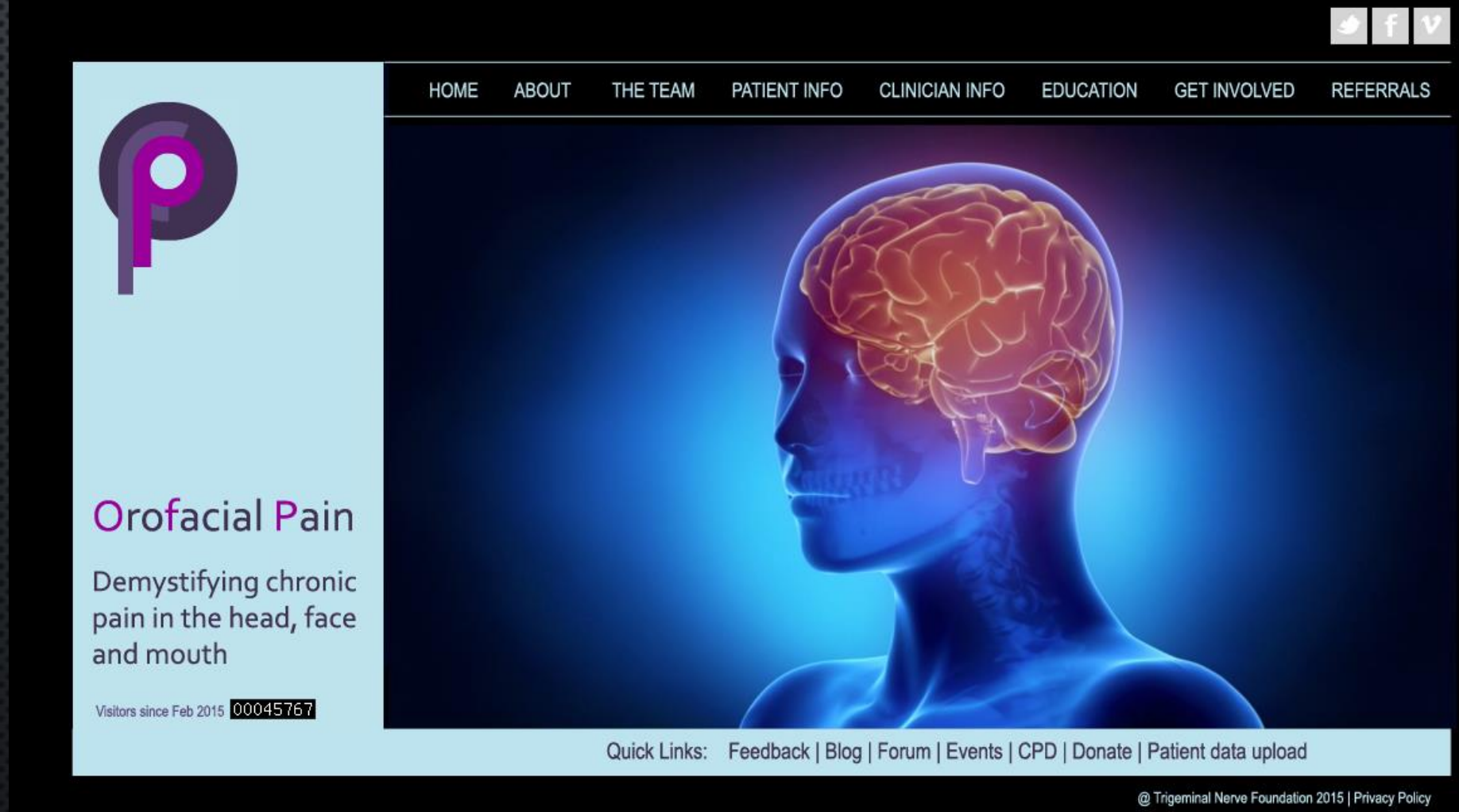


LEARNING OBJECTIVES

- To outline diagnostic criteria for BMS
- To provide a summary of aetiological factors and possible mechanisms
- To provide some key diagnostic tips and provide some novel strategies in management for patients with BMS
- To highlight the possible future management of patients with BMS

TYPES OF PAIN ……

Review series introduction

What is this thing called pain?

Clifford J. Woolf

Program in Neurobiology and Department of Neurology, Children's Hospital Boston, and Department of Neurobiology, Harvard Medical School, Boston, Massachusetts, USA.

To paraphrase Cole Porter's famous 1926 song, "What is this thing called pain? This funny thing called pain, just who can solve its mystery?" Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain. The substantial progress made over the last decade in revealing the genes, molecules, cells, and circuits that determine the sensation of pain offers new opportunities to manage it, as revealed in this Review series by some of the foremost experts in the field.

Classifying pain

What exactly, from a neurobiological perspective, is pain? Pain is actually three quite different things, although we and many of our physicians commonly fail to make the distinction. First, there is the pain that is an early-warning physiological protective system, essential to detect and minimize contact with damaging or noxious stimuli. This is the pain we feel when touching something too hot, cold, or sharp. Because this pain is concerned with the sensing of noxious stimuli, it is called *nociceptive* pain (Figure 1A), a high-threshold pain only activated in the presence of intense stimuli (1). The neurobiological apparatus that generates nociceptive pain evolved from the capacity of even the most primitive of nervous systems to signal impending or actual tissue damage from envi-

and other syndromes in which there exists substantial pain but no noxious stimulus and no, or minimal, peripheral inflammatory pathology. The clinical pain syndrome with the greatest unmet need, pathological pain is largely the consequence of amplified sensory signals in the central nervous system and is a low-threshold pain. By analogy, if pain were a fire alarm, the nociceptive type would be activated appropriately only by the presence of intense heat, inflammatory pain would be activated by warm temperatures, and pathological pain would be a false alarm caused by malfunction of the system itself. The net effect in all three cases is the sensation we call pain. However, because the processes that drive each are quite different, treatments must be targeted at the distinct mechanisms responsible.

TYPES OF PAIN

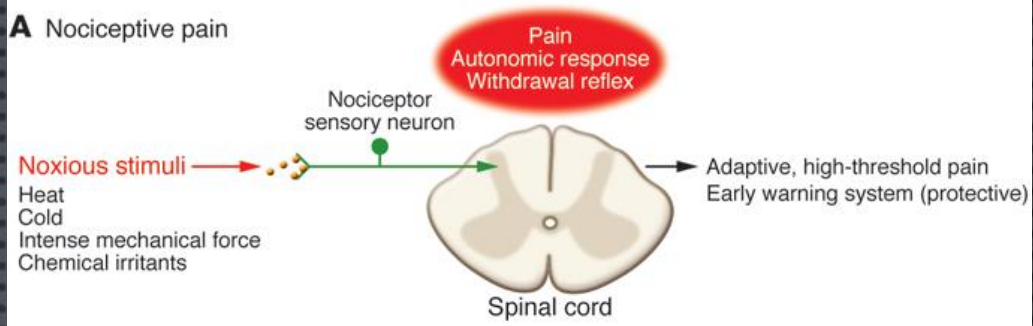
Healthy

- Nociceptive healthy feeling pain 'pain'
- Inflammatory pain health short lived after insult

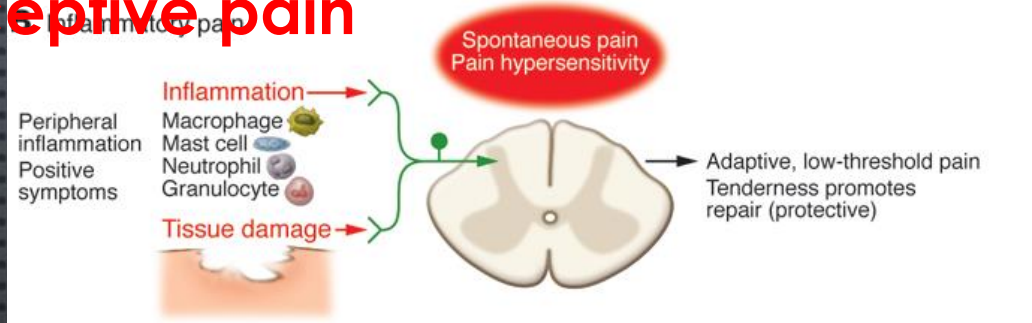
Unhealthy

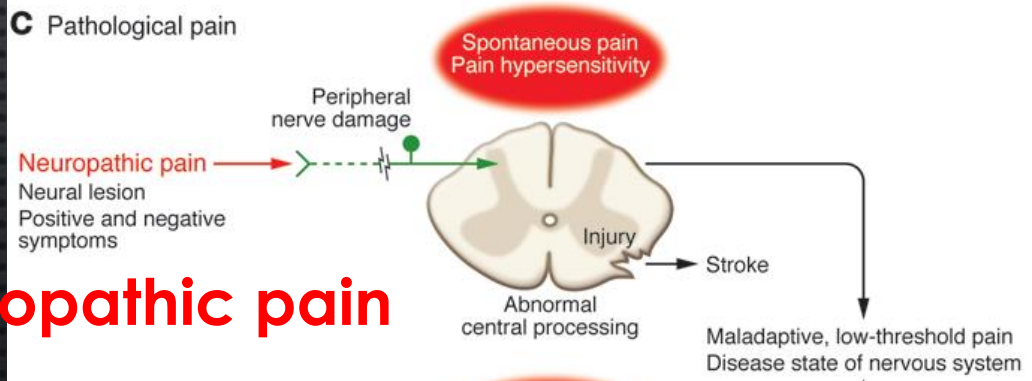
- Neuropathic pains
- Dysfunctional pain

Clifford J. Woolf. **What is this thing called pain?** J Clin Invest. Nov 1, 2010; 120(11): 3742–3744.

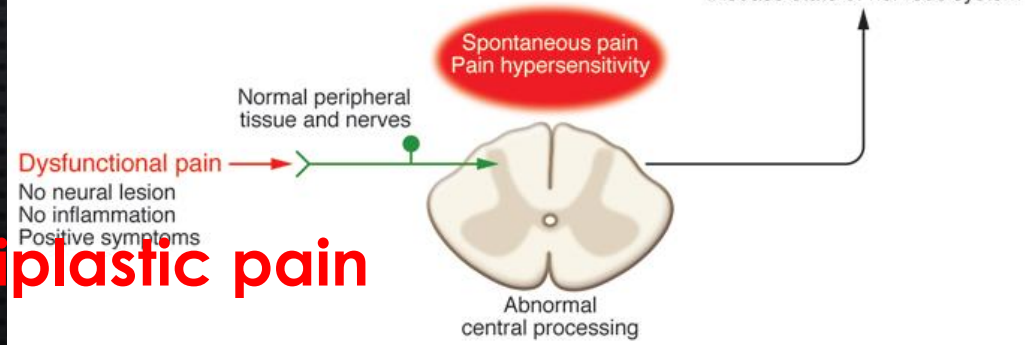


Nociceptive pain





Neuropathic pain



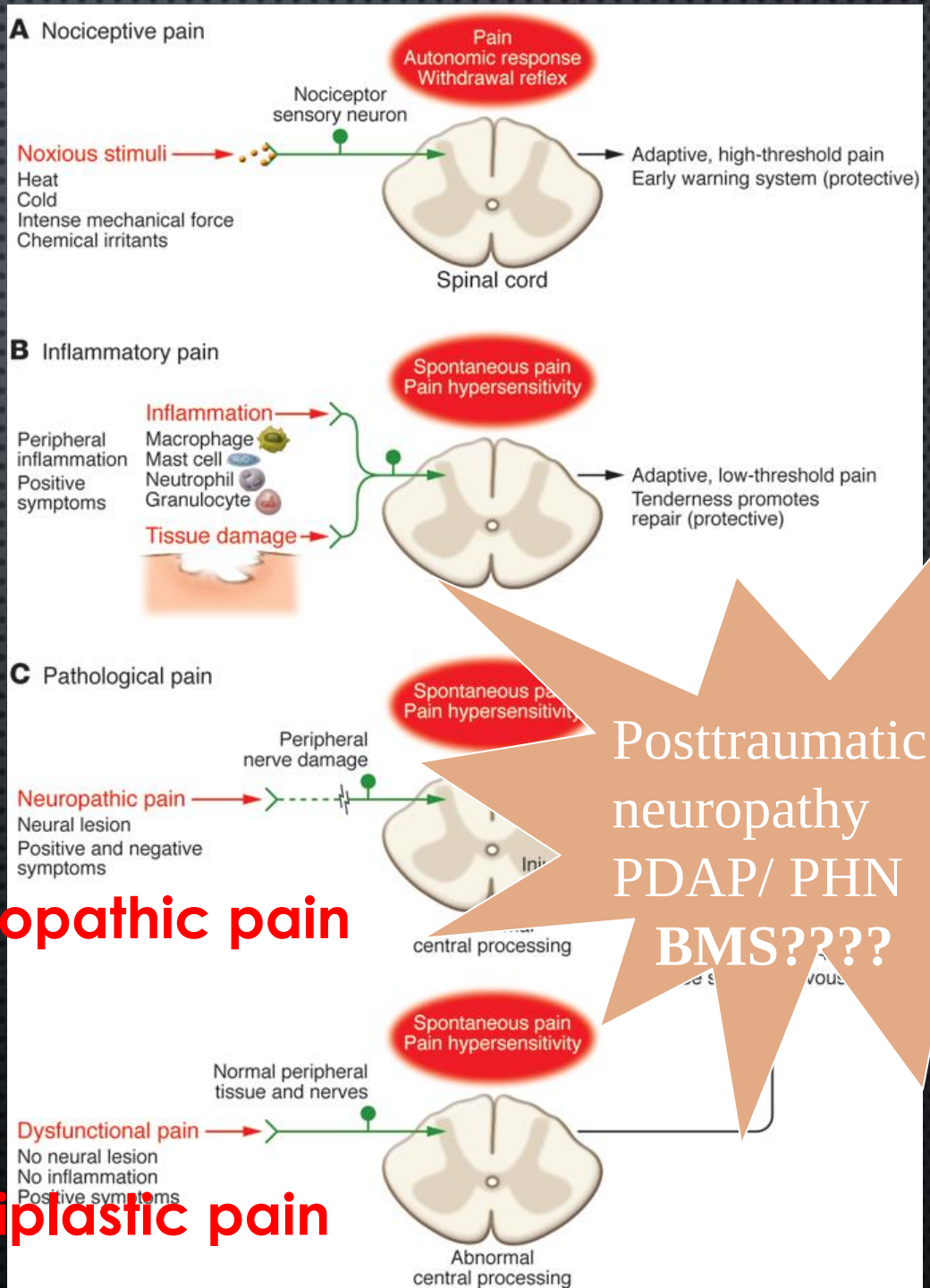
Nociplastic pain

Unhealthy Pain

BUT?

IS BURNING MOUTH SYNDROME NEUROPATHIC PAIN???

BURNING MOUTH DISORDER OR SECONDARY BMS **IS** NEUROPATHIC



Neuropathic pain

Posttraumatic neuropathy
PDAP/ PHN
BMS????

Nociplastic pain

UNHEALTHY PAIN

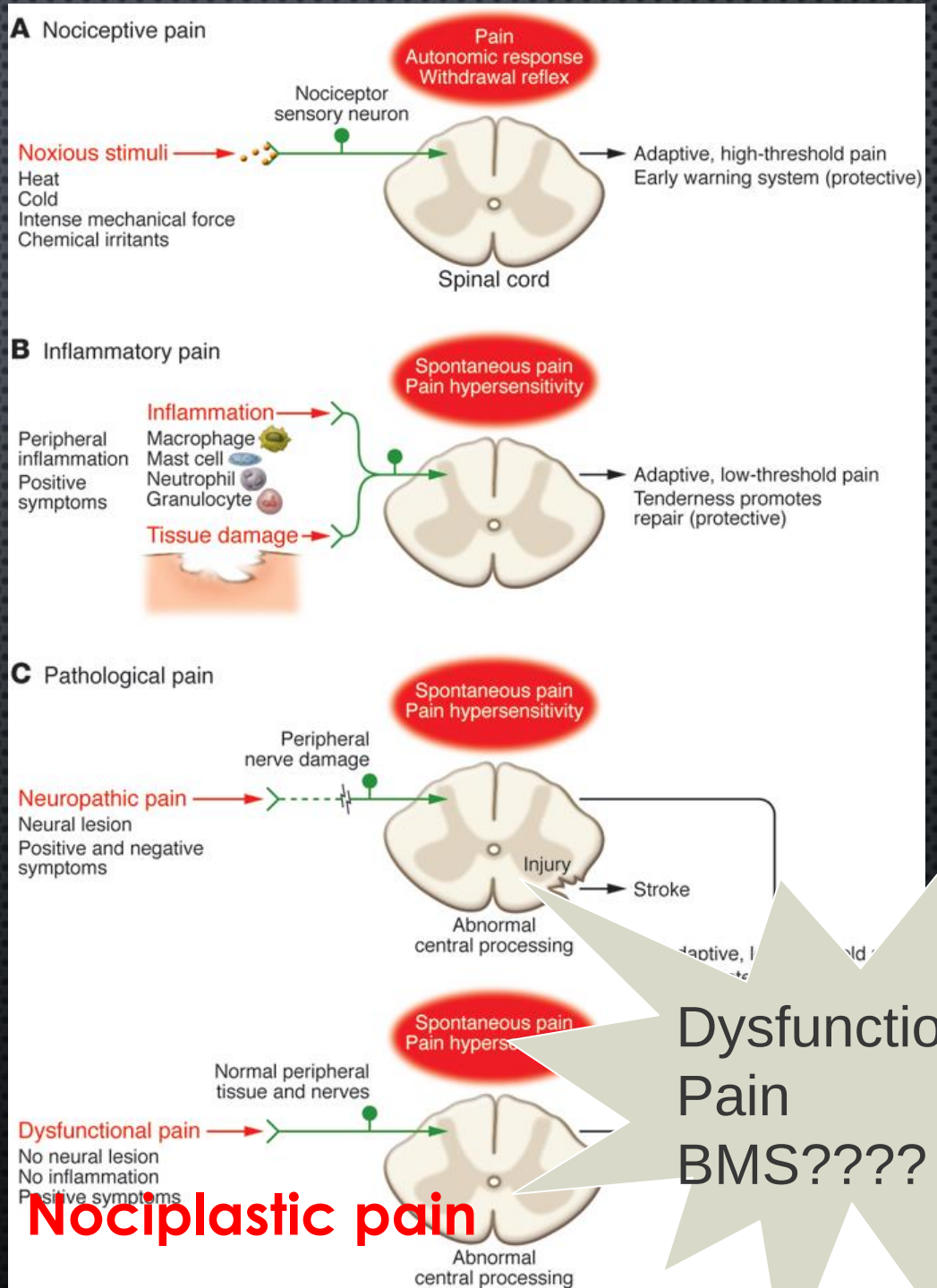
Neuropathic pain

Dysfunctional pain, Corresponds to a dysfunction of the central inhibitory processes of pain control (Crofford *et al*., 2005).

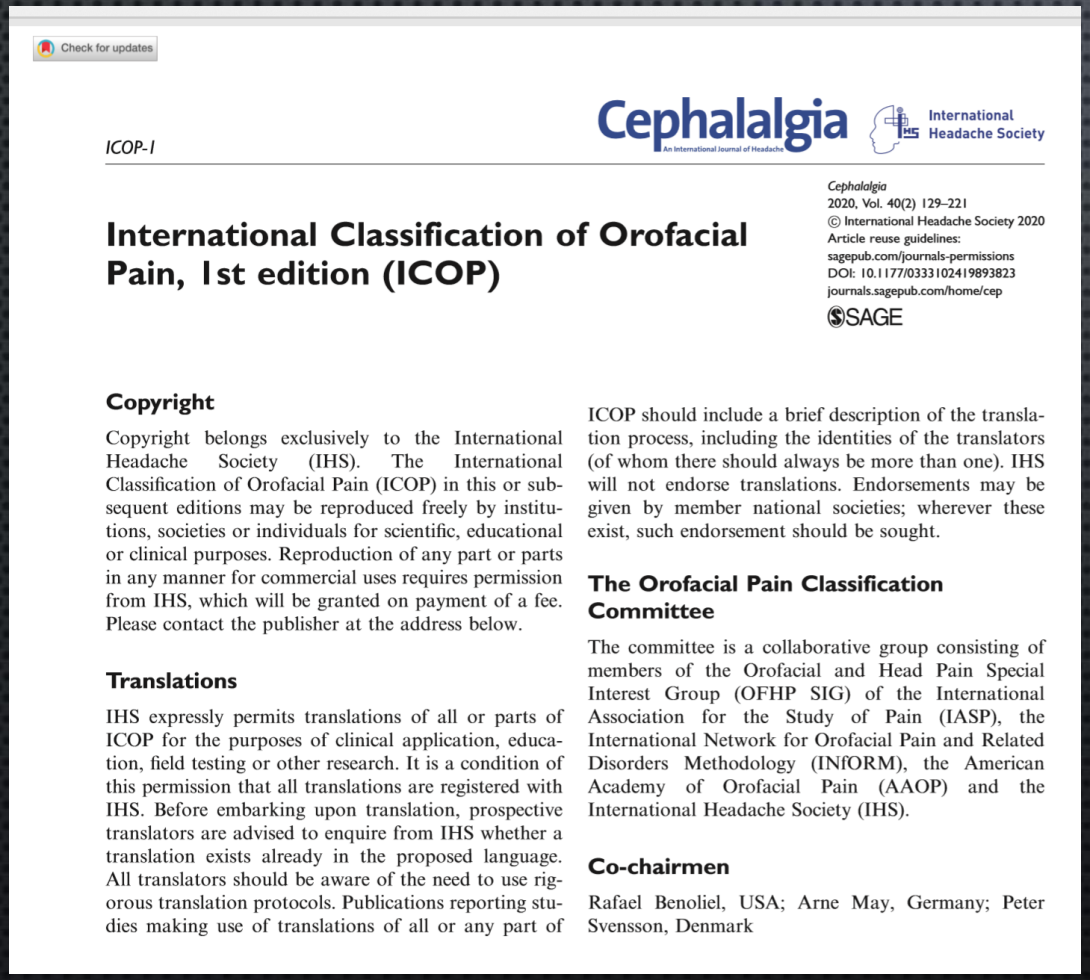
Including;

- fibromyalgia
- irritable bowel syndrome
- Tension headaches
- idiopathic orofacial pain
- complex regional pain syndrome
- **Burning mouth syndrome?**

With a marked co-morbidity between some of these pain syndromes (Kato *et al*., 2006).



ICOP STATES BMS IS IDIOPATHIC



Check for updates

ICOP-I

Cephalalgia
An International Journal of Headache
International Headache Society

Cephalalgia
2020, Vol. 40(2) 129–221

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International Classification of Orofacial Pain, 1st edition (ICOP)

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The Orofacial Pain Classification Committee

The committee is a collaborative group consisting of members of the Orofacial and Head Pain Special Interest Group (OFHP SIG) of the International Association for the Study of Pain (IASP), the International Network for Orofacial Pain and Related Disorders Methodology (INfORM), the American Academy of Orofacial Pain (AAOP) and the International Headache Society (IHS).

Co-chairmen

Rafael Benoliel, USA; Arne May, Germany; Peter Svensson, Denmark

IDIOPATHIC OROFACIAL PAIN

- 6.1 BURNING MOUTH SYNDROME (BMS)
  6.1.1 BURNING MOUTH SYNDROME WITHOUT SOMATOSENSORY CHANGES
- 6.1.2 BURNING MOUTH SYNDROME WITH SOMATOSENSORY CHANGES
- 6.1.3 PROBABLE BURNING MOUTH SYNDROME

Features of Neuropathic pain

- **Patient over 50 years**
  - Migraines
  - FM other chronic pain conditions
  - Genetics COMT

- Multiple insults
- Non respondent to anti inflammatory pain killers (NSAIDs Paracetamol)
- Better in mornings
- Does not disturb sleep
- Worsens during day
- Worsens with stress, tiredness and illness
- Either
  - Constant burning
  - Elicited neuralgic (electric shock)
  - Or combination

Table 2
Definitions of common features suggestive of neuropathic pain[29]

Paresthesia	An abnormal sensation, whether spontaneous or evoked
Dysesthesia	An unpleasant sensation, whether spontaneous or evoked
Hypoesthesia	Decreased sensitivity to stimulation (tactile or thermal; both are frequent)
Hyperesthesia	Increased sensitivity to stimulation (tactile or thermal; both are rare)
Hypoalgesia	Diminished pain response to a normally painful stimulus
Hyperalgesia	An increased response to a stimulus that is normally painful
Allodynia	Pain due to a stimulus that does not normally activate the nociceptive system

The Trigeminal nerve

Complex region

Consequences

- Social function
- Eating
- Drinking
- Speaking
- Kissing
- Make up / shaving
- Sleeping

IDENTITY?

Burning Mouth Syndrome

- First described in mid nineteenth century, this condition was further characterized in the early twentieth century by Butlin and Oppenheim as glossodynia
- Over the ensuing years, BMS has been referred to as glossopyrosis, oral dysesthesia, sore tongue, stomatodynia, and stomatopyrosis.
- 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."

IS BMS A SYNDROME?

- SHOULD BMS BE BURNING MOUTH DISORDER?

Vol. 127 No. 5 May 2019

EDITORIAL

Is burning mouth a syndrome or a disorder? A commentary

Why is it that burning mouth continues to be referred to as a "syndrome"? This enigmatic and long-described pain disorder has been defined by several international organizations.[1-3] In 1994, the International Association for the Study of Pain (IASP) defined burning mouth syndrome (BMS) "(also known as glossodynia, glossopyrosis, oral dysesthesia, or stomatodynia) as a chronic oral mucosal pain or discomfort that has no identifiable causative lesions and is not caused by any other condition or disease."[1] The IASP recognized the clinical features to include burning, tingling, pricking, or discomfort. In 2004, the International Headache Society [IHS]) defined BMS as "an intraoral burning sensation for which no medical or dental cause can be found."[4] In the latest IHS revision (2018), BMS is defined as "an intraoral burning or dysesthetic sensation, recurring daily for more than two hours/d over more than three months, without clinically evident causative lesions."[2] The World Health Organization [WHO]), which publishes the *International Classification of Diseases* (ICD), endorses a similar definition in their 2016 classification system (ICD-10 code). Here, glossodynia (K14.6), which includes additional terms, such as *glossopyrosis* and *painful tongue*, is described as "painful sensations in the tongue including a sensation of burning."[5] The definitions published by these organizations have been updated several times over the years, and many other entities and authors also have provided input into our understanding of this disorder.[3,6-12] These definitions provide clinical perspective, yet differences between the descriptions are clearly evident. Despite the many attempts to define this pain disorder more specifically, the name of the condition—"burning mouth syndrome"—has not been critically assessed and scrutinized for years.

Appropriately naming a medical condition is an important undertaking. The ICD, which is managed by the WHO, is responsible for disease nomenclature. The WHO recently called upon scientists and national organizations to follow best practices in naming new "human infectious" diseases to minimize unnecessary negative effects ...."[13] And, it is logical to extend this to all human disorders, with the goal of improving the understanding of diseases, disorders, and conditions to achieve optimal treatment outcomes. Best practices state that a "disease name should consist of generic descriptive terms, based on the disease symptoms and more specific descriptive terms when robust information is available on how the disease manifests, who it affects, its severity or seasonality."[13]

These guidelines promote consideration of why the word *syndrome* is being used for burning mouth. Merriam-Webster defines *syndrome* as "a group of signs and symptoms that occur together and characterize a particular abnormality or condition."[14] Implied in this definition is a common cause or biologic abnormality that leads to physiologic changes, contributing to a collection of clinical and physical features. Key to the definition of *syndrome* is a predictable group of clinical and physical features that are present in a wide range of persons affected by the *syndrome*.

Notably, patients who have burning mouth *syndrome* do not *always* display a consistent set of clinical features. Thus, the features are *not* present across the full gamut of affected persons, and the
sistent with the word *syndrome*.
features (i.e., anxiety, depression,
stomia [subjective feeling of dry
malities, and paresthesia have be
in this population,[2] the frequency
these clinical features is varia
addressed fully in the diagnostic
diagnostic and treatment outcom
For example, when a topical o
administered to affected individua
viates the burning sensation, and
anesthetic has no effect or w
fort.[8,23,24] In as much as the etiolo
ogy of burning mouth remain an
is lack of a predictable set of cl
than a burning sensation that each
it is time to consider this condition
an abnormal physical condition),

As such, we recommend that the
the IHS begin discussing a chan
"burning mouth disorder." These di
efit from the inclusion of practitio
patients and appropriate knowled
others addressed this topic 15 yea
been done to make a nomencl
recently rekindled this discussion
shop on Oral Medicine (WWOM)
tember 26–27, 2018, meeting in
and this meeting served as an impe
expertise and promote future disc
Our expectation is that this nam

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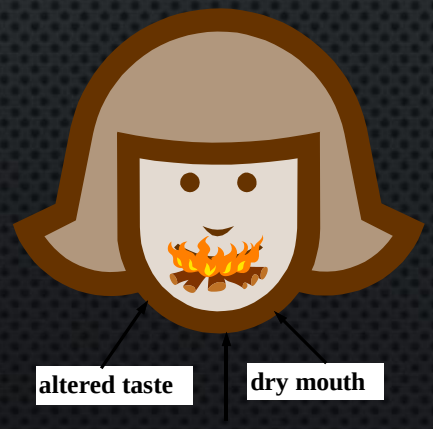
BURNING MOUTH SYNDROME DIAGNOSIS BY EXCLUSION

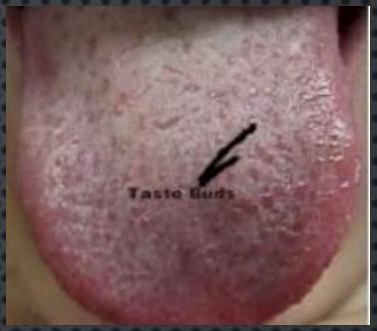
Burning mouth syndrome =The International Association for the Study of Pain (IASP) defines BMS as:

'A distinctive nosological entity' characterised by 'unremitting oral burning or similar pain in the absence of detectable oral mucosal changes' that can last <u>at least</u> 4-6 months. ***No known cause***

If cause found ……Burning mouth disorder
Or secondary BMS or Type 2 BM



BMS DIAGNOSTIC CRITERIA



Diagnostic criteria ICHD
Burning mouth syndrome (BMS)

- **Previously used terms:**
  Stomatodynia, or glossodynia when confined to the tongue.
- **Description:**
  An intraoral burning or dysaesthetic sensation, recurring daily for more than two hours per day over more than three months, without clinically evident causative lesions.
- **Diagnostic criteria:**
  A. Oral pain fulfilling criteria B and C
  B. Recurring daily for >2 hr per day for >3 months
  C. Pain has both of the following characteristics:
- 1. burning quality
  2. felt superficially in the oral mucosa
- D. Oral mucosa is of normal appearance and clinical examination including sensory testing is normal
  E. Not better accounted for by another ICHD-3 diagnosis.
- **Comments:**
  The pain of 13.10 Burning mouth syndrome (BMS) is usually bilateral and its intensity fluctuates. The most common site is the tip of the tongue.
- Subjective dryness of the mouth, dysaesthesia and altered taste may be present.
- There is a high menopausal female prevalence, and some studies show comorbid psychosocial and psychiatric disorders. Recent laboratory and brain imaging investigations have indicated changes

Research·Diagnostic·Criteria·for·Burning·Mouth·Syndrome·(BMS)¶
(Developed·at·IADR·2017)¶

Lead·Justin·Durham·and·Charlotte·Currie¶

• Introduction¶

This·research·diagnostic·criteria·(RDC)·has·been·developed·for·use·with·patients·with·Burning·Mouth·Syndrome·(BMS)·which·has·been·defined·as·"an·intraoral·burning·or·dysaesthetic·sensation,·recurring·daily·for·more·than·2·hours·per·day·over·more·than·3·months,·without·evident·causative·lesions·on·clinical·examination·and·investigation"·by·the·International·Classification·of·Orofacial·Pain·2019[1].··This·was·previously·referred·to·as·primary·BMS.·¶

The·aim·of·this·RDC·is·therefore·to·exclude·any·intraoral·burning·symptoms·which·can·be·attributed·to·a·causative·lesion(s).··An·exception·to·this·is·a·patient·who·has·intraoral·burning·symptoms·with·a·causative·lesion(s)·identified,·which·following·initiation·of·treatment·for·the·causative·lesion(s)·continues·to·report·a·persistent·burning·symptom.··In·this·case·the·patient·can·then·be·further·classified·as·having·BMS·by·the·RDC[2].··¶

The·criteria·will·be·developed·as·a·research·diagnostic·criteria,·which·includes·all·desirable·tests·which·would·be·included·for·research·purposes.··From·the·RDC·a·diagnostic·criteria·can·then·be·developed,·which·is·envisaged·to·be·a·shortened·version·of·the·RDC·but·practical·for·clinical·use.¶

The·RDC·will·form·four·parts/axes:·self-report,·examination,·psychosocial,·biomarkers.¶

MISDIAGNOSIS / DELAYED DIAGNOSIS

- 102 BMS PATIENTS 25.5% MISDIAGNOSED AS CANDIDIASIS

Vol. 129 No. 2 February 2020

Burning mouth syndrome: a diagnostic challenge

Jacob E. Freilich, BA,[a] Michal Kuten-Shorrer, DMD, DMSc,[b] Nathaniel S. Treister, DMD, DMSc,[a,c] Sook-Bin Woo, DMD, MMSc,[a,c] and Alessandro Villa, DDS, PhD, MPH[a,c]

Objectives. The aim of this study was to characterize the diagnostic process that patients with burning mouth syndrome (BMS) undergo and to identify the potential pitfalls encountered in the workup and management of BMS.

Study Design. A retrospective chart review of patients with BMS seen at the Oral Medicine clinic at Brigham and Women's Hospital (Boston, MA) was conducted from January 2014 to April 2017. Abstracted data focused on the period from onset of symptoms to referral to the Oral Medicine clinic for d tic tests performed, and provisional diagnc

Results. One hundred and two patients (86.3% females) were included (median age 60 years). Median time from onset of symptoms to referral to the Oral Medicine clinic was 12 months (range 4-370 months). Patients saw a median of 3 providers (range 1-7); 30.4% had undergone a diagnostic test; 63.7% had been given a provisional diagnosis; and 78.4% had received treatment. Candidiasis was the most common misdiagnosis (25.5%), and antifungal medication was the most frequently prescribed therapy (27.5%).

Conclusions. Patients with BMS experience delay in diagnosis and management despite seeking and receiving professional care. Many undergo unnecessary tests and tend to be misdiagnosed or receive no diagnosis at all. Even those correctly diagnosed with BMS often receive inappropriate or ineffective treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:120–124)

Table III. Provisional diagnoses received by patients for oral burning before the Oral Medicine consultation

*N = 102**	*n (%)*
BMS	30 (29.4%)
Candidiasis	26 (25.5%)
Viral Infection	8 (7.8%)
GERD	8 (7.8%)
Allergic reaction	6 (5.9%)
OLP	4 (3.9%)
Hyposalivation/Xerostomia	4 (3.9%)
Other†	13 (12.7%)
Total	99

*More than one provisional diagnosis per patient possible.
†Other past diagnoses included Sjogren syndrome, benign migratory glossitis, referred tooth pain, neuroma, laryngopharyngeal reflux, temporomandibular disorder, fibromyalgia, tongue ulceration, effects of cholesterol medication, denture irritation.*BMS,* burning mouth syndrome; *GERD,* gastroesophageal reflux disease; *OLP,* oral lichen planus.

Classification of Headache Disorders
intraoral burning or dysaesthetic ser
daily for greater than 2 hours per day
3 months, without clinically evident
The reported prevalence of BMS in th
tion ranges from 0.1% to 3.9%,[2–4] a
have a major impact on quality o
Despite its prevalence, BMS is not w

Talattof Z., et al. J Dent Shiraz Univ Med Sci., March 2019; 20(1): 42-47.
DOI: 10.30476/DENTJODS.2019.44562

Original Article

The Association between Burning Mouth Syndrome and Level of Thyroid Hormones in Hashimotos Thyroiditis in Public Hospitals in Shiraz, 2016

Zahra Talattof [1], Mohammad Hossein Dabbaghmanesh [2], Yasaman Parvizi [3], Negin Esnaashari [4], Azita Azad [5]

[1] Dept. of Oral and Maxillofacial Medicine, School of Dentistry, Azad Islamic University, Shiraz, Iran.
[2] Shiraz Endocrinology a
[3] Undergraduate Student,
[4] Postgraduate Dept. of C
[5] Dept. of Oral and Maxi

KEY WORDS
Burning Mouth Syndr
Hashimoto disease;
Hypothyroidism;
Visual Analog Scale;

Conclusion: The level of TSH, Anti-TPO, and Anti-TG, Free T3, and TSH indices of Hashimoto's patients were associated with the presence and severity of BSM. However, Free T4 level was only associated with the presence of BMS and not the intensity.

COMORBITIDIES

Vol. 129 No. 2 February 2020

Burning mouth syndrome: a diagnostic challenge

Jacob E. Freilich, BA,[a] Michal Kuten-Shorrer, DMD, DMSc,[b] Nathaniel S. Treister, DMD, DMSc,[a,c] Sook-Bin Woo, DMD, MMSc,[a,c] and Alessandro Villa, DDS, PhD, MPH[a,c]

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Study Design. A retrospective chart review of patients with BMS seen at the Oral Medicine clinic at Brigham and Women's Hospital (Boston, MA) was conducted from January 2014 to April 2017. Abstracted data focused on the period from onset of symptoms to referral to the Oral Medicine clinic for definitive diagnosis and included providers consulted, symptom characteristics, diagnostic tests performed, and provisional diagnoses and treatments offered.

Results. One hundred and two patients (86.3% females) were included (median age 60 years). Median time from onset of symptoms to referral to the Oral Medicine clinic was 12 months (range 4-370 months). Patients saw a median of 3 providers (range 1-7); 30.4% had undergone a diagnostic test; 63.7% had been given a provisional diagnosis; and 78.4% had received treatment. Candidiasis was the most common misdiagnosis (25.5%), and antifungal medication was the most frequently prescribed therapy (27.5%).

Conclusions. Patients with BMS experience delay in diagnosis and management despite seeking and receiving professional care. Many undergo unnecessary tests and tend to be misdiagnosed or receive no diagnosis at all. Even those correctly diagnosed with BMS often receive inappropriate or ineffective treatment. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:120−124)

Burning mouth syndrome (BMS) is defined by the International Headache Society in its International Classification of Headache Disorders (ICHD-3)[1] as an intraoral burning or dysaesthetic sensation, recurring daily for greater than 2 hours per day over greater than 3 months, without clinically evident causative lesions. The reported prevalence of BMS in the general population ranges from 0.1% to 3.9%,[2−4] and symptoms can have a major impact on quality of life (QoL).[5−7] Despite its prevalence, BMS is not well recognized or managed by physicians or dentists.[8−10] Studies that have investigated management strategies for BMS often are lacking in standardized outcome domains

reflux disorder (GERD), and irritable bowel syndrome, among others.[14,15]

The objective of this retrospective study was to characterize the diagnostic process that patients with BMS undergo and to identify the possible causes for delay in diagnosis and/or appropriate management.

MATERIALS AND METHODS

Study characteristics and inclusion criteria

A review of the electronic medical records of patients seen between January 2014 and April 2017 for initial consultation at the Division of Oral Medicine and Dentistry at the Brigham and Women's Hospital (BWH;

Table II. Reported comorbidities in patients with burning mouth syndrome

N = 102	*n (%)*
Psychiatric	
Anxiety	61 (59.8%)
Depression	51 (50.0%)
Panic Attacks	24 (23.5%)
PTSD	12 (11.9%)
OCD	7 (6.9%)
Pain	
Low back pain	43 (42.2%)
Neck and shoulder pain	41 (40.2%)
Headaches/Migraines	35 (34.3%)
TMD/Myofascial pain	22 (21.6%)
Extraoral dysesthesias	
Dry Eyes	35 (34.3%)
Skin	10 (9.8%)
Eyes (other than dryness)	9 (8.8%)
Genital	4 (3.9%)
Functional somatic syndromes	
IBS	15 (14.7%)
Fibromyalgia	13 (12.7%)
Chronic fatigue syndrome	10 (9.8%)
Other	
Current stressors	64 (62.7%)
Tinnitus	19 (18.6%)
Palpitations	26 (25.5%)

BMS, burning mouth syndrome; *IBS,* irritable bowel syndrome; *OCD,* obsessive-compulsive disorder; *PTSD,* post-traumatic stress disorder; *TMD,* temporomandibular disorder.

MEDICAL CO-MORBIDITIES

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DOI: 10.1111/odi.13186

LETTER TO THE EDITOR

ORAL DISEASES WILEY

Medical comorbidities of patients with burning mouth syndrome

Dear Editor,

Regarding recent original article named "World Workshop on Oral Medicine VII: Burning mouth syndrome: A systematic review of disease definitions and diagnostic criteria utilized in randomized clinical trials," the researchers conducted a systematic review of definitions and diagnostic criteria used for burning mouth syndrome (BMS) studies (Ariyawardana et al., 2019). In that study, sease, autoimmune diseases, and be often used as exclusion criteria is no strong evidence to suggest a AS and those mentioned diseases. hart review of new BMS patients to demonstrate their medial co- sical diagnoses were confirmed g doctors (family physicians and others) via referral letters. As shown in Table 1, the prevalence of diabetes mellitus, Parkinson's disease, autoimmune diseases, and thyroid diseases in BMS patients was constantly low: The average prevalence in 5 years is 4.5%, 0.2%, 1.8%, and 6.4%, respectively. Therefore, those diseases seem to have little influence on the majority of patients with BMS. On the other hand, Talattof et al. reported the association between thyroid hormones and BMS (Talattof, Dabbaghmanesh, Parvizi, Esnaashari, & Azad, 2019). Thus, the association between thyroid diseases and BMS is still controversial. Regarding diabetes mellitus, the prevalence of BMS in patients with diabetes mellitus is not significantly different with control group (Moore, Guggenheimer, & Orchard, 2007). Moreover, the prevalence of diagnosed diabetes in the United States is 9.1% (Menke, Casagrande, Geiss, & Cowie, 2015). Therefore, the prevalence of diabetes mellitus in BMS patients in our study is not much

TABLE 1 Chronological changes of patient demographics and physical comorbidities

	2014	2015	2016	2017	2018	Total
The number of patients with BMS	309	421	255	295	263	1,543
Age, mean ± *SD*, y	62.0 ± 13.2	64.3 ± 12.1	62.8 ± 13.5	64.9 ± 13.2	63.5 ± 13.0	63.6 ± 13.0
Male sex, No. %	43 (14.0%)	42 (10.0%)	41 16.1%)	39 (13.2%)	37 (14.1%)	202 (13.1%)
Hypertension, No. %	55 (17.8%)	72 (17.1%)	61 (23.9%)	53 (18.0%)	52 (19.8%)	293 (19.0%)
Hyperlipidemia, No. %	59 (19.1%)	90 (21.4%)	38 (14.9%)	46 (15.6%)	33 (12.5%)	266 (17.2%)
Cancer, No. %	29 (9.4%)	43 (10.2%)	28 (11.0%)	41 (13.9%)	35 (13.3%)	176 (11.4%)
Heart diseases, No. %	21 (6.8%)	35 (8.3%)	29 (11.4%)	27 (9.2%)	30 (11.4%)	142 (9.2%)
Uterine fibroid, No. %	24 (7.8%)	25 (5.9%)	11 (4.3%)	24 (8.1%)	25 (9.5%)	109 (7.1%)
Thyroid diseases, No. %	19 (6.1%)	27 (6.4%)	20 (7.8%)	16 (5.4%)	17 (6.5%)	99 (6.4%)
Cerebrovascular diseases, No. %	16 (5.2%)	20 (4.8%)	11 (4.3%)	20 (6.8%)	12 (4.6%)	79 (5.1%)
Diabetes mellitus, No. %	12 (3.9%)	25 (5.9%)	11 (4.3%)	10 (3.4%)	12 (4.6%)	70 (4.5%)
Glaucoma, No. %	8 (2.6%)	16 (3.8%)	9 (3.5%)	12 (4.1%)	19 (7.2%)	64 (4.1%)
Autoimmune diseases, No. %	8 (2.6%)	9 (2.1%)	2 (0.8%)	2 (0.7%)	7 (2.7%)	28 (1.8%)
Prostatomegaly, No. %	4 (1.3%)	7 (1.7%)	3 (1.2%)	2 (0.7%)	8 (3.0%)	24 (1.6%)
Epilepsy, No. %	1 (0.3%)	0 (0.0%)	2 (0.8%)	3 (1.0%)	1 (0.4%)	7 (0.5%)
Parkinson's disease, No. %	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.3%)	3 (0.2%)
No diseases, No. %	36 (11.7%)	34 (8.1%)	20 (7.8%)	36 (12.2%)	20 (7.6%)	146 (9.5%)

Abbreviation: BMS, burning mouth syndrome.

es of patient demographics and physical comorbidities

	2014	2015	2016	2017	2018	Total
	309	421	255	295	263	1,543
	62.0 ± 13.2	64.3 ± 12.1	62.8 ± 13.5	64.9 ± 13.2	63.5 ± 13.0	63.6 ± 13.0
	43 (14.0%)	42 (10.0%)	41 16.1%)	39 (13.2%)	37 (14.1%)	202 (13.1%)
	55 (17.8%)	72 (17.1%)	61 (23.9%)	53 (18.0%)	52 (19.8%)	293 (19.0%)
	59 (19.1%)	90 (21.4%)	38 (14.9%)	46 (15.6%)	33 (12.5%)	266 (17.2%)
	29 (9.4%)	43 (10.2%)	28 (11.0%)	41 (13.9%)	35 (13.3%)	176 (11.4%)
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	19 (6.1%)	27 (6.4%)	20 (7.8%)	16 (5.4%)	17 (6.5%)	99 (6.4%)
	16 (5.2%)	20 (4.8%)	11 (4.3%)	20 (6.8%)	12 (4.6%)	79 (5.1%)
	12 (3.9%)	25 (5.9%)	11 (4.3%)	10 (3.4%)	12 (4.6%)	70 (4.5%)
	8 (2.6%)	16 (3.8%)	9 (3.5%)	12 (4.1%)	19 (7.2%)	64 (4.1%)
	8 (2.6%)	9 (2.1%)	2 (0.8%)	2 (0.7%)	7 (2.7%)	28 (1.8%)
	4 (1.3%)	7 (1.7%)	3 (1.2%)	2 (0.7%)	8 (3.0%)	24 (1.6%)
	1 (0.3%)	0 (0.0%)	2 (0.8%)	3 (1.0%)	1 (0.4%)	7 (0.5%)
	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.3%)	3 (0.2%)
	36 (11.7%)	34 (8.1%)	20 (7.8%)	36 (12.2%)	20 (7.6%)	146 (9.5%)

syndrome.

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PSYCHOLOGICAL CO MORBIDITY IN BMS

- THE PSYCHIATRIC ASPECT OF BMS IS VERY IMPORTANT. A RELATIONSHIP HAS BEEN FOUND BETWEEN BMS AND DEPRESSION, INCREASED ANXIETY, HYPOCHONDRIA, CANCEROPHOBIA 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].

Burning mouth syndrome

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Burning mouth syndrome: pathogenic and therapeutic concepts

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Uniwersytet Medyczny w Poznaniu Klinika Psychiatrii Dorosłych UM w Poznaniu
Head: prof. dr hab. n med. J Rybakowski

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].

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FUNCTIONAL IMPACT

- BURNING MOUTH SYNDROME PATIENTS SHOWED POORER SCORES ON ALL SCALES COMPARED TO THE HEALTHY SUBJECTS WITH A LOWER OHRQOL.
- OHIP-14 GIVES A GREATER WEIGHT TO PSYCHOLOGICAL AND BEHAVIOURAL OUTCOMES IN EVALUATING ORAL HEALTH THAN GOHAI, AND THEREFORE, IT IS A MORE EFFECTIVE QUESTIONNAIRE IN TERMS OF THE EVALUATION OF THE TREATMENT RESPONSE.
- THE MANAGEMENT OF BMS CAN IMPROVE PAIN, ANXIETY AND DEPRESSION AND THE OHRQOL.

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DOI: 10.1111/joor.12864

ORIGINAL ARTICLE

JOURNAL OF ORAL REHABILITATION WILEY

Assessment of oral health-related quality of life, measured by OHIP-14 and GOHAI, and psychological profiling in burning mouth syndrome: A case-control clinical study

Daniela Adamo[1] | Giuseppe Pecoraro[1] | Giulio Fortuna[1] | Massimo Amato[2] | Gaetano Marenzi[1] | Massimo Aria[3] | Michele Davide Mignogna[1]

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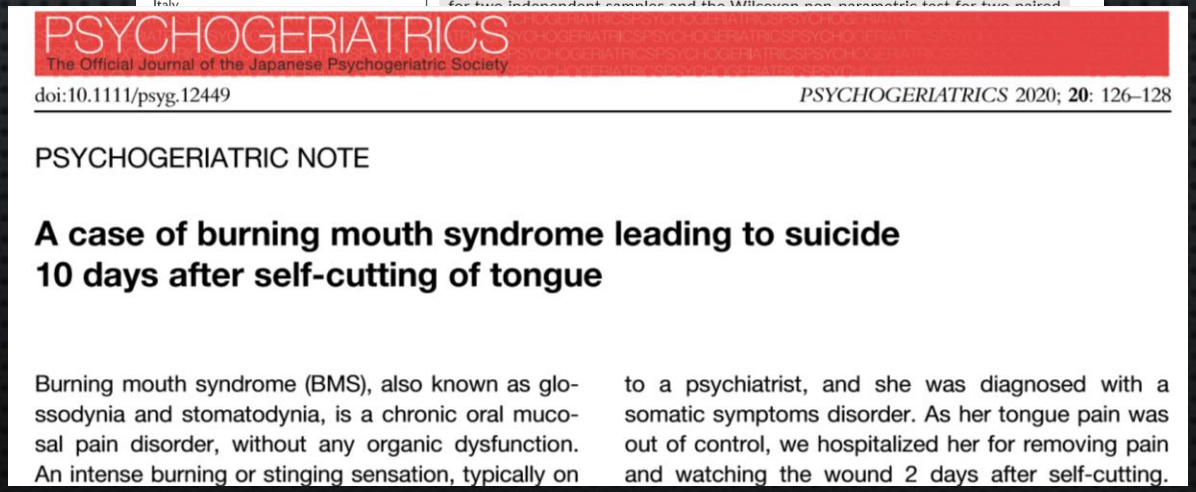
Abstract

Objectives: To evaluate the oral health-related quality of life (OHRQoL) of patients with burning mouth syndrome (BMS) by comparing the Oral Health Impact Profile-14 (OHIP-14) and Geriatric Oral Health Assessment Index (GOHAI) tests, assessing their dependence with pain, anxiety and depression and, secondly, to analyse the changes in time after treatment with psychotropic drugs.

Methods: Twenty-six patients and 26 controls were included. The GOHAI, OHIP-14, visual analogue scale (VAS) and the Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A) were performed at baseline (time 0) and after 6 months of treatment (time 1). Descriptive statistics, the Mann-Whitney non-parametric test



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PSYCHOGERIATRIC NOTE

A case of burning mouth syndrome leading to suicide 10 days after self-cutting of tongue

Burning mouth syndrome (BMS), also known as glossodynia and stomatodynia, is a chronic oral mucosal pain disorder, without any organic dysfunction. An intense burning or stinging sensation, typically on

to a psychiatrist, and she was diagnosed with a somatic symptoms disorder. As her tongue pain was out of control, we hospitalized her for removing pain and watching the wound 2 days after self-cutting.

Burning mouth syndrome

- Burning mouth syndrome by definition has no know cause=Primary (idiopathic) burning mouth syndrome
- Thus exclusion of secondary burning mouth syndrome (BMS) OR Burning mouth disorder is important in diagnosis
- The following conditions may produce BMS-like symptoms:

BMD DISORDER: SECONDARY NEUROPATHY

- Endocrine
  - Menopausal
  - Hypo thyroid
  - Diabetes
- Immunological

  Autoimune
  - Sjögren Syndrome
  - Scleroderma
- Vitamin deficiency (B1, B2, B6, B12, folate, iron)
- Medication reaction (eg, ACE inhibitors, ARBs, antiretrovirals, psychotropic, anticholinergic,clonazepam, [37] chemotherapeutic agents)
  Ciguatera neurotoxin exposure [38]
- Psychometric
- Allergy
- Supertasters
- Gastric reflux GERD
- Neuropathy ??

- Anemia
- Multiple sclerosis
- Anxiety
- Dehydration
- Mouth breathing/nasal obstruction
- Alcohol-based mouthwash
- Radiation-induced stomatitis
- Vesiculous bullou conditions
  - Aphthous stomatitis
  - Contact stomatitis
  - Erosive lichen planus
  - Pemphigoid
  - Pemphigus
  - Geographic tongue
- Leukoplakia
- Neoplasia
- Chewing tobacco use
- Areca nut extract exposure [39]
- INFECTION
  - Bacterial infection [40]
  - Candidiasis [28]
  - VIRAL

Are·you·taking,·or·have·you·taken,·any·of·the·following·medications·wh
symptoms:¶

- ☐→Antibiotics¶
- ☐→ACE·inhibitors¶
- ☐→ARB?¶
- ☐→Antiretrovirals¶
- ☐→Anticholinergic·¶
- ☐→Clonazepam¶
- ☐→Xerostomia·inducing·drugs¶
- ☐→Thiazide·diuretics¶
- ☐→Antihistamines¶
- ☐→Other·drugs·which·can·induce·taste·disturbance¶
- ☐→Corsodyl·and·alcohol·mouthwash¶
- ☐→Cinnamon·Aldehyde·toothpaste¶

Do·you·have·any·of·the·following·illnesses·or·medical·symptoms?¶

- ☐→Diabetes¶
- ☐→Thyroidism¶
- ☐→Menopause¶
- ☐→MS¶
- ☐→Scleroderma¶
- ☐→Anaemia¶
- ☐→Viral·infection¶
- ☐→Siogrens¶
- ☐→Ear·infection¶
- ☐→Heartburn/GORD¶
- ☐→Other·pain·conditions¶
- ☐→Dry·eyes/mouth¶
- ☐→Radiotherapy¶
- ☐→Chemotherapy¶
- ☐→Upper·respiratory·tract·infection¶
- ☐→Lichen·Planus¶
- ☐→Lupus·or·other·connective·tissue·disorders¶
- ☐→Vulvadynia¶

- Int J Dermatol. 2017 Sep;56(9):952-956. doi: 10.1111/ijd.13634. Epub 2017 Apr 23.
- Morr Verenzuela CS[1], Davis MDP[1], Bruce AJ[1], Torgerson RR[1]. **Burning mouth syndrome: results of screening tests for vitamin and mineral deficiencies, thyroid hormone, and glucose levels-experience at Mayo Clinic over a decade.**
- **BACKGROUND:** Burning mouth syndrome (BMS) is a disorder characterized by chronic mouth pain in the absence of objective clinical abnormalities. Vitamin or mineral deficiencies may have a role in BMS, but data regarding the prevalence and relevance of hematinic deficiencies are conflicting. We aimed to determine the frequency of specific laboratory abnormalities in patients with BMS.
- **METHODS:** We retrospectively reviewed the results of screening blood tests in patients with BMS at our institution between January 2003 and December 2013.
- **RESULTS: Among 659 patients with BMS, the most common decreased values or deficiencies were vitamin D_3 (15%), vitamin B_2 (15%), vitamin B_6 (5.7%), zinc (5.7%), vitamin B_1 (5.3%), thyrotropin (TSH) (3.2%), vitamin B_{12} (0.8%), and folic acid (0.7%). Laboratory values for fasting blood glucose and TSH were increased in 23.7% and 5.2%, respectively.**
- **CONCLUSIONS:** In patients with symptoms of BMS, our results suggest it is reasonable to screen for fasting blood glucose, vitamin D (D_2 and D_3), vitamin B_6, zinc, vitamin B_1, and TSH. Deficiencies of vitamin B_{12} and folic acid were rare (<1% abnormal).

MEDICATIONS CONTRIBUTING TO BMD

Table 2: Medications that possibly cause hyposalivation/ xerostomia as a side-effect

Medications	Examples (generic)
Tricyclic antidepressant	Amitriptyline, nortriptyline
Antipsychotic	Carbidopa/levodopa, chlorpromazine
Antihistaminic	Phenergan
Bronchodilator (anticholinergic and β−2 agonist)	Tiotropium, formoterol
Decongestant	Oxymetazoline
Antidepressant	Venlafaxine
Skeletal muscle relaxant	Tizanidine
Antihypertensives	Furosemide, clonidine, lisinopril, verapamil
Chemotherapy	Cyclophosphamide
Protease inhibitor (for HIV)	Reyataz, Norvir, Kaletra
Opioid	Hydrocodone, oxycodone
Benzodiazepine	Diazepam
Triptan	Rizatriptan

Atkinson *et al.*, 1989; Fox 1998; Bergdahl and Bergdahl 2000; Saleh *et al.*, 2015

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Review Article

Burning Mouth Syndrome: Aetiopathogenesis and Principles of Management

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Burning mouth syndrome (BMS) is a chronic debilitating oral condition characterised by a burning sensation of the oral mucosa in an otherwise apparently normal person. Its aetiology and pathogenesis are obscure, but both psychogenic factors and peripheral and central neuropathies appear to be implicated. There is no cure for BMS, and treatment with either local or systemic medications focuses on the relief of symptoms and on improving quality of life. In recalcitrant cases, psychological/psychiatric intervention may be helpful. In order to improve treatment outcomes, a better understanding of the pathogenesis of this syndrome might provide a basis for the development of more effective management strategies. In this short review, we discuss current knowledge of the diagnosis, aetiopathogenesis, and management of BMS.

1. Introduction

The International Association for the Study of Pain (IASP) has described burning mouth syndrome as a chronic condition characterised by a burning sensation of the oral mucosa for which no cause can be found [1]. The anterior part of the tongue is most commonly affected, followed by the labial mucosa and occasionally the palate. The burning pain is often accompanied by tingling or numbness and the sensation of dryness of the mouth [2–4]. Reduced taste intensity and a bitter or a metallic taste are experienced by about two-thirds of those with BMS. Despite all these symptoms, the oral mucosa and the salivary flow rate are normal [5, 6].

The burning sensation of BMS is moderate to severe in intensity, is usually bilaterally symmetrical, and is present every day for most of the day. It is minimal or even absent early in the morning and during mealtimes and it seldom interferes with sleep. In most cases, BMS starts spontaneously [2, 4–7] and continues for several years. Only about 3% of cases resolve over a 5-year observation period and even with treatment only about 30% of affected persons report any improvement [2, 3, 5, 8].

The worldwide prevalence of BMS is unknown because nearly all studies have been of European or North American populations and different diagnostic criteria have been used in different studies [2]. The frequency of BMS increases with age in both women and men and is highest in women aged 60–69 years [9]. The higher frequency of BMS in women (F : M = 5 : 1) [10] may very well be owing to biological, sociocultural, and psychological factors [11].

A diagnosis of BMS can be made only if the oral mucosa is clinically normal and all systemic and local causes for a burning sensation have been excluded (Table 1), bearing in mind that BMS may be superimposed upon a burning sensation of known systemic or local origin [5, 7, 8]. It is essential for treatment purposes thus to differentiate between BMS which is an idiopathic condition and oral mucosal burning sensations secondary to a known cause [12, 13].

BMS is frequently associated with stressful life events, anxiety, and depressive disorders [10, 14], and as these psychogenic factors can either enhance or reduce perception of pain (Figure 1), BMS can be managed by pharmacological or by psychological means or by a combination of the two [14, 15]. As with other chronic neuropathic pain conditions, BMS can induce or promote psychic symptoms or can itself be a somatic feature of a psychic disorder [11], but it is unclear, however, whether psychogenic factors are primary or secondary in any particular case of BMS.

Table 1: Some systemic and local causes of a burning sensation in the mouth, which, therefore, by definition is not BMS [4, 8, 12, 13, 18, 26].

(1) Oral mucosal conditions
(i) Erythema/erosion of whatever cause
(ii) Atrophic tongue
(iii) Candidosis
(iv) Geographic tongue
(v) Lichen planus
(vi) Pemphigoid, pemphigus
(2) Parafunctional habits
(i) Cheek sucking
(ii) Tongue thrusting
(3) Trauma: mechanical, chemical, thermal
(4) Xerostomia and altered salivary quality
(i) Radiotherapy
(ii) Chemotherapy
(iii) Other drugs
(iv) Sjögren's syndrome
(5) Systemic factors
(i) Diabetes
(ii) Decreased levels of vitamins B1, B2, B12, folate, iron, zinc
(iii) Abnormal thyroid function
(iv) Allergic reaction to food or dental materials
(v) Lichenoid tissue reactions
(vi) Autoimmune conditions
(vii) Hormonal disturbances
(viii) Parkinson disease
(6) Drugs
(i) Paroxetine
(ii) Angiotensin-converting enzyme inhibitors
(7) Local nerve damage
(i) Chemotherapy-associated neuropathy
(ii) Local physical irritation
(8) Various peripheral or central neuropathies

Systemic and topical medications (Table 2) have been used in the treatment of BMS with varying degrees of success [8]. Psychological/psychiatric intervention should be considered only when BMS does not respond favourably

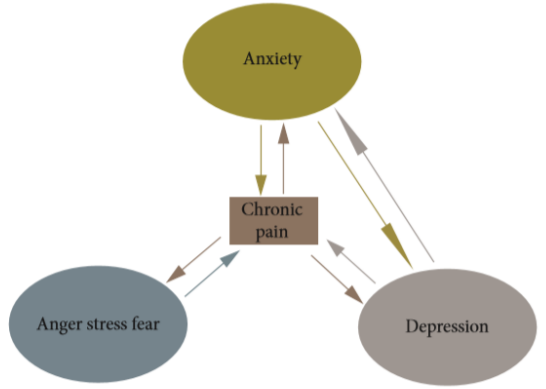


Figure 1: The interrelation between chronic pain, anxiety, depression, and other emotions. The greater the intensity of the pain the greater the suffering, and anxiety, depression, and the stressful emotions may aggravate the experience of pain.

Table 2: Available agents or strategies for the management of BMS based on expert opinion and common clinical practice. Adapted from [2].

Pharmacological agents
(1) *Topical*
(i) Clonazepam
(ii) Capsaicin
(iii) Doxepin
(iv) Lidocaine
(2) *Systemic*
(i) Tricyclic antidepressants
(ii) Selective serotonin reuptake inhibitors
(iii) Serotonin-adrenalin reuptake inhibitors
(iv) Anticonvulsants (e.g., gabapentin)
(v) Opioids
(vi) Benzodiazepines
(vii) Alpha-lipoic acid
Nonpharmacological therapy
(1) Cognitive-behavioural therapy
(2) Mindfulness meditation
(3) Other relaxation techniques

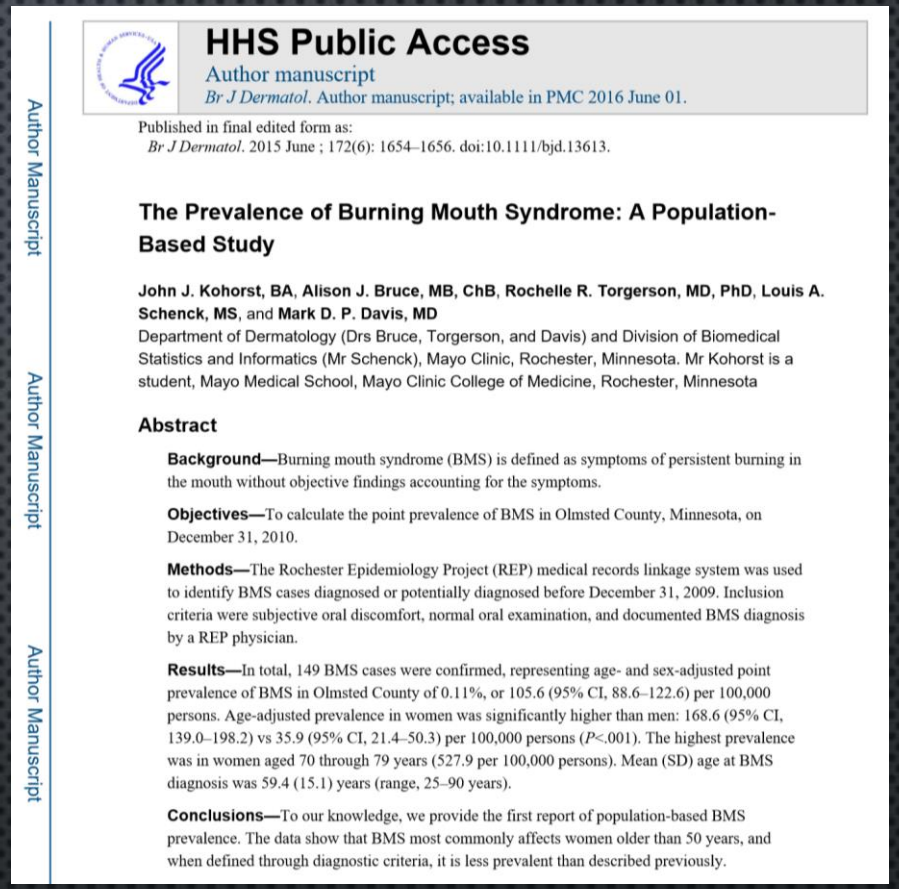
PREVALENCE: BMS

In a cross-sectional analysis of over 1000 randomly selected Swedish patients from Public Dental Health Service registers, 3.7% of subjects were diagnosed with BMS after reporting burning mouth symptoms and undergoing a subsequent physical examination.

In contrast, Lipton et al reported a prevalence of 0.7% based solely on self-reported symptoms from over 45 000 American households.

Haberland et al noted that 10% of new patients observed in his practice were diagnosed with BMS.

Most recently, a large retrospective study of over 3000 Brazilian patients referred to an oral pathology service reported a prevalence of about 1%.



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The Prevalence of Burning Mouth Syndrome: A Population-Based Study

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Abstract

Background—Burning mouth syndrome (BMS) is defined as symptoms of persistent burning in the mouth without objective findings accounting for the symptoms.

Objectives—To calculate the point prevalence of BMS in Olmsted County, Minnesota, on December 31, 2010.

Methods—The Rochester Epidemiology Project (REP) medical records linkage system was used to identify BMS cases diagnosed or potentially diagnosed before December 31, 2009. Inclusion criteria were subjective oral discomfort, normal oral examination, and documented BMS diagnosis by a REP physician.

Results—In total, 149 BMS cases were confirmed, representing age- and sex-adjusted point prevalence of BMS in Olmsted County of 0.11%, or 105.6 (95% CI, 88.6–122.6) per 100,000 persons. Age-adjusted prevalence in women was significantly higher than men: 168.6 (95% CI, 139.0–198.2) vs 35.9 (95% CI, 21.4–50.3) per 100,000 persons ($P<.001$). The highest prevalence was in women aged 70 through 79 years (527.9 per 100,000 persons). Mean (SD) age at BMS diagnosis was 59.4 (15.1) years (range, 25–90 years).

Conclusions—To our knowledge, we provide the first report of population-based BMS prevalence. The data show that BMS most commonly affects women older than 50 years, and when defined through diagnostic criteria, it is less prevalent than described previously.

1-15% Tammiala-Salomen et al 1993
5.3% - Locker & Grushka 1987,1988
0.7% - Lipton et al 1993
2.6% - Basker et al 1978
10.3% - Jaafar et al 1989
1.7% - Richards & Scourfield 1996

WHAT CAUSES BMS?

- BMD IS SECONDARY AND CAUSES CAN BE FOUND
- BMS (PRIMARY) NO CONSENSUS EXISTS REGARDING A DEFINITIVE CAUSE. RATHER, BURNING MOUTH SYNDROME (BMS) APPEARS TO BE MULTIFACTORIAL IN ORIGIN.
  - + SOMATOSENSORY CHANGES
  - - SOMATOSENSORY CHANGES
- MANY OF THE CURRENTLY PROPOSED ETIOLOGIES DESCRIBE SECONDARY, RATHER THAN PRIMARY BURNING MOUTH SYNDROME (BMS).
  - THERE MAY BE 3 TYPES OF BMS

Review Article

Burning mouth syndrome: Current concepts

Cibele Nasri-Heir, Julyana Gomes Zagury, Davis Thomas, Sowmya Ananthan

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Abstract

Burning mouth syndrome (BMS) is a chronic pain condition. It has been described by the International Headache Society as "an intra-oral burning or dysesthetic sensation, recurring daily for more than 2 h/day for more than 3 months, without clinically evident causative lesions." BMS is frequently seen in women in the peri-menopausal and menopausal age group in an average female/male ratio of 7:1. The site most commonly affected is the anterior two-thirds of the tongue. The patient may also report taste alterations and oral dryness along with the burning. The etiopathogenesis is complex and is not well-comprehended. The more accepted theories point toward a neuropathic etiology, but the gustatory system has also been implicated in this condition. BMS is frequently mismanaged, partly because it is not well-known among healthcare providers. Diagnosis of BMS is made after other local and systemic causes of burning have been ruled out as then; the oral burning is the disease itself. The management of BMS still remains a challenge. Benzodiazepines have been used in clinical practice as the first-line medication in the pharmacological management of BMS. Nonpharmacological management includes cognitive behavioral therapy and complementary and alternative medicine (CAM). The aim of this review is to familiarize healthcare providers with the diagnosis, pathogenesis, and general characteristics of primary BMS while updating them with the current treatment options to better manage this group of patients.

Key Words: Burning mouth syndrome, neuropathic pain, orofacial pain

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INTRODUCTION

Burning mouth syndrome (BMS) is an intraoral chronic pain condition characterized by intra-oral burning sensation. According to the International Headache Society, BMS is described as "an intra-oral burning or dysesthetic sensation, recurring daily for more than 2 h/day for more than 3 months, without clinically evident causative lesions."[1]

The International Association for the Study of Pain defines BMS as "burning pain of the tongue and/or other oral mucous membrane in the absence of clinical signs or laboratory findings."[2]

TERMINOLOGY/CLASSIFICATION

Various synonyms such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue, and oral

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TYPES OF BMS

Peripheral

- Approximately 20% of clinically diagnosed primary BMS patients belong to a subgroup that actually has a subclinical, neurophysiologically evident trigeminal system lesion that may be located within the peripheral nerves (lingual nerve, mandibular nerve, or entire trigeminal nerve) or within the brainstem (Jääskeläinen et al., 1997; Forssell et al., 2002)

Central

- Another 25–36% of primary BMS patients show signs of decreased inhibition of the blink reflex in the form of absent or deficient habituation of the reflex when stimulating the supraorbital nerve distribution outside the symptomatic intraoral trigeminal area (Jääskeläinen et al., 1997; Forssell et al., 2002). This may indicate a defect within the descending dopaminergic inhibitory system as similar loss of habituation occurs in Parkinson's disease (Kimura, 2001) due to deficient dopamine-mediated striatal inhibition of the brainstem (Evinger et al., 1993).

Mixed lesions both peripheral and central

Clinical classification of BMS

- Type 1 pain free waking and worsening during the day 35% linked to systemic disorders (BMD or secondary)
- Type 2 continuous symptoms throughout the day difficulty getting to sleep 55% associated with psychological disorders
- Type 3 intermittent symptoms with pain free periods during the day 10% of total and associated with allergic reaction

Lamey and Lewis classification of BMS

Sub type	Prevalence %	Clinical characteristics	Associated etiologies
1	35	Symptom free waking, progressive burning sensation developing in the late morning, gradually increasing in intensity, reaching its peak by evening	Nutritional deficiencies and endocrine disorders like diabetes mellitus, etc.
2	55	Continuous burning symptom throughout the day, present on awakening, difficulty in getting in to sleep	Associated psychological disorders, mood changes
3	10	Intermittent burning, present only on some days, affecting unusual sites	Display anxiety and allergic reactions

BMS: Burning mouth syndrome

- Subgroup 1 (50-65%) is characterized by peripheral small diameter fibre neuropathy of intraoral mucosa.
- Subgroup 2 (20-25%) consists of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be dissected with careful neurophysiologic examination but is clinically indistinguishable from the other two subgroups.
- Subgroup 3 (20-40%) fits the concept of central pain that may be related to hypofunction of dopaminergic neurons in the basal ganglia.

The peripheral subgroup demonstrates good analgesic response to local anesthesia, whereas the central subgroup shows no response or even hyperalgesia after peripheral nerve block.[16]

This easy procedure also seems to be able to predict the response to topical clonazepam treatment that was beneficial only in the peripheral subgroup of patients with BMS.

Nasri-Heir et al., 2011 demonstrated that BMS patients with complaints of longer durations presented with a significantly elevated tingling/taste electrical detection threshold ratio, indicating a possible neurodegenerative process, pointing to the hypofunction of the chorda tympani

The central subgroup showed higher scores in hospital anxiety and depression scores.

The Dopamine hypothesis of BMS pain comes from noninvasive brain stimulation studies showing that repetitive transcranial magnetic stimulation, by initially releasing dopamine in the striatum thereby activating the endogenous opioid system,[32] also effectively relieves BMS pain

Is burning mouth syndrome a neuropathic pain condition? Jääskeläinen, Satu, K. PAIN: March 2018 - Volume 159 - Issue 3 - p 610–613

Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, Ughetto S, Woda A. Effect of lingual nerve block on burning mouth syndrome (stomatodynia). A randomized crossover trial. PAIN 2010;149:27–32.

TYPES OF BMS

- IS BILATERAL BMS DIFFERENT CONDITION TO UNILATERAL BMS?

primary BMS were included. Among them, 324 patients who complained of oral symptoms on both sides of the oral cavity were assigned to the bilateral group and 97 patients who complained of symptoms only on one side of the oral cavity were assigned to the unilateral group. Clinical characteristics, psychological status, and salivary secretion were compared between the two groups. There were no significant differences in the mean age, sex ratio, unstimulated and stimulated salivary flow rates, or duration of symptoms between the two groups. The bilateral group had higher levels of psychological distresses compared with the unilateral group. The bilateral group had higher prevalence rates in burning, taste alteration, and xerostomia than the unilateral group. The proportion of patients who considered dental procedures as an initiating factor of BMS symptoms was higher in the unilateral group than in the bilateral group. Conclusively, BMS patients with

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Clinical Paper
Oral Medicine

Comparison of clinical characteristics between burning mouth syndrome patients with bilateral and unilateral symptoms

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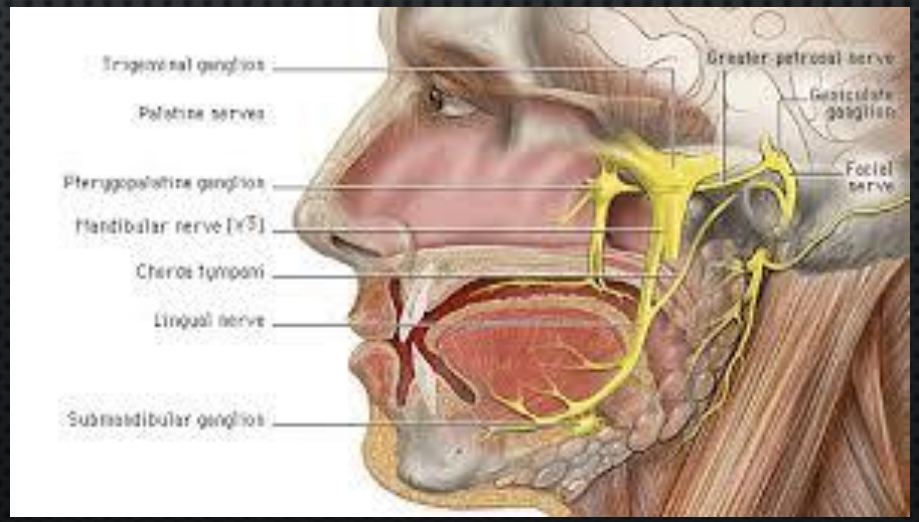
M.-J. Kim, J. Kim, H.-S. Kho: Comparison of clinical characteristics between burning mouth syndrome patients with bilateral and unilateral symptoms. Int. J. Oral Maxillofac. Surg. 2020; 49: 38–43.

CURRENT HYPOTHESES FOR (PRIMARY) BMS

- NEUROPATHIC PAIN MECHANISM
  - MEASURED ABNORMALITIES OF PHYSIOLOGIC RESPONSES OF THE TRIGEMINAL NERVE IN BURNING MOUTH SYNDROME (BMS) PATIENTS.[2, 3]
  - THERE IS ALSO EVIDENCE TO SUGGEST HISTOPATHOLOGIC CHANGES IN NOCICEPTIVE FIBRES IN BMS PATIENTS.[4]
  - THE DIFFERENTIATION BETWEEN A PERIPHERAL VERSUS A CENTRAL AETIOLOGY HAS NOT BEEN DETERMINED
- NOCI-PLASTIC PAIN
- PSYCHOGENIC ILLNESS
- SUPERTASTERS
- BRAIN CONNECTIVITY/ DOPAMINERGIC
- GENETIC



Sleep disorders increase the risk of burning mouth syndrome: A retrospective population-based cohort study

Article *in* Sleep Medicine 15(11) · November 2014 *with* 101 Reads

DOI: 10.1016/j.sleep.2014.06.009

Cite this publication

Burning Mouth Syndrome and Menopause

Article *in* International journal of preventive medicine · January 2013

REVIEW

Australian Dental Journal 2009; 54: 84–93

doi: 10.1111/j.1834-7819.2009.01099.x

Burning mouth syndrome and psychological disorders

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Review Article

Burning mouth syndrome: Current concepts

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Corneal Confocal Microscopy Detects Small-Fibre Neuropathy in Burning Mouth Syndrome: a cross-sectional study

Dr Francis O'Neill PhD, MBChB, FDS RCPS[1,2], Dr Andrew Marshall MBChB, BSc, FRCP [3,4], Dr Maryam Ferdousi BSc, MSc, PhD[3], Professor Rayaz A Malik PhD, MSc, MBChB,

Cephalalgia International Headache Society

Review

Cephalalgia
2019, Vol. 39(12) 1586–1594

DOI: 10.1177/0333102419854052
journals.sagepub.com/home/cep
SAGE

Cytokine levels and their role in the etiopathogenesis of Burning Mouth Syndrome: A systematic review

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CRANIOFACIAL PAIN

Check for updates

Relevance of sleep, pain cognition, and psychological distress with regard to pain in patients with burning mouth syndrome

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ABSTRACT

Objective: To clarify the influence of sleep, psychological distress, and pain catastrophizing on the pain experience in patients with burning mouth syndrome (BMS).

Methods: Ninety-three patients with BMS were investigated by reviewing medical records and questionnaires using the Brief Pain Inventory (BPI), Pittsburgh Sleep Quality Index (PSQI), Symptom Checklist-90 revised (SCL-90R), and pain catastrophizing scale (PCS).

Results: Of the 65 patients included in the study, 81.5% and 66% showed high PSQI and PCS scores, respectively. The PSQI, PCS, and SCL-90R scores correlated positively with pain interference. The result of multiple regression analysis demonstrated that helplessness and rumination of PCS significantly add to the prediction of pain interference.

Discussion: Pain catastrophizing rather than psychological distress and sleep quality seems to be associated with pain experience in patients with BMS. Therefore, targeting pain catastrophizing, specifically rumination and helplessness, might lead to reduction of pain-related disability in BMS patients.

KEYWORDS
Pain interference; psychological distress; pain catastrophizing; sleep quality; burning mouth syndrome

BMS AND NEUROPATHOGENIC AETIOLOGY

- Persistent peripheral neuropathy, the central afferent nociceptor terminals in the dorsal horn of the spinal cord release excitatory biological mediators which can activate postsynaptic NMDA receptors which under physiological conditions are silent, thus resulting in central sensitization with increased excitability[1].
- There may also be a decrease in the functional activity of the GABA-mediated pain-inhibitory interneuron circuits in the dorsal horn of the spinal cord which under physiological circumstances inhibit the glutamate/ NMDA-mediated central sensitization [1], possibly contributing to the neuropathic pain of BMS [2].
- Thus, central sensitization characterised by structural and functional neural plasticity results in increased excitability and increased tonic activity of central nociceptive neurons, playing an important role in the pathogenesis of BMS [3,4].
- However, surprisingly, despite the possible roles of central sensitization and of psychogenic factors such as anxiety or depression in BMS neuropathic pain, it appears that, in persons withBMS,the co-occurrence of other chronic neuropathic pain disorders(central sensitivity syndromes)including fibromyalgia, atypical facial pain, trigeminal neuralgia, temporomandibular joint pain, back pain, and vulvodynia is rare[4, 5.].
- This suggests that the neural pathogenic mechanisms of BMS are distinct, probably localised some where in thetrigeminal nerve pathway[5].

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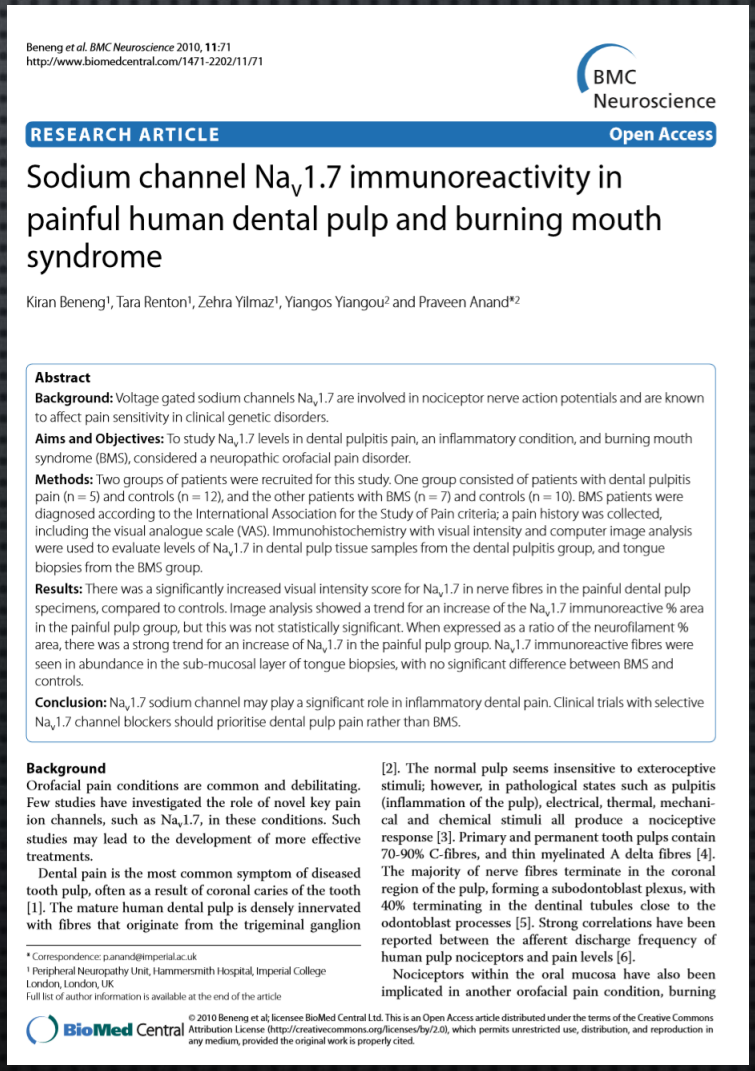
NEUROPATHY CAUSING NEUROPATHIC PAIN

- At the tip of the tongue compared to healthy controls (Grushka et al., 1987)
- With laser Doppler flowmetry, vasoreactivity of the intraoral mucosa to dry ice stimulation has been shown to be higher in BMS patients than controls (Heckmann et al., 2001), which, as a positive sign, is in line with the sensory phenomenon of decreased pain tolerance.
- More convincing evidence for focal involvement of the intraoral small fibre system came from a QST study utilizing argon laser stimulator (Svensson et al., 1993) and showing increased detection thresholds to warming and heat pain (hypoesthesia and hypoalgesia, i.e. negative signs) together with low pain to sensory threshold ratios on the tongue mucosa of BMS patients compared to control subjects.

- **Large and small fiber neuropathy.**
  - neuroanatomical studies applying methods developed for the investigation of intraepidermal nerve fibre density from skin biopsies to the study of epithelial density of small fibre endings (ENFD) in tongue mucosal biopsies (Lauria et al., 2005; Yilmaz et al., 2007; Beneng et al., 2010; Puhakka et al., 2010). These structural studies have now repeatedly shown significant loss of epithelial small diameter fibres in the tongue mucosa of BMS patients
  - Lauria et al., 2005; Albuquerque et al., 2006; Eliav et al., 2007; Yilmaz et al., 2007; Puhakka et al., 2010.
- **Lower threshold to blink reflex**
  - Another 25–36% of primary BMS patients show signs of decreased inhibition of the blink reflex in the form of absent or deficient habituation of the reflex when stimulating the supraorbital nerve distribution outside the symptomatic intraoral trigeminal area (Jääskeläinen et al., 1997; Forssell et al., 2002).



Beneng *et al. BMC Neuroscience* 2010, **11**:71
http://www.biomedcentral.com/1471-2202/11/71

BMC Neuroscience

RESEARCH ARTICLE Open Access

Sodium channel $Na_v1.7$ immunoreactivity in painful human dental pulp and burning mouth syndrome

Kiran Beneng[1], Tara Renton[1], Zehra Yilmaz[1], Yiangos Yiangou[2] and Praveen Anand*[2]

Abstract

Background: Voltage gated sodium channels $Na_v1.7$ are involved in nociceptor nerve action potentials and are known to affect pain sensitivity in clinical genetic disorders.

Aims and Objectives: To study $Na_v1.7$ levels in dental pulpitis pain, an inflammatory condition, and burning mouth syndrome (BMS), considered a neuropathic orofacial pain disorder.

Methods: Two groups of patients were recruited for this study. One group consisted of patients with dental pulpitis pain (n = 5) and controls (n = 12), and the other patients with BMS (n = 7) and controls (n = 10). BMS patients were diagnosed according to the International Association for the Study of Pain criteria; a pain history was collected, including the visual analogue scale (VAS). Immunohistochemistry with visual intensity and computer image analysis were used to evaluate levels of $Na_v1.7$ in dental pulp tissue samples from the dental pulpitis group, and tongue biopsies from the BMS group.

Results: There was a significantly increased visual intensity score for $Na_v1.7$ in nerve fibres in the painful dental pulp specimens, compared to controls. Image analysis showed a trend for an increase of the $Na_v1.7$ immunoreactive % area in the painful pulp group, but this was not statistically significant. When expressed as a ratio of the neurofilament % area, there was a strong trend for an increase of $Na_v1.7$ in the painful pulp group. $Na_v1.7$ immunoreactive fibres were seen in abundance in the sub-mucosal layer of tongue biopsies, with no significant difference between BMS and controls.

Conclusion: $Na_v1.7$ sodium channel may play a significant role in inflammatory dental pain. Clinical trials with selective $Na_v1.7$ channel blockers should prioritise dental pulp pain rather than BMS.

Background

Orofacial pain conditions are common and debilitating. Few studies have investigated the role of novel key pain ion channels, such as $Na_v1.7$, in these conditions. Such studies may lead to the development of more effective treatments.

Dental pain is the most common symptom of diseased tooth pulp, often as a result of coronal caries of the tooth [1]. The mature human dental pulp is densely innervated with fibres that originate from the trigeminal ganglion [2]. The normal pulp seems insensitive to exteroceptive stimuli; however, in pathological states such as pulpitis (inflammation of the pulp), electrical, thermal, mechanical and chemical stimuli all produce a nociceptive response [3]. Primary and permanent tooth pulps contain 70-90% C-fibres, and thin myelinated A delta fibres [4]. The majority of nerve fibres terminate in the coronal region of the pulp, forming a subodontoblast plexus, with 40% terminating in the dentinal tubules close to the odontoblast processes [5]. Strong correlations have been reported between the afferent discharge frequency of human pulp nociceptors and pain levels [6].

Nociceptors within the oral mucosa have also been implicated in another orofacial pain condition, burning

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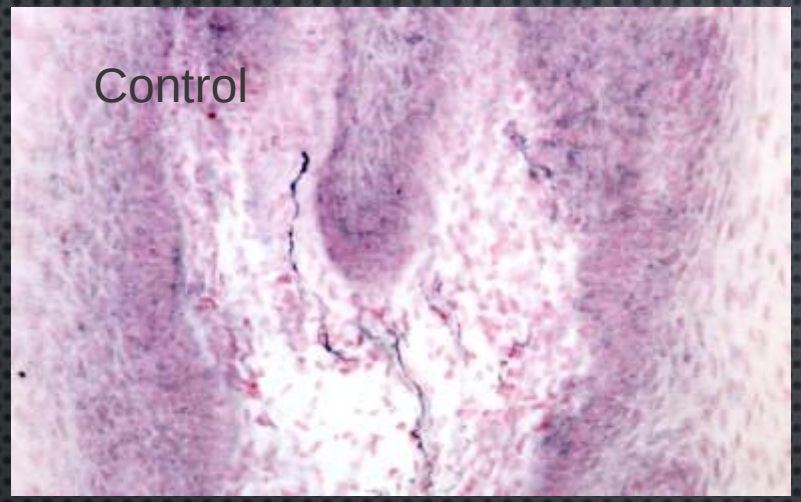
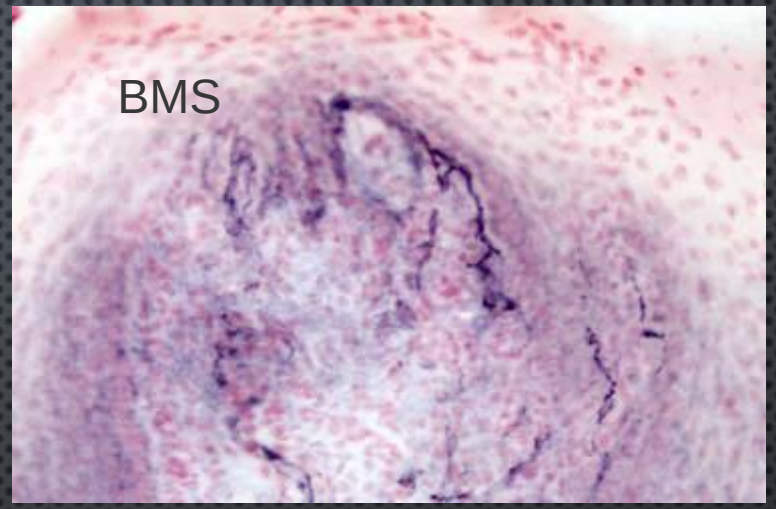
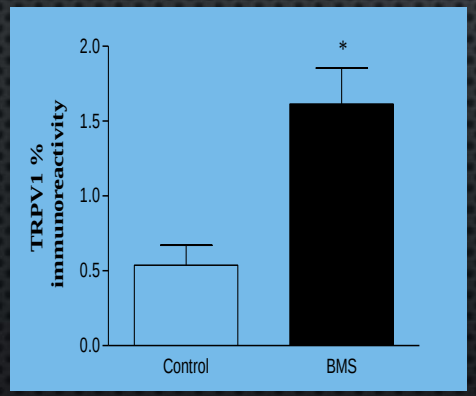
TRPV1 -IR







TRPV1 fibres staining in control and in BMS x20.

Bar chart shows the mean ± SEM of % area of TRPV1 fibres in control (n=10) and BM (n=10) tongue. * P =0.0011

Sodium channel Na v 1.7 immunoreactivity in painful human dental pulp and **burning mouth**syndrome.
Beneng K, Renton T, Yilmaz Z, Yiangou Y, Anand P.
BMC Neurosci. 2010 Jun 8;11:71. doi: 10.1186/1471-2202-11-71.
Sensory purinergic receptor P2X3 is elevated in **burning mouth** syndrome.
Beneng K, Yilmaz Z, Yiangou Y, McParland H, Anand P, Renton T.
Int J Oral Maxillofac Surg. 2010 Aug;39(8):815-9. doi: 10.1016/j.ijom.2010.03.013. Epub 2010 Apr 24.

‘SUPERTASTERS’

Studies report

- **increased fungiform papillae** (taste buds that are related to chorda tympani viability)
  - Med Oral Patol Oral Cir Bucal. 2012 May 1;17(3):e362-6. Fungiform papillae density in patients with burning mouth syndromeand xerostomia. Camacho-Alonso F, López-Jornet P, Molino-Pagán D
  - Laryngoscope. 2017 Aug 22. doi: 10.1002/lary.26828. **A case-control evaluation of fungiform papillae density in burning mouth syndrome.** Naud JM[1], Benca L[2], Drangsholt MT[3], LeResche L[3], Coldwell SE[3].

- **Increased taste sensitivity**
  - Oral Dis. 2017 Apr;23(3):395-402. doi: 10.1111/odi.12630. Epub 2017 Feb 8. **Taste function assessed by electrogustometry in burning mouth syndrome: a case-control study.** Braud A, Descroix V, Ungeheuer MN, Rougeot C, Boucher Y.

J Am Dent Assoc. 2007 May;138(5):628-33. **Evidence of chorda tympani dysfunction in patients with burning mouth syndrome.** Eliav E[1], Kamran B, Schaham R, Czerninski R, Gracely RH, Benoliel R.

Interaction taste nerve fibres and touch fibres in tongue mimicking 'phantom limb pain'

- One small study proposed that unilateral chorda tympani (taste) hypofunction results in lingual nerve (somatosensory) hyperfunction by disruption of a centrally mediated equilibrium between the two.[6]
- Observation in other conditions has shown that when a sensory circuit loses afferent signals that hyperactivity may result in hallucinatory sensations.
- Examples of this include phantom limb sensation following amputation and tinnitus in hearing loss. It would tend to account both for pain and for gustatory disturbances in burning mouth syndrome (BMS).
- Metallic or sour tastes are considered symptomatic manifestations of an understimulated gustatory circuit while understimulated sensory circuitry manifests burning sensations. The cause of this proposed neuropathy is unknown.

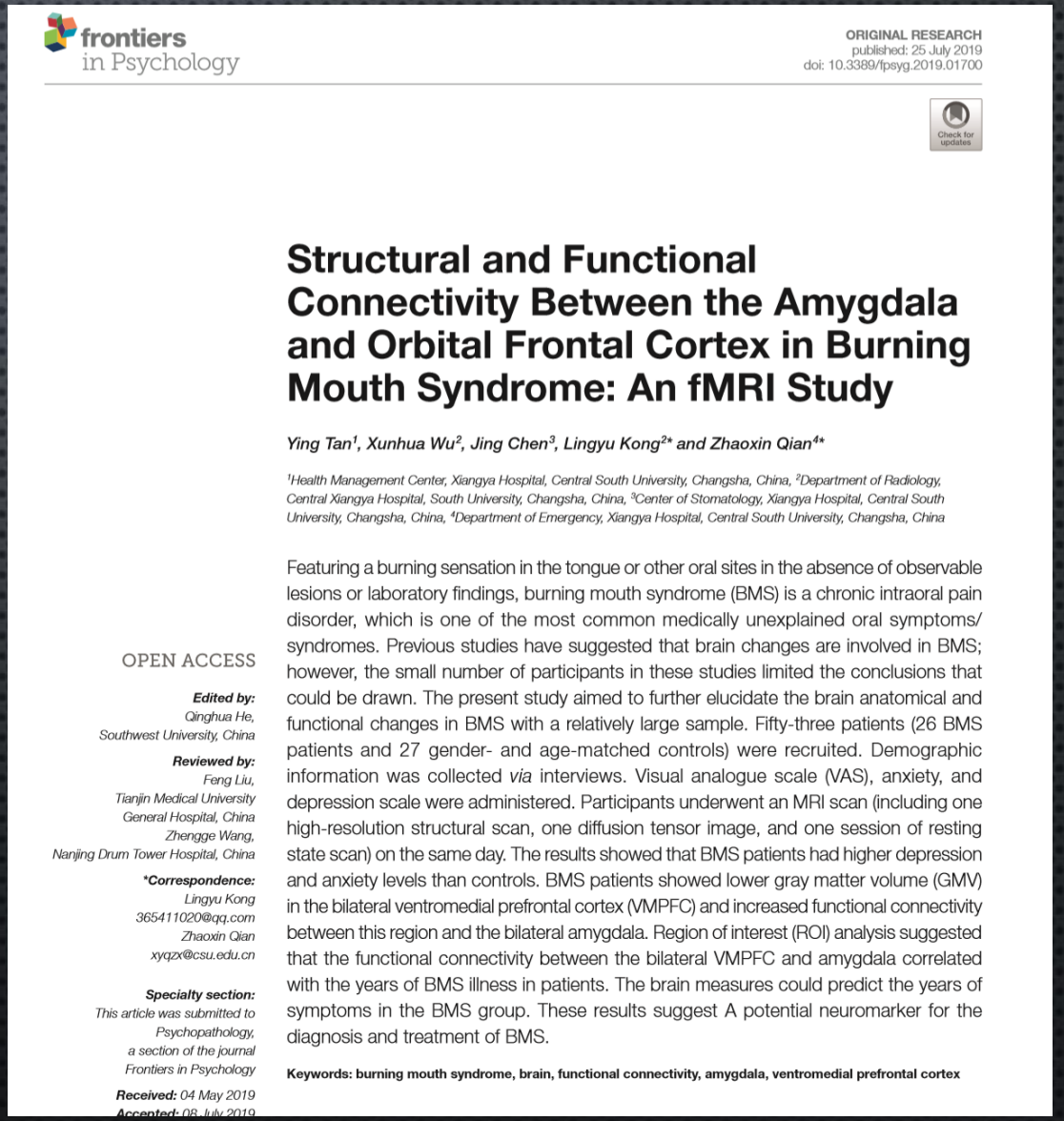
Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 Jul;112(1):65-72. doi: 10.1016/j.tripleo.2011.02.035. Epub 2011 May 20.**The role of sensory input of the chorda tympani nerve and the number of fungiform papillae in burning mouth syndrome.**Nasri-Heir C, Gomes J, Heir GM, Ananthan S, Benoliel R, Teich S, Eliav E

CENTRAL MECHANISMS

- fMRI studies has shown less volumetric activation in the entire brain to painful hot stimuli in primary BMS patients compared to control subjects and, more specifically, in the bilateral thalamus (Albuquerque et al., 2006); findings similar to those previously reported in neuropathic pain patients (Apkarian et al., 2005).
- The neurophysiologic phenomenon of deficient habituation of the R2 components of the blink reflex with supraorbital nerve stimulation in primary BMS patients initiated a series of studies on the role of brain dopamine system in pain (Jääskeläinen et al., 2001; Hagelberg et al., 2003, 2004).
- neurotransmitter positron emission tomography (PET) studies have demonstrated a significant decrease in fluoro-DOPA-tracer uptake in the presynaptic nerve terminals of the putamen on both sides indicating low level of dopamine in the nigrostriatal neurons of BMS patients compared to age matched controls (Jääskeläinen et al., 2001).
- However, on individual patient level, not all primary BMS patients show PET findings compatible with decrease in striatal dopamine. Deficient dopaminergic top-down inhibition may thus be a contributing factor to the clinical symptomatology in a subgroup of BMS patients, simultaneously with or independent of focal peripheral neuropathy.

CENTRAL FUNCTIONAL IMAGING STUDIES

- THE RESULTS SHOWED THAT BMS PATIENTS HAD HIGHER DEPRESSION AND ANXIETY LEVELS THAN CONTROLS.
- BMS PATIENTS SHOWED LOWER GRAY MATTER VOLUME (GMV) IN THE BILATERAL VENTROMEDIAL PREFRONTAL CORTEX (VMPFC) AND INCREASED FUNCTIONAL CONNECTIVITY BETWEEN THIS REGION AND THE BILATERAL AMYGDALA.
- REGION OF INTEREST (ROI) ANALYSIS SUGGESTED THAT THE FUNCTIONAL CONNECTIVITY BETWEEN THE BILATERAL VMPFC AND AMYGDALA CORRELATED WITH THE YEARS OF BMS ILLNESS IN PATIENTS.
- THE BRAIN MEASURES COULD PREDICT THE YEARS OF SYMPTOMS IN THE BMS GROUP. THESE RESULTS SUGGEST A POTENTIAL NEUROMARKER FOR THE DIAGNOSIS AND TREATMENT OF BMS.



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published: 25 July 2019
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Structural and Functional Connectivity Between the Amygdala and Orbital Frontal Cortex in Burning Mouth Syndrome: An fMRI Study

Ying Tan[1], Xunhua Wu[2], Jing Chen[3], Lingyu Kong[2] and Zhaoxin Qian[4]**

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Featuring a burning sensation in the tongue or other oral sites in the absence of observable lesions or laboratory findings, burning mouth syndrome (BMS) is a chronic intraoral pain disorder, which is one of the most common medically unexplained oral symptoms/syndromes. Previous studies have suggested that brain changes are involved in BMS; however, the small number of participants in these studies limited the conclusions that could be drawn. The present study aimed to further elucidate the brain anatomical and functional changes in BMS with a relatively large sample. Fifty-three patients (26 BMS patients and 27 gender- and age-matched controls) were recruited. Demographic information was collected *via* interviews. Visual analogue scale (VAS), anxiety, and depression scale were administered. Participants underwent an MRI scan (including one high-resolution structural scan, one diffusion tensor image, and one session of resting state scan) on the same day. The results showed that BMS patients had higher depression and anxiety levels than controls. BMS patients showed lower gray matter volume (GMV) in the bilateral ventromedial prefrontal cortex (VMPFC) and increased functional connectivity between this region and the bilateral amygdala. Region of interest (ROI) analysis suggested that the functional connectivity between the bilateral VMPFC and amygdala correlated with the years of BMS illness in patients. The brain measures could predict the years of symptoms in the BMS group. These results suggest A potential neuromarker for the diagnosis and treatment of BMS.

Keywords: burning mouth syndrome, brain, functional connectivity, amygdala, ventromedial prefrontal cortex

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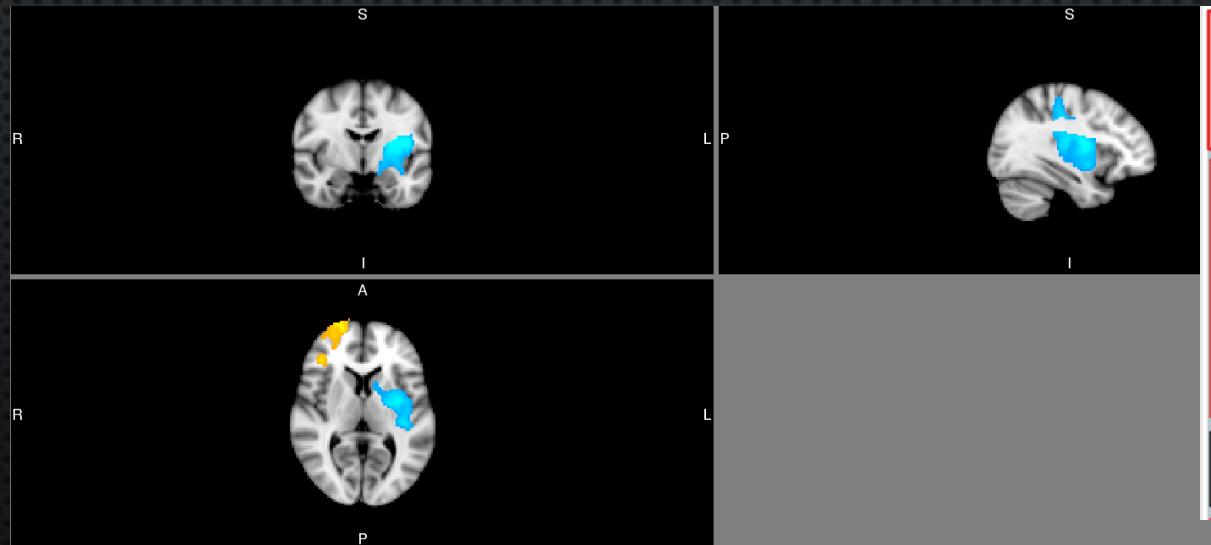
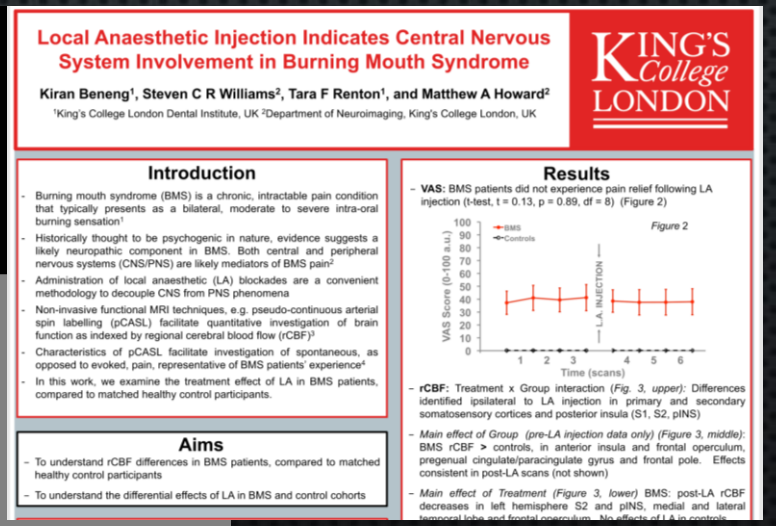
PERIPHERAL NERVE BLOCK (LINGUAL NERVE)

- UNILATERAL PERIPHERAL LINGUAL NERVE BLOCK WITH LIDOCAIN HAS BEEN SHOWN TO RESULT, ON THE GROUP LEVEL, IN SIGNIFICANT, IPSILATERAL OR BILATERAL SYMPTOM RESOLUTION IN PRIMARY BMS (GREMEAU-RICHARD ET AL., 2010).

- HOWEVER, ON INDIVIDUAL PATIENT LEVEL, PRIMARY BMS PATIENTS WERE SHOWN TO RESPOND IN TWO VERY DISTINCT WAYS, ONE SUBGROUP, CALLED "PERIPHERAL BMS", SHOWING CLINICALLY MEANINGFUL PAIN REDUCTION ON VISUAL ANALOGUE SCALE AND ANOTHER "CENTRAL" SUBGROUP SHOWING NO PAIN REDUCTION OR EVEN AN INCREASE IN BURNING PAIN AFTER TECHNICALLY SUCCESSFUL LINGUAL NERVE BLOCK.

- IN ADDITION, HOSPITAL ANXIETY AND DEPRESSION (HAD) SCORES WERE SIGNIFICANTLY HIGHER IN THE "CENTRAL" THAN THE "PERIPHERAL" BMS SUBGROUP.




Local Anaesthetic Injection Indicates Central Nervous System Involvement in Burning Mouth Syndrome

Kiran Beneng[1], Steven C R Williams[2], Tara F Renton[1], and Matthew A Howard[2]

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Introduction

- Burning mouth syndrome (BMS) is a chronic, intractable pain condition that typically presents as a bilateral, moderate to severe intra-oral burning sensation[1]
- Historically thought to be psychogenic in nature, evidence suggests a likely neuropathic component in BMS. Both central and peripheral nervous systems (CNS/PNS) are likely mediators of BMS pain[2]
- Administration of local anaesthetic (LA) blockades are a convenient methodology to decouple CNS from PNS phenomena
- Non-invasive functional MRI techniques, e.g. pseudo-continuous arterial spin labelling (pCASL) facilitate quantitative investigation of brain function as indexed by regional cerebral blood flow (rCBF)[3]
- Characteristics of pCASL facilitate investigation of spontaneous, as opposed to evoked, pain, representative of BMS patients' experience[4]
- In this work, we examine the treatment effect of LA in BMS patients, compared to matched healthy control participants.

Aims

- To understand rCBF differences in BMS patients, compared to matched healthy control participants
- To understand the differential effects of LA in BMS and control cohorts

Results

- **VAS:** BMS patients did not experience pain relief following LA injection (t-test, t = 0.13, p = 0.89, df = 8) (Figure 2)

Figure 2

- **rCBF:** Treatment x Group interaction (*Fig. 3, upper):* Differences identified ipsilateral to LA injection in primary and secondary somatosensory cortices and posterior insula (S1, S2, pINS)
- *Main effect of Group (pre-LA injection data only) (Figure 3, middle):* BMS rCBF > controls, in anterior insula and frontal operculum, pregenual cingulate/paracingulate gyrus and frontal pole. Effects consistent in post-LA scans (not shown)
- *Main effect of Treatment (Figure 3, lower)* BMS: post-LA rCBF decreases in left hemisphere S2 and pINS, medial and lateral

BRAIN CONNECTIVITY

- Burning mouth syndrome (BMS) is a chronic intraoral pain syndrome featuring idiopathic oral pain and burning discomfort despite clinically normal oral mucosa. The etiology of chronic pain syndrome is unclear, but preliminary neuroimaging research has suggested the alteration of volume, metabolism, blood flow, and diffusion at multiple brain regions. According to the neuromatrix theory of Melzack, pain sense is generated in the brain by the network of multiple pain-related brain regions. Therefore, the alteration of pain-related network is also assumed as an etiology of chronic pain. In this study, we investigated the brain network of BMS brain by using probabilistic tractography and graph analysis.
- **METHODS:** Fourteen BMS patients and 14 age-matched healthy controls underwent 1.5T MRI. Structural connectivity was calculated in 83 anatomically defined regions with probabilistic tractography of 60-axis diffusion tensor imaging and 3D T1-weighted imaging. Graph theory network analysis was used to evaluate the brain network at local and global connectivity.
- **RESULTS:** In BMS brain, a significant difference of local brain connectivity was recognized at the bilateral rostral anterior cingulate cortex, right medial orbitofrontal cortex, and left pars orbitalis which belong to the medial pain system; however, no significant difference was recognized at the lateral system including the somatic sensory cortex. A strengthened connection of the anterior cingulate cortex and medial prefrontal cortex with the basal ganglia, thalamus, and brain stem was revealed.
- **CONCLUSION:** Structural brain network analysis revealed the alteration of the medial system of the pain-related brain network in chronic pain syndrome.

Neuroradiology. 2017 May;59(5):525-532. doi: 10.1007/s00234-017-1830-2. Epub 2017 Mar 30. **Altered structural connectivity of pain-related brain network in burning mouth syndrome-investigation by graph analysis of probabilistic tractography** Wada A[1], Shizukuishi T[2], Kikuta J[2], Yamada H[2], Watanabe Y[2,3], Imamura Y[4], Shinozaki T[4], Dezawa K[4], Haradome H[2], Abe O[2,]

POTENTIAL BIOMARKERS IN BMS

Burning mouth syndrome (BMS) is a chronic pain disorder characterized by severe burning sensation in normal looking oral mucosa. Diagnosis of BMS remains to be a challenge to oral healthcare professionals because the method for definite diagnosis is still uncertain. In this study, a quantitative saliva proteomic analysis was performed in order to identify target proteins in BMS patients' saliva that may be used as biomarkers for simple, non-invasive detection of the disease. By using isobaric tags for relative and absolute quantitation labeling and liquid chromatography-tandem mass spectrometry to quantify 1130 saliva proteins between BMS patients and healthy control subjects, **we found that 50 proteins were significantly changed in the BMS patients when compared to the healthy control subjects ($p \leq 0.05$, 39 up-regulated and 11 down-regulated).**

Four candidates,

- **alpha-enolase**
- **interleukin-18 (IL-18)**
- **kallikrein-13 (KLK13)**
- **cathepsin G, were selected for further validation.**

Based on enzyme-linked immunosorbent assay measurements, three potential biomarkers

- **Alpha-enolase**
- **IL-18**
- **KLK13, were successfully validated**. The fold changes for alpha-enolase, IL-18, and KLK13 were determined as 3.6, 2.9, and 2.2 (burning mouth syndrome vs. control), and corresponding receiver operating characteristic values were determined as 0.78, 0.83, and 0.68, respectively.

Mol Pain. 2017 Jan;13:1744806916686796. doi: 10.1177/1744806916686796.
Potential protein biomarkers for burning mouth syndrome discovered by quantitative proteomics. Ji EH[1], Diep C[1], Liu T[2], Li H[2], Merrill R[1], Messadi D[1], Hu S[1].

ASSESSMENT OF PATIENT WITH BMS

INVESTIGATIONS DURHAM & CURRIE

Haematological:¶

- → CBC/FBC·(Hb,·MCV,·MCH,·WCC)¶
- → B12,·Fe,·Folate·(B1,·2,·6,·12)¶
- → Zinc¶
- → HbA_1C¶
- → TFT·(T3,·T4,·TSH)¶
- → LFT·(ALT,·GGT,·ALK·Phos,·Albumin)¶
- → ESR·**or**·CRP¶
- → ?Menopausal·index¶
- → ?H·pylori¶
- → Autoantibodies:¶
    - → Anti·Ro·and·Anti·La¶
    - → ANA¶
    - → ENA¶

Saliva·¶

Patch·test:·adjunctive·for·clinical·suspicion·¶

Candida¶

QST:·see·copy·and·pasted·table·taken·from·Devine·M·et·al·Prospero·review·of·diagnostic·criteria·for·PPTTN¶

Table VII. Proposed comprehensive test protocol

Test	*Description*	*Equipment*
Cool detection threshold	A small thermode applied to the affected nerve distribution is set at a baseline temperature and cools at a defined rate until the patient indicates when they first feel cold sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Warm detection threshold	A small thermode applied to the affected nerve distribution is set at a baseline temperature and warms at a defined rate until the patient indicates when they first feel warm sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Thermal sensory limen	The difference threshold for alternating cool and warm stimuli	Thermal QST apparatus
Cold pain threshold	A small thermode applied to the affected nerve distribution is set at a baseline temperature and cools at a defined rate until the patient indicates when they first feel pain caused by cold sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Heat pain threshold	A small thermode applied to the affected nerve distribution is set at a baseline temperature and warms at a defined rate until the patient indicates when he or she first feels pain caused by heat sensation. Test is repeated 3 times and an average value recorded.	Thermal QST apparatus
Mechanical detection threshold	Semmes Weinstein monofilaments are placed perpendicular to the skin in the affected nerve distribution and force is applied until the filament deforms. At this point, a known reproducible force is applied. An ascending and descending series of monofilaments applying different amounts of force is used to measure the contact detection threshold. This is repeated 5 times and a mean value taken.	Semmes Weinstein monofilaments
MPT	A custom-made weighted pinprick is applied to the affected nerve distribution. An ascending and descending series of pinpricks is used to measure the MPT. This is repeated 5 times and a mean value taken.	Weighted pinprick
MPS and DMA	MPS: Seven weighted pinprick stimuli of different intensities are applied in a random order and repeated five times for each test site. DMA involves moving innocuous stimuli such as a Q-tip, cotton wisp and soft toothbrush across the test site in between pinprick stimuli. The patient gives a numerical pain rating for each stimulus. A total of 50 stimuli (pinprick and tactile) should be given at each test site.	Weighted pinprick Q-tip Cotton wisp Soft toothbrush
Temporal summation of pain as wind up ration	10 pinprick stimuli of equal intensity are given at an interstimulus interval of 1 Hz. The patient is asked to give a numerical pain rating for this stimulus which is compared to the pain rating for a single stimulus. Each series of 10 stimuli is repeated 5 times in the affected nerve distribution and an average value is taken.	Weighted pinprick
VDT	Vibrating tuning forks are placed over a bony prominence in the affected nerve distribution. The patient indicates if they can feel vibration or not and three series of descending stimulus intensities are used to determine the VDT.	Vibrating tuning forks
Pressure pain detection threshold	A pressure algometer or pressure gauge device is applied to the affected nerve distribution. Three series of slowly ascending stimulus intensities are applied and the patient indicates when pain is felt. An average value of the 3 readings is taken.	Pressure algometer or pressure gauge

DMA, dynamic mechanical allodynia; *MPS*, mechanical pain sensitivity; *MPT*, mechanical pain threshold; *QST*, quantitative sensory testing; *VDT*, vibration detection threshold.

SENSORY TESTING ALL BMS PATIENTS

RECOMMENDED REGIME FOR RESEARCH

Step-wise diagnostic work-up of burning mouth patients. Step 1 examinations aid in the differential diagnostics of BM symptoms, Steps 2 and 3 examinations define the level and extent of neuropathic abnormalities in primary BMS, Step 4 reveals deficiencies in top-down inhibition. Different alternative tests for intraoral small fibre function can be used at Step 1, according to availability. Step 5 describes additional tests for further investigation of aetiology, exact location, and extent of nervous system pathology related to BMS.

	Test	Result	Interpretation
Step 1 alternative A	Electrogustatometry: Ratio of taste-to-tingling detection thresholds to electrical stimuli	High ratio	Primary BMS, neuropathic alteration of the taste afferent system
		Normal ratio	Secondary BMS/healthy
Step 1 alternative B	Thermal quantitative sensory testing (QST) on the tongue mucosa (small thermode, both sides: warm, cool, heat pain and cold pain detection thresholds; pain tolerance)	Thermal hypoesthesia/anaesthesia or thermal hypoalgesia/analgesia	Neuropathic pain due to small diameter fibre neuropathy or central pain
		Thermal allodynia/hyperesthesia	Possible small fibre neuropathy or central pain
		Normal	Confirm non-neuropathic nature with blink reflex or biopsy
Step 2	Blink reflex with stimulation of supraorbital, mental, and lingual nerve distributions Masseter reflex	Abnormal (afferent pattern)	Lingual/mandibular/trigeminal neuropathic pain
		Abnormal partial/mixed patterns	Central pain due to brainstem pathology
		Normal brainstem reflexes	Pure small fibre neuropathy or not neuropathic pain
Step 3	Tongue mucosal punch biopsy: epithelial (ENFD) and subepithelial (SENFD) nerve fibre density	Decreased ENFD only	Pure peripheral small fibre neuropathy
		Decreased ENFD and SENFD	Peripheral lingual/mandibular/trigeminal neuropathy
		Normal	Central or not neuropathic pain
Step 4	Habituation of the blink reflex: 1 Hz repetitive electrical stimulation of the supraorbital nerve	Abnormal excitability and normal findings at steps 1, 2 and 3	Central pain due to top-down disinhibition (maybe related to striatal dopamine depletion)
		Abnormal excitability and abnormal findings at steps 1A, 1B, 2 or 3	Neuropathic pain combined with deficient top-down inhibition
		Normal findings steps 1, 2, 3 and 4	Most likely not neuropathic pain
Step 5 Optional	a. ENMG: bulbar region, extremities	Abnormal	More exact localization of focal or generalized peripheral neuropathy
	b. Thermal QST or skin biopsy for ENFD in the extremities	Abnormal	Generalized small diameter fibre neuropathy
	c. MRI targeted according to abnormal findings at Step 2	Abnormal	Exact location of structural pathology, central pain

Satu K.Jääskeläinen Pathophysiology of primary burning mouth syndrome Clinical Neurophysiology Volume 123, Issue 1, January 2012, Pages 71-77

Review

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Burning mouth syndrome

Satu K Jääskeläinen[1] and Alain Woda[2]

Abstract

Objective: To review the clinical entity of primary burning mouth syndrome (BMS), its pathophysiological mechanisms, accurate new diagnostic methods and evidence-based treatment options, and to describe novel lines for future research regarding aetiology, pathophysiology, and new therapeutic strategies.

Description: Primary BMS is a chronic neuropathic intraoral pain condition that despite typical symptoms lacks clear clinical signs of neuropathic involvement. With advanced diagnostic methods, such as quantitative sensory testing of small somatosensory and taste afferents, neurophysiological recordings of the trigeminal system, and peripheral nerve blocks, most BMS patients can be classified into the peripheral or central type of neuropathic pain. These two types differ regarding pathophysiological mechanisms, efficacy of available treatments, and psychiatric comorbidity. The two types may overlap in individual patients. BMS is most frequent in postmenopausal women, with general population prevalence of around 1%. Treatment of BMS is difficult; best evidence exists for efficacy of topical and systemic clonazepam. Hormonal substitution, dopaminergic medications, and therapeutic non-invasive neuromodulation may provide efficient mechanism-based treatments for BMS in the future.

Conclusion: We present a novel comprehensive hypothesis of primary BMS, gathering the hormonal, neuropathic, and genetic factors presumably required in the genesis of the condition. This will aid in future research on pathophysiology and risk factors of BMS, and boost treatment trials taking into account individual mechanism profiles and subgroup-clusters.

Keywords

Burning mouth syndrome, epidemiology, pathophysiology, diagnosis, treatment

Date received: 5 November 2016; revised: 30 December 2016; 30 January 2017; accepted: 31 January 2017

Definition

The International Headache Society (1) defines burning mouth syndrome (BMS) as an "intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions". This definition does not regard BMS as a psychogenic pain, as it was generally held to be until two decades ago (2,3), but on the contrary lists it under the heading "painful cranial neuropathies" in the IHS classification (1) and includes "burning or dysaesthetic sensation", clearly referring to neuropathic mechanisms. This newer view has been substantiated by recent histological, neurophysiologic, brain imaging and quantitative sensory testing (QST) data, as will be described in detail further on.

Classification

The International Association for the Study of Pain (IASP) first recognized BMS in 1994 as an identified entity, labelled "glossodynia and sore mouth" (4). The initial proposal that BMS belonged to a group of idiopathic orofacial conditions, also including atypical odontalgia, atypical facial pain and some of the temporo-mandibular joint and masticatory muscle pains (5,6) was later confirmed when cluster analysis was applied to all types of chronic orofacial pain states in a prospective multicentre study (7). The analysis showed three main clusters, representing neuralgic, vascular, and idiopathic groups of orofacial pains. Within the idiopathic group, later called the dysfunctional group, BMS emerged as the most distinct subgroup with a homogeneous set of symptoms.

[1]Department of Clinical Neurophysiology, University of Turku and Turku University Hospital, Turku, Finland
[2]Université Clermont Auvergne, CROC and University Hospital, Odontology department; Clermont-Ferrand, France

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Table 1. Tests currently available for the diagnostic work-up of burning mouth (BMS) patients. With appropriate combinations, diagnosis and grading of subclinical trigeminal neuropathies and brainstem pathology can be done. In addition, multiple tests profile the pathophysiological processes on individual patient level, enabling a rational search for more specific aetiologies and mechanism-based treatment approaches.

Test and measured variables	Result	Interpretation in patients with intraoral burning pain
Electrogustatometry:		
Ratio of taste-to-tingling detection thresholds to electrical stimuli	High ratio	Primary BMS
	Normal ratio	Secondary BMS or healthy
Thermal quantitative sensory testing (QST) on the tongue mucosa:		
Warm, cool, heat pain and cold pain detection thresholds Pain tolerance	Thermal hypoesthesia/anaesthesia	Neuropathic pain due to small fibre neuropathy or central pain
	Thermal hypoalgesia/analgesia	Possible small fibre neuropathy or central pain
	Thermal allodynia/ hyperesthesia	May be neuropathic or non-neuropathic
	Normal	Central nigrostriatal dopamine deficit or healthy
Brainstem reflexes:		
Blink reflex with stimulation of supraorbital, mental, and lingual nerve distributions	Abnormal (afferent pattern)	Lingual/mandibular/trigeminal neuropathic pain
	Abnormal partial / mixed patterns	Central pain due to brainstem pathology
Masseter reflex	Normal brainstem reflexes	Not neuropathic pain, or pure small fibre neuropathy
Tongue mucosal biopsy:		
Epithelial (ENFD) and subepithelial (SENFD) nerve fibre density	Decreased ENFD, normal SENFD	Pure peripheral small fibre neuropathy
	Decreased ENFD and SENFD	Peripheral lingual/mandibular /trigeminal neuropathy
	Normal	Central or not neuropathic pain
Habituation of the blink reflex:		
Decrease in R2 component area with 1 Hz repetitive electrical stimulation of the supraorbital nerve	Abnormal excitability and normal findings in tests for peripheral nerves	Central pain due to top-down disinhibition (maybe related to striatal dopamine depletion)
	Abnormal excitability and abnormal findings in QST or brainstem reflex recordings	Neuropathic pain combined with deficient top-down inhibition
	Normal habituation	Normal dopamine mediated descending inhibition
Tests to further localize nervous system pathology		
ENMG: Face, bulbar region, extremities	Abnormal	More exact localization of peripheral neuropathy: Focal or generalized
Thermal QST or skin biopsy for ENFD in the extremities	Abnormal	Generalized peripheral small fibre neuropathy
MRI targeted according to abnormal findings in neurophysiologic tests	Abnormal	Exact location of structural central nervous system pathology

(continued)

Review

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MRI targeted according to abnormal findings in neurophysiologic tests	Abnormal	Exact location of structural central nervous system pathology

(continued)

Somatosensory Profiling of Patients with Burning Mouth Syndrome and Correlations with Psychologic Factors

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Aims: To compare somatosensory function profiles and psychologic factors in patients with primary burning mouth syndrome (BMS) and healthy controls and to evaluate correlations of subjective pain ratings with somatosensory and psychologic parameters. **Methods:** A quantitati
cold detection threshold (CDT), warm
limen (TSL), paradoxical heat sens
pain threshold (HPT), mechanical pa
pressure pain threshold (PPT)—was
buccal, and palatal sites in 30 Chine
50.9 ± 9.2 years) with primary BMS
controls (15 women and 3 men, mea
z scores and loss/gain scores were
in both groups using the Self-Ratin
Scale. Correlations of BMS patients
and psychologic profiles were asse
correlations and multiple linear re
had somatosensory abnormalities
controls ($P = .033$). The abnormaliti
to thermal nonnoxious stimuli (TSL
mechanical pressure stimuli (PPT =
thermal pain stimuli (CPT = 3.3%),
stimuli (WUR = 6.7%), pressure sti
(HPT = 3.3%). The most frequent l
somatosensory function with no so
and mechanical somatosensory fun
for gain of mechanical somatosens
elevations in anxiety scores were s
and 36.7% had mild and moderate
No anxiety or depression was detec
psychologic scores, were significa
ratings (PHS, Spearman coefficient
−0.370, $P = .034$; MPT, Pearson
coefficient 0.363, $P = .037$). **Cor**
distinct differences in somatosens
compared to controls, indicating
between impairments in nocicepti
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Keywords: *burning mouth syndrom
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Burning mouth syndrome (
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Review

Cephalalgia
International Headache Society

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SAGE

Burning mouth syndrome

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Abstract

Objective: To review the clinical entity of primary burning mouth syndrome (BMS), its pathophysiological mechanisms, accurate new diagnostic methods and evidence-based treatment options, and to describe novel lines for future research regarding aetiology, pathophysiology, and new therapeutic strategies.

Description: Primary BMS is a chronic neuropathic intraoral pain condition that despite typical symptoms lacks clear clinical signs of neuropathic involvement. With advanced diagnostic methods, such as quantitative sensory testing of small somatosensory and taste afferents, neurophysiological recordings of the trigeminal system, and peripheral nerve blocks, most BMS patients can be classified into the peripheral or central type of neuropathic pain. These two types differ regarding pathophysiological mechanisms, efficacy of available treatments, and psychiatric comorbidity. The two types may overlap in individual patients. BMS is most frequent in postmenopausal women, with general population prevalence of around 1%. Treatment of BMS is difficult; best evidence exists for efficacy of topical and systemic clonazepam. Hormonal substitution, dopaminergic medications, and therapeutic non-invasive neuromodulation may provide efficient mechanism-based treatments for BMS in the future.

Conclusion: We present a novel comprehensive hypothesis of primary BMS, gathering the hormonal, neuropathic, and genetic factors presumably required in the genesis of the condition. This will aid in future research on pathophysiology and risk factors of BMS, and boost treatment trials taking into account individual mechanism profiles and subgroup-clusters.

Keywords

Burning mouth syndrome, epidemiology, pathophysiology, diagnosis, treatment

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Definition

The International Headache Society (1) defines burning mouth syndrome (BMS) as an "intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions". This definition does not regard BMS as a psychogenic pain, as it was generally held to be until two decades ago (2,3), but on the contrary lists it under the heading "painful cranial neuropathies" in the IHS classification (1) and includes "burning or dysaesthetic sensation", clearly referring to neuropathic mechanisms. This newer view has been substantiated by recent histological, neurophysiologic, brain imaging and quantitative sensory testing (QST) data, as will be described in detail further on.

Classification

The International Association for the Study of Pain (IASP) first recognized BMS in 1994 as an identified entity, labelled "glossodynia and sore mouth" (4). The initial proposal that BMS belonged to a group of idiopathic orofacial conditions, also including atypical odontalgia, atypical facial pain and some of the temporo-mandibular joint and masticatory muscle pains (5,6) was later confirmed when cluster analysis was applied to all types of chronic orofacial pain states in a prospective multicentre study (7). The analysis showed three main clusters, representing neuralgic, vascular, and idiopathic groups of orofacial pains. Within the idiopathic group, later called the dysfunctional group, BMS emerged as the most distinct subgroup with a homogeneous set of symptoms.

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REVIEW ARTICLE

Pathophysiology of primary burning mouth syndrome with special focus on taste dysfunction: a review

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Primary burning mouth syndrome (BMS) is a chronic oral condition characterized by burning pain often accompanied with taste dysfunction and xerostomia. The most compelling evidence concerning BMS pathophysiology comes from studies on the somatosensory system using neurophysiologic or psychophysical methods such as blink reflex, thermal quantitative sensory testing, as well as functional brain imaging. They have provided convincing evidence for neuropathic involvement at several levels of the somatosensory system in BMS pain pathophysiology. The number of taste function studies trying to substantiate the subjective taste disturbances or studies on salivary factors in BMS is much more limited, and most of them suffer from definitional and methodological problems. This review aims to critically evaluate the existing literature on the pathophysiology of BMS, paying special attention to the correctness of case selection and the methodology used in published studies, and to summarize the current state of knowledge. Based on the recognition of several gaps in the current understanding of the pathophysiology of BMS especially as regards taste and pain system interactions, the review ends with future scenarios for research in this area.

Oral Diseases (2015) **21**, 937–948

Keywords: primary burning mouth syndrome; pathophysiology; taste dysfunction; saliva; taste

Introduction

Burning mouth syndrome (BMS) is a chronic oral condition characterized by burning pain, often accompanied with taste dysfunction (dysgeusia, taste phantoms) or dry mouth sensation (xerostomia). Noticeable is that hyposalivation by itself can also induce burning sensation in the mouth without being true BMS.

Burning mouth syndrome remained an enigma for a long time, but during the last years, knowledge of the pathophysiology of BMS has considerably increased. Research has particularly focused on the trigeminal somatosensory system to unravel the background of BMS pain, and various types of abnormalities have been found at several levels of the somatosensory system.

Much less attention has been paid to the other aspects of the syndrome, taste disorders and xerostomia. The numbers of taste function studies trying to substantiate the subjective taste disturbances or studies on salivary factors are much more limited. The aim of this article was to review the existing literature on the pathophysiology of BMS, with special focus on studies on taste dysfunction and xerostomia in BMS.

BMS – clinical features

Burning mouth syndrome is characterized by burning mucosal pain that is not due to any other local or systemic causes, and arises from a clinically normal, healthy mucosa (Bergdahl and Bergdahl, 1999; Woda and Pionchon, 1999; Zakrzewska and Hamlyn, 1999; Zakrzewska *et al*, 2005; Markman and Eliav, 2013). The International Classification of Headache Disorders defines BMS accordingly as 'an intraoral burning or dysesthetic sensation, recurring daily for more than 2 h per day over more than 3 months, without clinically evident causative lesions' (The International Classification of Headache Disorders, 2013). In addition to pain, BMS patients often complain of a feeling of oral dryness or taste disturbances justifying the use of the term 'syndrome' (Scala *et al*, 2003; Granot and Nagler, 2005; Zakrzewska *et al*, 2005).

Burning mouth syndrome diagnosis is in practice based on the exclusion of local and/or systemic factors that could cause the oral burning or other sensory symptoms. Many studies, especially earlier ones, have not distinguished between BMS and oral burning symptoms, that is

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52% of primary BMS patients have abnormal sensory responses Another theory is taste disturbance

GUSTATORY AND OLFACTORY FUNCTION

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RAPID COMMUNICATION

Central mechanisms in burning mouth syndrome involving the olfactory nerve: a preliminary study

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INTRODUCTION

Burning mouth syndrome (BMS) is characterized by a continuous sensation of burning or heat in the oral cavity, mainly on the tongue, palate and/or gingiva [1-3], in the absence of a primary cause [4-5]. Systemic diseases, such as diabetes mellitus or anemia, must be ruled out [3]. It is most common among postmenopausal women and causes intense discomfort and suffering.

There is no defined etiology for BMS other than precipitating causative factors, and it is still considered idiopathic. One of the most widely accepted theories is that the partial or total loss of chorda tympani (facial) nerve function disinhibits the trigeminal nerve, resulting in pain along trigeminal pathways, as both taste and pain systems are regulated by interneurons of the central nervous system

other lesions and no diseases included in the exclusion criteria.

Inclusion criteria: The study included 20 patients newly diagnosed with BMS who had not begun pharmacological treatment and 30 healthy controls with no complaint of facial or intraoral pain within the last 6 months who were consecutively selected from patients receiving dental treatment at the Dentistry Division of the hospital.

Exclusion criteria (for patients and controls): Exclusion criteria included Sjögren syndrome, rheumatological diseases (i.e., fibromyalgia and rheumatoid arthritis), diabetes, anemia, hyper- or hypothyroidism, generalized pain, and history of surgery in the facial/oral region. The patients and controls underwent a systematized evaluation by the hospital's general physician to investigate the presence of systemic diseases. In addition to the clinical exam, a

Sweet (glucose): 0.01; 0.032; 0.1; 0.32; 1.0.
Sour (citric acid): 0.01; 0.032; 0.1; 0.32; 1.0.
Salty (sodium chlorate): 0.01; 0.032; 0.1; 0.32; 1.0.
Bitter (urea): 0.01; 0.032; 0.1; 0.32; 1.0.

A single drop of each concentration was applied and swallowed by the patient; the results were compared to results from a single drop of distilled water. When the stimulus was not perceived, the next concentration was applied. The patient's mouth was washed with distilled water between different tastes.

(5) Olfactory threshold with isopropanol solutions (9.9; 15; 23.3; 32; 48; 53; 70%) [23-24]. Each concentration was offered to the patient along with a bottle of water, and the patient was asked to choose the bottle containing the substance three times. The threshold was established when the patient correctly chose all three times. If the patient chose incorrectly, the next concentration was offered along with a bottle of water.

All subjects were evaluated in the sitting position, with the head resting on a flat surface and the Frankfurt line parallel to the ground. All evaluations took place at the same time of day (between 1 and 4 pm) in a silent room with acoustic protection on the walls and with the door closed. Only the patient and the researcher were in the room during evaluations. All patients were evaluated by the same researcher. The subjects received the same instructions after being positioned, which were to keep their eyes closed during the exam and to identify and report whether they felt the stimuli being applied to the face (by saying ''yes'' or ''no'') and what they felt (by naming the stimulus). Only the researcher knew the order in which the stimuli would be presented. Finally, all findings were tabulated and statistically analyzed.

analyze facial and oral sensitivity. Finally, gustative and olfactory thresholds were evaluated with the Kruskall-Wallis test followed by Dunns test. The level of significance was $p<0.05$.

RESULTS

Demographic characteristics

The mean age of subjects was 60.95, and there were 16 women and 4 men in the BMS group. There was a significant age difference between groups (Table 1).

Somatosensory findings

There were no between-group differences in the somatosensory results for the ophthalmic branch, and similar cold thresholds were noted between the groups. The BMS patients had higher tactile thresholds at the maxillary branch ($p=0.001$) and higher warm thresholds at the maxillary ($p=0.032$) and mandibular ($p=0.001$) branches (Table 2). The BMS patients had higher pain thresholds at the ophthalmic and maxillary branches ($p<0.05$) (Table 3). There were no intraoral sensibility differences between the studied groups ($p=0.87$).

Gustative evaluation

The gustative evaluation showed significant differences in all basic tastes (sweet $p<0.001$; salty $p=0.004$; sour $p=0.001$; bitter $p=0.001$). The BMS patients had higher salty, sweet and bitter thresholds but lower sour thresholds (Figure 1). Neither group exhibited difficulties with taste identification.

Olfactory evaluation

The BMS patients had higher olfactory thresholds (Figure 2).

DISCUSSION

Will it get better?

- For patients with primary burning mouth syndrome (BMS), an estimated 50-66% may have improvement in symptoms after 6-7 years.[11]
- A small study of 32 patients reported near universal improvement in symptoms within 16 weeks for patients receiving ongoing multidisciplinary treatment.[42]
- Spontaneous remission is rare but does occur in roughly 3% of patients.[43]
- These findings are similar to other idiopathic chronic pain syndromes and support the idea that treatment should be individualized based on symptoms

HOW CAN WE FIX SOMETHING WHEN WE DON'T KNOW THE CAUSE?

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REVIEW ARTICLE

Burning mouth syndrome: a review and update

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Burning mouth syndrome (BMS) is characterized by the presence of burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. It occurs more commonly in middle-aged and elderly women and often affects the tongue tip and lateral borders, lips, and hard and soft palate. In addition to a burning sensation, the patients with BMS may also complain unremitting oral mucosal pain, dysgeusia, and xerostomia. BMS can be classified into two clinical forms: primary and secondary BMS. The primary BMS is essential or idiopathic, in which the organic local/systemic causes cannot be identified and a neuropathological cause is likely. The diagnosis of primary BMS depends mainly on exclusion of etiological factors. The secondary BMS is caused by local, systemic, and/or psychological factors; thus, its diagnosis depends on identification of the exact causative factor. When local, systemic or psychological factors are present, treatment or elimination of these factors usually results in a significant clinical improvement of BMS symptoms. Vitamin, zinc, or hormone replacement therapy has been found to be effective for

Introduction

Burning mouth syndrome (BMS) is typically described by the patients as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. It occurs more commonly in middle-aged and elderly women, with an overall prevalence ranging from 0.7% to 7% and a prevalence up to 12% to 18% for post-menopausal women with BMS (1–6). BMS often affects the tongue (particularly the tip and lateral borders), lips, and hard and soft palate. In addition to a burning sensation, the patients may present unremitting oral mucosal pain, dysgeusia, and xerostomia (1).

Diagnostic criteria

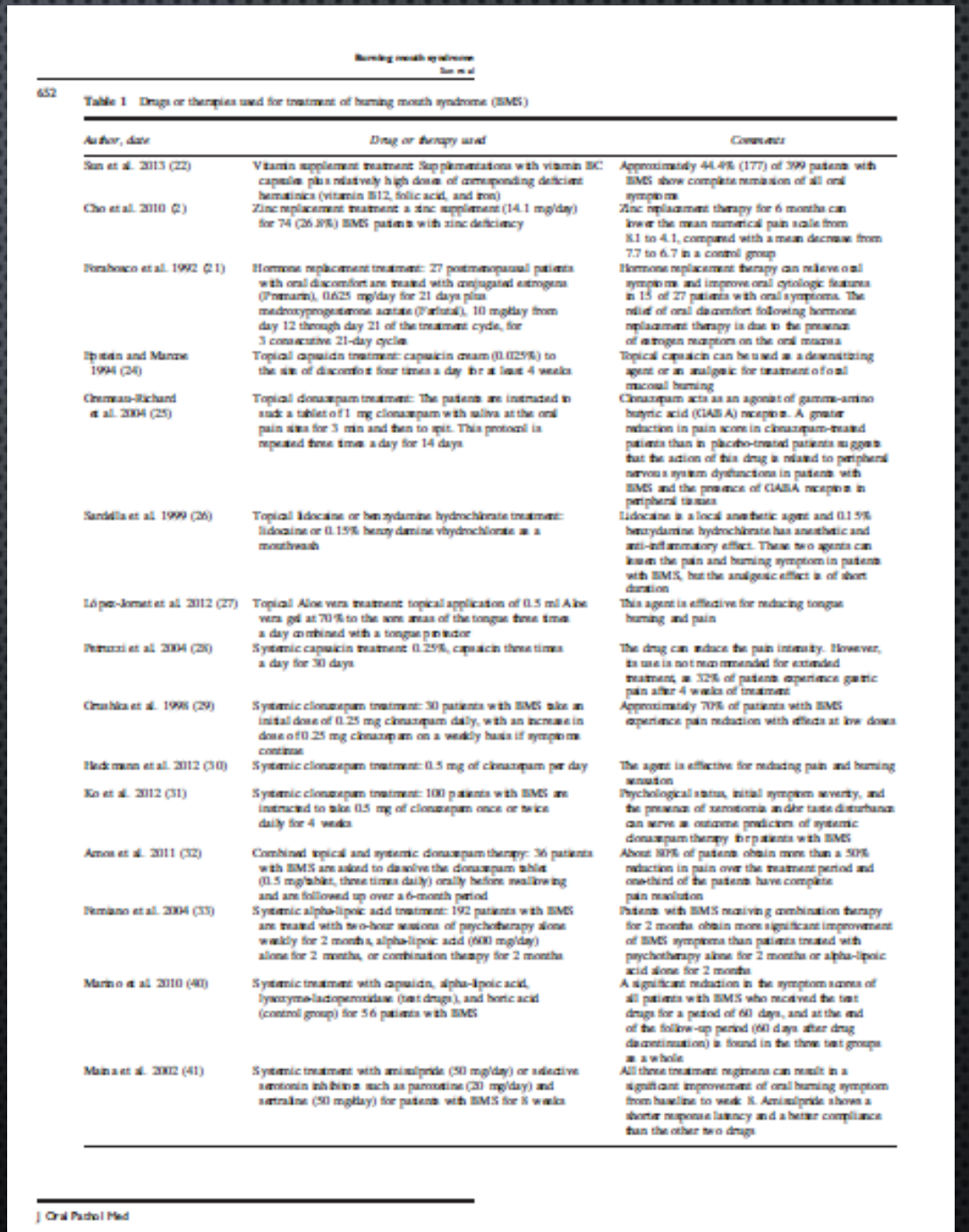
The diagnosis of BMS needs a careful analysis of the symptom pattern experienced by each patient. The main symptoms of oral burning or pain should be experienced deep within the oral mucosa, unremitting for at least 4–6 months, and continuous throughout almost all the day.

MANAGEMENT CONSENSUS

TREAT THE PATIENT -HOLISTIC CARE WITH INFORMED EDUCATION

- MANAGE PATIENTS EXPECTATIONS
- EXPLAIN DIAGNOSIS
- EXCLUDE CAUSES FOR BMD CONFIRM DIAGNOSIS BMS
  - RECTIFY NUTRITIONAL DEFICIENCIES (B COMPLEX, ZINC,
  - ANXIOLYSIS
- PSYCHOLOGICAL SUPPORT
- MEDICAL INTERVENTIONS
  - TOPICAL
  - SYSTEMIC
- ALTERNATIVE
  - ACUPUNCTURE
  - HYPNOTHERAPY
- OTHER
  - LASER
  - DBS

Tricyclic antidepressants
Alpha-lipoic acid [45]
Hormone replacement therapy
SSRIs
Gabapentin or pregabalin
Topiramate [50]
Olanzapine [51]



Burning mouth syndrome
Soo et al

652

Table 1 Drugs or therapies used for treatment of burning mouth syndrome (BMS)

Author, date	Drug or therapy used	Comments
Sun et al. 2013 (22)	Vitamin supplement treatment: Supplementations with vitamin BC capsules plus relatively high doses of corresponding deficient hematinics (vitamin B12, folic acid, and iron)	Approximately 44.4% (177) of 399 patients with BMS show complete remission of all oral symptoms
Cho et al. 2010 (2)	Zinc replacement treatment: a zinc supplement (14.1 mg/day) for 74 (26.8%) BMS patients with zinc deficiency	Zinc replacement therapy for 6 months can lower the mean numerical pain scale from 8.1 to 4.1, compared with a mean decrease from 7.7 to 6.7 in a control group
Fotinhoco et al. 1992 (21)	Hormone replacement treatment: 27 postmenopausal patients with oral discomfort are treated with conjugated estrogens (Premarin), 0.625 mg/day for 21 days plus medroxyprogesterone acetate (Farlutal), 10 mg/day from day 12 through day 21 of the treatment cycle, for 3 consecutive 21-day cycles	Hormone replacement therapy can relieve oral symptoms and improve oral cytologic features in 15 of 27 patients with oral symptoms. The relief of oral discomfort following hormone replacement therapy is due to the presence of estrogen receptors on the oral mucosa
Epstein and Marcoe 1994 (24)	Topical capsaicin treatment: capsaicin cream (0.025%) to the site of discomfort four times a day for at least 4 weeks	Topical capsaicin can be used as a desensitizing agent or an analgesic for treatment of oral mucosal burning
Grenman-Richard et al. 2004 (25)	Topical clonazepam treatment: The patients are instructed to suck a tablet of 1 mg clonazepam with saliva at the oral pain sites for 3 min and then to spit. This protocol is repeated three times a day for 14 days	Clonazepam acts as an agonist of gamma-amino butyric acid (GABA) receptors. A greater reduction in pain scores in clonazepam-treated patients than in placebo-treated patients suggests that the action of this drug is related to peripheral nervous system dysfunctions in patients with BMS and the presence of GABA receptors in peripheral tissues
Sardella et al. 1999 (26)	Topical lidocaine or benzydamine hydrochlorate treatment: lidocaine or 0.15% benzydamine chydrochloride as a mouthwash	Lidocaine is a local anesthetic agent and 0.15% benzydamine hydrochlorate has anesthetic and anti-inflammatory effect. These two agents can lessen the pain and burning symptoms in patients with BMS, but the analgesic effect is of short duration
López-Jornet et al. 2012 (27)	Topical Aloe vera treatment: topical application of 0.5 ml Aloe vera gel at 70% to the sore areas of the tongue three times a day combined with a tongue protector	This agent is effective for reducing tongue burning and pain
Petruzzi et al. 2004 (28)	Systemic capsaicin treatment: 0.25%, capsaicin three times a day for 30 days	The drug can reduce the pain intensity. However, its use is not recommended for extended treatment, as 32% of patients experience gastric pain after 4 weeks of treatment
Grushka et al. 1998 (29)	Systemic clonazepam treatment: 30 patients with BMS take an initial dose of 0.25 mg clonazepam daily, with an increase in dose of 0.25 mg clonazepam on a weekly basis if symptoms continue	Approximately 70% of patients with BMS experience pain reduction with effects at low doses
Heckmann et al. 2012 (30)	Systemic clonazepam treatment: 0.5 mg of clonazepam per day	The agent is effective for reducing pain and burning sensation
Ko et al. 2012 (31)	Systemic clonazepam treatment: 100 patients with BMS are instructed to take 0.5 mg of clonazepam once or twice daily for 4 weeks	Psychological status, initial symptom severity, and the presence of xerostomia and/or taste disturbance can serve as outcome predictors of systemic clonazepam therapy for patients with BMS
Arnos et al. 2011 (32)	Combined topical and systemic clonazepam therapy: 36 patients with BMS are asked to dissolve the clonazepam tablet (0.5 mg/tablet, three times daily) orally before swallowing and are followed up over a 6-month period	About 80% of patients obtain more than a 50% reduction in pain over the treatment period and one-third of the patients have complete pain resolution
Femiano et al. 2004 (33)	Systemic alpha-lipoic acid treatment: 192 patients with BMS are treated with two-hour sessions of psychotherapy alone weekly for 2 months, alpha-lipoic acid (600 mg/day) alone for 2 months, or combination therapy for 2 months	Patients with BMS receiving combination therapy for 2 months obtain more significant improvement of BMS symptoms than patients treated with psychotherapy alone for 2 months or alpha-lipoic acid alone for 2 months
Marino et al. 2010 (40)	Systemic treatment with capsaicin, alpha-lipoic acid, lysozyme-lactoperoxidase (test drugs), and boric acid (control group) for 56 patients with BMS	A significant reduction in the symptom scores of all patients with BMS who received the test drugs for a period of 60 days, and at the end of the follow-up period (60 days after drug discontinuation) is found in the three test groups as a whole
Main a et al. 2002 (41)	Systemic treatment with amisulpride (50 mg/day) or selective serotonin inhibitors such as paroxetine (20 mg/day) and sertraline (50 mg/day) for patients with BMS for 8 weeks	All three treatment regimens can result in a significant improvement of oral burning symptom from baseline to week 8. Amisulpride shows a shorter response latency and a better compliance than the other two drugs

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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].

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

Topical treatment

- Clonazepam – anxiolytic drug
- Lidocaine – anaethetic drug
- Capsaicin – atypical analgesic drug
- Doxepin (cream) – tricyclic antidepressant
- Bensidamine – non-steroidal antiinflammatory drug
- Lactopeoxidase – antibacterial drug
- Sulphacrate – protective agent for mucous membrane

Oral administration

- Alpha-lipoic acid – antioxidant
- Capsaicin – atypical analgesic drug
- Clonazepam, chlordiazepoxide - benzodiazepines
- Gabapentin, pregabalin, topiramate – anticonvulsant drugs
- Amitriptyline, imipramine, nortriptyline, dezipramine – tricyclic antidepressants
- Paroxetine, sertraline – selective serotonin reuptake inhibitors
- Trazodone - serotonin antagonist and reuptake inhibitor
- Milnacipran, duloxetine – selective serotonin and norepinephine reuptake inhibitors
- Amisulpride, olanzapine – atypical antipsychotic drugs
- Pramipeksol – dopamine D2 receptor agonist
- Lafutidine – histamine receptor antagonist
- Hypericin
- Pilocarpine, sialor, cevimiline, betanechol - stimulants of saliva secretion
- Proton pump inhibitors

Other methods

- Cognitive-behavioral therapy
- Group therapy
- Electroconvulsive therapy
- Acupuncture
- Laser therapy
- Tongue protector (shield)
- Biofeedback

OPTIMAL TREATMENT FOR BMS BEST EVIDENCE?

- The interventions were grouped into:
  - **Medical**
    - antidepressants and antipsychotics
    - the anticonvulsant gabapentin (one study, 100 participants) **RR 4.00, 95% CI 2.09 to 7.67**
    - topical benzodiazepine (two studies, 111 participants) **MD -1.89 95% CI -2.19 to -1.59. Long term symptom relief was achieved with topical benzodiazepine (one study, 66 participants) MD -1.39 95% CI -1.96 to 0.83**
  - **dietary supplements**
  - **electromagnetic radiation**
  - **psychological therapies**
  - **topical treatments. Short-term symptom relief was demonstrated by:**
  - **Laser energy waves (one study, 58 participants) MD -30.36, 95% CI -44.22 to -16.50,**
  - **physical barriers (one study, 50 participants) MD -1.1 95% CI -2.14 to 0.06,**
- **Conclusions From studies mostly classified as high risk of bias, there is insufficient evidence to support or refute the use of any particular intervention for the management of BMS.**

Evid Based Dent. 2017 Jun 23;18(2):57-58. doi: 10.1038/sj.ebd.6401244. Cochrane Review **Little evidence to support or refute interventions for the management of burning mouth syndrome.** Fischoff DK[1], Spivakovsky S[1].

OPTIMAL TREATMENT FOR BMS BEST EVIDENCE?

Abstract

- **BACKGROUND:** Burning mouth syndrome (BMS) is a term used for oral mucosal pain (burning pain or discomfort in the tongue, lips or entire oral cavity) without identifiable cause. General population prevalence varies from 0.1% to 3.9%. Many BMS patients indicate anxiety, depression, personality disorders and impaired quality of life (QoL). This review updates the previous versions published in 2000 and 2005.
- **OBJECTIVES:** To determine the effectiveness and safety of any intervention versus placebo for symptom relief and changes in QoL, taste, and feeling of dryness in people with BMS.
- **SEARCH METHODS:** Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 31 December 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 11) in the Cochrane Library (searched 31 December 2015), MEDLINE Ovid (1946 to 31 December 2015), and Embase Ovid (1980 to 31 December 2015). We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for ongoing trials. We placed no restrictions on the language or date of publication when searching the electronic databases SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing any treatment against placebo in people with BMS. The primary outcomes were symptom relief (pain/burning) and change in QoL. Secondary outcomes included change in taste, feeling of dryness, and adverse effects.
- **DATA COLLECTION AND ANALYSIS:** We used standard methodological procedures expected by Cochrane. Outcome data were analysed as short-term (up to three months) or long-term (three to six months).
- **MAIN RESULTS:** We included **23 RCTs (1121 ANALYSED PARTICIPANTS**; 83% female). Interventions were categorised as: antidepressants and antipsychotics, anticonvulsants, benzodiazepines, cholinergics, dietary supplements, electromagnetic radiation, physical barriers, psychological therapies, and topical treatments.Only one RCT was assessed at low risk of bias overall, four RCTs' risk of bias was unclear, and 18 studies were at high risk of bias. Overall quality of the evidence for effectiveness was very low for all interventions and all outcomes.Twenty-one RCTs assessed short-term symptom relief. There is very low-quality evidence of benefit from electromagnetic radiation (one RCT, 58 participants), topical benzodiazepines (two RCTs, 111 participants), physical barriers (one RCT, 50 participants), and anticonvulsants (one RCT, 100 participants). We found insufficient/contradictory evidence regarding the effectiveness of antidepressants, cholinergics, systemic benzodiazepines, dietary supplements or topical treatments. No RCT assessing psychological therapies evaluated short-term symptom relief.Four studies assessed long-term symptom relief. There is very low-quality evidence of a benefit from psychological therapies (one RCT, 30 participants), capsaicin oral rinse (topical treatment) (one RCT, 18 participants), and topical benzodiazepines (one RCT, 66 participants). We found no evidence of a difference for dietary supplements or lactoperoxidase oral rinse. No studies assessing antidepressants, anticonvulsants, cholinergics, electromagnetic radiation or physical barriers evaluated long-term symptom relief.Short-term change in QoL was assessed by seven studies (none long-term).The quality of evidence was very low. A benefit was found for electromagnetic radiation (one RCT, 58 participants), however findings were inconclusive for antidepressants, benzodiazepines, dietary supplements and physical barriers.Secondary outcomes (change in taste and feeling of dryness) were only assessed short-term, and the findings for both were also inconclusive.With regard to adverse effects, there is very low-quality evidence that antidepressants increase dizziness and drowsiness (one RCT, 37 participants), and that alpha lipoic acid increased headache (two RCTs, 118 participants) and gastrointestinal complaints (3 RCTs, 138 participants). We found insufficient/contradictory evidence regarding adverse events for anticonvulsants or benzodiazepines. Adverse events were poorly reported or unreported for cholinergics, electromagnetic radiation, and psychological therapies. No adverse events occurred from physical barriers or topical therapy use.
- **AUTHORS' CONCLUSIONS:** Given BMS' potentially disabling nature, the need to identify effective modes of treatment for sufferers is vital. Due to the limited number of clinical trials at low risk of bias, **THERE IS INSUFFICIENT EVIDENCE TO SUPPORT OR REFUTE THE USE OF ANY INTERVENTIONS IN MANAGING BMS**. Further clinical trials, with improved methodology and standardised outcome sets are required in order to establish which treatments are effective. Future studies are encouraged to assess the role of treatments used in other neuropathic pain conditions and psychological therapies in the treatment of BMS.

Cochrane Database Syst Rev. 2016 Nov 18;11:CD002779. **Interventions for treating burning mouth syndrome.** McMillan R[1], Forssell H, Buchanan JA, Glenny AM, Weldon JC, Zakrzewska JM.

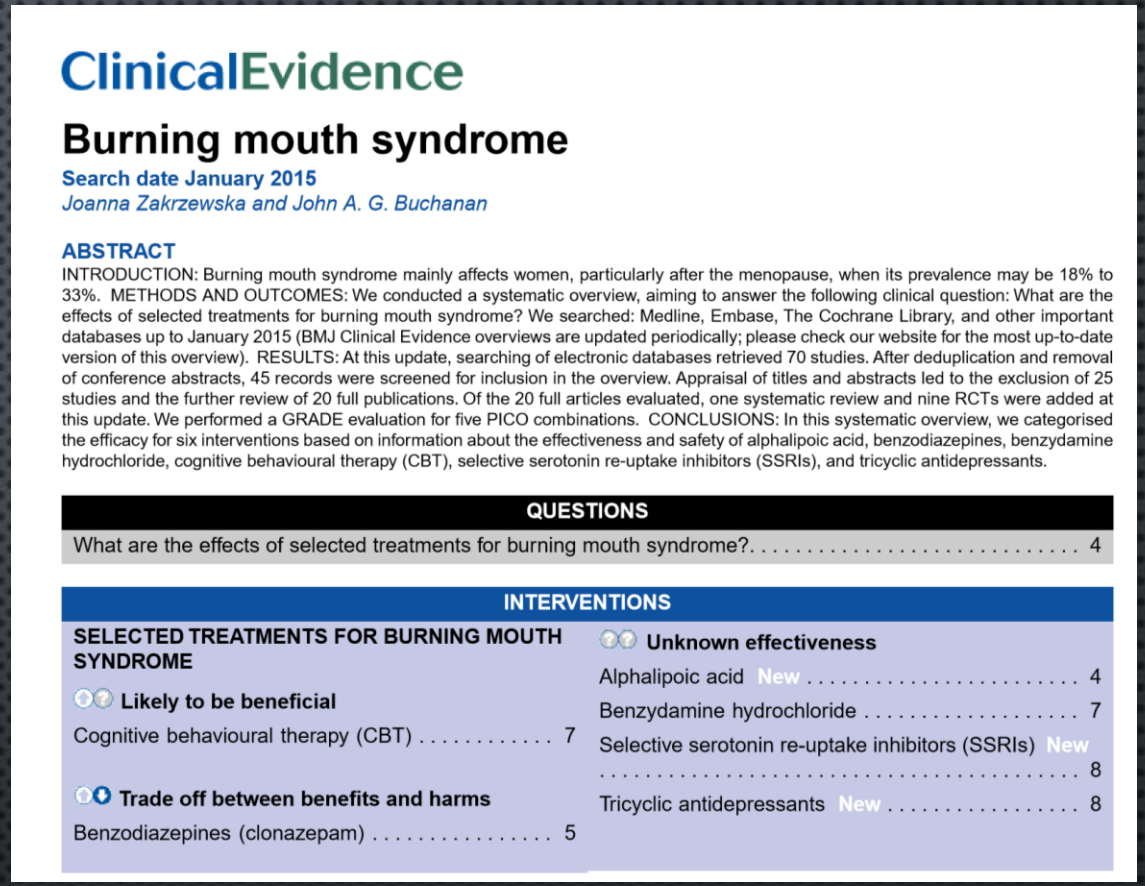
J Oral Rehabil. 2017 Oct;44(10):800-826. doi: 10.1111/joor.12539. Epub 2017 Jul 29.

Pharmacological treatment of oro-facial pain - health technology assessment including a systematic review with network meta-analysis.

Häggman-Henrikson B[1,2,3], Alstergren P[1,4,5], Davidson T[3,6], Högestätt ED[7], Östlund P[2,8], Tranaeus S[2,8], Vitols S[8,9], List T[1,4,5].

This health technology assessment evaluated the efficacy of pharmacological treatment in patients with oro-facial pain. Randomised controlled trials were included if they reported pharmacological treatment in patients ≥18 years with chronic (≥3 months) oro-facial pain. Patients were divided into subgroups: TMD-muscle [temporomandibular disorders (TMD) mainly associated with myalgia]; TMD-joint (TMD mainly associated with temporomandibular joint pain); and burning mouth syndrome (BMS). The primary outcome was pain intensity reduction after pharmacological treatment. The scientific quality of the evidence was rated according to GRADE. An electronic search in PubMed, Cochrane Library, and EMBASE from database inception to 1 March 2017 combined with a handsearch identified 1552 articles. After screening of abstracts, 178 articles were reviewed in full text and 57 studies met the inclusion criteria. After risk of bias assessment, 41 articles remained: 15 studies on 790 patients classified as TMD-joint, nine on 375 patients classified as TMD-muscle and 17 on 868 patients with BMS. Of these, eight studies on TMD-muscle, and five on BMS were included in separate network meta-analysis. The narrative synthesis suggests that NSAIDs as well as corticosteroid and hyaluronate injections are effective treatments for TMD-joint pain. **The network meta-analysis showed that clonazepam and capsaicin reduced pain intensity in BMS, and the muscle relaxant cyclobenzaprine, for the TMD-muscle group**. In conclusion, based on a limited number of studies, evidence provided with network meta-analysis showed that clonazepam and capsaicin are effective in treatment of BMS and that the muscle relaxant cyclobenzaprine has a positive treatment effect for TMD-muscle pain.

- We searched for evidence from RCTs and systematic reviews of RCTs on selected interventions in people with burning mouth syndrome.
- **Cognitive behavioural therapy may improve symptom intensity compared with placebo** in people with burning mouth syndrome, although we found no good-quality studies.
- **Clonazepam may reduce pain compared with placebo** in people with burning mouth syndrome, but even when it is administered topically it may be absorbed systemically, with increased risk of dependence over time.
- **We don't know whether tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or benzydamine hydrochloride can improve symptoms of burning mouth, as we found few studies.**
- Given the lack of knowledge about mechanisms involved, both local and centrally acting treatments may be effective. Given its significant impact on quality of life and mood, antidepressants may have a role to play.
- **There is insufficient evidence to show that the dietary supplement alphalipoic acid**, used in a variety of forms, has an impact on symptom relief.
- Concerning the evidence overall, it was important to ascertain that the diagnostic criteria were fulfilled. Outcome measures are varied and, even if the same ones are used, they are applied differently, thus making comparisons of trials difficult.There is a high risk of bias in the majority of studies.



ClinicalEvidence

Burning mouth syndrome

Search date January 2015

Joanna Zakrzewska and John A. G. Buchanan

ABSTRACT

INTRODUCTION: Burning mouth syndrome mainly affects women, particularly after the menopause, when its prevalence may be 18% to 33%. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of selected treatments for burning mouth syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2015 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 70 studies. After deduplication and removal of conference abstracts, 45 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 25 studies and the further review of 20 full publications. Of the 20 full articles evaluated, one systematic review and nine RCTs were added at this update. We performed a GRADE evaluation for five PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for six interventions based on information about the effectiveness and safety of alphalipoic acid, benzodiazepines, benzydamine hydrochloride, cognitive behavioural therapy (CBT), selective serotonin re-uptake inhibitors (SSRIs), and tricyclic antidepressants.

QUESTIONS

INTERVENTIONS

SELECTED TREATMENTS FOR BURNING MOUTH SYNDROME

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

SYSTEMIC CAPSAICIN!

- J Oral Pathol Med. 2004 Feb;33(2):111-4. **Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study** Petruzzi M[1], Lauritano D, De Benedittis M, Baldoni M, Serpico R.
- **BACKGROUND:** Burning mouth syndrome (BMS) is a major diagnostic and therapeutic problem. Systemic and topical treatments (capsaicin, lidocaine, anti-histamines, sucralfate and benzydiamine) have been tried, but they appear to be inadequate. Topical capsaicin is bitter, may cause burning and has low therapeutic efficacy. We hypothesized that systemic administration of capsaicin could reduce the limitations of topical administration and have better therapeutic efficacy; this hypothesis was tested in a controlled trial.
- **METHODS:** Systemic oral capsaicin 0.25% was used for patients with BMS, recruited in our single centre. After the diagnosis of BMS, patients were dentally and medically examined. They were alternatively assigned to treatment with capsaicin or to a shape/smell/taste/color matched placebo. The severity of symptoms was scored at trial entry and 30 days thereafter by investigators who were unaware of the assigned intervention. The visual analogical scale (VAS) measure was used to score the severity of pain, and results for the treated and untreated groups were compared by Fisher's exact test. Analysis was performed by intention-to-treat. Statistical significance was considered for values of $P < 0.05$. Data are expressed as mean +/- SD.
- **RESULTS:** Fifty patients were enrolled (25 assigned to systemic capsaicin and 25 to placebo). The VAS score was significantly lower in treated patients (5.84 +/- 1.17) as compared to the placebo-control group (6.24 +/- 0.96). The use of systemic capsaicin implied significant gastric toxicity (referred gastric pain) with eight cases (32%) documented in the treatment group as compared to zero cases (0%) in the placebo control group.
- **CONCLUSION:** Systemic capsaicin is therapeutically effective for the short-term treatment of BMS but. This preliminary study suggests that more, adequately powered, randomized controlled trials are n**major gastrointestinal side-effects may threaten its large-scale, long-term use**ecessary and worthy to come to a definitive assessment of this matter.

MANAGEMENT OF COMORBID PSYCHOLOGICAL ISSUES ANXIETY, DEPRESSION ETC

- Non pharmacological
  - Psychotherapy (cognitive behavioral modification, relaxation) [45]
  - Education
  - Counselling
  - Interpersonal skills -reassurance
  - Hypnosis
  - Acupuncture
  - TENS
- Pharmacological anti-anxiety treatments
  - Single drug sedation (conscious)
  - Multiple drug sedation (deep)
  - Medical treatment f underlying anxiety disorders

Thirty-five patients with primary BMS were included in the study: 31 % of them had a DN4i score in favour of neuropathic pain and 34.3 % had a HADS overall score in favour of anxiety and depressive disorder.

Bilateral BMS had higher levels of psychological distresses compared with the unilateral group.

Vitamins recommended for Migraine

- Riboflavin 400ug BD
- Q10 co enzyme A 100ug TDS
- Magnesium 550ug/day Or Melatonin 4ug90mins before bed

Am J Clin Dermatol. 2016 Apr;17(2):171-8. doi: 10.1007/s40257-015-0170-4.
Primary Burning Mouth Syndrome: A Questionnaire Study of Neuropathic and Psychological Components. Sevrain M[1], Brenaut E[2,3], Le Toux G[4], Misery L[1,5].
Int J Oral Maxillofac Surg. 2020 Jan;49(1):38-43. doi: 10.1016/j.ijom.2019.06.013. Epub 2019 Jun 21.
Comparison of clinical characteristics between burning mouth syndrome patients with bilateral and unilateral symptoms.
Kim MJ[1], Kim J[1], Kho HS[2].

MANAGEMENT PSYCHOLOGICAL

Psychological interventions show great promise in treating patients with BMS. Weekly one-hour sessions of cognitive behavioral therapy lasting for 12-15 week significantly reduced BMS symptoms in all study patients compared to placebo control group, with an estimated 27% of patients remaining symptom-free at 6 month follow up (none in placebo group)[2].

Weekly group psychotherapy administered for three consecutive months achieved symptom improvement in 70% of the patients[3].

Femiano et al[4] noted a statistically significant symptom improvement with cognitive psychotherapy (40%),

1. Bergdahl J, Anneroth G, Perris H. Cognitive therapy in the treatment of patients with resistant burning mouth syndrome: a controlled study. J Oral Pathol Med 1995; 24: 213-215 [PMID: 7616460]
2. Netto FO, Diniz IM, Grossmann SM, de Abreu MH, do Carmo MA, Aguiar MC. Risk factors in burning mouth syndrome: a case-control study based on patient records. Clin Oral Investig 2011; 15: 571-575 [PMID: 20440632]
3. Miziara ID, Filho BC, Oliveira R, Rodrigues dos Santos RM. Group psychotherapy: an additional approach to burning mouth syndrome. J Psychosom Res 2009; 67: 443-448 [PMID: 19837207]
4. Femiano F, Gombos F, Scully C. Burning Mouth Syndrome: open trial of psychotherapy alone, medication with alphalipoic acid (thioctic acid), and combination therapy. Med Oral 2004; 9: 8-13 [PMID: 14704612

- Homeopathic
  - Arnica reduces bruising and swelling
- Hypnotherapy
  - self hypnosis
  - induced hypnosis
- Biofeedback
  - training in changing function to reduce pain
- Tens shown to reduce the discomfort of ID blocks
- Pet therapy

MANAGEMENT TOPICAL MEDICATIONS

Topical Medical interventions

- Clonazepam (low-dose) dissolvable wafers (may be better than tablets) [45] A literature review by Miziara et al of treatment studies indicated that topical clonazepam, although not a cure, offers short-term improvement of burning mouth syndrome, with studies on alpha-lipoic acid and cognitive therapy showing their effectiveness as well. However, the investigators found few randomized, controlled studies demonstrating the long-term effectiveness of alpha-lipoic acid, although they reported that research did indicate that cognitive therapy produces lasting results.[53]
  - Capsaicin
    - Topical capsaicin [1]
    - Intermittent oral capsaicin [46]
  - CBD oil
  - Local anaesthetic agents
  - Pregabalin No evidence

CLONAZEPAM

Studies have shown a decrease of pain levels with clonazepam, a gamma amino butyric acid (GABA) agonist. GABA is a neurotransmitter possibly involved with taste,[46] reinforcing the evidence that BMS is probably a neuropathic pain condition involved with the gustatory system.

Grushka et al. reported a 70% reduction in pain levels with the oral administration of clonazepam, 0.5–1.5 mg/day in divided doses to a maximum of 3 mg/day.

Heckmann etal., demonstrated in a double-blind randomized controlled study that treatment with clonazepam 0.5 mg/day significantly reduced pain levels in BMS patients compared to controls after 9 weeks of treatment. However, there was no follow-up.

Interestingly, Ko etal. (2012) evaluated the outcome predictors affecting the efficacy of clonazepam and they found that those with greater symptom severity of taste disturbance and xerostomia at baseline, showed better therapeutic results after clonazepam therapy than those without those complaints; and patients with tongue symptoms had a significantly decrease in pain compared to those with intraoral symptoms excluding the tongue.

Topical

Woda et al., in a study with 25 patients, dissolved clonazepam 1.0 mg, 3 times/day for 3 min in the mouth with 66% of patients reporting a reduction in symptoms, and 29% reporting partial reduction in symptoms after 6 months.[70] Gremeau-Richard et al. (2004), in a randomized placebo-controlled study instructed the patients to suck a tablet of 1 mg of clonazepam (or placebo) and hold their saliva near the pain location without swallowing for 3 min and then tospit. This protocol was repeated 3 times a day for 14 days. The authors then concluded that topical administration of clonazepam improves intraoral burning sensation in some but not in all BMS patients.

Rodríguez de Rivera Campillo etal. also reported benefits of using clonazepan topically.

J Oral Facial Pain Headache. 2017 Summer;31(3):257-263. doi: 10.11607/ofph.1754. **Topical Clonazepam Solution for the Management of Burning Mouth Syndrome: A Retrospective Study.** Kuten-Shorrer M, Treister NS, Stock S, Kelley JM, Ji YD, Woo SB, Lerman MA, Palmason S, Sonis ST, Villa A.

TOPICAL CLONAZEPAM

- **OBJECTIVES:** CLONAZEPAM HAS BEEN USED IN THE TREATMENT OF BURNING MOUTH SYNDROME (BMS) FOR SEVERAL DECADES. WE CONDUCTED A META-ANALYSIS TO INVESTIGATE THE EFFICACY OF CLONAZEPAM IN THE TREATMENT OF BMS.
- **METHODS:** WE CONDUCTED A SEARCH OF THE PUBMED, MEDLINE, EMBASE, WEB OF SCIENCE (TS), AND THE COCHRANE LIBRARY DATABASES FOR RELEVANT STUDIES THAT MET OUR ELIGIBILITY CRITERIA (UP TO SEPTEMBER 22, 2015). STATISTICAL ANALYSES WERE CONDUCTED USING REVMAN 5.2 AND STATA 11.0 SOFTWARE.
- **RESULTS:** THREE RANDOMIZED CONTROLLED TRIALS (RCTS) AND TWO HIGH-QUALITY CASE-CONTROL STUDIES INVOLVING 195 BMS PATIENTS WERE SELECTED FOR THIS STUDY. OUR RESULTS SHOW THAT CLONAZEPAM CAN REDUCE THE ORAL PAIN SENSATION IN PATIENTS WITH BMS (WMD: -3.72, 95% CI: -4.57, -2.86; P < 0.05; FOR ALL FIVE STUDIES). A POSITIVE THERAPEUTIC EFFECT WAS DEMONSTRATED FOR BOTH SHORT-TERM (≤10 WEEKS) APPLICATION (WMD: -1.44, 95% CI: -2.06, -0.82; P < 0.05) AND LONG-TERM (>10 WEEKS) APPLICATION (WMD: -4.50, 95% CI: -4.98, -4.03; P < 0.05). BOTH TOPICAL (WMD: -1.50, 95% CI: -2.14, -0.85; P < 0.05) AND SYSTEMIC (WMD: -3.81, 95% CI: -4.63, -2.98; P < 0.05) ADMINISTRATION OF CLONAZEPAM WERE CONFIRMED TO BE EFFECTIVE.
- **CONCLUSION: CLONAZEPAM IS EFFECTIVE IN INDUCING SYMPTOM REMISSION IN PATIENTS WITH BMS.**

Topical·Clonazepam·for·Burning·Mouth·Syndrome·(BMS)¶

This· prescription· is· for· symptomatic· treatment· of· burning· mouth· syndrome.· Clonazepam· is· a· benzodiazepine·and·often·being·used·as·an·anxiolytic,·hypnotic·and·anticonvulsant·agent.·¶

Clonazepam·expresses·the·analgesic·effect·in·BMS·by·potentiating·the·inhibitory·gamma-aminobutyric· acid· (GABA)· signalling· pathways· and· antagonise· the· hyperexcitability· of· neurotransmission.· Clonazepam·binding·to·the·$GABA_A$·receptor·acts·as·a·positive·allosteric·modulator·by·facilitates·the· opening·of·GABA-activated·chloride·channels·and·reduce·the·firing·of·action·potentials.·The·$GABA_A$· receptor· is· widely· found· in· central· nervous· systems· and· peripheral· tissues.· Clonazepam· is· rapidly· absorbed·after·oral·administration,·reaching·maximum·plasma·concentrations·within·2·to·4·hours.· This·change·may·require·regular·use·of·clonazepam·over·two·weeks·and·above.·You·are·advised·to· review· regularly· with· your· doctor· to· find· the· right· dose· for· you· for· optimal· analgesic· effect· and· minimal·adverse·drug·reactions.·¶

Clonazepam·dosage¤	Frequency¤	Instructions¤
0.25mg·¤	Twice·daily·or·¶	To·suck·the·tablet;·¶
0.50mg·¤	Three·times·daily;¶	Retain·saliva·in·mouth·near·the·pain·sites·for·
1.00·mg·¤	After·meal¤	3·to·5·minutes;·¶
		Followed·by·expectorating·of·saliva¤

There·is·no·need·to·increase·the·dose·further·if·the·pain·has·settles·and·may·be·reduced·to·twice·daily· topically·usage.¶

Despite·the·promising·results·of·clonazepam·for·pain·relief·symptoms,·there·are·possible·side·effects· that·may·occur·at·low·doses.·If·any·of·the·following·side·effects·continue·or·become·troublesome,·you· are·advised·to·seek·immediate·review·with·your·doctor.·Below·are·the·reported·adverse·drug·reactions· of·topical·clonazepam·(Gremeau-Richard·et·al.,·2004;·Kuten-Shorrer·et·al.,·2017).·¶

Adverse·Drug·Reaction¤	Symptoms¤
Drowsiness·/·Sedation·¤	Decreased·in·alertness;·Feeling·sleepy·during·the· day.·¶ DO·NOT·DRIVE·A·MOTOR·VEHICLE·OR·OPERATE· MACHINERY·WHEN·YOU·HAVE·THIS·SYMPTOM·¤
Dizziness·/·Ataxia¤	Loss· of· balance;· Unsteadiness;· Instability,· Feeling·of·spinning.·¶ DO·NOT·DRIVE·A·MOTOR·VEHICLE·OR·OPERATE· MACHINERY·WHEN·YOU·HAVE·THIS·SYMPTOM¤
Altered·mental·status/·Euphoric·behaviour·¤	Confusion;·Altered·mood;·Anxiety¤
Burning·sensation·¤	Increased·in·burning·feeling·¤
Dry·mouth·¤	Feeling·of·dryness·in·the·mouth·but·no·clinical· saliva·flow·changes.·¤
Gastrointestinal·disorder¤	Nausea;·Gastro-oesophageal·reflux¤
Others¤	Skin·reaction,·Spasmophilia¤

¶

Other· possible· side· effects· (NICE· BNF· 2019)· are· alopecia;· concentration· impaired;°coordination· abnormal;· increased· risk· of· fall;· increased· risk· of· fracture;°muscle· tone· decreased;· nystagmus;· seizures;· tremor;· sexual· dysfunction;· speech· impairment;· vertigo;· vision· disorders;· withdrawal·

Oral Dis. 2016 Sep;22(6):503-11. doi: 10.1111/odi.12422. Epub 2016 Jan 20. **Efficacy evaluation of clonazepam for symptom remission in burning mouth syndrome: a meta-analysis.** Cui Y[1], Xu H[1,2], Chen FM[1], Liu JL[1], Jiang L[1], Zhou Y[1], Chen QM[1].

TOPICAL CAPSAICIN (TOBASCO SAUCE!)

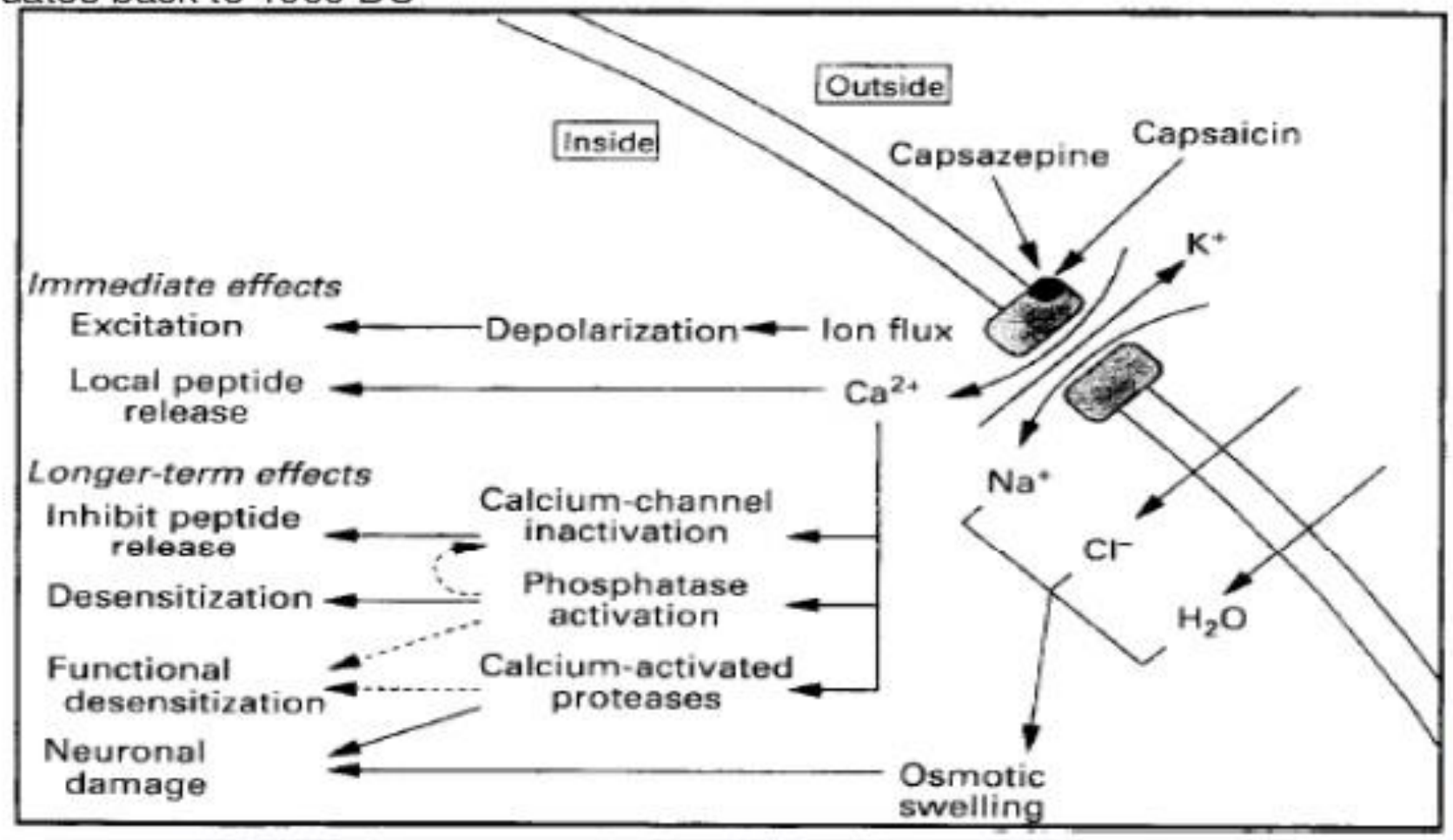
Burning mouth syndrome is defined as an intraoral burning sensation for which no medical or dental cause can be found. Recently, researchers have demonstrated an altered trophism of the small nerve fibres and alterations in the numbers of TRPV-1 vanilloid receptors. Capsaicin is a molecule that is contained in hot peppers and is specifically detected by TRPV-1 vanilloid receptors that are distributed in the oral mucosae. We aimed at verifying if **topical capsaicin** could prove to be an effective treatment of Burning Mouth Syndrome. A group of 99 BMS patients were recruited. We subdivided the BMS patients into two groups: the collaborative patients, who expressed a predominantly neuropathic pattern of symptoms, and the non-collaborative patients, who were characterised by stronger psychogenic patterns of the syndrome. Both groups underwent topical therapy with capsaicin in the form of a **mouthrinse 3 times a day for a long period. After 1 year of treatment, the final overall success rate was approximately 78%,** but with a significant difference in the success rates of the two groups of patients (87% and 20% among the collaborative and non-collaborative patients, respectively; p=0.000).

The **use of topical capsaicin can improve the oral discomfort of BMS patients, especially during the first month of therapy, but it is more effective for those patients in which the neuropathic component of the syndromeis predominant**. Our hypothesis is that chronic stimulation with capsaicin leads to decreases in burningsymptoms. This phenomenon is called desensitisation and is accompanied by substantial improvements in oral symptoms.

J Biol Regul Homeost Agents. 2017 Apr-Jun;31(2 Suppl 1):89-95. **A burning therapy for burning mouth syndrome: preliminary results with the administration of topical capsaicin.** Azzi L[1], Croveri F[1], Pasina L[2], Porrini M[3], Vinci R[4], Manfredini M[1], Tettamanti L[1], Tagliabue A[1], Silvestre-Rangil J[5], Spadari F[3].

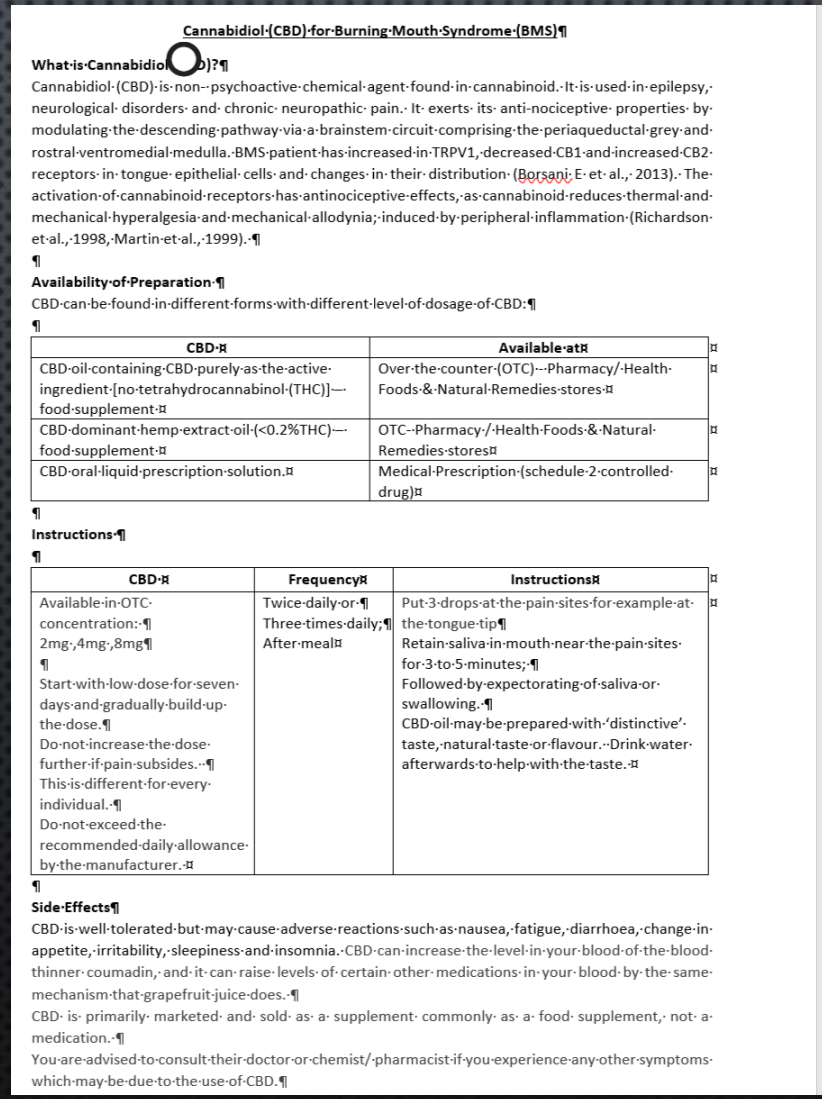
Capsacian

- Capsaicinoids first recorded use, in the form of chilies, for the treatment of pain dates back to 4000 BC



TOPICAL CANNIBIDIOL (CBD)

- ‘BUT I HAVE EXPERIMENTED ON MYSELF WITH CBD OIL (SWISH FOR 30/30 SEC) AND EXPECTORATE, AND I DO GET IMMEDIATE RELIEF WHICH LASTS LONG ENOUGH FOR ME TO GET TO SLEEP.’
- START WITH .025%. AS AN ALTERNATIVE YOU CAN INSTRUCT THE PATIENT TO USE TABASCO SAUCE IN A 1 TO 4 DILUTION WITH WATER. THEY CAN INCREASE THE DILUTION AS TOLERABLE. AS WITH MOST THERAPIES FOR BURNING MOUTH, THE EFFICACY IS LOW TO MODERATE.



Cannabidiol·(CBD)·for·Burning·Mouth·Syndrome·(BMS)¶

What·is·Cannabidiol·(CBD)?¶

Cannabidiol·(CBD)·is·non-·psychoactive·chemical·agent·found·in·cannabinoid.·It·is·used·in·epilepsy,·neurological· disorders· and· chronic· neuropathic· pain.· It· exerts· its· anti-nociceptive· properties· by·modulating·the·descending·pathway·via·a·brainstem·circuit·comprising·the·periaqueductal·grey·and·rostral·ventromedial·medulla.·BMS·patient·has·increased·in·TRPV1,·decreased·CB1·and·increased·CB2·receptors· in· tongue· epithelial· cells· and· changes· in· their· distribution· (Borsani· E· et· al.,· 2013).· The·activation·of·cannabinoid·receptors·has·antinociceptive·effects,·as·cannabinoid·reduces·thermal·and·mechanical·hyperalgesia·and·mechanical·allodynia;·induced·by·peripheral·inflammation·(Richardson·et·al.,·1998,·Martin·et·al.,·1999).·¶

¶

Availability·of·Preparation·¶

CBD·can·be·found·in·different·forms·with·different·level·of·dosage·of·CBD:¶

¶

CBD·¤	Available·at¤
CBD·oil·containing·CBD·purely·as·the·active·ingredient·[no·tetrahydrocannabinol·(THC)]·—·food·supplement·¤	Over·the·counter·(OTC)·—·Pharmacy/·Health·Foods·&·Natural·Remedies·stores·¤
CBD·dominant·hemp·extract·oil·(<0.2%THC)·—·food·supplement·¤	OTC·-·Pharmacy·/·Health·Foods·&·Natural·Remedies·stores¤
CBD·oral·liquid·prescription·solution.¤	Medical·Prescription·(schedule·2·controlled·drug)¤

¶

Instructions·¶

¶

CBD·¤	Frequency¤	Instructions¤
Available·in·OTC·concentration:·¶ 2mg·,4mg·,8mg¶ ¶ Start·with·low·dose·for·seven·days·and·gradually·build·up·the·dose.¶ Do·not·increase·the·dose·further·if·pain·subsides.··¶ This·is·different·for·every·individual.·¶ Do·not·exceed·the·recommended·daily·allowance·by·the·manufacturer.·¤	Twice·daily·or·¶ Three·times·daily;¶ After·meal¤	Put·3·drops·at·the·pain·sites·for·example·at·the·tongue·tip¶ Retain·saliva·in·mouth·near·the·pain·sites·for·3·to·5·minutes;·¶ Followed·by·expectorating·of·saliva·or·swallowing.·¶ CBD·oil·may·be·prepared·with·‘distinctive’·taste,·natural·taste·or·flavour.··Drink·water·afterwards·to·help·with·the·taste.·¤

¶

Side·Effects¶

CBD·is·well·tolerated·but·may·cause·adverse·reactions·such·as·nausea,·fatigue,·diarrhoea,·change·in·appetite,·irritability,·sleepiness·and·insomnia.·CBD·can·increase·the·level·in·your·blood·of·the·blood·thinner·coumadin,·and·it·can·raise·levels·of·certain·other·medications·in·your·blood·by·the·same·mechanism·that·grapefruit·juice·does.·¶

CBD· is· primarily· marketed· and· sold· as· a· supplement· commonly· as· a· food· supplement,· not· a·medication.·¶

You·are·advised·to·consult·their·doctor·or·chemist/·pharmacist·if·you·experience·any·other·symptoms·which·may·be·due·to·the·use·of·CBD.¶

Efficacy·and·Safety·of·CBD·¶

There·is·no·evidence-based·medicine·research·on·the·use·of·CBD·for·BMS.·The·above·suggestion·is·based·on·anecdotal·records·of·patients·with·BMS.·There·is·on-going·research·on·the·use·of·topical·CBD·for·other·chronic·neuropathic·pain·of·the·limbs.·¶

¶

The·Legal·Standpoint¶

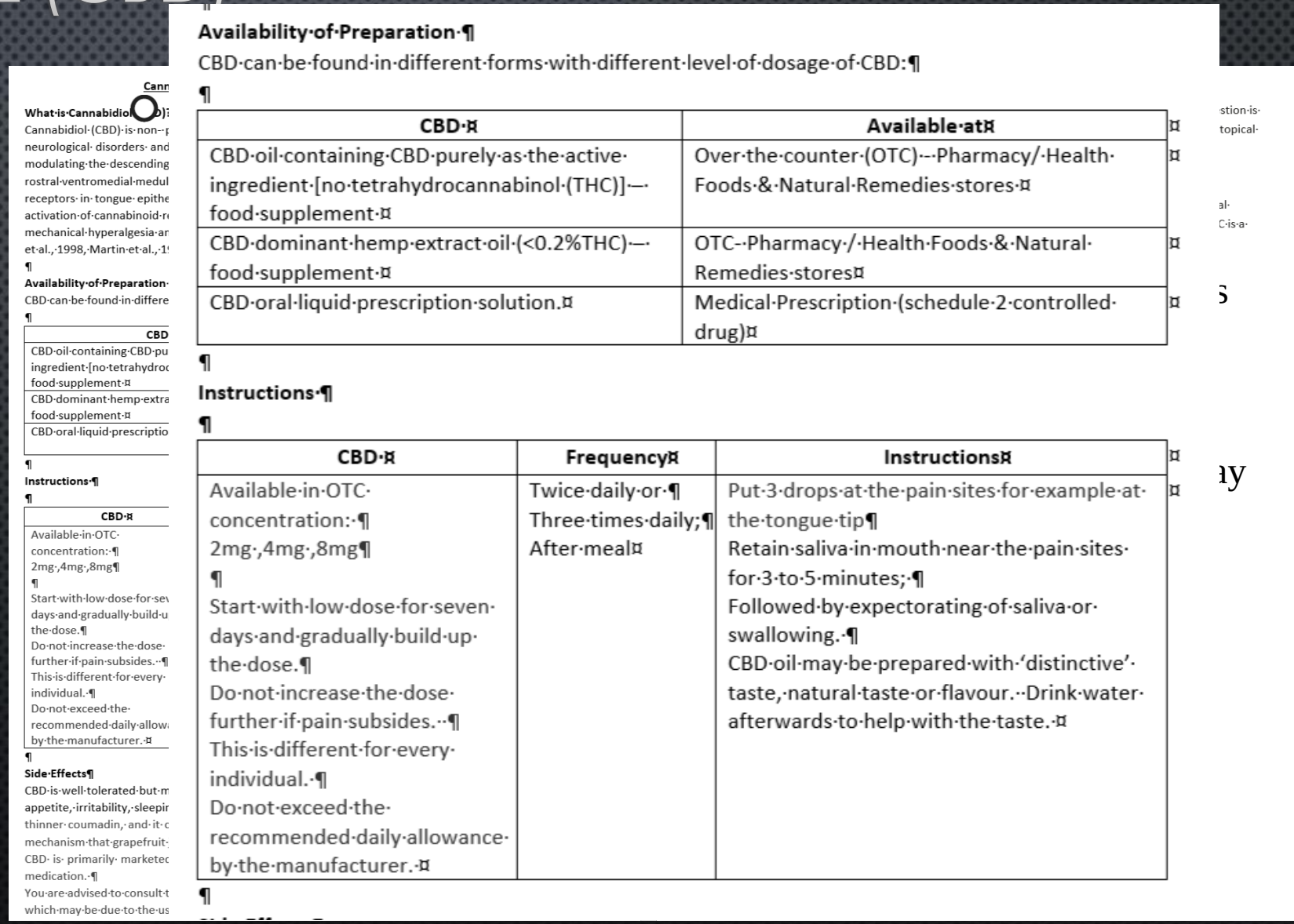
Under·UK·law:·Misuse·of·Drugs·Act·1971·and·Misuse·of·Drugs·Regulations·2001,·CBD·is·legal·provided·that·it·contains·no·more·than·0.2%·THC·which,·due·to·its·psychoactive·effects.·THC·is·a·controlled·substance·under·the·Guidelines.··¶

¶

A literature review, observed trials dosing up to 1500mg/day of oral CBD in human patients, with no consequential adverse reactions, however future clinical studies may be needed to further investigate potential drug interactions with CBD. 9,10 CBD exhibits anticonvulsant, anxiolytic, antipsychotic, anti-inflammatory, antibacterial, and neuroprotective effect

TOPICAL CANNIBIDIOL (CBD)

- ‘BUT I HAVE EXPERIMENTED ON MYSELF WITH CBD OIL (SWISH FOR 30/30 SEC) AND EXPECTORATE, AND I DO GET IMMEDIATE RELIEF WHICH LASTS LONG ENOUGH FOR ME TO GET TO SLEEP.’
- START WITH .025%. AS AN ALTERNATIVE YOU CAN INSTRUCT THE PATIENT TO USE TABASCO SAUCE IN A 1 TO 4 DILUTION WITH WATER. THEY CAN INCREASE THE DILUTION AS TOLERABLE. AS WITH MOST THERAPIES FOR BURNING MOUTH, THE EFFICACY IS LOW TO MODERATE.



Availability·of·Preparation·¶

CBD·can·be·found·in·different·forms·with·different·level·of·dosage·of·CBD:¶

¶

CBD·¤	Available·at¤
CBD·oil·containing·CBD·purely·as·the·active·ingredient·[no·tetrahydrocannabinol·(THC)]·—·food·supplement·¤	Over·the·counter·(OTC)·—·Pharmacy/·Health·Foods·&·Natural·Remedies·stores·¤
CBD·dominant·hemp·extract·oil·(<0.2%THC)·—·food·supplement·¤	OTC·-·Pharmacy·/·Health·Foods·&·Natural·Remedies·stores¤
CBD·oral·liquid·prescription·solution.¤	Medical·Prescription·(schedule·2·controlled·drug)¤

¶

Instructions·¶

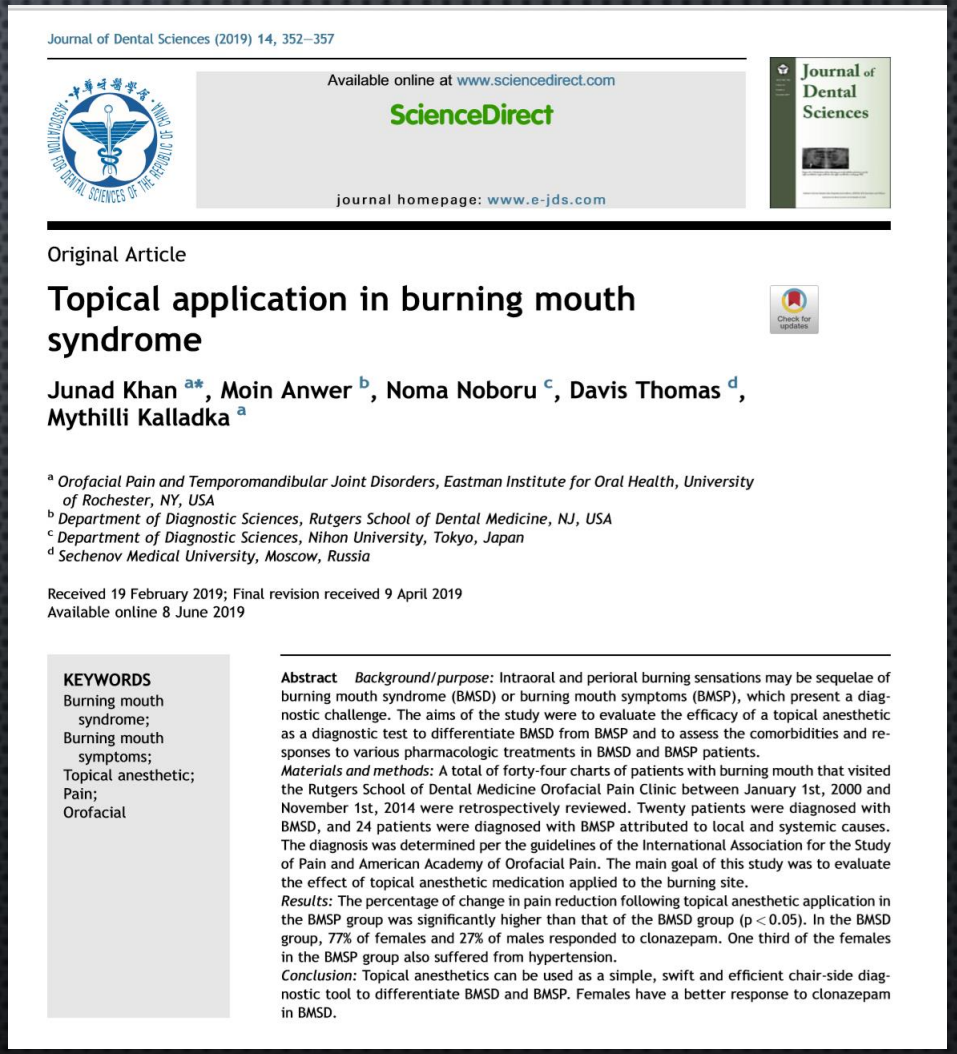
¶

CBD·¤	Frequency¤	Instructions¤
Available·in·OTC·concentration:·¶ 2mg·,4mg·,8mg¶ ¶ Start·with·low·dose·for·seven·days·and·gradually·build·up·the·dose.¶ Do·not·increase·the·dose·further·if·pain·subsides.··¶ This·is·different·for·every·individual.·¶ Do·not·exceed·the·recommended·daily·allowance·by·the·manufacturer.·¤	Twice·daily·or·¶ Three·times·daily;¶ After·meal¤	Put·3·drops·at·the·pain·sites·for·example·at·the·tongue·tip¶ Retain·saliva·in·mouth·near·the·pain·sites·for·3·to·5·minutes;·¶ Followed·by·expectorating·of·saliva·or·swallowing.·¶ CBD·oil·may·be·prepared·with·‘distinctive’·taste,·natural·taste·or·flavour.··Drink·water·afterwards·to·help·with·the·taste.·¤

¶

TOPICAL DESENSITISATION

- BENZYDAMINE AS A MOUTH RINSE IS ALSO CONTROVERSIAL. SARDELLA (1999) IN A DOUBLE-BLIND, RANDOMIZED LONGITUDINAL STUDY FOUND NO SIGNIFICANT EFFICACY BETWEEN PLACEBO/ BENZYDAMINE HYDROCHLORIDE 0.15% ORAL MOUTHWASHES 3 TIMES A DAY FOR 4 WEEKS/NO TREATMENT GROUP



Journal of Dental Sciences (2019) 14, 352–357

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ScienceDirect

journal homepage: www.e-jds.com

Journal of Dental Sciences

Original Article

Topical application in burning mouth syndrome

Junad Khan [a*], Moin Anwer [b], Noma Noboru [c], Davis Thomas [d], Mythilli Kalladka [a]

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Available online 8 June 2019

KEYWORDS
Burning mouth syndrome;
Burning mouth symptoms;
Topical anesthetic;
Pain;
Orofacial

Abstract *Background/purpose:* Intraoral and perioral burning sensations may be sequelae of burning mouth syndrome (BMSD) or burning mouth symptoms (BMSP), which present a diagnostic challenge. The aims of the study were to evaluate the efficacy of a topical anesthetic as a diagnostic test to differentiate BMSD from BMSP and to assess the comorbidities and responses to various pharmacologic treatments in BMSD and BMSP patients.
Materials and methods: A total of forty-four charts of patients with burning mouth that visited the Rutgers School of Dental Medicine Orofacial Pain Clinic between January 1st, 2000 and November 1st, 2014 were retrospectively reviewed. Twenty patients were diagnosed with BMSD, and 24 patients were diagnosed with BMSP attributed to local and systemic causes. The diagnosis was determined per the guidelines of the International Association for the Study of Pain and American Academy of Orofacial Pain. The main goal of this study was to evaluate the effect of topical anesthetic medication applied to the burning site.
Results: The percentage of change in pain reduction following topical anesthetic application in the BMSP group was significantly higher than that of the BMSD group ($p < 0.05$). In the BMSD group, 77% of females and 27% of males responded to clonazepam. One third of the females in the BMSP group also suffered from hypertension.
Conclusion: Topical anesthetics can be used as a simple, swift and efficient chair-side diagnostic tool to differentiate BMSD and BMSP. Females have a better response to clonazepam in BMSD.

INTERVENTIONAL PAIN MANAGEMENT FOR BMS

- **Botoxin injections** these have to be placed at nerve endings with obvious risk of causing temporary 3 month motor palsy to local nerves
- **Neurostimulation**
  - Spinal cord stimulation (not for OFP)
  - Deep brain stimulation
  - Superficial sessional neurostimulation
  - Ganglia implanted neurostimulation
  - Transmagnetic stimulation
- **Ablative techniques**
  - Gasserian Ganglion interventions
    - Pulsed Radiofrequency ablation
    - Thermocoagulation
    - Balloon compression
    - Glycerolysis
  - Sphenopalatine ganglion injections
  - Stereotactic radiosurgery
  - Gamma knife may be indicated If there is medical contraindications to MVD

Not indicated for BMS

BUT ONE STUDY ON BOTULINUM TOXIN FOR BMS

- STUDY ON THREE PATIENTS

Annals of Internal Medicine®

LETTERS | 16 MAY 2017

Botulinum Toxin for Burning Mouth Syndrome

Domenico A. Restivo, MD, PhD; Giuseppe Lauria, MD; Rosario Marchese-Ragona, MD; Riccardo Vigneri, MD

Article, Author, and Disclosure Information

Background: Burning mouth syndrome is characterized by burning pain in the oral mucosa (mainly the tongue and lips) in the absence of medical causes (1). It is also known as oral dysesthesia. It is common; mostly affects women of advanced age; and is often associated with systemic diseases, such as diabetes, nutritional deficiencies, depression, and anxiety (1). The etiopathogenesis of burning mouth syndrome is unclear, although some studies of biopsy specimens suggest an underlying trigeminal small-fiber neuropathy (2). No effective treatment is available for this condition; antidepressants, analgesics, clonazepam, topical capsaicin, and psychotherapy have...

PHOTOBIOMODULATION

- Near infrared irradiation of the stellate ganglion, to inhibit sympathetic discharge and improve blood flow to the tongue in glossodynia (still experimental) [47]
- Laser therapy [48, 49]Near infrared irradiation of the stellate ganglion, to inhibit sympathetic discharge and improve blood flow to the tongue in glossodynia (still experimental) [47] Juliana Cassol Spanemberg ; José López López ; Maria Antonia Zancanaro de Figueiredo ; Karen Cherubini ; Fernanda Gonçalves Salum J. Biomed. Opt. 20(9), 098001 (Sep 11, 2015).
- Abstract. The aim of the present study was to assess the effect of low-level laser therapy (LLLT) in the treatment of burning mouth syndrome (BMS). A diode laser was used in 78BMS patients who were randomly assigned into four groups: IR1W, n=20 (830 nm, 100 mW, 5 J, 176 J/cm2, 50 s, LLLT weekly sessions, 10 sessions); IR3W, n=20 (830 nm, 100 mW, 5 J, 176 J/cm2, 50 s, three LLLT weekly sessions, 9 sessions); red laser, n=19 (685 nm, 35 mW, 2 J, 72 J/cm2, 58 s, three LLLT weekly sessions, 9 sessions); and control-group (CG), n=19. Symptoms were assessed at the end of the treatment and eight weeks later; quality of life related to oral health was assessed using the Oral Health Impact Profile (OHIP-14). Statistical analysis was carried out using repeated measures analysis of variance followed by the posthoc Tukey test. There was significant reduction of the symptoms in all groups at the end of the treatment, which was maintained in the follow-up. The scores of the IR1W and IR3W laser groups differed significantly from those of the CG.
- **There was also a decrease in the OHIP-14 scores in the four groups. The IR3W laser group scores differed significantly from those of the CG. LLLT reduces the symptoms of BMS and may be an alternative therapeutic strategy for the relief of symptoms in patients with BMS**

PHOTOBIOMODULATION

- Group A (laser treatment) was composed of 43 patients while group B (sham therapy) of 42 patients.
- Patients treated with PBMT showed a significant decrease in symptoms (p=0.0008) and improved quality of life related to oral health (p=0.0002).
- Conclusions: PBMT has demonstrated to have a positive effect in relieving BMS symptoms and in improving a patient's overall quality of life.
- No significant difference in pain but improved OHIP 14?

Journal section: Oral Medicine and Pathology
Publication Types: Research

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http://dx.doi.org/doi:10.4317/medoral. 23143

Efficacy of the photobiomodulation therapy in the treatment of the burning mouth syndrome

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Accepted: 07/07/2019

Bardellini E, Amadori F, Conti G, Majorana A. Efficacy of the photobiomodulation therapy in the treatment of the burning mouth syndrome. Med Oral Patol Oral Cir Bucal. 2019 Nov 1;24 (6):e787-91.
http://www.medicinaoral.com/pubmed/medoralv24_i6_p787.pdf

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Indice Médico Español

Abstract

Background: This study aims to evaluate the efficacy of the photobiomodulation therapy (PBMT) - in terms of pain and of quality of life- in patients affected by burning mouth syndrome (BMS).

Material and Methods: This study was designed as a randomised double-blinded prospective study. Patients diagnosed with BMS in the period from June 2015 to June 2018 were recruited. The patients were randomised into two groups and each received treatment once a week for ten weeks: group A received laser therapy (K Laser Cube 3®) while group B was given sham therapy (placebo). Pain was evaluated through the Visual Analogue Scale (VAS) and quality of life was assessed with the short form of the Oral Health Impact Profile (OHIP-14). Assessment was done at baseline and after every therapy session. The researchers were blind to the randomised allocations.

Results: A total of 85 patients were analysed. Group A (laser treatment) was composed of 43 patients while group B (sham therapy) of 42 patients. Patients treated with PBMT showed a significant decrease in symptoms (p=0.0008) and improved quality of life related to oral health (p=0.0002). Conclusions: PBMT has demonstrated to have a positive effect in relieving BMS symptoms and in improving a patient's overall quality of life.

Key words: *Burning mouth syndrome, oral cavity, lasers, life quality.*

WHAT DO WE DO?

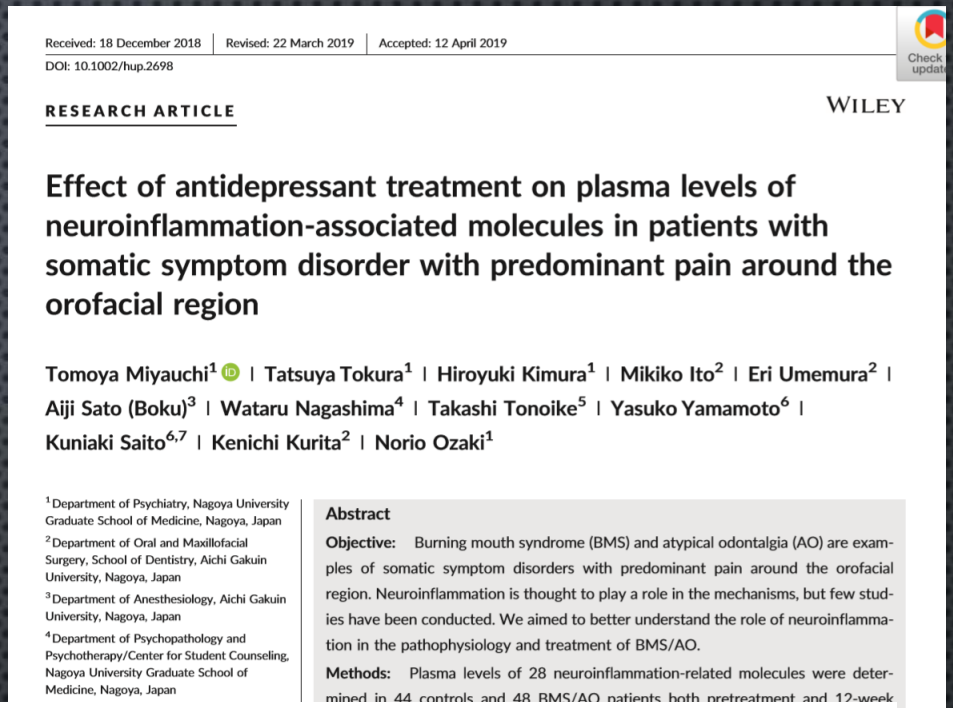
CANDID CONSULTATION WITH REALISTIC PROGNOSIS AND BASIC EXPLANATION OF THEORIES OF CAUSE

PSYCHOLOGICAL SUPPORT

- SINGLE AND GROUP THERAPY

MEDICAL

- TOPICAL CLONAZEPAM
- JUST STARTED RECOMMENDING CBD
- NORTIPTYLINE
  - STEP UP DOSES 10MG NOCTE FIRST WEEK, 20MG SECOND WEEK, 30MG THIRD WEEK, 40MG 4TH WEEK
  - PATIENT TO TITRATE UP ACCORDING TO PAIN RELIEF AND SIDE EFFECT BENEFIT BALANCE
  - 12 WEEKS
  - SEEMS TO WORK WELL DESPITE LACK OF EVIDENCE
  - OCCASIONALLY CONSIDER DULOXETINE
  - RARELY USE PREGABALIN OR GABAPENTIN



Received: 18 December 2018 | Revised: 22 March 2019 | Accepted: 12 April 2019
DOI: 10.1002/hup.2698

RESEARCH ARTICLE

WILEY

Effect of antidepressant treatment on plasma levels of neuroinflammation-associated molecules in patients with somatic symptom disorder with predominant pain around the orofacial region

Tomoya Miyauchi[1] | Tatsuya Tokura[1] | Hiroyuki Kimura[1] | Mikiko Ito[2] | Eri Umemura[2] | Aiji Sato (Boku)[3] | Wataru Nagashima[4] | Takashi Tonoike[5] | Yasuko Yamamoto[6] | Kuniaki Saito[6,7] | Kenichi Kurita[2] | Norio Ozaki[1]

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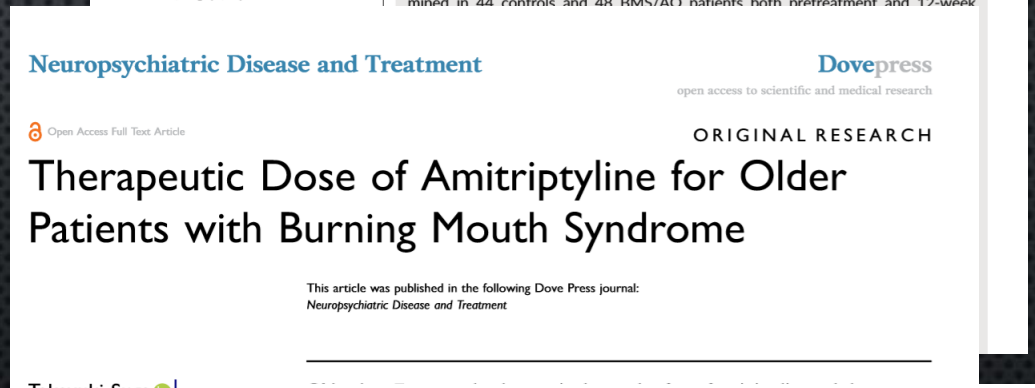
[3]Department of Anesthesiology, Aichi Gakuin University, Nagoya, Japan
[4]Department of Psychopathology and Psychotherapy/Center for Student Counseling, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abstract

Objective: Burning mouth syndrome (BMS) and atypical odontalgia (AO) are examples of somatic symptom disorders with predominant pain around the orofacial region. Neuroinflammation is thought to play a role in the mechanisms, but few studies have been conducted. We aimed to better understand the role of neuroinflammation in the pathophysiology and treatment of BMS/AO.

Methods: Plasma levels of 28 neuroinflammation-related molecules were determined in 44 controls and 48 BMS/AO patients both pretreatment and 12-week



Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Therapeutic Dose of Amitriptyline for Older Patients with Burning Mouth Syndrome

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Takayuki Suga[1]
Miho Takenoshita[1]
Takeshi Watanabe[1]
Trang TH Tu[1]
Lou Mikuzuki[1]
Chaoli Hong[1]
Kazuhito Miura[2]
Tatsuya Yoshikawa[1]
Takahiko Nagamine[3]
Akira Toyofuku[1]

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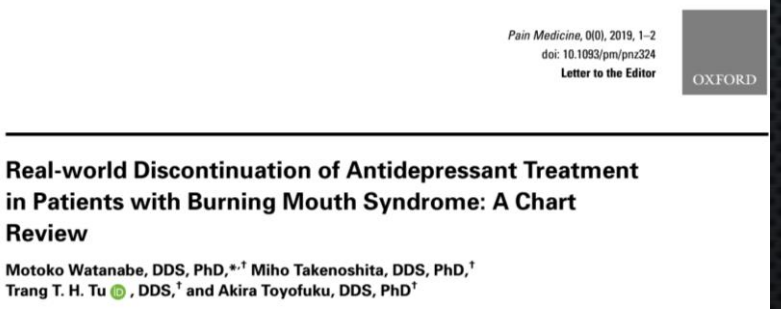

Pain Medicine, 0(0), 2019, 1–2
doi: 10.1093/pm/pnz324
Letter to the Editor

OXFORD

Real-world Discontinuation of Antidepressant Treatment in Patients with Burning Mouth Syndrome: A Chart Review

Motoko Watanabe, DDS, PhD,*,† Miho Takenoshita, DDS, PhD,†
Trang T. H. Tu, DDS,† and Akira Toyofuku, DDS, PhD†

WHERE NEXT?

- CHRONIC PAIN IS BEST MANAGED BY MAXIMISING THE PATIENTS OWN RESOURCES FOR ENDOGENOUS PAIN SUPPRESSION AND REDUCE FACILITATION
  - WEBSITES ONLINE INFORMATION
  - FACEBOOK GROUPS
- FUTURE RESEARCH
  - IDENTIFY SOMATOSENSORY CHANGES
  - IDENTIFY PERIPHERAL OR CENTRAL BMS USING LA INFILTRATIONS
  - PRECISION MEDICINE

Received: 6 January 2019 | Revised: 27 January 2019 | Accepted: 29 January 2019
DOI: 10.1111/odi.13053

WWOM PROCEEDINGS

WILEY ORAL DISEASES

World Workshop in Oral Medicine VII: Reporting of IMMPACT-recommended outcome domains in randomized controlled trials of burning mouth syndrome: A systematic review

Arwa M. Farag[1,2] | Rui Albuquerque[3] | Anura Ariyawardana[4,5] | Milda Chmieliauskaite[6] | Heli Forssell[7] | Cibele Nasri-Heir[8] | Gary D. Klasser[9] | Andrea Sardella[10] | Michele D. Mignogna[11] | Mark Ingram[12] | Charles R. Carlson[13] | Craig S. Miller[14]

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Funding information
American Academy of Oral Medicine; European Association of Oral Medicine; The British Society for Oral Medicine; The National Institute of Dental and Craniofacial Research; Colgate-Palmolive; Henry Schein Cares Foundation; AFYX; Unilever; The World Dental Education Foundation

Abstract

Objectives: To determine the frequency of use of the core outcome domains published by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) in burning mouth syndrome (BMS) randomized controlled trials (RCTs).

Methods: This systematic review, conducted as part of the World Workshop on Oral Medicine VII (WWOM VII), was performed by searching the literature for studies published in PubMed, Web of Science, PsycINFO, Cochrane Database/Cochrane Central, and Google Scholar from January 1994 (when the first BMS definition came out) through October 2017.

Results: A total of 36 RCTs (n = 2,175 study participants) were included and analyzed. The overall reporting of the IMMPACT core and supplemental outcome domains was low even after the publication of the IMMPACT consensus papers in 2003 and 2005 (mean before IMMPACT consensus publication = 2.6 out of 6; mean after IMMPACT

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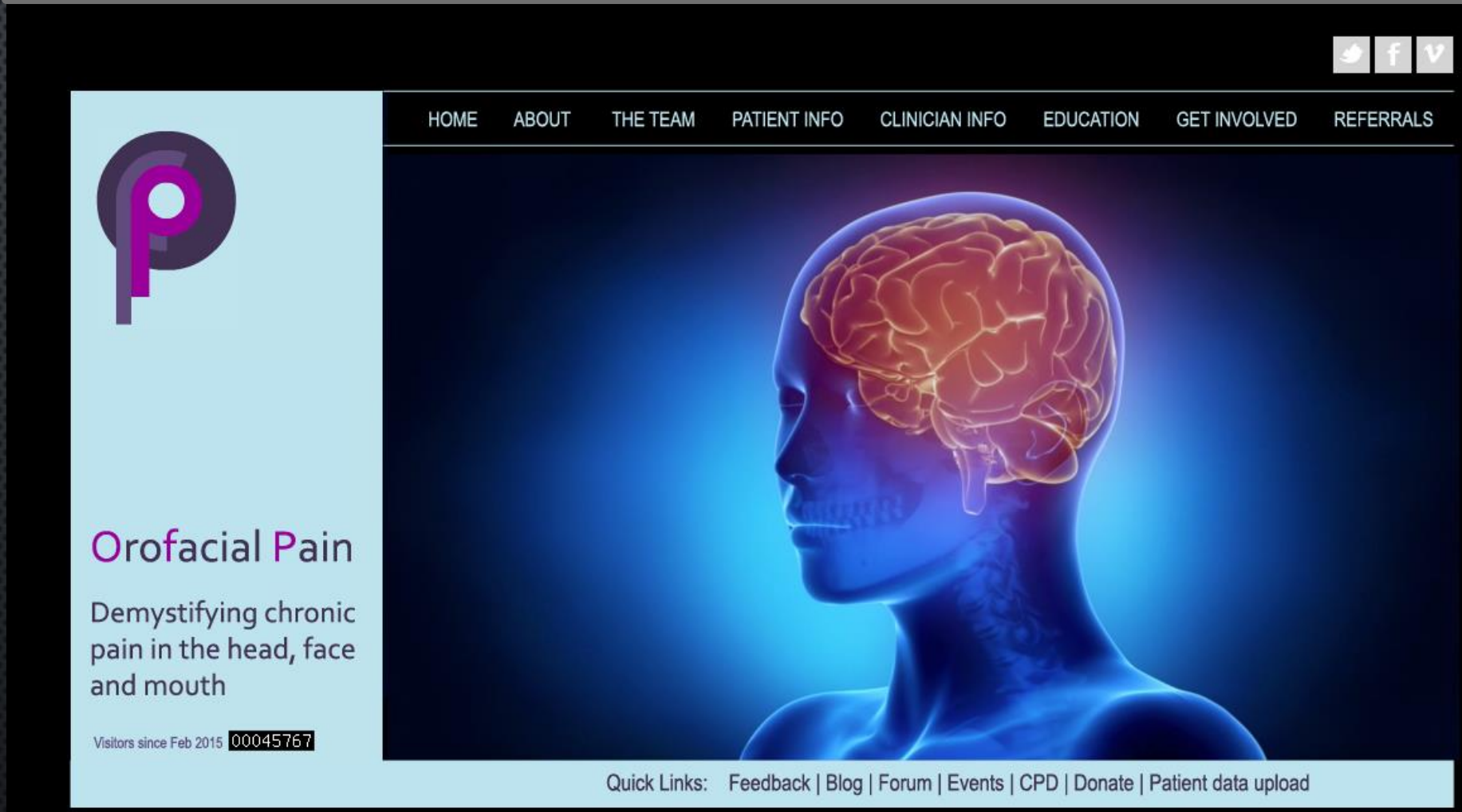

PATIENT INFO

Burning Mouth Syndrome

What is Burning Mouth Syndrome?

Burning mouth syndrome (BMS) is a chronic intra-oral burning sensation that has no identifiable medical or dental cause either local or systemic condition or disease. BMS usually lasts for more than six months with no visible signs of oral mucosa pathology. It is also known as glossodynia, glossopyrosis, stomatodynia or oral dysesthesia.

Who does it affect?

The lack of universally consistent on BMS diagnostic criteria, the epidemiology data collected are of poor quality. Prevalence of BMS in general populations varies from 1% to 15%. BMS affects more on women and usually at menopause or post-menopause age (5th to 7th decade of age).

What causes BMS?

The aetiology of BMS remains not fully understood. However, studies have been showing increasing evidence of BMS as neuropathic pain with central and peripheral nervous system involvement. BMS may be associated with systemic factors such as diabetes, hormonal changes, nutritional deficiencies and psychological disorders; or local causes including oral infections, allergies, salivary gland dysfunction, dental treatment and ill-fitting dentures, are known as secondary BMS and is not true BMS.

What kind of problems might I have?

Location	Usually bilateral burning oral mucosal pain Affects commonly on the tongue, followed by palate, lips and oropharynx
Onset	Spontaneous with continuous gradually continuous increasing of burning pain
Character	Burning pain
Severity	Moderate to severe intensity that may vary during the day. It is usually at the lowest heat upon awake, worsening after the first meal and reach maximum intensity in late evening.
Associated features	Altered taste (bitter, metallic taste, 'supertaster') and dry mouth Psychology disorders such as anxiety, irritability and depression

How is it diagnosed?

The diagnose of BMS is by exclusion of local or systemic conditions or diseases. Based on history and detailed clinical examination, the burning sensation secondary to a primary cause is differentiated from a true BMS.

PEER SUPPORT FACE BOOK GROUP

BMS Profile

Name

Email

Age

Gender

Ethnicity

Country

Date BMS Began

Was there an initiating event for the BMS (yes/no)

If yes, describe the event

Have you been given a BMS diagnosis (yes/no)

Current State of BMS (Pain level 0 = no pain; 10 = pain as bad as it can be)

What words do you use to describe your symptoms?

What areas of your mouth does it affect (list in order of worst to least)

GOOD PAPERS

Cephalalgia. 2017 Jun;37(7):627-647. doi: 10.1177/0333102417694883. Epub 2017 Mar 15.
Burning mouth syndrome.
Jääskeläinen SK[1], Woda A[2].

Ann Intern Med. 2017 May 16;166(10):762-763. doi: 10.7326/L16-0451. Epub 2017 Apr 11.
Botulinum Toxin for Burning Mouth Syndrome.
Restivo DA[1], Lauria G[1], Marchese-Ragona R[1], Vigneri R[1].

IMPAIRED TASTE SENSITIVITY IN BMS PATIENTS

- Oral Dis. 2017 Apr;23(3):395-402. doi: 10.1111/odi.12630. Epub 2017 Feb 8.

- **Taste function assessed by electrogustometry in burning mouth syndrome: a case-control study.**

- Braud A[1], Descroix V[1,2], Ungeheuer MN[3], Rougeot C[3], Boucher Y[1,2].
- **Author information**

- **Abstract**
- **OBJECTIVE:**
- Idiopathic burning mouth syndrome (IBMS) is characterized by oral persistent pain without any clinical or biological abnormality. The aim of this study was to evaluate taste function in IBMS subjects and healthy controls.
- **MATERIAL AND METHODS:**
- Electrogustometric thresholds (EGMt) were recorded in 21 IBMS patients and 21 paired-matched controls at nine loci of the tongue assessing fungiform and foliate gustatory papillae function. Comparison of EGMt was performed using the nonparametric Wilcoxon signed-rank test. A correlation between EGMt and self-perceived pain intensity assessed using a visual analogic scale (VAS) was analyzed with the Spearman coefficient. The level of significance was fixed at $P < 0.05$.
- **RESULTS:**
- Mean EGMt were significantly increased with IBMS for right side of the dorsum of the tongue and right lateral side of the tongue ($P < 0.05$). In the IBMS group, VAS scores were significantly correlated to EGMt at the tip of the tongue ($r = -0.59$; $P < 0.05$) and at the right and left lateral sides of the tongue (respectively, $r = -0.49$ and $r = -0.47$; $P < 0.05$).
- **CONCLUSION:**
- These data depicted impaired taste sensitivity in IBMS patients within fungiform and foliate taste bud fields and support potent gustatory/nociceptive interaction in IBMS.

FUNGIFORM PAPILLAE COUNT?

- Laryngoscope. 2017 Aug 22. doi: 10.1002/lary.26828. [Epub ahead of print]
- **A case-control evaluation of fungiform papillae density in burning mouth syndrome.**
- Naud JM[1], Benca L[2], Drangsholt MT[3], LeResche L[3], Coldwell SE[3].
- **Author information**
- **Abstract**
- **HYPOTHESIS:**
- It has been hypothesized that high fungiform papillae density may be a risk factor for developing the taste and pain alterations characteristic of burning mouth syndrome.
- **OBJECTIVE:**
- Evaluate whether fungiform papillae density, taste sensitivity, and mechanical pain sensitivity differ between burning mouth syndrome cases and controls.
- **STUDY DESIGN:**
- This case-control study compared cases diagnosed with primary burning mouth syndrome with pain-free controls.
- **METHODS:**
- Participants (17 female cases and 23 female controls) rated the intensity of sucrose, sodium chloride, citric acid, and quinine applied separately to each side of the anterior tongue and sampled whole mouth. Mechanical pain sensitivity was assessed separately for each side of the tongue using weighted pins. Digital photographs of participants' tongues were used to count fungiform papillae.
- **RESULTS:**
- Burning mouth syndrome cases had increased whole mouth taste intensity. Cases also had increased sensitivity to quinine on the anterior tongue, as well as increased mechanical pain sensitivity on the anterior tongue. Fungiform papillae density did not differ significantly between cases and controls. Fungiform papillae density on the left and right sides of the tongue were correlated in controls; however, there was no left/right side correlation in cases.
- **CONCLUSION:**
- Cases had increased pain and taste perception on the anterior tongue. The lack of correlation between left and right fungiform papillae density in cases may be an indication of asymmetrical lingual innervation in these patients.

INTRAORAL CAMERA FOR FFP COUNT

- Med Oral Patol Oral Cir Bucal. 2012 May 1;17(3):e362-6.
- **Fungiform papillae density in patients with burning mouth syndromeand xerostomia.**
- Camacho-Alonso F[1], López-Jornet P, Molino-Pagán D.
- **Author information**
- **Abstract**
- **OBJECTIVE:**
- The aim of this study was to analyze fungiform papillae density in patients with burning mouth syndrome (BMS) and xerostomia.
- **STUDY DESIGN:**
- In this cross-sectional clinical study, sixty patients were included (20 with BMS, 20 with xerostomia and 20 healthy controls). The fungiform papillae density was analyzed over a small region on the anterior tip of the tongue with the aid of a digital camera. The number of papillae was measured in an area of 19 mm^2.
- **RESULTS:**
- The patients with BMS showed significantly higher fungiform papillae density than the patients with xerostomia; though no statistically significant differences were recorded versus the control group. In the BMS group, 65% of all cases presented a density of 71-90 papillae (within an area of 19 mm^2), while 10% had more than 90 papillae. On the contrary, 70% of the patients with xerostomia had fewer than 70 papillae in the studied area.
- **CONCLUSIONS:**
- The digital camera offers a rapid, noninvasive and relatively simple way to study fungiform papillae density. The patients with BMS have higher fungiform papillae density than the patients with xerostomia.

J Clin Exp Dent. 2016 Apr 1;8(2):e153-9. doi: 10.4317/jced.52560. eCollection 2016 Apr.

Continuous neurophatic orofacial pain: A retrospective study of 23 cases.

Sotorra-Figuerola D[1], Sánchez-Torres A[1], Valmaseda-Castellón E[2], Gay-Escoda C[3].

Author information

Abstract

BACKGROUND:

To determine the clinical characteristics of Continuous Neuropathic Orofacial Pain in patients that suffer Persistent Idiopathic Facial Pain (PIFP), Painful Post-Traumatic Trigeminal Neuropathy (PPTTN) or Burning Mouth Syndrome (BMS) and to describe their treatment.

MATERIAL AND METHODS:

A retrospective observational study was made, reviewing the clinical history of the patients diagnosed with Continuous Neuropathic Orofacial Pain between 2004 and 2011 at the Orofacial Pain Unit of the Master of Oral Surgery and Implantology of the University of Barcelona and at the Orofacial Pain Unit of the Teknon Medical Center of Barcelona.

RESULTS:

The average age of the patients with Continuous Neuropathic Orofacial Pain was 54.5, with a clear female predominance (86.9%, n=20). Of all patients, 60.9% (n=14) were suffering a PIFP, 21.7% (n=5) had a BMS and 17.4% (n=4) were presenting a PPTTN. The pain quality described by the patients with Continuous Neuropathic Orofacial Pain was oppressive (43.47%, n=10), widely represented by patients with PIFP, and burning (39.13%, n=9) being the only quality that described patients with BMS. The treatment carried out with the patients was only pharmacologic. The most used drugs for the treatment of PIFP and PPTTN were clonazepam (50%, n=9) and amitriptyline (44.44%, n=8). However, a 55.5% (n=10) of the patients with PIFP or PPTTN required the association of two or more drugs for a correct pain control. All the patients with BMS responded satisfactorily to clonazepam.

CONCLUSIONS:

Continuous Neuropathic Orofacial Pain is a little known condition among the general population, physicians and dentists. This favors a late diagnosis and inaccurate treatments which entail unnecessary suffering. It is important to inform both the general population and health professionals concerning this painful condition.

KEY WORDS:

Continuous neuropathic orofacial pain, persistent idiopathic facial pain, painful post-traumatic trigeminal neuropathy, burning mouth syndrome, atypical odontalgia.