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A systematic review of randomized trials for the treatment of burning mouth syndrome

Steve Kisely [a,b,c,d,*], Malcolm Forbes [a,e,f], Emily Sawyer [g], Emma Black [h], Ratilal Lalloo [i]

[a] School of Medicine, The University of Queensland, Woolloongabba, Australia
[b] Griffith Health Institute, Gold Coast, Queensland, Australia
[c] Department of Psychiatry, Dalhousie University, Halifax, Canada
[d] Department Community Health and Epidemiology, Dalhousie University, Halifax, Canada
[e] Department of Psychiatry, Royal Melbourne Hospital, 300 Grattan St, Parkville, Australia
[f] Melbourne Medical School, University of Melbourne, Melbourne, Australia
[g] School of Medicine, James Cook University, Queensland, Australia
[h] Rural Clinical School, The University of Queensland, Toowoomba, Australia
[i] School of Dentistry, The University of Queensland, Herston, Queensland, Australia

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ABSTRACT

Objectives: Burning mouth syndrome (BMS) is characterized by burning of the oral mucosa in the absence of underlying dental or medical causes. The results of previous systematic reviews have generally been equivocal. However, findings for most interventions are based on searches of 5–10 years ago. This study therefore updates previous searches of randomized controlled trials (RCTs) for pain as assessed by Visual Analogue Scales (VAS). Secondary outcomes included quality of life, mood, taste and salivary flow.
Methods: A search of MEDLINE and Embase up to 2016.
Results: 24 RCTs were identified. Meta-analyses were impossible because of wide variations in study method and quality. The commonest interventions were alpha-lipoic acid (ALA) (8 comparisons), capsaicin or an analogue (4 comparisons), clonazepam (3 comparisons) and psychotherapy (2 comparisons). ALA and capsaicin led to significantly greater improvements in VAS (4 studies each), as did clonazepam (all 3 studies), at up to two month follow-up. However, capsaicin led to prominent dyspepsia. Psychotherapy significantly improved outcomes in one study at two and 12 month follow-up. Catauma and tongue-protectors also showed promise (one study each). There were no significant differences in any of the secondary outcomes except in the one study of tongue protectors.
Conclusions: At least in some studies and for some outcomes, ALA, clonazepam, capsaicin and psychotherapy may show modest benefit in the first two months. However, these conclusions are limited by generally short follow-up periods, high study variability and low participant numbers. Further RCTs with follow-up of at least 12 months are indicated.

1. Introduction

There is a strong interaction between oral and mental health. In one direction, several psychiatric disorders such as schizophrenia, bipolar affective and eating disorders can lead to poor oral health because of poor oral hygiene, sugary drinks, barriers to accessing health care, chronic medical conditions, poor nutrition and comorbid substance misuse [1–3].

In the other direction, perception of dental pain may be exacerbated by someone's mental state, regardless of the degree of oral pathology. One example is burning mouth syndrome (BMS), a somatic symptom disorder characterized by a burning sensation in clinically healthy oral mucosa [4].

BMS is a poorly-understood but important chronic pain disorder that affects more than 1 million people in the United States [5]. BMS may be classified into three types [6]. In Type 1, patients are free of pain on waking but experience increasing symptoms as the day goes on. About a third of patients have this type of disorder and this is generally associated with organic disorders such as nutritional deficiency, auto-immune conditions and diabetes mellitus. In Type 2, patients have continuous pain throughout the day; this type accounts for 55% of patients and has the strongest association with psychological disorders [4]. In Type 3, patients have intermittent symptoms with pain-free periods during the day. These constitute 10% of patients with BMS and are associated with allergic reactions.

An alternative classification involves defining BMS as primary or secondary [7]. Patients with a primary or idiopathic BMS present with

* Corresponding author at: School of Medicine, The University of Queensland, Level 4, Building 1, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia.
E-mail address: s.kisely@uq.edu.au (S. Kisely).

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stinging or burning in the mouth, accompanied by a clinically normal oral mucosa with the absence of medical or dental diseases. By contrast, in patients with secondary BMS, symptoms arise from local or systemic organic conditions such as dry mouth, oral infections, autoimmune disorders, nutritional deficiencies, allergies, gastro-oesophageal reflux, medication side-effects, and some endocrine disorders.

Uncertainty concerning the diagnostic criteria for BMS means that it is difficult to estimate the prevalence of the disorder with figures of between 0.7 and 4.6% in the general population [6]. However, estimates for the broader syndrome have been as high as 15% [8]. It is more common among older people and women [6].

While treatment of secondary BMS is directed to treating the underlying organic cause, a wide range of interventions have been proposed for primary BMS [9]. Of these the most common are anti-oxidants or vitamins, capsaicin, anaesthetic agents and clonazepam [6,9,10]. Many are used both systematically and topically. Each of these will be considered in turn.

Alpha-lipoic acid (ALA) is a mitochondrial coenzyme with both antioxidant and neuroprotective effects. ALA may also stimulate the production of neural growth factors [6]. Capsaicin is responsible for the burning sensation experienced with hot chili pepper, and acts on the sensory afferent neuron [6,10]. It binds to TRPV1, a potent calcium channel-specific receptor, thereby inactivating neuronal responses to heat [11]. Prolonged exposure depletes TRPV1 leading to desensitization of pain receptors [11]. Topical capsaicin can also be used as a desensitizing agent or analgesic although its taste reduces acceptability [6,10].

Clonazepam acts as an agonist of gamma-amino butyric acid (GABA) receptors. In oral form, it leads to central nervous system inhibition resulting in an anticonvulsant action, sedation, muscular relaxation, and tranquilisation [6,10]. Topically, clonazepam can reduce burning symptoms without the adverse effects of systemic use.

Lidocaine is commonly used as a local anaesthetic in dental clinics while benzydamine hydrochlorate has both anaesthetic and anti-inflammatory effects [6,10]. These two agents can be used as a mouthwash to lessen the pain or burning symptom in BMS. However, the short duration of the analgesic effect limits their efficacy.

Additional physical treatments have included antidepressants, antipsychotics, St John's Wort, *Aloe vera* and tongue protectors [6,10]. Because of the strong psychological component of the illness, psychotherapy has also been tried [6,10].

The results of previous systematic reviews of possible interventions were equivocal [10–12]. However, they were based on searches of 5 to 10 years ago. The one exception was a systematic review that was restricted to clonazepam [13]. This study therefore updates previous searches of randomized controlled trials (RCTs) of all available treatments where the primary outcome was pain intensity.

2. Method

The review was registered with PROSPERO, an international database of prospectively registered systematic reviews in health and social care based in the United Kingdom (Registration number: CRD42016032778) [14]. In addition, we followed recommendations for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement including background, search strategy, methods, results, discussion and conclusions [15].

2.1. Health outcomes

The primary outcome of this study was pain as assessed by Visual Analogue Scale (VAS) or standardised instruments such as the McGill Pain Questionnaire [16]. Secondary outcomes included quality of life and psychological status a measured by standardised questionnaires. In the case of quality of life, this was divided into instruments that assessed general health such as the 36-item short-form health survey (SF-36) [17], and others that targeted the impact of oral health on quality of life such as the Oral Health Impact Profile (OHIP). The latter has 14- and 49-item versions that explore oral function and quality of life, including speech, taste, eating, and problems with dentures [18,19]. Psychological status was measured through instruments such as the Hospital Anxiety and Depression Scale [20].

2.2. Inclusion and exclusion criteria

We included placebo-controlled RCTs of patients with a diagnosis of primary or idiopathic BMS who presented with stinging or burning in the mouth accompanied by a clinically normal oral mucosa in the absence of medical or dental diseases. This comparison was chosen given the high response to placebo in some studies of BMS [21]. An active agent that had potential side-effects should therefore be superior to an inactive one with little such possibility. For inclusion, papers had to state somewhere that allocation to active treatment or placebo was random. We excluded studies of secondary BMS arising from local or systemic organic conditions such as dry mouth, oral infections, autoimmune disorders, nutritional deficiencies, allergies, oesophageal reflux, medication side-effects, and some endocrine disorders.

2.3. Search strategy

We searched Medline and EMBASE up till January 2016 using the following text, MeSH or Emtree terms as appropriate: ("stomatodynia") OR ("burning mouth syndrome"[MeSH Terms] OR ("burning"[All Fields] AND "mouth"[All Fields] AND "syndrome"[All Fields]) OR "burning mouth syndrome"[All Fields]) AND Randomized Controlled Trial[ptyp]. We searched for further publications by scrutinizing the reference lists of initial studies identified and other relevant review papers. We made attempts to contact selected authors and experts. Two reviewers (SK and MF or ES) independently assessed titles, abstracts and papers, as well as extracted and checked the data for accuracy. EB was available to advise and RL provided dental expertise. In the case of disagreements, consensus was reached on all occasions.

2.4. Study quality

We assessed the quality of included studies using the following criteria of the risk of bias assessment tool, developed by the Cochrane Collaboration to assess possible sources of bias in RCTs: 1. Adequate generation of allocation sequence; 2. Concealment of allocation to conditions; 3. Prevention of knowledge of the allocated intervention to participants and personnel; 4. Prevention of knowledge of the allocated intervention to assessors of outcome 5. Dealing with incomplete outcome data; 6. Selective reporting of outcomes, and; 7. Other sources of bias [22].

2.5. Statistical analysis

If appropriate we combined data from different studies using the standardised mean difference (SMD) for continuous data [23] and the relative risk (RR) for any dichotomous outcome, assessing for publication bias where there were at least 10 studies.

3. Results

We found 295 citations of interest in the initial electronic searches, of which 87 abstracts were screened. Of these, 35 full-text papers were potentially relevant and assessed for eligibility. Thirteen papers were excluded for reasons listed in Fig. 1. Two additional papers were found from the reference lists of other papers from the database search. This left 24 papers (Fig. 1). Participants were predominately females of older age.

The most common interventions were alpha-lipoic acid (ALA) (8 comparisons), capsaicin or an analogue (4 comparisons), clonazepam (3 comparisons and psychotherapy (2 comparisons) (Table 1)).