Burning Mouth Syndrome: Etiopathogenesis, Clinical Concepts, and Emerging Management Trends

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***Abstract*—Burning Mouth Syndrome (BMS) represents a complex, chronic intraoral neuropathic pain condition characterized by a persistent scalding or dysesthetic sensation in the absence of observable mucosal lesions or organic laboratory abnormalities (Canfora et al., 2024; Bookout, 2023). Historically dependent on non-specific empirical pharmacotherapy, contemporary clinical paradigms are evolving toward individualized regimens aimed at complete functional recovery (Nasri-Heir et al., 2015). This narrative synthesis highlights the underlying neurobiological mechanisms, diagnostic frameworks, and therapeutic advancements in BMS, emphasizing emerging low-toxicity modalities such as photobiomodulation therapy (PBMT), non-invasive neurostimulation (rTMS, tDCS), multimodal psychotropics, micro-dosed opioid antagonists, and targeted phytotherapy.**

***Index Terms*—BMS, Treatment\, Modalities ,Therapeutic interventions.**

I. INTRODUCTION & PATHOPHYSIOLOGICAL MECHANICS

Epidemiological data indicate a pronounced predilection of Burning Mouth Syndrome for peri- and post-menopausal women, with global prevalence estimates spanning from 0.7% to 15% depending on diagnostic criteria (Bookout, 2023). Symptom presentation is characteristically bilateral and symmetrical, localized primarily to the anterior two-thirds of the tongue, the hard palate, labial mucosa, and lower lip (Nasri-Heir et al., 2015).

Clinical classification divides the disorder into two primary variants (Canfora et al., 2024):

- Primary (Idiopathic) BMS: Intraoral mucosal dysesthesia occurring in the complete absence of clinical, histological, or systemic abnormalities.
- Secondary BMS: Intraoral burning symptoms resulting from underlying systemic or localized pathologies, including oral candidiasis, salivary hypofunction, essential micronutrient deficiencies (iron, folate, B12), geographic tongue, or hypersensitivity to dental restoration materials (Asl et al., 2026; Canfora et al., 2024).

From a pathophysiological standpoint, primary BMS is categorized as a nociplastic pain state stemming from dysregulation across three key neurological pathways (Shemesh, 2026; Nasri-Heir et al., 2015):

- Peripheral Small-Fiber Neuropathy: Involves axonal degeneration and diminished density of unmyelinated intraepithelial C-fibers and thin A-delta fibers in lingual tissue, alongside upregulation of local Transient Receptor Potential Vanilloid 1 (TRPV1) channels (Nasri-Heir et al., 2015).
- Central Sensory Disinhibition: Marked by impaired central pain-gating processes associated with altered thalamocortical signaling and reduced nigrostriatal dopaminergic tone (Shemesh, 2026).
- Psychoneuroendocrine Dysregulation: Involves hypothalamic-pituitary-adrenal (HPA) axis dysfunction, strongly correlated with psychological stress, generalized anxiety, sleep architecture disruption, and altered salivary steroid profiles (Bookout, 2023).

II. CONVENTIONAL THERAPEUTIC INTERVENTIONS

Historical interventions relied predominantly on systemic medications to suppress pain signals. Although effective for certain patient populations, systemic side effects and variable response rates

restrict their long-term utility (Nasri-Heir et al., 2015; Canfora et al., 2024):

- GABAergic Agents (Topical & Systemic): Clonazepam (0.25–2 mg/day orally or 1 mg topical rinse-and-spit) enhances GABAA-mediated central and peripheral inhibition. Topical application allows localized mucosal action while avoiding systemic sedation (Bookout, 2023).
- Gabapentinoids: Gabapentin (300–1200 mg/day) and pregabalin bind to voltage-gated calcium channel alpha-2-delta subunits, dampening central sensitization (Canfora et al., 2024).
- Monoaminergic Antidepressants: Low-dose Tricyclic Antidepressants (e.g., amitriptyline, nortriptyline) and SNRIs (duloxetine) strengthen descending pain inhibition; however, anticholinergic side effects like xerostomia may aggravate oral discomfort (Nasri-Heir et al., 2015).
- Metabolic Antioxidants: Alpha-Lipoic Acid (ALA, 400–600 mg/day) acts as a neuroprotective scavenger to attenuate peripheral oxidative neural damage (Canfora et al., 2024).

III. CONTEMPORARY TRENDS & NEXT-GENERATION PARADIGMS

Current research reflects a shift toward targeted, non-invasive therapies designed to stimulate peripheral nerve regeneration, foster central cortical plasticity, and balance psychoneuroendocrine function (Canfora et al., 2024).

3.1. Photobiomodulation Therapy (PBMT / LLLT)

Application of low-level red to near-infrared diode lasers (630–980 nm) serves as a key non-pharmacological strategy. Light energy absorbed by cytochrome c oxidase within mitochondrial chains enhances ATP synthesis, reduces reactive oxygen species (ROS), downregulates pro-inflammatory cytokines (TNF-α, IL-1β), and promotes peripheral nerve recovery alongside endogenous opioid release (Canfora et al., 2024).

3.2. Central Non-Invasive Neuromodulation

To mitigate central thalamocortical dysfunction, repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) are applied in refractory primary BMS. Targeting the primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) supports adaptive plasticity and restores dopaminergic and endogenous opioid signaling (Shemesh, 2026).

3.3. Novel Targeted Pharmacotherapies

Emerging pharmacotherapeutic strategies focus on high receptor specificity and lower systemic toxicity:

- Vortioxetine: A multimodal antidepressant (5-HT3, 5-HT1D, 5-HT7 antagonist and 5-HT1A agonist) that alleviates pain and cognitive impairment without worsening anticholinergic dry mouth (Canfora et al., 2024).
- Low-Dose Naltrexone (LDN): Administered at 1.5–4.5 mg/day, LDN induces transient opioid receptor blockade, triggering endorphin upregulation and suppressing central microglial neuroinflammation.
- TRPV1 Desensitizers & Phytomedicines: Formulations such as topical capsaicin, crocin (saffron extract), melatonin, and targeted botanicals help modulate channel kinetics and local neurogenic inflammation (Nasri-Heir et al., 2015).

3.4. Integrative Biopsychosocial Care & Digital Health

Recognizing the frequent co-occurrence of secondary mood and anxiety disturbances, comprehensive care models combine Cognitive Behavioral Therapy (CBT), Mindfulness-Based Stress Reduction (MBSR), and digital health platforms to manage anxiety and facilitate multidisciplinary monitoring (Bookout, 2023).

IV. COMPARATIVE SYNTHESIS OF TREATMENT MODALITIES

Category	Modality / Agent	Primary Mechanism	Clinical Profile & Considerations
Emerging Non-Pharm.	Photobiomodulation (PBMT)	Mitochondrial stimulation & ROS suppression	Non-invasive, well-tolerated, strong local analgesia; requires

			outpatient administration.
Neuromodulation	rTMS / tDCS	Cortical stimulation (M1/DLPFC) to restore gating mechanisms	Effective for central refractory pain; requires specialized clinical setups.
Novel Pharm.	Vortioxetine / LDN	Multimodal serotonergic & microglial inhibition	Simultaneously addresses mood and pain; low risk of xerostomia or heavy sedation.
Traditional Pharm.	Clonazepam (Topical/Oral)	GABAA receptor hyperpolarization	Rapid onset; risk of tolerance, dependence, and systemic sedation.

V. CONCLUSION & FUTURE OUTLOOK

The clinical approach to Burning Mouth Syndrome is rapidly transitioning from empirical monotherapy toward personalized, integrative care paradigms. Combining non-invasive modalities such as PBMT and neuromodulation with novel pharmacotherapeutics and biopsychosocial interventions targets both peripheral and central pain circuits, optimizing long-term therapeutic outcomes and functional recovery.

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