Pharmacological and non-pharmacological management of burning mouth syndrome: A systematic review

Leczenie farmakologiczne i niefarmakologiczne zespołu pieczenia jamy ustnej – przegląd piśmiennictwa

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Abstract

Burning mouth syndrome (BMS) is idiopathic chronic oral pain, associated with depression, anxiety and pain symptoms. The BMS symptoms include a burning sensation in the tongue and/or other oral mucosa with no underlying medical or dental reasons. As many BMS patients suffer from psychiatric comorbidities, several psychotropic drugs are included in the management of BMS, reducing the complaint, while managing anxiety, depression and pain disorders.

In this review, a search of the published literature regarding the management of BMS was conducted. We discuss the BMS etiology, clinically associated symptoms and available treatment options. The current evidence supports some BMS interventions, including alpha-lipoic acid (ALA), clonazepam, capsaicin, and low-level laser therapy (LLLT); however, there is a lack of robust scientific evidence, and large-scale clinical trials with long follow-up periods are needed to establish the role of these BMS management options. This knowledge could raise the awareness of dentists, psychiatrists and general practitioners about these challenges and the available kinds of treatment to improve multidisciplinary management for better health outcomes.

Key words: burning mouth syndrome, neuropathic pain, orofacial pain, clonazepam, oral conditions

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Introduction

Burning mouth syndrome (BMS) is oral dysesthesia characterized by a burning sensation in the tongue and/or other oral mucosa. It is associated with dry mouth and taste changes in the absence of clinical/laboratory findings or underlying medical or dental reasons, and it can be debilitating in some patients.1–3 Burning mouth syndrome is a painful cranial neuropathy, similar to trigeminal neuralgia,4 with mostly unknown etiology. As described by the international classification of headache disorders, BMS recurs daily for more than 2 h/day over more than 3 months without clinically evident causative lesions; the pain is usually bilateral with fluctuating intensity.5 The syndrome can also lead to sleep disturbances, especially in the elderly.6

Burning mouth syndrome is commonly associated with depression and anxiety.7 It has a prevalence of 0.7–5% and appears to be more frequent in females,6 especially in post-menopausal women, where its prevalence is 12–18%.9 Females report more paresthesia, oral mucosal pain, dysgeusia and xerostomia, while taste changes are less common in males.10

Burning mouth syndrome is common in psychiatric patients; there are reports that it affects up to 20% of the older hospitalized psychiatric patients11–13 and 10–20% of elderly outpatients.14 It could be associated with oral or systemic abnormalities, such as changes in hormone levels, infections, nutritional disturbances, denture-related lesions, and pharmacological treatment.15 The BMS characteristics include changes in the mucosal blood flow.16

Burning mouth syndrome has been described as a psychosomatic disorder predisposed by psychological stress or neuropathic pain, affecting the peripheral and central nervous system in the trigeminal pathways,5 the prefrontal cortex and the hippocampus.17 Patients with BMS process thermal stimulation differently, with changes in tactile sensory functions, including a lower threshold for cold detection, while warmth, heat and pain detection thresholds are higher.18–20

Immune and endocrine functions are also involved in BMS; a lower level of plasma adrenaline, a low level of CD8(+) cells and a high CD4(+) /CD8(+) ratio represent a suppressed immune system.21 A significant increase in the genetic polymorphisms associated with interleukin-1β (IL-1β) has also been suggested.22

Changes in scores on psychiatric assessment scales have been identified. With the Temperament and Character Inventory (TCI), BMS patients have lower novelty-seeking scores and self-directedness scores, while their harm-avoidance scores are higher.23 A Visual Analog Scale (VAS) study supported higher frequencies of depression, anxiety and cancer phobia in BMS patients.24 This is reflected in the F3 classification of BMS as a mood/affective disorder.25

Risk factors for developing BMS include stroke, a low level of education, depression, life events, anxiety, personality disorders, the excessive use of hexetidine mouthwashes, and vitamin deficiency.26,27 Burning mouth syndrome is common in Parkinson’s disease, characterized by dopamine dysregulation, especially in the nigrostriatal dopaminergic pathway, as confirmed by positron emission tomography (PET).28,29

Material and methods

A literature search for studies investigating different forms of BMS management was performed in PubMed, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials (CENTRAL), using the Population/Interest/Context (PICO) framework and the following search terms: “burning mouth syndrome”, “BMS”, “alpha-lipoic acid” AND “burning mouth syndrome”, and “clonazepam” AND “burning mouth syndrome”.30 No restrictions on the study size, year or duration were set. Titles were screened for relevance and duplicates were removed, while abstracts were screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.31 Trials that investigated the efficacy of different management approaches for BMS were included (Tables 1,2). The study populations included adult patients undergoing pharmacological or non-pharmacological treatment compared to placebos/controls for BMS management, with randomized controlled trials (RCTs) and case studies screened for relevancy.

Outcome measures

The primary efficacy outcome was the improvement in the VAS and Oral Health Impact Profile (OHIP) scores. Pharmacological management included alpha-lipoic acid (ALA), clonazepam, capsaicin, amisulpride, fluoxetine, trazodone, milnacipran, St. John’s wort (Hypericum perforatum extract), melatonin, bupivacaine, benzodiazepine, and lidocaine lingual nerve injection (Table 1).

Results

Pharmacological management of burning mouth syndrome

As BMS appears to be associated with psychiatric comorbidities, a number of psychotropic drugs are used in its management, including antidepressants and clonazepam (Table 1); psychotherapy has also been used (Table 2).
<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Dose</th>
<th>Efficacy assessment</th>
<th>Control</th>
<th>No. of patients</th>
<th>Main findings</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
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<tr>
<td><strong>Alpha-lipoic acid</strong></td>
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</tr>
<tr>
<td>Carbon 200933</td>
<td>400 mg BID</td>
<td>– change in VAS – responders</td>
<td>Pa</td>
<td>16 ALA</td>
<td>20 Pla</td>
<td>– ALA: 20.0 ± 2.59 vs Pla: 1.60 ± 2.41</td>
<td>–</td>
</tr>
<tr>
<td>Carbon 200934</td>
<td>800 mg/day</td>
<td>change in VAS</td>
<td>Pa</td>
<td>23 ALA</td>
<td>16 Pla</td>
<td>ALA: 2.2 ± 2.6 vs Pla: 3.8 ± 3.7 no sign differences ALA: 1 case of GI side</td>
<td>effects</td>
</tr>
<tr>
<td>Marino 201037 (open-label study)</td>
<td>800 mg/day</td>
<td>– change in VAS – improvement</td>
<td>Pa</td>
<td>14 in each group</td>
<td>ALA −2.1 ± 2.5 vs Pla: 0.5 ± 22 ALA: 8/14 vs Pla: 0/14 no side effects reported</td>
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<tr>
<td>Femiano 200036</td>
<td>600 mg/day for 20 days, then 200 mg/day</td>
<td>improvement</td>
<td>Pa</td>
<td>21 in each group</td>
<td>ALA: −2.1 ± 2.5 vs Pla: 0.5 ± 22 ALA: 8/14 vs Pla: 0/14 no side effects reported</td>
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<tr>
<td>Femiano 200237</td>
<td>200 mg TID</td>
<td>improvement</td>
<td>Pa</td>
<td>30 in each group</td>
<td>ALA: −2.9 vs Pla: −1.2</td>
<td></td>
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<tr>
<td>Femiano 200238</td>
<td>200 mg TID</td>
<td>improvement</td>
<td>Pa</td>
<td>22 in each group</td>
<td>ALA: −2.9 vs Pla: −1.2</td>
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<tr>
<td>Femiano 200239</td>
<td>200 mg TID</td>
<td>improvement</td>
<td>Bet</td>
<td>20 in each group</td>
<td>ALA: −18 vs Pla: −10 Bel: 0% Lac: 0% Pla: 0%</td>
<td>ALA: GI side effects (4/20) Bel: nausea, dizziness, blood pressure fall</td>
<td></td>
</tr>
<tr>
<td>Femiano 200440</td>
<td>600 mg/day</td>
<td>improvement</td>
<td>ALA Psy Com Pla</td>
<td>48 in each group</td>
<td>ALA: −30 vs Pla: −30 Com: 48 Pla: 648</td>
<td></td>
<td></td>
</tr>
<tr>
<td>López-D’Alessandro 201141</td>
<td>ALA: 600 mg/day Gab: 300 mg/day</td>
<td>improvement</td>
<td>ALA Gab Com Pla</td>
<td>20 ALA</td>
<td>20 Gab 20 Com 60 Pla</td>
<td>ALA: 11 vs Pla: 10 Gab: 10 Com: 14 Pla 0/60</td>
<td></td>
</tr>
<tr>
<td>Palacios-Sánchez 201532</td>
<td>200 mg TID for 2 weeks</td>
<td>improvement</td>
<td>Pla</td>
<td>25 ALA</td>
<td>29 Pla</td>
<td>ALA: 16 vs Pla: 8 Pla: 8/9</td>
<td></td>
</tr>
<tr>
<td>Cavalcanti 200943</td>
<td>200 mg TID</td>
<td>improvement</td>
<td>Pla</td>
<td>17 ALA</td>
<td>14 Pla</td>
<td>ALA: 14 vs Pla: 11 Pla: 11</td>
<td></td>
</tr>
<tr>
<td>Gremmeau-Richard 20043097</td>
<td>topical 3 mg/day</td>
<td>change in VAS</td>
<td>Pla</td>
<td>24 in each group</td>
<td>a significant decrease in pain scores Clo: −24 ± 6 vs Pla: −6 ± 0.4</td>
<td>–</td>
<td></td>
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<tr>
<td>Heckmann 201248</td>
<td>0.5 mg/day</td>
<td>BDI</td>
<td>Pla</td>
<td>10 in each group</td>
<td>a significant decrease regarding pain Clo: −3.5 ± 2.9 vs Pla: −1.4 ± 2.4</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Rodríguez de Rivera Campillo 201049</td>
<td>0.5 mg mouth-dissolving tablet</td>
<td>– change in VAS – improvement</td>
<td>Pla</td>
<td>33 in each group</td>
<td>a decrease in pain scores Clo: 4.8 vs Pla: 3.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Barker 200550</td>
<td>Clonazepam: 0.25 mg BID</td>
<td>improvement</td>
<td>–</td>
<td>21 Clo</td>
<td>70 Dia</td>
<td>Clonazepam: partial or complete resolution of symptoms in 71.4% of patients</td>
<td></td>
</tr>
<tr>
<td>Barker 200559</td>
<td>Dia: 2 mg BID</td>
<td>–</td>
<td>–</td>
<td>21 Clo</td>
<td>70 Dia</td>
<td>Dia: partial or complete resolution of symptoms in 71.1% of patients</td>
<td></td>
</tr>
<tr>
<td>Fenelon 201798</td>
<td>VNS</td>
<td>–</td>
<td>Amit</td>
<td>23 Clo drops 16 Amit</td>
<td>Clonazepam: −2.7 ± 2.0 vs Amit: −3.4 ± 2.7 both effective (no difference between the 2 kinds of treatment)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>De Castro 201499</td>
<td>Oral rinse 1 mg/10 mL</td>
<td>change in VAS</td>
<td>–</td>
<td>16 in each group</td>
<td>a decrease in the VAS scores from −5.56 ± 1.77 to 3.50 ± 3.19</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
Continued Table 1

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Dose</th>
<th>Efficacy assessment</th>
<th>Control</th>
<th>No. of patients</th>
<th>Main findings</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin</td>
<td>Marino 2010&lt;sup&gt;36&lt;/sup&gt; (open-label study)</td>
<td>oral rinse TID</td>
<td>change in VAS</td>
<td>Pla</td>
<td>14 in each group</td>
<td>Cap −3.2 ±2.6 vs Pla 0.5 ±2.2</td>
<td>–</td>
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<tr>
<td></td>
<td>Petruzzi 2004&lt;sup&gt;43&lt;/sup&gt;</td>
<td>oral rinse 0.25% TID</td>
<td>change in VAS</td>
<td>Pla</td>
<td>25 in each group</td>
<td>Cap a greater decrease in VAS scores vs Pla 7%</td>
<td>Cap gastric pain (8/25)</td>
</tr>
<tr>
<td></td>
<td>Lauritano 2003&lt;sup&gt;34&lt;/sup&gt;</td>
<td>3×50 mg of red pepper powder with 0.29% of Cap</td>
<td>change in VAS</td>
<td>Pla</td>
<td>42 in each group</td>
<td>High VAS scores (8–10) vs Pla 5% (2/42), Pla 57% (24/42)</td>
<td>–</td>
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<tr>
<td></td>
<td>Toida 2009&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Laf 10 mg BID</td>
<td>improvement</td>
<td>Pla</td>
<td>34 Laf 30 Pla</td>
<td>Laf a greater decrease in VAS scores</td>
<td>Laf mild abdominal pain (2/34)</td>
</tr>
<tr>
<td></td>
<td>Jørgensen 2017&lt;sup&gt;96&lt;/sup&gt;</td>
<td>Cap gel at 2 different doses 0.01% or 0.025%</td>
<td>change in VAS</td>
<td>–</td>
<td>9 in each group, no Pla</td>
<td>0.01% −17 ±2.3 vs 0.025% −10 ±2.8</td>
<td>4 cases of GI side effects</td>
</tr>
<tr>
<td></td>
<td>Silvestre 2012&lt;sup&gt;97&lt;/sup&gt;</td>
<td>oral rinse TID</td>
<td>change in VAS</td>
<td>Pla</td>
<td>15 in each group</td>
<td>significant differences (data not extractable)</td>
<td>–</td>
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<tr>
<td></td>
<td>Amisulpride</td>
<td>Maina 2002&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Ami: 50 mg/day Par: 20 mg/day Ser: 50 mg/day</td>
<td>– change in VAS</td>
<td>Ami 27 Ami: −4.0 ±1.2 vs Par: −3.7 ±1.2 vs Ser: −4.4 ±1.0</td>
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<tr>
<td></td>
<td>Fluoxetine</td>
<td>Zoric 2018&lt;sup&gt;100&lt;/sup&gt;</td>
<td>20 mg/day</td>
<td>– change in VAS</td>
<td>Flu: −4.0 ±2.5 vs Pla: −3.3 ±2.8</td>
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<tr>
<td></td>
<td>Trazadone</td>
<td>Tammai-Saaren 1999&lt;sup&gt;101&lt;/sup&gt;</td>
<td>100 mg/day, then 200 mg/day</td>
<td>– change in VAS</td>
<td>Tra: −2.1 ±1.2 vs Pla: −1.2 ±1.2</td>
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<td></td>
<td>Milnacipran</td>
<td>Ito 2010&lt;sup&gt;106&lt;/sup&gt;</td>
<td>60 mg/day</td>
<td>– change in VAS</td>
<td>–</td>
<td></td>
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<tr>
<td></td>
<td>St. John’s wort</td>
<td>Sardella 2008&lt;sup&gt;102&lt;/sup&gt;</td>
<td>900 mg/day</td>
<td>– change in VAS</td>
<td>Sj: −2.0 ±0.5 vs Pla: −1.2 ±0.5</td>
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<tr>
<td></td>
<td>Melatonin</td>
<td>Varoni 2018&lt;sup&gt;103&lt;/sup&gt;</td>
<td>–</td>
<td>– change in VAS</td>
<td>Mel 0.6 ±0.4 vs Pla 1.2 ±0.5</td>
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<td></td>
<td>Bupivacaine</td>
<td>Trelle 2016&lt;sup&gt;104&lt;/sup&gt;</td>
<td>5 mg TDI</td>
<td>– change in VAS</td>
<td>treatment more effective −6.8 (−8.6, −4.9)</td>
<td></td>
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<tr>
<td></td>
<td>Benzydamine</td>
<td>Sardella 1999&lt;sup&gt;105&lt;/sup&gt;</td>
<td>oral rinse 0.15%</td>
<td>– change in VAS</td>
<td>Ben 1/10 vs Pla 2/10</td>
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<tr>
<td></td>
<td>Lidocaine lingual nerve injection</td>
<td>Gémeau-Richard 2018&lt;sup&gt;106&lt;/sup&gt;</td>
<td>–</td>
<td>– change in VAS</td>
<td>Lid −2.7 ±3 vs Pla 2.0 ±2.6</td>
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</table>

BID – twice a day; VAS – Visual Analog Scale; ALA – alpha-lipoic acid; Pla – placebo; GI – gastrointestinal; TID – 3 times a day; Bet – bethanol; Lac – lactoperoxidase; Psy – psychotherapy; Com – combination; Gab – gabapentin; Clo – clonazepam; BDI – Beck Depression Inventory; Dia – diazepam; VNS – Visual Numeric Scale; Amit – amitriptyline; Cap – capsaicin; Laf – lafutidine (capsaicin analog); Ami – amisulpride; Par – paroxetine; Ser – sertraline; Ham-D – Hamilton Depression Rating Scale; Flu – fluoxetine; Tra – trazodone; GOHAI – General Oral Health Assessment Index; Sj – St. John’s wort; Mel – melatonin; Ben – benzydamine; Lid – lidocaine.
## Table 2. Non-pharmacological management of burning mouth syndrome (BMS)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Efficacy assessment</th>
<th>Control</th>
<th>No of patients</th>
<th>Main findings</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasers</td>
<td>Barbosa 2018&lt;sup&gt;45&lt;/sup&gt;</td>
<td>– changes in VAS – salivary flow</td>
<td>ALA</td>
<td>10 LLLT 5 ALA</td>
<td>– LLLT: −20 vs ALA: −3.5</td>
<td>no side effects reported</td>
</tr>
<tr>
<td></td>
<td>Arbabi-Kalati 2015&lt;sup&gt;78&lt;/sup&gt;</td>
<td>– changes in VAS – QoL</td>
<td>Pla</td>
<td>10 females in each group</td>
<td>– LLLT: −4.4 ±3.0 vs Pla: −0.2 ±1.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Spanemberg 2015&lt;sup&gt;79&lt;/sup&gt;</td>
<td>– change in VNS – change in VAS – OHIP</td>
<td>3 groups vs Pla</td>
<td>20 LLLT II 19 LR 19 Pla</td>
<td>– LLLT: −5.00 ±2.52 vs LLLT II −5.00 ±2.31 vs LR −3.76 ±2.68 vs Pla −2.95 ±1.70</td>
<td>no side effects reported</td>
</tr>
<tr>
<td></td>
<td>Spanemberg 2019&lt;sup&gt;80&lt;/sup&gt;</td>
<td>change in VAS</td>
<td>Pla</td>
<td>12 LLLT 9 Pla</td>
<td>LLLT: −4.2 vs Pla: −3.2</td>
<td>–</td>
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<tr>
<td></td>
<td>Valenzuela 2017&lt;sup&gt;77&lt;/sup&gt;</td>
<td>– change in VAS – OHIP</td>
<td>2 groups vs Pla</td>
<td>16 LLLI 16 LLLII 12 Pla</td>
<td>– LLLT: −1.18 ±1.60 vs LLLT II −1.32 ±1.80 vs Pla: −0.18 ±1.160</td>
<td>no side effects reported</td>
</tr>
<tr>
<td></td>
<td>Bardellini 2019&lt;sup&gt;92&lt;/sup&gt;</td>
<td>– changes in VAS – OHIP</td>
<td>Pla</td>
<td>43 LLLT 42 Pla</td>
<td>significant improvement</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Sugaya 2016&lt;sup&gt;100&lt;/sup&gt;</td>
<td>complete remission</td>
<td>Pla</td>
<td>13 LLL 10 Pla</td>
<td>LLLT: −6.13 ±4.10 vs Pla: 4.10</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Antonić 2017&lt;sup&gt;110&lt;/sup&gt;</td>
<td>change in VAS 660 nm and 810 nm</td>
<td>20 in each group</td>
<td>20 LLLT 16 LLLII 12 Pla</td>
<td>−2.5 vs −20 improvement in both cases</td>
<td>–</td>
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<tr>
<td></td>
<td>dos Santos 2015&lt;sup&gt;111&lt;/sup&gt;</td>
<td>change in VAS prospective study</td>
<td>20</td>
<td>–</td>
<td>LLLT effective</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>dos Santos 2011&lt;sup&gt;112&lt;/sup&gt;</td>
<td>change in VAS 10 patients follow-up</td>
<td>–</td>
<td>–</td>
<td>a reduction in the VAS scores by 58%</td>
<td>–</td>
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<tr>
<td></td>
<td>Brailo 2013&lt;sup&gt;113&lt;/sup&gt;</td>
<td>change in VAS 16 patients follow-up</td>
<td>–</td>
<td>–</td>
<td>a decrease in burning by 55.2%</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Arduino 2016&lt;sup&gt;114&lt;/sup&gt;</td>
<td>– change in VAS – MPQ – OHIP</td>
<td>topical Clo</td>
<td>18 LLLT 15 Clo</td>
<td>– LLLT: −2.78 ±4.80 vs Clo: −1.15 ±1.80</td>
<td>Clo: fever, dizziness and headache in 32% of patients</td>
</tr>
<tr>
<td></td>
<td>Sikora 2018&lt;sup&gt;115&lt;/sup&gt;</td>
<td>change in VAS data not extractable</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>Femiano 2004&lt;sup&gt;40&lt;/sup&gt;</td>
<td>CBT (two 1-hour sessions per week)</td>
<td>improvement</td>
<td>ALA 48 in each group</td>
<td>ALA: 39/48</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Miziara 2009&lt;sup&gt;83&lt;/sup&gt;</td>
<td>improvement</td>
<td>Pla</td>
<td>24 Psy 20 Pla</td>
<td>Psy: 17/24 vs Pla: 8/20</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Bergdahl 1995&lt;sup&gt;116&lt;/sup&gt;</td>
<td>pain symptoms using VAS</td>
<td>Pla</td>
<td>15 in each group</td>
<td>Psy: 27% symptom-free (4 pts) vs Pla: none</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Komiyaama 2013&lt;sup&gt;117&lt;/sup&gt;</td>
<td>pain symptoms (not a trial)</td>
<td>no comparison</td>
<td>–</td>
<td>group intervention helpful in persistent pain</td>
<td>–</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Juricic Kasic 2015&lt;sup&gt;107&lt;/sup&gt;</td>
<td>– change in VAS – BDQ</td>
<td>Clo</td>
<td>19 in each group</td>
<td>–</td>
<td>Clo: nausea, dizziness, drowsiness</td>
</tr>
<tr>
<td></td>
<td>Zavoreo 2017&lt;sup&gt;110&lt;/sup&gt;</td>
<td>– change in VAS – OHIP – Ham-D</td>
<td>vitamin C</td>
<td>21 in each group</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

LLL – low-level laser therapy; QoL – quality of life; OHIP – Oral Health Improvement Profile; LR – Laser Red; MPQ – Multiple Personality Questionnaire; CBT – cognitive behavioral therapy; Acu – acupuncture; Vit.C – vitamin C.
**Alpha-lipoic acid**

Alpha-lipoic acid is a free-radical scavenger, and its metabolite – dihydrolipoic acid – has antioxidant properties and can regenerate endogenous antioxidants (vitamin E, vitamin C and glutathione).32 Alpha-lipoic acid is considered an effective medication for BMS management, as highlighted by the evidence obtained from trials measuring its efficacy by means of various methods,33–44 with some heterogeneity among the studies (Table 1). An interesting comparison with low-level laser therapy (LLLT) showed that both LLLT and ALA were efficient in treating BMS.45

**Benzodiazepines**

Benzodiazepines are hypnotics/sedatives that potentiate the action of the inhibitory neurotransmitter gamma aminobutyric acid (GABA).46 We found 3 trials that compared the efficacy of clonazepam against a placebo using the VAS scores.47–49 The overall results proved the effectiveness of clonazepam, as highlighted by a significant reduction in the VAS scores. Systemic clonazepam presented the best efficacy, with more than 70% of patients showing the partial or complete resolution of their oral symptoms as compared to just over 55% of patients on diazepam.50 Topical clonazepam was also effective, and considered more cost-effective than amisulpride, paroxetine and sertraline,51 while prazepam showed some efficacy as well.52

**Capsaicin**

We found 4 studies that measured the efficacy of capsaicin.35,53–55 The overall results showed a positive effect and a possible beneficial role of capsaicin in BMS management.

**Antidepressants**

Selective serotonin reuptake inhibitors (SSRIs) have low side-effect profiles and are particularly efficient in psychogenic BMS management.56 At low doses, they inhibit serotonin reuptake, and at high doses, they may inhibit noradrenaline reuptake as well.56 There have not been many trials pitting SSRIs against a placebo or control medication (Table 1), and most of the available evidence comes from case studies. Sertraline, a widely used antidepressant, resulted in a reduction in the severity of stomatodynia.57 Paroxetine proved to be efficacious, with complete pain remission in more than 70% of patients.58 In 1 study, painful burning sensations were elicited with fluoxetine treatment, and citalopram used as an alternative led to the remission of BMS associated with depression.59 On the other hand, clomipramine reduced pain in BMS patients at a level similar to a placebo.60

Venlafaxine and duloxetine are serotonin-norepinephrine reuptake inhibitors (SNRIs). Venlafaxine with clonazepam were successful in patients unresponsive to anticonvulsants and antidepressants.11 Duloxetine was observed to significantly relieve pain in case reports, and led to symptom remission and improvement in the quality of life (QoL).61,62 Moclobemide is a reversible inhibitor of monoamine oxidase, and it reduced anxiety, depression and the VAS scores among BMS patients.63 Milnacipran blocks serotonin and norepinephrine reuptake. It has a simple pharmacokinetics profile and no inhibitory effects on cytochrome P450 enzymes, so it is recommended for patients with multiple treatment regimens.64 Low-dose milnacipran (30 mg daily) had a poor response; the cumulative improvement rate increased to 68% when the daily dose was increased from 60 mg to 90 mg.65 Milnacipran reportedly brought about significant reductions in the VAS scores,66 reduced depression and improved patients’ QoL,67 but there have not been enough trials comparing milnacipran to a placebo or control medication (Table 1). Most of the available evidence of the efficacy of milnacipran comes from case studies, such as that of a 71-year-old with no satisfactory response to psychotropic drugs who recovered from BMS when sertraline was replaced with milnacipran.68

**Antipsychotics and anti-Parkinson medications**

For antipsychotics and anti-Parkinson drugs, there is not enough data comparing a placebo or control medication with these medications, and most of the evidence comes from case studies. Olanzapine, an antipsychotic, caused rapid significant improvement in treating BMS,69 even in patients unresponsive to milnacipran or paroxetine.70 Aripiprazole ameliorated chronic burning pain,71 while levosulpiride and amisulpride alleviated oral symptoms.72,73 A case of refractory BMS showed complete relief after treatment with pramipexol.74 The BMS symptoms also responded to levodopa.7

**Anticonvulsants**

Pregabalin was successful in patients unresponsive to milnacipran or duloxetine.75 Gabapentin – a structural analog of GABA – reduced oral burning, while nortriptyline and sertraline were contraindicated.76 However, another study failed to confirm the efficacy of gabapentin in BMS.77

**Non-pharmacological management of burning mouth syndrome**

The most common non-pharmacological interventions are LLLT, psychotherapy and acupuncture.

We found 4 trials measuring the efficacy of LLLT using the VAS scores78–81 and 3 trials measuring its efficacy
using OHIP (Table 2). The overall results showed positive effects on both VAS and OHIP. Interestingly, a comparison with ALA showed similar efficacy.

Two trials measured the efficacy of psychotherapy in alleviating the BMS symptoms, but there have not been enough trials studying the efficacy of acupuncture as compared to a placebo or control medication (Table 2).

Discussion

Both the diagnosis and management of BMS are unclear. Burning mouth syndrome is known as a chronic condition with pain intensity increasing from morning to evening. The tongue is the most commonly affected site, followed by the lower lip and the hard palate. Burning mouth syndrome could be due to immunological or endocrine etiology, and some recent evidence suggests neurophysiological mechanisms, such as a peripheral small-fiber neuropathy or central neuropathic disturbances. Risk factors include metabolic disorders, vitamin deficiencies or medications, i.e., angiotensin-converting enzyme inhibitors and anticoagulants.

The prevalence of BMS can be especially high in psychiatric patients, and it is associated with comorbidities such as depression and anxiety. Assessment and outcome measurements include the VAS scores, QoL ratings, taste, and the salivary flow.

Multiple kinds of pharmacological treatment have been tried, including ALA, milnacipran, benzodiazepines, antidepressants, anticonvulsants, and atypical antipsychotics (Table 3). Topical clonazepam is used for peripheral BMS, while central BMS is managed with antidepressants, anti-seizure medications or antipsychotics, but the evidence of their efficacy is weak, as the power of the studies and the numbers of patients have been relatively low, and most studies have had short follow-up periods with high variability.

Burning mouth syndrome could have a neuropathic origin, and experts recommend neuropathic pain agents, such as amitriptyline, gabapentin, benzodiazepines, antipsychotics, or mood-altering interventions. Our study highlights that ALA, clonazepam and capsaicin may bring promising results (Table 4); however, more studies are needed, with longer follow-up periods and larger numbers of patients. Alpha-lipoic acid and clonazepam have shown modest evidence of decreasing BMS. The overall quality of the evidence of effectiveness remains low for all pharmacological and non-pharmacological interventions.

Our review has some limitations. There was high heterogeneity among the studies and there were few clinical trials for most of the management options. Different methods were used to present the findings, while some trials had missing data (Tables 1,2).

Combination treatment has shown promising results. Alpha-lipoic acid with gabapentin, sertraline with cognitive behavioral therapy, and tranylcypromine with low-dose anxiolytics and psychotherapy have been effective in refractory BMS. Non-pharmacological interventions, such as LLLT or psychotherapy, have shown some efficacy. However, large-scale clinical trials with long follow-up periods are still needed to confirm these findings. Treatment should be tailored with careful history-taking and consultations among a variety of health professionals, including psychiatrists, dentists, pain specialists, and neurologists with a special interest in headaches, to avoid potential delays in diagnosis. A clinical diagnosis should include the assessment of the nutritional status and comprehensive dental evaluation. The management of BMS should include managing anxiety, depression and pain disorders, ruling out treatable conditions,
and discussing different management options with the patient. Non-pharmacological interventions could be tried first, if clinically appropriate, and compatible with the patient’s preferences and the severity of the symptoms. If pharmacotherapy is appropriate, ALA or capsaicin could be first choice because of favorable side-effect profiles, while clonazepam or milnacipran could be second-line medications for BMS management due to their side effects – particularly cognitive ones – and an increased risk of dependence associated with benzodiazepines.

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**References**


50. Barker KE, Batstone MD, Savage NW. Comparison of treatment moda-

49. Guarneri F, Guarneri C, Marini H. Contribution of neuroinflamma-


47. Feiamento F, Gomos F, Scully C. Burning mouth syndrome: The effi-


