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## Interventions for the treatment of burning mouth syndrome (Review)

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## TABLE OF CONTENTS

HEADER .....	1
ABSTRACT .....	1
PLAIN LANGUAGE SUMMARY .....	2
BACKGROUND .....	3
OBJECTIVES .....	3
METHODS .....	3
RESULTS .....	4
DISCUSSION .....	7
AUTHORS' CONCLUSIONS .....	7
ACKNOWLEDGEMENTS .....	8
REFERENCES .....	9
CHARACTERISTICS OF STUDIES .....	11
DATA AND ANALYSES .....	16
Analysis 2.1. Comparison 2 Cognitive behavioural therapy versus placebo, Outcome 1 Intensity of BMS at 6 months. ....	17
Analysis 3.1. Comparison 3 Analgesics versus placebo, Outcome 1 Partial/complete improvement in symptoms. ....	17
Analysis 5.1. Comparison 5 Alpha-lipoic versus placebo, Outcome 1 Improvement in symptoms. ....	17
Analysis 6.1. Comparison 6 Anticonvulsants versus placebo, Outcome 1 Decrease in mean pain intensity. ....	18
ADDITIONAL TABLES .....	18
APPENDICES .....	18
WHAT'S NEW .....	19
HISTORY .....	19
CONTRIBUTIONS OF AUTHORS .....	19
DECLARATIONS OF INTEREST .....	19
SOURCES OF SUPPORT .....	19
INDEX TERMS .....	20

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[Intervention Review]

# Interventions for the treatment of burning mouth syndrome

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## ABSTRACT

### Background

The complaint of a burning sensation in the mouth can be said to be a symptom of other disease or a syndrome in its own right of unknown aetiology. In patients where no underlying dental or medical causes are identified and no oral signs are found, the term burning mouth syndrome (BMS) should be used. The prominent feature is the symptom of burning pain which can be localised just to the tongue and/or lips but can be more widespread and involve the whole of the oral cavity. Reported prevalence rates in general populations vary from 0.7% to 15%. Many of these patients show evidence of anxiety, depression and personality disorders.

### Objectives

The objectives of this review are to determine the effectiveness and safety of any intervention versus placebo for relief of symptoms and improvement in quality of life and to assess the quality of the studies.

### Search methods

We searched the Cochrane Oral Health Group Trials Register (20 October 2004), CENTRAL (*The Cochrane Library* 2004, Issue 4), MEDLINE (January 1966 to October 2004), EMBASE (January 1980 to October). Clinical Evidence Issue No. 10 2004, conference proceedings and bibliographies of identified publications were searched to identify the relevant literature, irrespective of language of publication.

### Selection criteria

Studies were selected if they met the following criteria: study design - randomised controlled trials (RCTs) and controlled clinical trials (CCTs) which compared a placebo against one or more treatments; participants - patients with burning mouth syndrome, that is, oral mucosal pain with no dental or medical cause for such symptoms; interventions - all treatments that were evaluated in placebo-controlled trials; primary outcome - relief of burning/discomfort.

### Data collection and analysis

Articles were screened independently by two reviewers to confirm eligibility and extract data. The reviewers were not blinded to the identity of the studies. The quality of the included trials was assessed independently by two reviewers, with particular attention given to allocation concealment, blinding and the handling of withdrawals and drop outs. Due to both clinical and statistical heterogeneity statistical pooling of the data was inappropriate.

### Main results

Nine trials were included in the review. The interventions examined were antidepressants (two trials), cognitive behavioural therapy (one trial), analgesics (one trial), hormone replacement therapy (one trial), alpha-lipoic acid (three trials) and anticonvulsants (one trial). Diagnostic criteria were not always clearly reported. Out of the nine trials included in the review, only three interventions demonstrated a

reduction in BMS symptoms: alpha-lipoic acid (three trials), the anticonvulsant clonazepam (one trial) and cognitive behavioural therapy (one trial). Only two of these studies reported using blind outcome assessment. Although none of the other treatments examined in the included studies demonstrated a significant reduction in BMS symptoms, this may be due to methodological flaws in the trial design, or small sample size, rather than a true lack of effect.

### **Authors' conclusions**

Given the chronic nature of BMS, the need to identify an effective mode of treatment for sufferers is vital. However, there is little research evidence that provides clear guidance for those treating patients with BMS. Further trials, of high methodological quality, need to be undertaken in order to establish effective forms of treatment for patients suffering from BMS.

## **PLAIN LANGUAGE SUMMARY**

### **Interventions for the treatment of burning mouth syndrome**

There is insufficient evidence to show the effect of painkillers, hormones or antidepressants for 'burning mouth syndrome' but there is some evidence that learning to cope with the disorder, anticonvulsants and alpha-lipoic acid may help.

A burning sensation on the lips, tongue or within the mouth is called 'burning mouth syndrome' when the cause is unknown and it is not a symptom of another disease. Other symptoms include dryness and altered taste and it is common in people with anxiety, depression and personality disorders. Women after menopause are at highest risk of this syndrome. Painkillers, hormone therapies, antidepressants have all been tried as possible cures. This review did not find enough evidence to show their effects. Treatments designed to help people cope with the discomfort and the use of alpha-lipoic acid may be beneficial. More research is needed.

## BACKGROUND

The complaint of a burning sensation in the mouth which can be localised to the lips or tongue or be more widespread within the mouth can be said to be a symptom of other disease or a syndrome in its own right of unknown aetiology (Zakrzewska 1999). Burning mouth is said to be a symptom of other disease when local or systemic factors are found to be implicated. In other patients, however, no underlying dental or medical causes are identified and no 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 paraesthesia and altered taste or smell. There is confusion in the literature as a wide variety of different terms have been used to describe the sensation of a burning mouth (Bergdahl 1993). These include glossodynia, glossopyrosis, stomatodynia, stomatopyrosis, sore tongue, burning mouth and oral dysaesthesia. The International Association for the Study of Pain (IASP) classification of chronic pain defines glossodynia and sore mouth (also known as burning tongue or oral dysaesthesia) as a burning pain in the tongue or other oral mucous membranes but it does not draw the distinction between burning as a symptom and burning as part of a syndrome (Merksey 1994). However the revised classification of the International Headache Society (Headache Classification Subcommittee 2004) does make this distinction and defines it as a burning sensation for which no dental or medical cause can be found. They also highlight that the condition can be confined to the tongue alone and that it can be associated with dryness and loss of taste.

The epidemiological data on BMS are generally poor due in part to lack of strict adherence to diagnostic criteria (Zakrzewska 1999; Bergdahl 1999). Reported prevalence rates in general populations vary from 15% (Tammiala 1993) to 0.7% (Lipton 1993) and relate to burning mouth as a symptom. BMS predominantly affects females with an increased prevalence with age and following menopause (Basker 1978).

The cause of burning mouth syndrome is essentially unknown although a wide range of factors has been suggested (Zakrzewska 1999). Unfortunately, most of the studies are small, uncontrolled, lack replication and standardised outcome measures. Risk factors and high risk patients have not been identified although it would appear that post-menopausal women are at highest risk. The natural history of burning mouth syndrome has not been clearly defined and there are no reports of longitudinal cohort studies (Zakrzewska 1999). There is anecdotal evidence of at least partial spontaneous remission in approximately half of these patients within 6 to 7 years (Grushka 1991).

The clinical features of burning mouth syndrome have been described (Grushka 1987; Bergdahl 1999). The prominent feature is the symptom of burning pain which can be localised just to the tongue and/or lips but can be more widespread and involve the whole of the oral cavity. In most patients the symptoms are bilateral. Sometimes words such as 'discomfort', 'tender' and 'annoying' instead of burning are used. In most cases the symptoms have continued for many months and the intensity of pain tends to increase towards 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 burning

mouth syndrome show an increased tendency for somatisation as well as several other psychiatric features when measured on the SCL -90 questionnaire (Eli 1994). On standard clinical examination of the oral cavity no abnormalities are identified and there are no clinically useful investigations that would help to support a diagnosis of burning mouth syndrome. However, more sophisticated testing indicates that neuronal mechanisms may be involved. Grushka et al (Grushka 1987) and Svensson et al (Svensson 1993) have shown altered sensory and pain thresholds in these patients. Two recent studies using blink reflex and thermal quantitative sensory tests have demonstrated signs of neuropathy in a great majority of BMS patients (Jääskeläinen 1997; Forssell 2002). The management of this condition has centred on correction of systemic factors such as vitamins, hormone balance and psychological management (Buchanan 2000). The recent neuropathological findings in BMS may suggest the need for alternative treatment strategies. This review will only include patients with the diagnosis of burning mouth syndrome.

## OBJECTIVES

The objectives of this review are to determine the effectiveness and safety of any intervention versus placebo for relief of symptoms and improvement in quality of life and to assess the quality of the studies.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCTs) and controlled clinical trials (CCTs) which compared a placebo against one or more treatments.

#### Types of participants

Patients with burning mouth syndrome (BMS), that is, oral mucosal pain with no dental or medical cause for such symptoms. Trials recruiting patients with other types of pain will only be included if data on BMS patients can be separated out.

#### Types of interventions

All treatments that were evaluated in placebo-controlled RCTs or CCTs.

#### Types of outcome measures

- (A) Primary outcome: relief of burning/discomfort.
- (B) Secondary outcomes:
  - (1) Changes in taste
  - (2) Changes in feeling of dryness
  - (3) Changes in quality of life e.g. depression, anxiety.

### Search methods for identification of studies

The current review is an update of a previously published version (first published in *The Cochrane Library* 2001, Issue 3).

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

- (1) Electronic databases:
  - (a) Cochrane Oral Health Group's Trials Register (20 October 2004)

- (b) Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2004, Issue 4)
- (c) MEDLINE (January 1966 to October 2004)
- (d) EMBASE (January 1980 to October (week 42) 2004)
- (e) Clinical Evidence Issue No. 10, 2004.

A search strategy based on the terms used for searching MEDLINE (OVID) ([Appendix 1](#)) was used to search the above electronic databases.

(2) Handsearching: conference proceedings for British Society for Oral Medicine (BSOM), British Society for Dental Research (BSDR), International Association for Dental Research (IADR).

(3) Bibliographies of identified publications and reviews.

(4) Authors of relevant studies were asked to identify missing data and unreported trials.

## Data collection and analysis

### Selection of trials

A pool of titles and abstracts of potential studies were first screened in duplicate for placebo-controlled RCTs and CCTs. The full article of each selected trial was screened independently by two reviewers to confirm eligibility, assess quality and extract data. The reviewers were not blinded to the identity of the study authors.

### Data extraction

The following study features were extracted.

- (1) Adequacy of randomisation and assignment methods.
- (2) Details of blinding.
- (3) Whether the trial was of parallel or cross-over design.
- (4) Length of study period and first cross-over period.
- (5) Method of diagnosis.
- (6) Comparability of treatment groups at baseline.
- (7) Treatments and number randomised.
- (8) Outcome measures used that were appropriate and the basis of statistical analyses.
- (9) Drop outs and reasons.
- (10) Side effects and toxicities.
- (11) Whether an intention-to-treat analysis was used.

Trialists 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*. Allocation concealment, blinding and the handling of withdrawals and drop outs were assessed, but no overall summary score was calculated.

### Data analysis

Drop outs due to treatment side effects were regarded as treatment failures. If cross-over 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. The criteria for pooling studies was based on similarity of patient type, form of disease, treatment and outcome measures.

## RESULTS

### Description of studies

Details of the trial participants, interventions and outcomes measured can be seen in the [Characteristics of included studies](#).

The first version of this review included six trials ([Bergdahl 1995a](#); [Loldrup 1989](#); [Sardella 1999](#); [T-S 1999](#); [Femiano 2000](#); [Pisanty 1975](#)). The update includes a further four randomised controlled trials (RCTs) ([Bogetto 1999](#); [Femiano 2002a](#); [Femiano 2002b](#); [Gremeau-Richard 2004](#)), but excludes a previously included trial ([Loldrup 1989](#)), bringing the total number of included trials to nine. The trial by Loldrup has been excluded due to the fact that BMS patients were evaluated alongside patients with tension headache, abdominal pain and low back pain, and the data for patients with BMS could not be separated out. The authors will be contacted to see if the data for BMS patients alone can be provided and, if so, included in a subsequent update.

Of the nine included trials, eight were RCTs ([Bergdahl 1995a](#); [Sardella 1999](#); [T-S 1999](#); [Femiano 2000](#); [Femiano 2002a](#); [Femiano 2002b](#); [Bogetto 1999](#); [Gremeau-Richard 2004](#)) and one a controlled clinical trial (CCT) ([Pisanty 1975](#)). All trials were published in English, however, the countries of origin were Finland ([T-S 1999](#)), Italy ([Sardella 1999](#); [Femiano 2000](#); [Femiano 2002a](#); [Femiano 2002b](#); [Bogetto 1999](#)), Sweden ([Bergdahl 1995a](#)), France ([Gremeau-Richard 2004](#)) and Israel ([Pisanty 1975](#)).

### Characteristics of participants

Eight trials defined their participants as BMS or stomatodynia sufferers ([Bergdahl 1995a](#); [Sardella 1999](#); [T-S 1999](#); [Femiano 2000](#); [Femiano 2002a](#); [Femiano 2002b](#); [Bogetto 1999](#); [Gremeau-Richard 2004](#)). Diagnostic criteria for BMS included "daily, or almost daily, oral burning pain that had lasted 6 months or longer and had a moderate to severe intensity" (all patients whose pain could possibly be related to some physical findings were excluded) ([T-S 1999](#)), and "all forms of burning sensation in the mouth, including complaints described as stinging sensation or pain, in association with an oral mucosa that appears clinically normal in the absence of local or systemic diseases or alterations" ([Sardella 1999](#)). In a third trial ([Bergdahl 1995a](#)) all patients were odontologically and medically examined and treated according to the protocol for the management of BMS proposed by Bergdahl et al ([Bergdahl 1993](#)). If treatment for odontologically and medically diagnosed diseases had no effect on burning sensations, patients were classed as suffering from resistant BMS. Femiano et al ([Femiano 2000](#); [Femiano 2002a](#); [Femiano 2002b](#)) only included BMS patients with absence of identifiable oral pathological lesions, with normal salivary secretion and normal laboratory results. Bogetto et al ([Bogetto 1999](#)) diagnosed BMS using criteria 'supplied by the literature' ([Gorsky 1987](#); [Gorsky 1991](#)). An eighth trial screened patients with stomatodynia, defined as chronic burning pain in the oral mucosa with a normal clinical examination. Patients with continuous pain, present for more than 4 months, were included ([Gremeau-Richard 2004](#)). One trial recruited post-menopausal ([Pisanty 1975](#)) participants complaining of dry, burning sensation in the mouth.

The age of the participants ranged from 22 years to 85 years. Data on duration of BMS symptoms were not always reported, but ranged

from 6 months to 20 years in those trials that did report such data (Bogetto 1999; Sardella 1999; T-S 1999).

## Characteristics of interventions

### Antidepressants

Two trials examined the effectiveness of antidepressants for the treatment of BMS (T-S 1999; Bogetto 1999). Trazodone was compared to placebo in an 8 week RCT (T-S 1999). Amisulpride, paroxetine, clordemetildiazepam and amitriptyline were all compared with placebo in a second 8 week trial (Bogetto 1999).

### Cognitive behavioural therapy

One trial compared a 12 to 15 week programme of cognitive behavioural therapy with a placebo/attention programme (Bergdahl 1995a).

### Analgesics

One trial compared an analgesic mouthwash, benzydamine hydrochloride, 15 ml three times daily for 4 weeks, with a placebo group and a no treatment control group (Sardella 1999).

### Hormone replacement therapy in post-menopausal women

One CCT was identified that examined hormone replacement therapy (Pisanty 1975). The trial compared three ointments (estrone alone, estrone plus progesterone, and placebo base) that were to be massaged into the oral mucosa, three times a day for 30 days (Pisanty 1975).

### Alpha-lipoic acid

A study of 42 patients with BMS compared the coenzyme alpha-lipoic acid (thioctic acid), 600 mg/day reducing to 200 mg/day, with cellulose starch in a 30 day RCT (Femiano 2000). As a second stage to the study, the control patients were subsequently treated with the alpha-lipoic acid. A second trial comparing alpha-lipoic acid 600 mg/day with cellulose starch was conducted over a 2 month period (Femiano 2002a). Patients showing an improvement at 2 months were given a further month of treatment using a protocol identical to that used previously.

A third trial by the same authors compared alpha-lipoic acid (thiotic acid) with two 'active placebos' (lactoperoxidase mouthrinse and bethanecol) and a placebo group (xylitol in distilled water) (Femiano 2002b).

### Anticonvulsants

A trial of 48 people with stomatodynia compared clonazepam tablets (1 mg) with placebo. Tablets were sucked three times a day after each meal. The trial lasted for 2 weeks, but the patients were followed up for 6 months (Gremeau-Richard 2004).

## Characteristics of the outcome measures

Four of the nine included trials used a visual analogue scale (VAS) to measure the intensity of the BMS symptoms (Bergdahl 1995a; Sardella 1999; T-S 1999; Gremeau-Richard 2004). 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, saliva flow, tissue change and ordinal scales of changes in symptomology.

## Risk of bias in included studies

Additional Table 1.

### Allocation concealment

In only two of the RCTs was allocation concealment ascertainable (T-S 1999; Gremeau-Richard 2004). In both trials block randomisation was undertaken by a third party. Sardella et al (Sardella 1999) used a random number table in order to allocate participants to treatment groups, however, whether this process was concealed or not is unclear. The remaining five RCTs stated that they were randomised but gave no further information regarding randomisation or allocation concealment.

### Blinding

Four of the RCTs reported that they were double-blind (Sardella 1999; T-S 1999; Femiano 2002a; Gremeau-Richard 2004). However, one of the three groups in the trial by Sardella et al (Sardella 1999) did not receive any treatment, therefore could not be blind. The remaining RCTs either did not report on blinding (Bergdahl 1995a) or it was clear that the investigators were not blind to treatment allocation (Femiano 2000; Femiano 2002b; Bogetto 1999). The CCT by Pisanty et al (Pisanty 1975) was double-blind, with both the clinician and the patients unaware of the ointment used until after the final assessment.

### Withdrawals

In five of the nine included studies there were no drop outs (Femiano 2000; Bergdahl 1995a; Pisanty 1975; Sardella 1999; Femiano 2002b). In a trial by Femiano and Scully (Femiano 2002a) all patients randomised were available at the 2 month evaluation. However, only those showing improvements at 2 months were followed up at 1 year. Tammiala-Salonen and Forssell (T-S 1999) indicate that in their study of trazodone versus placebo, 7/18 in the treatment group and 2/19 in the placebo group dropped out due to side effects (mainly dizziness). Bogetto et al (Bogetto 1999) reported a total of 54/121 drop outs across five groups. The group with the lowest number of drop outs 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. Drop outs for the other treatment groups were 9/24 (paroxetine), 14/23 (amitriptyline), 11/26 (clordemetildiazepam) and 19/24 (placebo). The difference between the number of drop outs across between the five groups is statistically significant ( $P < 0.001$ ). Gremeau-Richard (Gremeau-Richard 2004) reported 2/24 drop outs in the active treatment group (clonazepam) and 1/24 in the placebo group. An intention-to-treat analysis was undertaken, including the three drop outs in the analysis.

### Sample size

The sample size of the included studies ranged from 22 (Pisanty 1975) to 121 (Bogetto 1999). Only one of the studies undertook an a priori calculation of sample size (Gremeau-Richard 2004).

### Outcome assessment

The outcomes assessed are described in the [Characteristics of included studies](#). Only one of the trials specified how large a change was required on the measures to be classified as a clinically important change (Gremeau-Richard 2004). In their trial of clonazepam versus placebo, they considered clonazepam to

be effective when the score of the pre-treatment pain intensity was reduced by two or more units. Sardella et al (Sardella 1999) reported a 4 mm change (also a 50% reduction) on the visual analogue scale (VAS) as partial improvement whereas in other pain trials this would be considered clinically important. Bergdahl et al (Bergdahl 1995a), using a one to seven VAS scale, did not indicate what constituted clinically significant burning intensity and what indicated a clinically important improvement. Other outcome measures only reported presence, absence or changes in symptoms (Femiano 2000; Pisanty 1975; Femiano 2002a; Femiano 2002b). Quality of life was not measured in any of the trials but anxiety and depression were measured in two trials (T-S 1999; Bogetto 1999).

## Effects of interventions

### Antidepressants

A trial of antidepressants demonstrated no significant difference between the active treatment and the placebo group in terms of pain or pain related symptoms (T-S 1999).

In this 8 week, double-blind RCT trazodone (200 mg/day) was compared with placebo for the treatment of chronic burning mouth pain. The groups had a baseline difference in pain intensity at the start of medication, with the mean VAS in the trazodone group being 12.6 mm higher than in the placebo group ( $P < 0.05$ ). Nine people failed to finish the trial due to side effects (mainly dizziness), two in the placebo group and seven in the trazodone group. Pain and pain related symptoms were measured at 2 week intervals for the duration of the trial. The authors report no statistically significant differences between the groups at any time point. The possibility of false negative results was discussed, and was considered unlikely in the light of the calculated confidence intervals.

In a second, open trial, comparing amisulpride, paroxetine, clordemetildiazepam and amitriptyline to placebo, no statistically significant between group differences were shown with regard to BMS symptoms and depression and it should be noted that the trial had a 45% drop-out rate (Bogetto 1999). A statistically significant reduction from baseline in BMS symptoms and depression was shown for patients receiving 50 mg/day amisulpride (Bogetto 1999).

### Cognitive behavioural therapy

One RCT examined the effect of cognitive therapy on resistant BMS in comparison to a 'placebo', attention programme (Bergdahl 1995a). Participants in the treatment group received 1 hour of cognitive therapy once a week for 12 to 15 weeks. Those in the 'placebo' group returned for three visits over the 12-15 week period, during which an evaluation of BMS intensity and an oral examination were undertaken. All randomised participants were accounted for in the analysis. The intensity of BMS was evaluated using a VAS (1 to 7). The authors report a statistically significant difference in reduction in pain intensity for those receiving cognitive behavioural therapy compared to placebo was shown immediately following the therapy and at 6 month follow up (Comparison 2, Outcome 2.1).

### Analgesics

A small, double-blind RCT of benzydamine hydrochloride oral rinse (15 ml to be used three times a day) compared to both a

placebo and a no treatment group, was undertaken by Sardella et al (Sardella 1999). The duration of the trial was 4 weeks. The groups were comparable at baseline, diagnostic criteria for BMS clearly stated and all randomised participants included in the analysis. A VAS was used to assess the severity of BMS symptoms. The trial was unable to demonstrate any statistically significant difference between the three groups at the end of the 4 week period (Comparison 3, Outcome 3.1) (only data for benzydamine hydrochloride versus placebo presented). No adverse events were reported.

### Hormone replacement therapy

One CCT examined the role of hormone replacement therapy in post-menopausal women with BMS (Pisanty 1975). The diagnostic criteria and outcome measures were unclear. There were fewer than 10 participants in each treatment arm (estrone alone  $n = 6$ ; estrone plus progesterone  $n = 9$ ; placebo  $n = 7$ ) and comparability of groups at baseline was not discussed. Due to methodological flaws, there is insufficient data to draw any reliable conclusions on the effectiveness of hormone replacement therapy for post-menopausal women with BMS.

### Alpha-lipoic acid

In a 30 day RCT, alpha-lipoic acid was compared to cellulose starch (Femiano 2000). Twenty-one patients were randomised to each group. Outcomes were assessed according to changes in BMS symptomology (worsening, unchanged, slight improvement, decided improvement, resolution). At the end of the trial, 16/21 (76%) patients in the treatment group demonstrated some level of improvement (7/21 slight improvement; 9/21 decided improvement; 5/21 remained unchanged). In the cellulose starch group only 3/21 patients demonstrated slight improvement in their symptoms, 14/21 remained unchanged, and 4/21 worsened.

A subsequent, double-blind trial was undertaken making the same comparison between alpha-lipoic acid and cellulose starch over a 2 month period (Femiano 2002a). Twenty-nine (97%) of those receiving the treatment showed some level of improvement at 2 months (3/30 slight improvement; 22/30 decided improvement; 4/30 resolution). Only 12/30 (40%) of those receiving placebo showed slight improvement.

A 60 day trial of alpha-lipoic acid compared to bethanecol, lactoperoxidase or placebo (xylitol in distilled water) (Femiano 2002b). Twenty patients were randomised to each group. The same outcome measures were used as for Femiano 2000. By the end of the 60 days, 18/20 (90%) of the patients receiving alpha-lipoic acid showed some level of improvement in symptoms (2/20 slight improvement; 16/20 decided improvement). Four patients reported heartburn in this group. No improvements were seen in those receiving the xylitol placebo or lactoperoxidase. Two patients receiving bethanecol had slight improvements in BMS symptoms. It is unclear from the paper whether or not there is some overlap between the patients recruited to this trial and the earlier Femiano 2000 trial.

Pooling of these three studies using a random-effects model showed statistically significant heterogeneity ( $P = 0.02$ ), with an  $I^2$  value of 75.5%. Examination of the studies shows a much greater number of patients showing some level of improvement in the placebo group for the double-blind trial when compared to the two open-label trials. This may account for some of the

heterogeneity. Given the variation in results, and the potential for overlap in patients in two of the trials, it was felt inappropriate to provide an overall estimate of effect, although all three trials showed a statistically significant improvement with alpha-lipoic acid (Comparison 5, Outcome 5.1). Given the subjective nature of the outcome assessment the results for the open-label trials should be interpreted with caution.

### Anticonvulsants

In a 14 day trial, with 6 month follow up, 48 stomatodynia sufferers were randomised to clonazepam or placebo. Twenty-four people were randomised to each group. Pain intensity was scored using a numerical scale with 0 representing 'no pain' and 10 representing 'worst imaginable pain'. At the end of the treatment period a statistically significant difference in mean decrease in pain intensity was seen in favour of clonazepam, with a mean difference of 1.60 (95% confidence interval (CI) 1.31 to 1.89) (analysed on an intention-to-treat basis, with drop-outs considered to have not been modified by the treatment) (Comparison 6, Outcome 6.1).

## 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. 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. The varying treatments used, however, 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, however, often lack support from controlled studies. The current review has identified several methodological flaws in the included trials. The methodological quality of the studies assessing treatment efficacy is of great importance with regard to the credibility of the results achieved. Low quality trials are at greater risk of bias, and thus the results of the studies should 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 nine identified trials included in this review, the definitions of the patient samples varied. In all cases, except for the study of Pisanty (Pisanty 1975), it seemed clear that the included patients suffered from BMS. Pisanty, however, included post-menopausal 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 participants included in the nine identified trials reported suffering from BMS from 6 months to 20 years. This difference in length of disease may be relevant to outcomes as chronicity of pain leads to increased potential for intractability.

The RCTs included in the review provided little information with regard to the method of randomisation used and in only two RCTs was allocation concealment ascertainable (T-S 1999; Gremeau-Richard 2004). Without adequate randomisation a trial can be susceptible to selection bias, with treatment groups being unbalanced with regard to baseline characteristics. In addition,

given the subjective nature of the outcomes assessed within the included trials, blinding should have been used in all trials to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviours (performance bias) or outcome assessment (detection bias). 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 (Femiano 2000; Femiano 2002b) and Bogetto et al (Bogetto 1999), have been shown to overestimate the treatment effects by 35% (Juni 1999). Indeed, this may explain why the two open-label trials of alpha-lipoic acid (Femiano 2000; Femiano 2002b) provided greater estimates of effect than the double-blind trial of the same intervention (Femiano 2002a). Bergdahl et al (Bergdahl 1995a) attempted to standardise 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 and it is not clear whether the visual analogue scale (VAS) used was validated.

Only one of the included trials defined the clinical outcomes that would be considered clinically significant (Gremeau-Richard 2004). There remains considerable debate on defining the clinically important differences in pain outcome measures which were not addressed by any of the studies (Farrar 2000). All included studies measured intensity of symptoms but no study assessed how these symptoms affected the quality of life of the patients and only two studies used surrogate measures (depression, anxiety) (Bogetto 1999; T-S 1999).

Out of the nine trials included in the review, three interventions demonstrated a reduction in BMS symptoms in comparison to placebo; alpha-lipoic acid (Femiano 2000; Femiano 2002a; Femiano 2002b), the anticonvulsant, clonazepam (Gremeau-Richard 2004) and cognitive behavioural therapy (Bergdahl 1995a). 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 recognised that differences in patients' psychological 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. However, only one of these trials was methodologically sound (Gremeau-Richard 2004). Due to methodological weaknesses, the findings of the remaining trials should be interpreted with caution, particularly as only one of the studies reported a reduction in BMS symptoms used blind outcome assessment (Femiano 2002a). The interventions need to be re-evaluated 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 also be due to methodological flaws in the trials design, or small sample size, rather than a true lack of effect.

## AUTHORS' CONCLUSIONS

### Implications for practice

To date, there is little research evidence that provides clear guidance for those treating patients with BMS. It does stress the importance of assessing whether burning mouth is a symptom of other disease or a distinct syndrome. Clinicians should ensure that treatable causes of burning mouth are first identified before labelling patients as suffering from BMS. In the case of BMS,

however, it is equally important that the clinician recognises the situation and gives a credible explanation about the condition and its benign nature to the patient. One RCT included in the review did provide some evidence that cognitive behavioural therapy may be beneficial in helping to relieve symptoms (Bergdahl 1995a), although the problems associated with the outcome assessment should not be ignored. In addition, the authors of the trial recognise that differences in patients' psychological 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. RCTs of alpha-lipoic acid also provide promising evidence for its effectiveness at reducing BMS symptoms, although given the subjective nature of the outcome assessment the results for the open-label trials should be interpreted with caution. A single, but high quality RCT of clonazepam has shown promising results for short-term relief of pain.

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 methods which help patients to cope with symptoms may be of some use, but require further evaluation. These types of interventions have been shown to be of value in all chronic pain sufferers.

### Implications for research

Further trials, of high methodological quality, need to be undertaken in order to establish effective forms of treatment for patients suffering from BMS. The inclusion/exclusion of patients needs to be based on clearer diagnostic criteria, excluding those with medical or odontological causes as has been suggested in the literature (Tourne 1992; Bergdahl 1993). Comparability of groups at baseline is of great importance, particularly with regard to intensity of symptoms, the chronicity of the condition, gender and psychological background. True randomisation 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. Given the subjectivity of the symptoms to be assessed, patients, trialists, healthcare providers and outcome assessors should be blind to the intervention.

Validated scales/questionnaires should be used for the assessment of pain. 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 and it could be that this is too high and 30% would be more realistic. Farrar et al (Farrar 2000) argue that use of consistent clinically important cut off points for pain outcomes would not only enhance validity and comparability but would also have more clinical applicability. Other outcome measures such as change in taste, feeling of dryness and quality of life need to be considered. The inclusion of a quality of life assessment would

be 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 the lives then a significant result could be said to have been reached even though the patients may still have the same intensity of burning. Psychological methods which help patients to cope with symptoms require further evaluation for BMS sufferers.

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. Larger studies are essential and multicentre 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.

It is recognised that the prevalence of BMS is greater in females, particularly post-menopausal women (Basker 1978), however, the underlying cause of BMS is essentially unknown. Identification of the cause and associated risk factors of BMS may help in the identification of effective treatment strategies as may more objective, quantitative investigation. 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 aetiologies, it should be possible to assess and treat pain according to the underlying neurophysiological mechanisms involved (Woolf 1998). It is feasible that some of the drugs which 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 have been shown in the study of benzodiazepine (clonazepam - a GABA agonist), rather than the tricyclic antidepressants. However, only a single (but high quality) RCT has been conducted to date (Gremeau-Richard 2004). As regards to BMS, there is increasing evidence suggesting alterations in the peripheral or central nervous system specific to nociceptive or taste pathways (Ship 1995; Svensson 1993; Jääskeläinen 1997; Jääskeläinen 2001; Forssell 2002), and progress in the treatment of BMS symptoms may also come along with these findings in the future.

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**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Bergdahl 1995a**

Methods	Single-centre RCT.
Participants	30 BMS patients. Mean age 54 years (range 38 to 69). M/F 6/24.  Mean duration of BMS not stated.
Interventions	Group 1: cognitive therapy 1 hour, weekly sessions for 12 to 15 visits (n = 15).  Group 2: attention placebo 3 visits over 12 to 15 weeks (n = 15).  Duration: 12 to 15 weeks.
Outcomes	BMS symptoms measured on VAS (1 to 7).
Notes	Diagnostic criteria stated. Groups comparable at baseline.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Bogetto 1999**

Methods	Single-centre RCT.
Participants	121 BMS patients. Mean age 65.4 years (sd 10.6 years). M/F not stated. Mean duration of BMS 5.7 years (sd 3.2 years).
Interventions	Group 1: paroxetine 20 mg/day (n = 24).  Group 2: amitriptyline 25 mg/day (n = 23).

**Interventions for the treatment of burning mouth syndrome (Review)**

**Bogetto 1999** (Continued)

Group 3: clordemetildiazepam 1 mg/day (n = 26).

Group 4: amisulpride 50 mg/day (n = 24).

Group 5: placebo (n = 24).

Duration: 8 weeks.

Outcomes	Montgomery Asberg Depression Rating Scale; Clinical Global Impression-Improvement; Hamilton Anxiety Rating Scale.
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Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Femiano 2000**

Methods	Single-centre RCT, matched for age and sex.
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Participants	42 BMS patients. Median age 63 years (range 43 to 78). M/F 10/32. 20 had removable prostheses. Mean duration of BMS not stated.
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Interventions	Group 1: alpha-lipoic acid (thioctic acid) 600 mg/day for 20 days, followed by 200 mg/day for 10 days (n = 21).  Group 2: cellulose starch 100 mg/day for 30 days (n = 21).  Duration: 30 days.
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Outcomes	Changes in symptomatology were scored as worsening, unchanged, slight improvement, decided improvement, resolution.
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Notes	Diagnostic criteria stated. Comparability of groups at baseline unclear.
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Femiano 2002a**

Methods	RCT (unclear whether single or multicentre).
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Participants	60 BMS patients.
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**Interventions for the treatment of burning mouth syndrome (Review)**

**Femiano 2002a** (Continued)

Median age 45 years (range 22 to 68).  
 M/F 18/42.

Interventions	<p>Group 1: alpha-lipoic acid (thioctic acid) in 200 mg oral pills, three times a day (n = 30).</p> <p>Group 2: cellulose starch 100 mg/day, three times a day (n = 30).</p> <p>Duration: 2 months (note: those showing improvement in symptoms at 2 months given a further month of treatment and followed for 1 year).</p>
Outcomes	Changes in symptomatology were scored as worsening, unchanged, slight improvement, decided improvement, resolution.
Notes	<p>Diagnostic criteria stated.</p> <p>Comparability of groups at baseline unclear.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Femiano 2002b**

Methods	Single-centre RCT matched for age and sex.
Participants	<p>80 BMS patients (16 patients had used anxiolytic drugs).</p> <p>Median age 63 years (range 30 to 74).</p> <p>M/F 32/48.</p>
Interventions	<p>Group 1: bethanecol 5 mg orally every 8 hours between meals (n = 20).</p> <p>Group 2: lactoperoxidase in oral solution topically 5 to 6 times daily (n = 20).</p> <p>Group 3: Lipoic acid (ALA) 200 mg orally every 8 hours (n = 20).</p> <p>Group 4: Xylitol 3% in distilled water (n = 20).</p> <p>Duration: 60 days.</p>
Outcomes	Changes in symptomatology were scored as worsening, unchanged, slight improvement, decided improvement, resolution.
Notes	Diagnostic criteria stated. Comparability of groups at baseline unclear.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

### Gremeau-Richard 2004

Methods	Multi-centre (6 centres) RCT.
Participants	48 patients with isolated complaint of chronic pain in the oral mucosa with normal clinical examination, with duration of pain greater than 4 months. Mean age 65 years (sd 2.1 years). M/F 4/44.
Interventions	Group 1: clonazepam tablet 1 mg to be sucked without swallowing for 3 min, three times a day (after each meal) for 2 weeks (n = 24).  Group 2: placebo, as for Group 1 (n = 24).  Duration: 2 weeks intervention, 6 month open follow up.
Outcomes	Mean pain intensity (0 'no pain' to 10 'maximal pain imaginable'). Compliance and adverse events were also recorded.
Notes	Diagnostic criteria stated. Groups comparable at baseline.

#### **Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Low risk	A - Adequate

### Pisanty 1975

Methods	Single-centre, double-blind, CCT.
Participants	22 post-menopausal women complaining of dry, burning sensation in the mouth.
Interventions	Group 1: estrone ointment (50,000 U per gm) (n = 6).  Group 2: estrone (10,000 U per gm) + progesterone (50 mg per gm) ointment (n = 9).  Group 3: placebo base ointment (n = 7).  Duration: ointment massaged into oral mucosa 3x daily for 30 days.
Outcomes	Improvement of symptoms (burning sensation, dryness, bad taste, saliva flow, tissue change).
Notes	Diagnostic criteria unclear. Comparability of groups at baseline unclear.

#### **Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Unclear risk	D - Not used

**Sardella 1999**

Methods	Single-centre, double-blind RCT.
Participants	30 BMS patients. Mean age 69 years (range 54 to 85). M/F 4/26. Duration of BMS 18 months.
Interventions	Group 1: benzydamine HCl oral rinse (15 ml) 3 times daily (n = 10).  Group 2: placebo (n = 10).  Group 3: no treatment (n = 10).  Duration: 4 weeks.
Outcomes	VAS (ineffective to complete response) for severity of symptoms.
Notes	Diagnostic criteria stated. Groups comparable at baseline. Study only double-blind for groups 1 and 2.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**T-S 1999**

Methods	Single-centre, double-blind RCT.
Participants	37 BMS women. Mean age 59 years (range 39 to 71). Duration of BMS 2.9 years (6 months to 20 years).
Interventions	Group 1: trazodone 200 mg daily (n = 18).  Group 2: placebo (n = 19).  Duration: 8 weeks.
Outcomes	VAS and McGill Pain questionnaire for severity of pain. Beck Depression inventory.
Notes	Diagnostic criteria stated. Groups differed at baseline with regard to pain intensity.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

BMS = burning mouth syndrome; CCT = controlled clinical trial; RCT = randomised controlled trial; sd = standard deviation; VAS = visual analogue scale.

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
<a href="#">Bessho 1998</a>	Does not use a placebo group. Compares Kampo medicine with diazepam.
<a href="#">Campisi 1997</a>	Does not use a placebo group. Compares two different comparisons of two different forms of su-cralfate - 20% suspension versus 1 g chewable tablet.
<a href="#">Ferguson 1981</a>	Single-centre, double-blind CCT of 145 oophorectomised patients comparing mestranol with placebo. The study was excluded as no baseline or change data were presented.
<a href="#">Forabosco 1992</a>	Not a RCT or CCT. All subjects included in the study with BMS symptoms received the same intervention (hormone replacement therapy).
<a href="#">Grechko 1996</a>	Does not use a placebo group. Compares electrical stimulation therapy with standard methods of treatment (novocaine blockade, analgesics, etc.).
<a href="#">Grushka 1998</a>	Not a RCT or CCT. All 30 subjects received clonazepam (starting dose was 0.25 mg daily, with an increase in dose of 0.25 mg on a weekly basis if symptoms continued).
<a href="#">Hugoson 1991</a>	Not a RCT or CCT. Patients grouped according to presence of BMS symptoms and/or vitamin deficiency. Only those with both symptoms and vitamin deficiency received therapy.
<a href="#">Lamey 1986</a>	Patients initially divided according to whether they were vitamin deficient or not. The non-vitamin deficient group were randomly allocated to various vitamin replacement regimen, although results are not broken down according to regimen.
<a href="#">Loldrup 1989</a>	Patients randomly allocated one of three groups: clomipramine, mianserin or placebo. The trial included patients with pain of no known organic cause. Data for BMS sufferers could not be separated out from other types of pain.
<a href="#">Maina 2002</a>	Does not use a placebo group. Compares SSRIs (paroxetine 20 mg/day or sertraline 50 mg/day) with amisulpride 50 mg/day.
<a href="#">Peng 2001</a>	Does not use a placebo group. Compares livial (a synthetic hormone) with oryzanol and vitamin E.
<a href="#">Woda 1998</a>	Not a RCT or CCT. All 25 subjects received clonazepam (0.5 or 1 mg) two or three times daily.

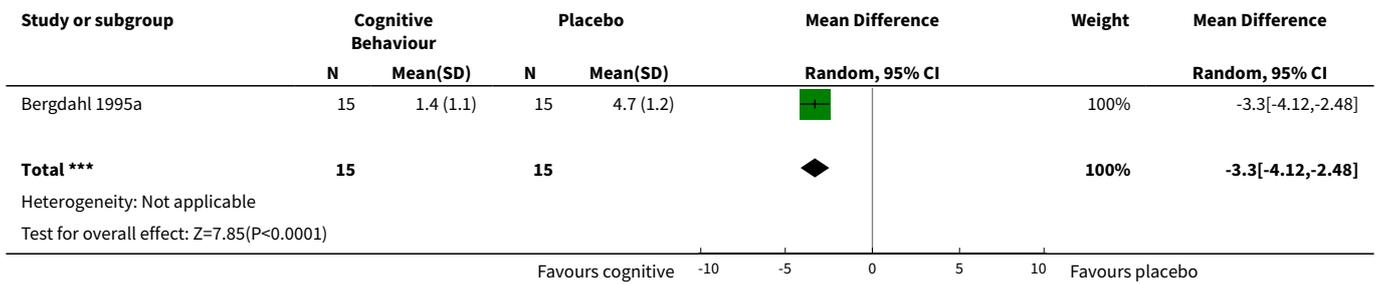
CCT = controlled clinical trial; RCT = randomised controlled trial.

## DATA AND ANALYSES

### Comparison 2. Cognitive behavioural therapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Intensity of BMS at 6 months</a>	1	30	Mean Difference (IV, Random, 95% CI)	-3.30 [-4.12, -2.48]

**Analysis 2.1. Comparison 2 Cognitive behavioural therapy versus placebo, Outcome 1 Intensity of BMS at 6 months.**



**Comparison 3. Analgesics versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Partial/complete improvement in symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

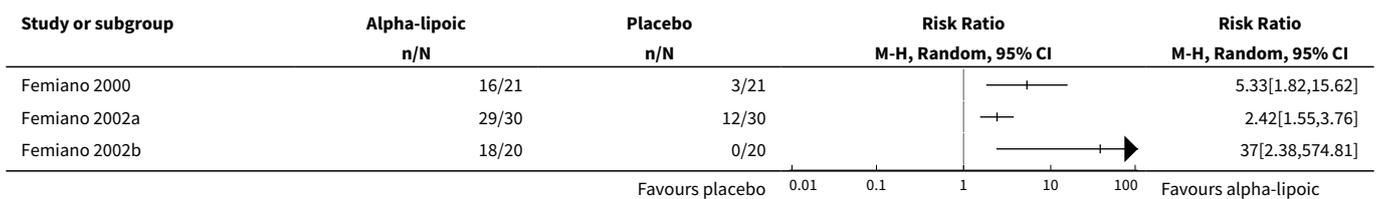
**Analysis 3.1. Comparison 3 Analgesics versus placebo, Outcome 1 Partial/complete improvement in symptoms.**



**Comparison 5. Alpha-lipoic versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in symptoms	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

**Analysis 5.1. Comparison 5 Alpha-lipoic versus placebo, Outcome 1 Improvement in symptoms.**



**Comparison 6. Anticonvulsants versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Decrease in mean pain intensity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

**Analysis 6.1. Comparison 6 Anticonvulsants versus placebo, Outcome 1 Decrease in mean pain intensity.**

Study or subgroup	Treatment		Control		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Gremeau-Richard 2004	24	2.2 (0.6)	24	0.6 (0.4)	+	1.6[1.31,1.89]

Favours placebo    -10    -5    0    5    10    Favours anticonvuls.

**ADDITIONAL TABLES**

**Table 1. Quality assessment of included studies**

Study	Sequence generation	Concealed allocation	Blinding	Drop outs listed
Bergdahl 1995a	Unclear	Unclear	Unclear	No drop outs
Bogetto 1999	Unclear	Unclear	Not used	54/121 (45%) drop outs
Femiano 2000	Unclear	Unclear	Not used	No drop outs
Femiano 2002a	Unclear	Unclear	Adequate	No drop outs at 2 month evaluation only
Femiano 2002b	Unclear	Unclear	Not used	No drop outs
Gremeau-Richard 2004	Adequate	Adequate	Adequate	3/28 (6%) drop outs. Drop outs included in the analysis
Pisanty 1975	Unclear	Unclear	Adequate	No drop outs
Sardella 1999	Adequate	Unclear	Adequate (for two groups)	No drop outs
T-S 1999	Adequate	Adequate	Adequate	9/37 (24%) drop outs

**APPENDICES**

**Appendix 1. MEDLINE (OVID) search strategy**

(MeSH terms appear in upper case, free text terms in lower case):

1. BURNING MOUTH SYNDROME
2. Burning adj3 mouth
3. Burning adj3 tongue
4. GLOSSALGIA

5. Glossalgia\$
6. Glossodynia\$
7. Glossopyros\$
8. Stomatodynia\$
9. Stomatopyros\$
10. Oral adj dysaesthesia
11. Oral adj dysesthesia
12. or/1-11

## WHAT'S NEW

Date	Event	Description
16 April 2012	Amended	Additional table linked to text.

## HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 3, 2001

Date	Event	Description
19 August 2008	Amended	Converted to new review format.
15 November 2004	New search has been performed	Searches updated to October 2004.
15 November 2004	New citation required and conclusions have changed	Substantive amendment. Two studies previously awaiting assessment have been excluded; a further four randomised controlled trials have been included and one previously included trial excluded.

## CONTRIBUTIONS OF AUTHORS

Joanna Zakrzewska (JZ) was responsible for the initiation and development of the review, following on from her chapter in Clinical Evidence, BMJ Publishing.

Anne-Marie Glenny (AMG), JZ and Heli Forssell (HF) were all responsible for screening of papers, data extraction and validity assessment. JZ and HF were responsible for any handsearching undertaken.

AMG was responsible for data management, input into RevMan and production of the first draft of the review.

It should be noted that the search results were shared between Clinical Evidence (BMJ Publishing) and the Cochrane Oral Health Group.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- St Bartholomew's and the Royal London, UK.
- University Dental Hospital of Manchester, UK.
- Turku University Central Hospital, Finland.

### External sources

- No sources of support supplied

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**INDEX TERMS****Medical Subject Headings (MeSH)**

Analgesics [therapeutic use]; Anticonvulsants [therapeutic use]; Antidepressive Agents [therapeutic use]; Benzodiazepines [therapeutic use]; Burning Mouth Syndrome [\*therapy]; Clinical Trials as Topic; Cognitive Behavioral Therapy; Electromagnetic Radiation; Hormone Replacement Therapy; Quality of Life; Randomized Controlled Trials as Topic; Vitamins [therapeutic use]

**MeSH check words**

Female; Humans; Male