Appropriate dental prescribing should also use antibiotics only in an adjunctive role to the use of active local treatment that addresses the source of the infection. Patients should receive counseling on how to take the antibiotic so that errors in administration can be avoided. Patient education can also address problems related to individuals expecting or requesting antibiotics that are incorrect and persons who are unwilling to accept local treatment.

Teoh L, Stewart K, Marino R, et al: Antibiotic resistance and relevance to general dental practice in Australia. *Austral Dent J* 63:414-421, 2018

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BURNING MOUTH

Advances in the causation and treatment of burning mouth syndrome

BACKGROUND

Burning mouth syndrome (BMS) is poorly understood in terms of its etiology, making management challenging. Generally, BMS is characterized by oral pain and discomfort in a patient with normal-appearing mucosa and no local or systemic condition typically associated with stomatodynia. This rare condition is likely caused by multiple factors, which makes it more difficult to diagnose. The current state of knowledge regarding the causes and treatment of BMS was detailed.

PUTATIVE CAUSES

Pain Perception

Recent studies suggest that about 30% to 60% of patients with BMS suffer from neuropathic pain, along with reduced sensitivity to cold and warmth and diminished thermal pain thresholds compared to healthy control subjects. BMS patients can be grouped into those who experience peripheral small fiber neuropathy, those with major subclinical central trigeminal neuropathy, and those who have inhibitory dopaminergic deficiency.

Patients with BMS have structural and functional deficits in key brain regions related to pain perception, specifically the medial prefrontal cortex and the hippocampus. Changes in the gray matter of the pain matrix are also described. Low cerebral blood flow may be present in patients with BMS and depression. Dopamine levels in the putamen may also be diminished in BMS patients.

Activity in the postcentral gyrus is stronger in those with BMS in response to angry facial expressions, which may link psychological disorders with brain function in BMS. The peripheral nervous system is also implicated and includes specific defects in pain sensory pathways. Some study indicates that blockade of the artemin/GFRα3/TRPV1 axis may prove therapeutically efficacious.

Dysgeusia

Although the finding is poorly understood, several studies report abnormal taste sensation among BMS patients. Electrogustometry (EGMt) is a technique that estimates taste detection thresholds and assesses the integrity of the taste pathways. One study found that patients with BMS had diminished taste sensitivity in the fungiform and foliate taste buds. The EGMt values at the tongue's lateral borders and tips correlated with visual analog scale scores for these patients. Alterations in salivary composition could affect the salivary pH and alter EGMt results, but the results so far indicate that pain perception and dysgeusia may be interrelated among BMS patients.

Neuroendocrine and Hormonal Problems

Patients with BMS have neuroendocrine and endocrine system dysfunction. Compared to control patients, their plasma adrenaline levels are significantly lower and cortisol levels are slightly increased. Significant decreases are seen in dehydroepiandrosterone (DHEA), the precursor of testosterone and estradiol. Salivary 17β-estradiol levels correlate with disease severity, whereas cortisol levels and cortisol/DHEA ratios in whole saliva have demonstrated an inverse relationship to the severity of oral burning. It has been hypothesized that these alterations may be caused by abnormal oscillations in the hypothalamic-pituitary-adrenal (HPA) axis, which controls the secretion of adrenal hormones. Decreased DHEA levels are indicative of HPA dysfunction, so dysregulation of these systems likely contributes to chronic pain conditions, including BMS.

Psychological Factors

Patients with BMS tend to experience higher levels of psychogenic disturbances compared to the general population. Nearly all studies performed since 2000 report an association between psychological factors and BMS. Anxiety and depression are more common among BMS patients, with women experiencing psychological factors more often than men. The specific factors seen in women are somatization, obsessive compulsive disorder, and paranoid ideation. The depression in those with BMS correlates with plasma noradrenaline and cortisol levels as well.

Sleep Disorders

Self-reported poor sleep quality is greater for BMS patients that for controls. In addition, depressed mood and anxiety were positively correlated with sleep disturbances. Having a sleep disorder may also increase the risk of BMS development. Many BMS patients appear to suffer from poor sleep quality, which may be related to the significant number of mood disorders these patients experience.

Circadian Rhythm

One emerging area of research is circadian clock dysfunction. Circadian rhythm is controlled by complex networks and mechanisms that have profound effects on health and disease. The proteins encoded by clock genes are critical in establishing and maintaining chronobiology. A number of human pathological conditions are related to clock genes, including disorders of mood and sleep. Those relevant to BMS and linked to circadian rhythm include pain perception, depression and anxiety, and sleep disorders. The HPA axis is regulated by circadian output, with dopamine a primary modulator of the circadian rhythm in the central nervous system. Alterations occur in BMS, with pathologic changes underlying the anxiety, depression, sleep disturbances, HPA axis dysfunction, and chronic pain experienced by patients with BMS (Figure 2). Further study of the regulatory mechanisms that control circadian rhythm will likely lead to the identification of disease-related networks in patients with BMS and other chronic pain disorders. These findings may carry significant diagnostic and therapeutic implications.

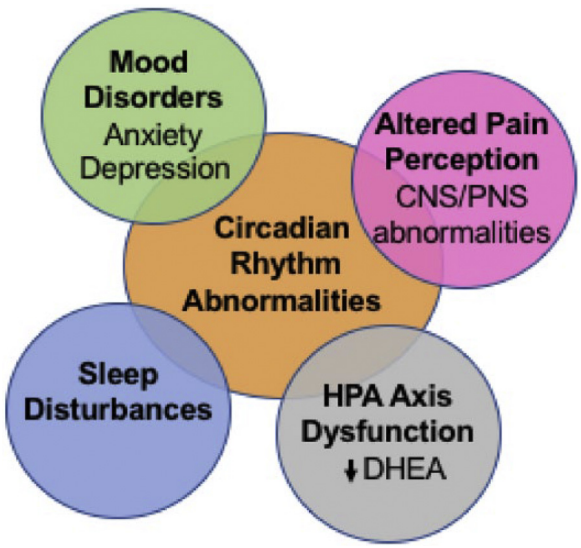

Figure 2. Emerging evidence for circadian rhythm dysfunction in the etiopathogenesis of burning mouth syndrome. Pathologic alterations in circadian rhythm oscillations may underlie the elevated pain perception, depression and anxiety, sleep disorders, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction that are described for patients with burning mouth syndrome. *CNS,* Central nervous system; *DHEA,* dehydroepiandrosterone; *PNS,* peripheral nervous system. (Courtesy of Ritchie A, Kramer JM: Recent advances in the etiology and treatment of burning mouth syndrome. *J Dent Res* 97:1193-1199, 2018.)

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
		Asthenia
Capsaicin	Diminished burning sensation	Increased burning sensation immediately following topical application
		Dyspepsia associated with oral therapy
Low-level laser therapy	Diminished burning sensation	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).
(Courtesy of Ritchie A, Kramer JM: Recent advances in the etiology and treatment of burning mouth syndrome. *J Dent Res* 97:1193-1199, 2018.)

MANAGEMENT

Patients diagnosed with BMS may receive a number of treatments. Evidence is lacking concerning which treatments are best, requiring further study. Current therapy can be divided into topical, systemic, and behavioral and emerging strategies (Table 2).

Topical Therapies

Among the topical treatments are clonazepam, capsaicin, and low-level laser therapy (LLLT). Clonazepam effectively reduces symptoms associated with BMS, with topical application helping both short term and long term. Side effects include xerostomia, lethargy, and fatigue. Clonazepam can cause dependence.

Capsaicin is an analgesic that controls neuropathic pain and inactivates neuronal responses to heat. In a carefully selected population of patients, capsaicin can significantly improve burning symptoms compared with placebo. However, it also causes the adverse effects of an increased burning sensation immediately after topical application and dyspepsia when the capsaicin is delivered orally, especially when the patient has a history of gastric-related disorders.

LLLT reduces the burning sensation by increasing the synthesis and release of serotonins and β-endorphins and decreasing the secretion of bradykinin. LLLT also blocks the depolarization of C-fibers, which transmit heat and pain stimuli. Laser therapy reduces stomatodynia, but the wide variations in laser use parameters make it difficult to determine the best treatment guidelines.

Systemic Therapies

Clonazepam, alpha lipoic acid (ALA), gabapentin, and amitriptyline are the primary systemic therapies used for BMS. Systemic clonazepam can significantly improve the pain BMS patients experience and is particularly helpful for those with normal salivary production, those with the most severe symptoms when initially seen, and those who do not use psychotropics. Although this drug offers good short-term benefits, it does not improve mood, taste dysfunction, or xerostomia.

ALA may stimulate the production of neuronal growth factors, but how this yields therapeutic benefits for BMS patients remains unknown. ALA is accompanied by headaches and gastric upset, but these are not more significant than those seen with placebo.

Gabapentin is an anticonvulsant medication that is effective treatment for related conditions such as glossopharyngeal neuralgia and general neuropathic pain. When combined with ALA, 1 study found that 70% of patients experienced diminished pain.

The tricyclic antidepressant amitriptyline also has analgesic properties. It relieves the pain of BMS, but is accompanied by asthenia and dry mouth. Care should be taken in prescribing drugs that cause dry mouth for patients with BMS because they can contribute to the oral discomfort when given for an extended period of time.

Behavioral and Emerging Therapies

Cognitive behavioral therapy (CBT) is a psychological method for managing depression and anxiety as well as physical symptoms. Relaxation and cognitive restructuring are most relevant to BMS management. Relaxation techniques include progressive muscle relaxation and focused breathing that alleviates discomfort. Cognitive restructuring is used to identify and modify destructive thoughts that relate to emotional and behavioral problems. Pain catastrophizing, which is a heightened negative cognitive-affective orientation toward pain, is targeted for BMS patients and can be predictive of pain outcomes. CBT overall focuses on patient education, distraction, evaluation of harmful automatic thoughts, and the replacement of those thoughts with more beneficial ones. Twelve to 15 CBT sessions have been able to reduce the severity of pain and discomfort in BMS patients, with maintenance of the improvement for 6 months after therapy ended. Symptoms were most responsive to treatments emphasizing reducing dysfunctional cognitive factors. The combination of cognitive therapy and ALA may be more effective than either therapy in isolation. Further study is needed to identify the best combinations of treatment for BMS relief.

Among the emerging therapeutic approaches used for BMS are topical bupivacaine, paroxetine, and melatonin. In addition, an herbal supplement from Brazil, catuama, has been suggested to offer antinociceptive, antidepressant, and vasorelaxant properties. Further research is needed to better understand these possible treatments for BMS.

DISCUSSION

BMS causes oral and systemic disease manifestations that can significantly diminish a patient's quality of life. Continued study is required to identify the causes of BMS and to establish the best evidence-supported treatment approaches.

Clinical Significance

Evidence-based methods of addressing the discomfort and pain of BMS remain elusive. Further study is needed both to identify the best of the current strategies and to uncover additional methods that may prove effective.

Ritchie A, Kramer JM: Recent advances in the etiology and treatment of burning mouth syndrome. *J Dent Res* 97:1193-1199, 2018

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