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Burning mouth syndrome (BMS):

- Etiology remains poorly understood
 - o Complex and multifactorial
 - o Emerging data suggests role of circadian rhythm dysfunction
- Pain and discomfort with normal appearance of mucosa
- A diagnosis of exclusion

Putative causes of BMS

Altered Pain Perception

- Nociceptive pain: noxious insult (inflammation/mechanical) or thermal stimuli.
- Neuropathic pain: generated and maintained by the nervous system. Affects central and peripheral nervous systems
 - o burning, electric shock–like, prickling, and/or numbness.
 - o ~ 30% to 60% of BMS patients suffer from neuropathic pain
- Structural and functional deficits in brain regions associated with pain perception.
- Possible diminished dopamine levels in the putamen
- Possible mechanism linking psychological disorders with brain function
- Elevated artemin (Artn) and TRPV1 expression in BMS patients
 - o Artn a ligand for the GDNF (glial cell line–derived neurotrophic factor), regulates expression of TRPV1 (transient receptor potential vanilloid 1)
 - o Role of TRP channels in temperature perception and nociception.
 - o Increased TRP levels could contribute to heightened pain sensation
- Mouse model studies reveal Artn-neutralizing antibody diminishes heat hyperalgesia

Dysgeusia

- Abnormal taste among patients who have BMS (reason poorly understood)
- Use of electrogustometry (EGMt) to examine taste disturbances
 - o Assess the integrity of taste pathways.
 - o A case-control study reveals diminished taste sensitivity in fungiform and foliate taste buds
 - o Alterations in salivary composition in BMS can affect the salivary pH
 - pH of the saliva critical factor in signal transmission in EGMt

Neuroendocrine and Hormonal Disturbances

- In BMS patients:
 - o Plasma adrenaline levels significantly lower
 - o Serum cortisol levels are slightly higher
 - o Dehydroepiandrosterone (DHEA) significantly lower
- Salivary 17 β -estradiol levels correlated with disease severity
- Cortisol levels and the cortisol/DHEA ratio in saliva shows an inverse relationship with the severity of oral burning
- Alterations may be due to abnormal oscillations in the HPA axis
 - o Data suggest decreased DHEA is indicative of HPA dysfunction

Psychological Factors

- Higher levels of psychogenic disturbances in BMS patients
- Systematic review of 14 controlled studies found an association between psychological factors and BMS
 - o Anxiety and depression are most common observed in BMS patients
 - o Higher levels of somatization, obsessive compulsive disorder, and paranoid ideation in females with BMS
 - o Depression in BMS correlates with plasma noradrenaline and cortisol levels
 - further evidence underlying HPA abnormalities may contribute to the psychological disturbances seen in BMS.

Sleep Disorders

- Self-reported poor sleep quality higher for patients who have BMS
- Sleep disorders may increase the risk of BMS development, however:
 - o studies relied exclusively on self-reporting,
 - o technique to evaluate sleep quality not validated for BMS patients

Circadian Rhythm

- Dysfunction in circadian clock an emergent area of research
- Clock genes are implicated in numerous human pathoses, including mood and sleep disorders
 - o Pain perception, depression and anxiety, and sleep disorders intimately linked with circadian disturbances
 - o HPA axis regulated by circadian outputs
 - o Dopamine is primary modulator of the circadian rhythm in the central nervous system
- Data suggest that continued identification of regulatory mechanisms that control the circadian rhythm can have diagnostic and therapeutic significance

Management

- Rule out systemic conditions or local factors or if the cause is idiopathic.
 - o Systemic conditions include esophageal reflux, diabetes, and nutritional deficiencies.
 - o Local factors include parafunctional habits, candidiasis, geographic tongue, and xerostomia,
- According to recent Cochrane database systematic, evidence lacking for specific treatment recommendations
 - o Need placebo-controlled, double-blind studies with long-term follow-up
- Current treatment divided into 3 categories:
 - o Topical therapies
 - o Systemic treatments
 - o Behavioral strategies

Topical Therapies

Clonazepam

- Effectively reduces symptoms associated with BMS both short-term (<10 wk) and long-term (>10 wk)
- Good for patients unwilling/unable to take systemic medications.

Capsaicin

- Binds to TRPV1, inactivating neuronal responses to heat
 - o Prolonged exposure = desensitization of pain receptors
- Increased burning sensation immediately after application and dyspepsia, especially if the capsaicin ingested as a capsule
 - o Important for patients with a history of gastric-related disorders.

Low level laser Therapy (LLLT)

- Associated with analgesic, anti-inflammatory, and biostimulatory properties.
- Decrease burning sensation by increasing synthesis and release of serotonin and β -endorphins and decreasing bradykinin secretion.
- Blocks C-fiber depolarization therefore heat, and pain stimuli not transmitted

Systemic Therapies

Clonazepam

- Significant improvement in pain among patients who have BMS
- Most effective for patients with:
 - o Normal salivary production
 - o Those with greatest severity of symptoms at initial presentation,
 - o Those who did not use psychotropic medications
- Mood, taste dysfunction, and xerostomia not improved
- Good short-term option (long term use safety and effectiveness unknown)

Alpha Lipoic Acid (ALA)

- Mitochondrial coenzyme may stimulate production of neural growth factors
- Therapeutic benefits of ALA for BMS are unclear
- ALA as BMS treatment shows promise but more studies are needed

Gabapentin

- Agonist of the inhibitory neurotransmitter GABA.
- Crossover placebo-controlled trial where BMS patients were administered gabapentin, ALA, or a combination
 - 50% in the gabapentin group reported improvements in pain vs 15% in the placebo group
 - 70% reduction in pain with gabapentin +ALA

Amitriptyline

- Amitriptyline is a tricyclic antidepressant with analgesic properties.
- No significant differences between amitriptyline and gabapentin in reducing oral pain

Table 2. Local and Systemic Therapies for Burning Mouth Syndrome.

Therapy: Medication	Advantages	Disadvantages
Topical		
Clonazepam	Relieves symptoms associated with burning mouth syndrome	May cause drowsiness and dry mouth Possible dependence
Capsaicin	Diminished burning sensation	Asthenia Increased burning sensation immediately following topical application
Low-level laser therapy	Diminished burning sensation	Dyspepsia associated with oral therapy Optimal parameters not established
Systemic		
Clonazepam	Diminished burning sensation	No improvement in mood, taste, or xerostomia
Alpha lipoic acid	Diminished burning sensation	May need to be used in concurrence with cognitive behavioral therapy
Gabapentin	Improved pain scores, particularly when used with alpha lipoic acid	Drowsiness
Amitriptyline	Diminished pain	May cause dry mouth Asthenia

Miziara et al. (2015), Kisely et al. (2016), McMillan et al. (2016), Al-Maweri et al. (2017), Liu et al. (2017).

Emerging Therapeutic Approaches

- Most studies are single reports → Need for larger patient cohorts
- Topical bupivacaine may be effective anesthetic to relieve BMS symptoms
- Paroxetine showed promise in an increase dose study

- Although clinically unclear, preliminary work suggests melatonin improves anxiety among patients with BMS,
- Catuama:
 - o Herbal product that combines 4 medicinal plants:
 - *Paullinia cupana* (guarana), *Trichilia catigua* (catuaba), *Zingiber officinale* (ginger), and *Ptychopetalum olacoides* (muira puama).
 - o Antinociceptive, antidepressant, and vasorelaxant properties
 - o Reduced symptoms in the BMS
- Promising preliminary studies warranting further research

Behavioral Strategies

- Cognitive behavioral therapy (CBT) used to manage depression and anxiety as well as physical symptoms
- Specific techniques include:
 - o Biofeedback, relaxation, exposure, and cognitive restructuring.
 - Relaxation techniques: progressive muscle relaxation and focused breathing to alleviate discomfort,
 - Cognitive restructuring: identify and modify destructive thoughts related to emotional and behavioral problems
- Several CBT sessions required for patient education, distraction, evaluation of harmful automatic thoughts, and replacement with more beneficial thoughts
- 12 to 15 sessions reduced pain severity and discomfort
- Improved symptoms maintained for 6 months
- Cognitive therapy + ALA may be more effective than either approach alone

Reference

Ritchie, A. and Kramer, J. (2018). *Recent Advances in the Etiology and Treatment of Burning Mouth Syndrome*. [online] Journals.sagepub.com. Available at: https://journals.sagepub.com/doi/full/10.1177/0022034518782462?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed [Accessed 1 Oct. 2018].