Interventions for the Treatment of Burning Mouth Syndrome: A Systematic Review

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Aims: *To carry out a systematic review of previous studies to determine the effectiveness of any intervention vs placebo for relief of symptoms and improvement in quality of life of patients with burning mouth syndrome (BMS) and to assess the quality of the studies.* ***Methods:*** *Electronic databases, conference proceedings, and bibliographies of identified publications were searched (up to September 2001) to identify relevant literature, irrespective of language of publication. Randomized controlled trials and controlled clinical trials of interventions used for the treatment of BMS in comparison to a placebo were included. The primary outcome was relief of burning/discomfort. The screening of studies, validity assessment, and data extraction were undertaken independently and in duplicate. Since statistical pooling of data was inappropriate, a qualitative assessment was undertaken.* ***Results:*** *Seven trials, evaluating antidepressants, cognitive behavioral therapy, analgesics, hormone replacement therapy, and vitamin complexes, met the inclusion criteria. None of the trials was able to provide conclusive evidence of effectiveness. However, cognitive behavioral therapy may be beneficial in reducing the intensity of the symptoms.* ***Conclusion:*** *Given that the research evidence is, as yet, unable to provide clear, conclusive evidence of an effective intervention, clinicians need to provide support and understanding when dealing with BMS sufferers. Psychological interventions that help patients to cope with symptoms may be of some use, but promising and new approaches to treatment still need to be evaluated in good-quality randomized controlled trials.* J OROFAC PAIN 2003;17:293–300.

Key words: burning mouth syndrome, randomized controlled trials, systematic review

The complaint of a burning sensation in the mouth, which can be localized to the lips or tongue or be more widespread within the mouth, can be a symptom of other disease or a syndrome in its own right of unknown etiology.[1] Burning mouth is said to be a symptom of other disease when local or systemic factors are implicated and their treatment results in resolution of burning mouth. In other patients, however, no underlying dental or medical causes are identified and no gross oral signs are found, and it is in these instances that the term burning mouth syndrome (BMS) should be used. The word syndrome is justified in that many patients will also have subjective xerostomia (dryness), oral paresthesia, and altered taste or smell. There is confusion in the literature because a wide variety of different terms and definitions have been used to describe the sensation of a burning mouth.[2] These include glossodynia, glossopyrosis, stomatodynia, stomatopyrosis, sore tongue, burning mouth, and oral dysesthesia.

The epidemiologic data on BMS is generally poor due, in part, to lack of strict adherence to diagnostic criteria.[1,3] Reported prevalence rates in general populations vary from 0.7%[4] to 15%,[5] and most relate to burning mouth as a symptom rather than the syndrome. BMS predominantly affects females with an increased prevalence with age and following menopause.[6]

The cause of BMS is essentially unknown, although a wide range of factors has been suggested.[1,2,6,7] Unfortunately, most of the studies are small, uncontrolled, and lack replication and standardized outcome measures. Risk factors and high-risk patients have not been identified, although it would appear that postmenopausal women are at highest risk. The natural history of BMS has not clearly been defined and there are no reports of longitudinal cohort studies.[1] There is an anecdotal report of at least partial spontaneous remission within 6 to 7 years in approximately half of these patients.[7]

Case control methodology[3,7] has been used to describe the clinical features of BMS. The prominent feature is the symptom of burning pain/discomfort or even an annoying/tender sensation, which can be localized just to the tongue and/or lips but can be more widespread and involve the whole oral cavity. In most patients the symptoms are bilateral and have been present for many months, with the intensity of pain tending to increase toward the end of the day. Altered taste sensation and dryness are frequently reported. Many of these patients show evidence of anxiety, depression, and personality disorders, and it has been demonstrated that patients with BMS show an increased tendency for somatization as well as several other psychiatric features when measured on the Symptom Checklist-90 (SCL-90) questionnaire.[8] Standard clinical examination of the oral cavity identifies no abnormalities and there are no clinically useful investigations that would help to support a diagnosis of BMS. However, more sophisticated testing indicates that neuronal mechanisms may be involved. Grushka[9] and Svensson et al[10] have suggested that these patients may have altered sensory and pain thresholds. Two recent studies using blink reflex and thermal quantitative sensory tests have demonstrated signs of neuropathy in a great majority of BMS patients.[11,12] It has also been postulated that BMS represents an oral pain phantom induced in susceptible individuals by damage to the taste system.[13] To date, the management of this condition has centered on the use of vitamins, hormones, and psychologic treatment.[14]

The objectives of this systematic review of previous studies were to determine the effectiveness of any intervention vs placebo for relief of symptoms and improvement in quality of life of patients with BMS and to assess the quality of the studies. The review was carried out in collaboration with the Cochrane Oral Health Group.

Materials and Methods

Inclusion Criteria

For a trial to be included in the review it had to:

- Be a randomized controlled trial (RCT) or controlled clinical trial (CCT) (where participants were allocated to different interventions, but the study did not specify how)
- Include patients with BMS, that is, oral mucosal pain or discomfort with no dental or medical cause for such symptoms
- Evaluate any intervention used for the treatment of BMS compared to placebo
- Have measured relief of burning/discomfort (secondary outcome measures of changes in taste, feeling of dryness, and quality of life were also recorded when available)

Search Strategy for Identification of Studies

Electronic databases (including The Cochrane Library [Issue 3, 2001], MEDLINE [1966 to September 2001], EMBASE [1980 to September 2001], and Best Evidence 5 [2001]) were searched by the use of both controlled vocabulary (eg, MeSH terms) and free-text words. The search strategy was developed around the following terms: burning mouth syndrome (MeSH), burning NEAR mouth, burning NEAR tongue, glossodynia, glossopyrosis, stomatodynia, stomatopyrosis, oral NEXT dysesthesia.

Handsearching of conference proceedings and screening of bibliographies of identified trials and reviews were undertaken to identify further studies. In addition, authors of relevant studies were contacted to identify missing data and unreported trials.

Non–English-language papers were considered where translation was available.

Assessment of Relevance. A pool of titles and abstracts of potential studies were first screened for placebo-controlled RCTs and CCTs. The full article describing each selected trial was screened independently by 2 reviewers to confirm eligibility.

The reviewers were not blinded to the identity of the study authors.

Data Extraction

The following study features were extracted independently by 2 reviewers:

1. Adequacy of randomization and assignment methods
2. Details of blinding
3. Whether the trial was of parallel or crossover design
4. Length of study period and first crossover period
5. Method of diagnosis
6. Comparability of treatment groups at baseline
7. Treatments and number randomized
8. Outcome measures used
9. Dropouts and reasons
10. Side effects and toxicities
11. Whether an intention-to-treat analysis was used

Study authors were contacted to supply missing information and to clarify points where necessary.

Quality Assessment

Two reviewers independently assessed the quality of each study according to the guidelines in the Cochrane Reviewers' Handbook.[15] Allocation concealment (where participants/investigators are unaware of treatment group until after assignment), blinding, and the handling of withdrawals and dropouts were assessed, but no overall summary score was calculated.

Data Analysis

All data were managed in the Review Manager 4.1 software (Cochrane Collaboration, 2000). Dropouts were regarded as treatment failures. If crossover trials had been identified for inclusion in the review they were to be combined with parallel group studies, provided that the appropriate standard errors were available, using the statistical software package Stata.

Results

Due to differences in patient type, interventions, and outcome measures, statistical pooling of data was not possible. The results are therefore presented in a narrative.

Seven trials were identified as meeting the inclusion criteria, 6 RCTs[16–21] and 1 CCT.[22] Six trials defined their participants as BMS sufferers[16–21] and 1 recruited postmenopausal participants complaining of a dry, burning sensation in the mouth.[22] The age of the participants ranged from 38 years to 85 years, with reported duration of BMS symptoms ranging from 6 months to 21 years. The interventions evaluated were antidepressants,[17,20,21] cognitive behavioral therapy,[16] analgesics,[18] hormone replacement therapy,[22] and vitamin complexes.[19] Four of the 7 included trials used a visual analog scale (VAS) to measure the intensity of the BMS symptoms.[16–18,20] The Clinical Global Impression Scale and the McGill Pain Questionnaire were also used to measure the severity of pain. Other outcomes assessed included dryness, bad taste, psychiatric status, personality, psychosocial stressors, social functioning, plasma levels, saliva flow, and tissue change. Further characteristics of the included studies are presented in Table 1.

Methodological Quality of Included Studies

Allocation Concealment. In only 1 of the RCTs was allocation concealment ascertainable.[20] In this trial, randomization was performed in blocks of 6 by a third party (Orion Pharma). Identical capsules of trazodone and placebo were manufactured and packaged in the same way. Sardella et al[18] used a random number table to allocate participants to treatment groups; however, whether this process was concealed or not is unclear. The remaining RCTs stated that they were randomized but gave no further information regarding randomization or allocation concealment.

Blinding. Two of the RCTs reported that they were double-blind.[18,20] However, 1 of the 3 groups in the trial by Sardella et al[18] did not receive any treatment and, therefore, could not be double-blind. The remaining RCTs either did not report on blinding,[16,17] or it was clear that neither the patients nor the investigators were blind to treatment allocation.[19,21] The CCT by Pisanty et al[22] was double-blind, with both the clinician and the patients unaware of the ointment used until after the final assessment.

Withdrawals

In 4 of the 7 included studies there were no dropouts.[16,18,19,22] Tammiala-Salonen and Forssell[20] indicate that in their study of trazodone vs placebo, 7/18 in the treatment group and 2/19 in the placebo

Table 1 Characteristics of Included Studies

	Antidepressants			Cognitive behavioral therapy	Analgesics	Hormone replacement therapy	Vitamin complexes
	Bogetto et al[21]	Loldrup et al[17]	Tammiala-Salonen and Forssell[20]	Bergdahl et al[16]	Sardella et al[18]	Pisanty et al[22]	Femiano et al[19]
Country of origin	Italy	Denmark	Finland	Sweden	Italy	Israel	Italy
Design	Single-center RCT	Multicenter RCT stratified by classification of depression	Single-center RCT	Single-center RCT	Single-center RCT	Single-center CCT	Single-center RCT matched for age and sex
Allocation concealment	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Blinding	No	Not reported	Double-blind	Not reported	Double-blind	Double-blind	No
Participants	121 BMS patients	77 BMS patients	37 BMS women	30 BMS patients	30 BMS patients	22 postmenopausal women with dry, burning sensation in mouth	42 BMS patients (20 of whom had removable prostheses)
Diagnostic criteria	Unclear	Unclear*	Stated	Stated	Stated	Unclear	Stated
Mean age (y)	65.4 ± 10.6	63 (range 38–80)	59 (range 39–71)	54 (range 38–69)	69 (range 54–85)	Not stated	63 (range 43–78)
Male-female ratio	Not stated	6:71	0:37	6:24	4:26	0:22	10:32
Mean duration of BMS (y)	5.7 ± 3.2	3 (range 0.5–21)	2.9 (range 0.5–20)	Not stated	1.5	Not stated	Not stated
Interventions							
Group 1	Paroxetine 20 mg/d (n = 24)	Clomipramine 75 mg increased to max 150 mg after 3 wk (n unclear)	Trazodone 200 mg daily (n = 18)	Cognitive therapy 1h, weekly sessions for 12–15 visits (n = 15)	Benzydamine, HCl oral rinse (15 mL) 3 times daily (n = 10)	Estrone ointment 50,000 U/g (n = 6)	Alpha-lipoic acid (thioctic acid) 600 mg/d for 20 d, 200 mg/d for 10 d (n = 21)
Group 2	Amitriptyline 25 mg/d (n = 23)	Mianserin 30 mg increased to max 60 mg after 3 wk (n unclear)	Placebo (n = 19)	Attention placebo 3 visits over 12–15 wk (n = 15)	Placebo (n = 10)	Estrone 10,000 U/g + progesterone 50 mg/g ointment (n = 9)	Cellulose starch 100 mg/d for 30 d (n = 21)
Group 3	Clordemetildiazepam 1 mg/d (n = 26)	Placebo (n unclear)	—	—	No treatment (n = 10)	Placebo base ointment (n = 7)	—
Group 4	Amisulpride 50 mg/d (n = 24)	—	—	—	—	—	—
Group 5	Placebo (n = 24)	—	—	—	—	—	—
Duration	8 wk	6 wk	8 wk	12–15 wk	4 wk	3 times/d for 30 d	30 d
Comparability of groups at baseline	Unclear	Unclear	Differed with regard to pain intensity	Comparable	Comparable	Unclear	Unclear
Results	SS reduction in MADRS and CGI-I at both 4 and 8 wk for amisulpride; SS reductions in mean scores on HARS for groups 1–4; no SS reduction in placebo group	No significant difference between 3 groups regarding improvement over time, as defined by the area under the curve spanned by VAS (0–100 mm) of pain	No significant differences between groups in VAS or McGill Pain Questionnaire data	Intensity of BMS symptoms (measured on VAS [1–7]) significantly reduced in cognitive therapy group at end of trial and 6-mo follow-up; no decrease of symptoms in control group	No significant differences between groups in VAS (ineffective to complete response) data for severity of symptoms	Reported moderate improvement in subjective complaints (burning sensation, dryness, bad taste) for all 3 groups	16/21 patients in treatment group showed some improvement compared to 3/21 in placebo group (outcome assessment subjective and no blinding)
No. of dropouts	Group 1: 9/24 Group 2: 14/23 Group 3: 11/26 Group 4: 1/24 Group 5: 19/24	Total: 20/77	Group 1:7/18 Group 2: 2/19	None	None	None	None
Reason for dropouts	Not stated (unclear whether analysis was carried out on ITT basis)	Not stated	Side effects, especially dizziness	—	—	—	—

*Other forms of pain included in study, but not reported here.
RCT = randomized controlled trial; CCT = controlled clinical trial; BMS = burning mouth syndrome; SS = statistically significant; MADRS = Montgomery Asberg Depression Rating Scale; CGI-I = Clinical Global Impression-Improvement; HARS = Hamilton Anxiety Rating Scale; ITT = intention-to-treat analysis; VAS = visual analog scale.

group dropped out due to side effects (mainly dizziness). In a large study of clomipramine, mianserin, and placebo, patients with a variety of chronic idiopathic pain syndromes were included.[17] It is clear that 20/77 BMS patients included in the study dropped out due to side effects or insufficient improvement in symptoms. However, it is not clear to which treatment groups the dropouts were allocated. Bogetto et al[21] reported a total of 54/121 dropouts across 5 groups (Table 1). The group with the lowest number of dropouts was the amisulpride group (1/24). The authors stated that this lower rate may have been due to the low number of side effects associated with the drug, though details of side effects were not presented for any group.

Sample Size

The sample size of the included studies ranged from 22 subjects[22] to 121 subjects.[21] None of the studies undertook an a priori calculation of sample size.

Outcome Assessment

The outcomes assessed are described in Table 1. Only one study stated that success of treatment would be based on a 50% reduction in VAS and Clinical Global Impression Scale scores.[17] None of the other studies specified how large a change was required on the measures to be classified as a clinically significant change. Other outcome measures only reported presence or absence of symptoms.[19,22] Quality of life was not measured in any of the studies, although anxiety and depression were measured in 3 studies.[17,20,21]

Antidepressants

Two trials of antidepressants demonstrated no significant difference between the active treatment and the placebo groups in terms of pain or pain-related symptoms, as shown in Table 1.[17,20] In an open trial Bogetto et al[21] demonstrated a statistically significant reduction in BMS symptoms and depression in patients receiving amisulpride. A statistically significant reduction in anxiety levels was seen in all 4 active treatments. No significant reduction in symptoms was achieved in the placebo group.

Cognitive Behavioral Therapy

One RCT examined the effect of cognitive therapy on resistant BMS in comparison to a 'placebo' program. The study showed a statistically significant reduction in pain intensity for those receiving cognitive therapy both immediately following the therapy and at 6-month follow-up, as shown in Table 1.[16]

Analgesics

A small, double-blind RCT of benzydamine hydrochloride (oral rinse) compared to both a placebo and a no-treatment group was unable to demonstrate any statistically significant difference between the 3 groups at the end of the 4-week period (Table 1).[18] No adverse events were reported.

Hormone Replacement Therapy

One CCT examined the role of hormone replacement therapy in postmenopausal women with BMS,[22] but there is insufficient data to draw any reliable conclusions on its effectiveness due to methodologic flaws (Table 1).

Vitamin Complexes

The positive findings from a 30-day randomized controlled trial of the coenzyme alpha-lipoic acid (thioctic acid)[19] as compared to cellulose starch should be interpreted with caution given the subjective nature of the outcome assessment and the fact that the study was an open trial (Table 1).

Discussion

Given the chronic nature and prevalence of BMS, the need to identify an effective mode of treatment for sufferers is vital since, to date, there is insufficient evidence to provide clear guidance for those treating patients with BMS.

This review has identified several methodologic flaws in the currently available trials. These flaws need to be highlighted, because low-quality trials are at greater risk of bias,[23] and therefore the results of the studies need to be interpreted with caution.

Strict diagnostic criteria have rarely been reported in these studies, and many study populations seem to represent a heterogeneous patient population with regard to the background of the oral burning. In the 7 identified trials included in this review, the definitions of the patient samples varied, and were not clearly given in 1 study.[17] In all cases, except for the study of Pisanty et al,[22] it

seemed clear that the included patients suffered from BMS. Pisanty et al,[22] however, included postmenopausal women complaining of dry, burning sensation of the mouth. Whether these patients suffered from BMS, or oral discomfort connected to menopause, is not clear. The inclusion/exclusion of patients into trials needs to be based on clear diagnostic criteria, excluding those with medical or odontological causes, as has been suggested in the literature.[3,24] Comparability of groups at baseline is of great importance, particularly with regard to intensity and duration of symptoms, gender, and psychologic background. The participants included in the 7 identified trials reported suffering from BMS from 6 months to 21 years. This difference in length of disease may be relevant to outcomes because chronicity of pain leads to increased potential for intractability. True randomization with concealed allocation to treatment groups should provide comparable groups, although details of baseline characteristics should still be provided and an estimate of comparability undertaken. The power of the study should also be estimated.

Given the subjectivity of the symptoms to be assessed, trials should ideally be double-blind to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviors (performance bias), or outcome assessment (detection bias). None of the studies demonstrating a reduction in BMS symptoms reported using blind outcome assessment.[16,19,21] Blind outcome assessment has been shown to be of particular importance when evaluating subjective outcomes such as pain. Trials with open assessment of the outcome, as described by Femiano et al[19] and Bogetto et al,[21] have been shown to overestimate the treatment effects by 35%.[25] Bergdahl et al[16] attempted to standardize outcome assessment, ensuring each patient evaluated burning mouth intensity with the same dentist. However, it is not reported whether or not the dentist was blind to treatment allocation.

More than 1 validated scale/questionnaire should be used for the assessment of pain (its intensity, character, and duration). Other outcome measures such as change in taste, feeling of dryness, and quality of life need to be included. The inclusion of a quality-of-life assessment is of great importance, as the impact of this condition on daily activities is potentially high. Several measures, including anxiety and depression, should be included to give an improved estimate of the clinical significance of the results of treatment. If patients are able to cope with their symptoms after treatment and accept that they may have to live with them for the rest of their lives, then a significant result could be said to have been reached even though the patients may still have the same intensity of burning. Only 1 study defined the outcomes that would be considered clinically significant.[17] There remains considerable debate on defining the clinically important differences in pain outcome measures; this issue was not addressed by any of the studies.[26] A decision regarding how large a treatment effect constitutes an adequate outcome also needs to be made. Most treatments for chronic pain aim for a 50% reduction in pain scores from baseline. This may be too high; 30% may be more realistic. Farrar et al[26] argued that use of consistent, clinically important cutoff points for pain outcomes would not only enhance validity and comparability but would also have more clinical applicability. All included studies measured intensity of symptoms but no study assessed how these symptoms affected the quality of life of the patients.

All patients included in a trial should be accounted for in the analysis of the results, with the analysis undertaken on an intention-to-treat basis (where participants are analyzed according to the treatment to which they were initially randomized, whether they received it or not). Larger studies are essential and multicenter studies may be the only way of ensuring that the power of the study is great enough to yield statistically significant results and that consensus views are reached in respect of outcome measures.

A wide variety of different treatments have been used in attempts to alleviate burning mouth symptoms. Unfortunately, most of the studies reporting on these have been uncontrolled, and are thus not included in the present review. Out of the 7 trials included in the review, 3 demonstrated a reduction in BMS symptoms: vitamin complexes,[19] the antidepressant amisulpride,[21] and cognitive behavioral therapy.[16] In the latter, although not all patients were symptom-free following therapy, they did report a reduction in intensity of BMS symptoms. The authors of the trial recognized that differences in patients' psychologic backgrounds may have an impact on the outcome of cognitive therapy and suggest that an individual approach is necessary regarding assessment and treatment of BMS sufferers. Due to methodologic weaknesses, the findings of these 3 trials should be interpreted with caution, particularly those with open outcome assessment. The interventions need to be reevaluated in methodologically sound trials before strong conclusions about their effectiveness can be drawn.

Although none of the other treatments examined in the included studies demonstrated a significant reduction in BMS symptoms, this may again be due to methodologic flaws in the trial design, or small sample size, rather than a true lack of effect.

The varying treatments used reflect the situation regarding the state of knowledge and understanding of the burning mouth symptoms. Most treatments are tailored to the suspected causal factors, which often lack support from controlled studies.

There is increasing evidence suggesting BMS may involve alterations in the peripheral or central nervous system specific to nociceptive or taste pathways,[10–13,27,28] and progress in the treatment of BMS symptoms may also come along with these findings in the future. Due to the recent explosive growth in the understanding of the mechanisms of different pain entities, it has also been suggested that instead of focusing on the different etiologies, it should be possible to assess and treat pain according to the underlying neurophysiologic mechanisms involved.[29] It is feasible that some of the drugs that have been shown to be effective for neuropathic pains in general might prove to be useful in the treatment of BMS pain. In addition, promising results of interventions evaluated in uncontrolled trials may also require further exploration. For example, studies of a benzodiazepine (clonazepam—a GABA agonist), rather than the tricyclic antidepressants, have shown favorable results but require evaluation in the form of well-conducted RCTs.[30,31] Psychologic methods which help patients to cope with symptoms may also be of some use, but require further evaluation. These types of interventions have been shown to be of value in all chronic pain sufferers.

A systematic review of the current evidence has highlighted the need for further good-quality RCTs to be undertaken to establish the effectiveness of promising and new approaches to treating BMS. The systematic review will continue to be updated every 2 years within the Cochrane Library, adding in the results of emerging trials. However, given that the research evidence is, as yet, unable to provide clear, conclusive evidence of an effective intervention, clinicians need to provide support and understanding when dealing with BMS sufferers. It is important that clinicians recognize the syndrome, give a credible explanation of our present understanding of it, and reassure patients of its benign nature.

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