ClinicalEvidence

Burning mouth syndrome

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Joanna Zakrzewska and John A. G. Buchanan

ABSTRACT

INTRODUCTION: Burning mouth syndrome mainly affects women, particularly after the menopause, when its prevalence may be 18% to 33%. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of selected treatments for burning mouth syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2015 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 70 studies. After deduplication and removal of conference abstracts, 45 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 25 studies and the further review of 20 full publications. Of the 20 full articles evaluated, one systematic review and nine RCTs were added at this update. We performed a GRADE evaluation for five PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for six interventions based on information about the effectiveness and safety of alphalipoic acid, benzodiazepines, benzydamine hydrochloride, cognitive behavioural therapy (CBT), selective serotonin re-uptake inhibitors (SSRIs), and tricyclic antidepressants.

QUESTIONS

INTERVENTIONS

Key points

- Burning mouth syndrome is characterised by discomfort or pain of the mouth, with no known medical or dental cause. It is often localised to the tongue and/or lips but can be more widespread and involve all the oral mucosa. It may affect up to one third of postmenopausal women and up to 15% of adults overall. It is a diagnosis of exclusion once other causes of possible burning have been ruled out.

  Symptoms of burning mouth can also be caused by infections, allergies, vitamin deficiencies, and ill-fitting dentures, leading to problems identifying effective treatments.

  Patients with burning mouth syndrome often also report subjective xerostomia, oral paraesthesia, and/or altered taste.

  Psychogenic factors may be involved in some people, such as anxiety, depression, or personality disorders, and could be related to dopaminergic hypofunction.

  People with burning mouth syndrome may show altered sensory and pain thresholds, or other signs of neuropathy. However, it remains unclear whether central or peripheral mechanisms are involved.

  Complete spontaneous remission occurs in only a small percentage of people, and up to 30% will note moderate improvement with or without treatment.
- We searched for evidence from RCTs and systematic reviews of RCTs on selected interventions in people with burning mouth syndrome.
- Cognitive behavioural therapy may improve symptom intensity compared with placebo in people with burning mouth syndrome, although we found no good-quality studies.
- Clonazepam may reduce pain compared with placebo in people with burning mouth syndrome, but even when it is administered topically it may be absorbed systemically, with increased risk of dependence over time.
- We don't know whether tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or benzydamine hydrochloride can improve symptoms of burning mouth, as we found few studies.

  Given the lack of knowledge about mechanisms involved, both local and centrally acting treatments may be effective. Given its significant impact on quality of life and mood, antidepressants may have a role to play.
- There is insufficient evidence to show that the dietary supplement alphalipoic acid, used in a variety of forms, has an impact on symptom relief.
- Concerning the evidence overall, it was important to ascertain that the diagnostic criteria were fulfilled. Outcome measures are varied and, even if the same ones are used, they are applied differently, thus making comparisons of trials difficult. There is a high risk of bias in the majority of studies.

Clinical context

GENERAL BACKGROUND

Burning mouth syndrome is characterised by discomfort or pain of the mouth, with no known medical or dental cause. It is often localised to the tongue and/or lips but can be more widespread and involve all the oral mucosa. It has increasing prevalence in older women, affecting up to one third of postmenopausal women and up to 15% of adults overall.

FOCUS OF THE REVIEW

Despite being relatively common, burning mouth syndrome is rarely recognised by medical practitioners, and yet it has a significant impact on quality of life. For this update, we have examined the evidence for selected interventions that may be considered to manage the symptoms.

COMMENTS ON EVIDENCE

Many studies do not provide diagnostic criteria, and it cannot be ascertained whether medical or dental causes for burning mouth were excluded. There is a wide heterogeneity of treatments used, and outcome measures vary, with few providing measures of quality of life, which makes it difficult to compare treatments. The adverse effects of treatments are poorly documented. In some RCTs, there is a high placebo response (one systematic review evaluating the placebo response in studies on treatments for burning mouth syndrome found a positive placebo response in 6 out of 12 RCTs). [1] More attention needs to be paid to this effect when designing trials.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, November 2009, to January 2015. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 70 studies. After deduplication and removal of conference abstracts 45 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 25 studies and the further review of 20 full publications. Of the 20 full articles evaluated, one systematic review and nine RCTs were added at this update.

ADDITIONAL INFORMATION

Acknowledgement that this condition has a neurophysiological basis and is not purely psychiatric helps patients come to terms with the disorder, especially if they meet fellow sufferers.

DEFINITION

Burning mouth syndrome (BMS) is an idiopathic burning discomfort or pain affecting people with clinically normal oral mucosa, in whom a medical or dental cause has been excluded. [2] [3] [4] Terms previously used to describe what is now called burning mouth syndrome include glossodynia, glossopyrosis, stomatodynia, stomatopyrosis, sore tongue, and oral dysaesthesia. [5] A survey of 669 men and 758 women randomly selected from 48,500 people aged 20 to 69 years found that people with burning mouth also have subjective dryness (66%), take some form of medication (64%), report other systemic illnesses (57%), and have altered taste (11%). [6] Local and systemic factors (such as infections, allergies, ill-fitting dentures, [7] hypersensitivity reactions, [8] and hormone and vitamin deficiencies [9] [10] [11]), as well as side effects of drugs, may cause the symptom of burning mouth and should be excluded before diagnosing burning mouth syndrome. This overview deals only with idiopathic BMS. The new classification of the International Headache Society (ICHD) supports these criteria. [12]

INCIDENCE/ PREVALENCE

The epidemiological data are of poor quality. Incidence and prevalence vary according to diagnostic criteria, [5] and many studies have included people with the symptom of burning mouth, rather than with BMS as defined above. BMS mainly affects women, [13] [14] [15] particularly after the menopause, when its prevalence may be 18% to 33%. [16] One study in Sweden found a prevalence of 4% for the symptom of burning mouth without clinical abnormality of the oral mucosa (11/669 [2%] men, mean age 59 years; 42/758 [6%] women, mean age 57 years), with the highest prevalence (12%) in women aged 60 to 69 years. [6] Reported prevalence in general populations varies from 1% to 15%. [13] However, there may be several aetiological factors behind BMS. One oral clinical examination survey in the general adult population in Finland found that 15% of the individuals surveyed had experienced BMS. However, when people with mucosal lesions, oral candidiasis, or both were excluded, the frequency decreased to 8%. Less than 1% of people reported continuous BMS complaints. [13]

AETIOLOGY/ RISK FACTORS

Although the aetiology remains unknown, there are increasing numbers of studies providing evidence that both peripheral and central changes are involved, and that BMS may be a neuropathic pain.

Neurophysiological changes have been reported both when using thermal quantitative sensory testing (QST) and with blink reflexes. [17] [18] [19] Electrogustatometric studies have provided evidence for dysfunction of the chordi tympani. [20] [21] [22] Biopsies from the tongue have shown loss of epithelial nerve fibres. [23] [24] [25] [26] Changes on functional MRIs have also been demonstrated; these changes are similar to those seen in neuropathic pain. Positron emission tomography (PET) studies support the theory that there is a decrease of endogenous dopamine. [27] [28] Psychological factors have been extensively studied for many years, [29] [30] and the high psychological or psychiatric comorbidity could be mediated by dysfunctional brain dopamine activity.

PROGNOSIS

We found no prospective cohort studies describing the natural history of BMS. [31] We found anecdotal reports of at least partial spontaneous remission in about 50% of people with BMS within 6 to 7 years. However, a retrospective study assessing 53 people with BMS (48 women and 5 men, mean duration of BMS 5.5 years, mean follow-up 56 months) found a complete spontaneous resolution of oral symptoms in 4% of people who received no treatment. Overall, 28% of people (15/53) experienced a moderate improvement with or without treatment. [32] One study in 32 patients who were provided with individual treatments for BMS did show improvement in all patient-reported outcome measures at 16 weeks. [33]

AIMS OF INTERVENTION

To alleviate symptoms, with minimal adverse effects.

OUTCOMES

Symptom relief self-reported relief of symptoms (burning mouth, altered taste, dry mouth, pain); visual analogue scale (VAS) (measure of severity of BMS pain/discomfort or relief); incidence and severity of anxiety and depression (e.g., the Beck Depression Inventory, Hospital Anxiety and Depression Scale [HADS], Hamilton Anxiety rating scale); quality of life using a validated ordinal scale (e.g., Medical Outcome Short Form Health Survey [SF-36]) and the impact of oral health on patients' quality of life (Oral Health Impact Profile [OHIP-14 or 49]). **Adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date January 2015. Databases used to identify studies for this systematic overview include: Medline 1966 to January 2015, Embase 1980 to January 2015, The Cochrane Database of Systematic Reviews 2015, issue 1 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have split the previously reported option on Antidepressants into two separate options, Selective serotonin re-uptake inhibitors and Tricyclic antidepressants. We have removed the previously reported options on HRT, local anaesthetics, and dietary supplements and added the option, Alphalipoic acid. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and

odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this overview (see table, p 11). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *BMJ Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of selected treatments for burning mouth syndrome?

OPTION ALPHALIPOIC ACID New

Symptom relief

Alphalipoic acid compared with placebo We don't know whether the dietary supplement alphalipoic acid is more effective than placebo at improving symptoms in people with burning mouth syndrome. There may be some short-term symptom relief, but there was considerable heterogeneity in the trials so it is difficult to draw any firm conclusions (low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 11 .

Benefits:

Alphalipoic acid versus placebo:

We found one systematic review (search date 2012), [34] which identified seven RCTs meeting *BMJ Clinical Evidence* reporting criteria. [35] [36] [37] [38] [39] [40] [41] The review did not perform a meta-analysis, so we report data from the individual RCTs.

Three of the RCTs identified by the review evaluated outcomes on a 5-point scale (symptoms 'worsening', 'unchanged', 'slight improvement', 'decided improvement', or 'resolution'). [35] [36] [37]

The first RCT identified by the review compared alphalipoic acid (600 mg/day for 20 days, followed by 200 mg/day for 10 days) with placebo. [35] It found that alphalipoic acid significantly improved symptoms compared with placebo (42 people; proportion of people with 'slight improvement' or 'decided improvement': 16/21 [76%] with alphalipoic acid *v* 3/14 [21%] with placebo; RR 3.6, 95% CI 1.6 to 7.7; NNT 2, 95% CI 1 to 3; follow-up period unclear).

The second RCT identified by the review found that alphalipoic acid (200 mg 3 times daily) significantly improved symptoms after 2 months compared with placebo (60 people; proportion of people with 'slight improvement', 'decided improvement', or 'resolution': 29/30 [97%] with alphalipoic acid *v* 12/30 [40%] with placebo; P <0.0001). [36]

The third RCT identified by the review compared alphalipoic acid (200 mg 3 times daily), lactoperoxidase mouth rinse (5–6 times daily), bethanecol (5 mg 3 times daily), and placebo. [37] It found that alphalipoic acid increased the proportion of people reporting improvement on the symptom scale at 60 days compared with the three other treatment options (80 people; 18/20 [90%] with alphalipoic acid *v* 0/20 [0%] with lactoperoxidase *v* 2/20 [10%] with bethanecol *v* 0/20 [0%] with placebo; it is unclear to which comparison the reported P <0.0001 refers).

The fourth and fifth RCTs identified by the review evaluated outcomes using an 11-point scale (0 = no pain to 10 = most severe burning pain experienced). [39] [40] The fourth RCT (66 people) compared three interventions: alphalipoic acid (400 mg twice daily), alphalipoic acid plus multivitamins, and placebo. [39] Symptoms were evaluated by a visual analogue scale (VAS; 10-cm vertical line marked from 0 [no pain] to 10 [most severe pain experienced]) and the McGill Pain Questionnaire (MPQ). The RCT found that all three interventions reduced VAS scores from baseline, but found no significant difference among groups in symptoms at 16 weeks (mean reduction in VAS score from baseline: –2.00 with alphalipoic acid *v* –1.78 with alphalipoic acid plus multivitamins *v* –1.25 with placebo; P = 0.79 for among-group comparison). Similarly, there was no significant difference in MPQ scores among groups at 16 weeks (reported as not significant, P value and absolute numbers not reported). Rate of withdrawal from the study was high, with 10 people withdrawing because of non-compliance and four people because of lack of effect. [39]

The fifth RCT was a four-armed study (56 people; 14 people per arm) comparing alphalipoic acid (400 mg twice a day), capsaicin, lysozyme-lactoperoxidase, and placebo. [40] Treatment was given

for 8 weeks, with a subsequent 2-month follow-up period. The RCT found that alphalipoic acid was associated with a reduction in VAS score at 8 weeks, compared with an increase in score in the placebo group (28 people; mean change in VAS score from baseline: from 5.8 to 3.7 with alphalipoic acid *v* from 4.8 to 5.3 with placebo; significance of between-group difference not assessed). At 2 months' follow-up after the end of treatment, only 64% of people were followed up, which is below *BMJ Clinical Evidence* reporting criteria and, therefore, data for this time point have not been reported here.

The sixth RCT (38 people, median age 62.9 years) compared alphalipoic acid (200 mg 3 times daily) with placebo in a crossover design involving two treatment cycles of 30 days, with a 20-day washout period between treatments. [38] The RCT found no significant difference in symptoms between alphalipoic acid and placebo at the end of the first treatment cycle (pre-crossover) and at the end of the second treatment cycle (proportion of people with 'slight improvement', 'decided improvement', or 'resolution' after first cycle: 14/17 [82%] with alphalipoic acid *v* 11/14 [79%] with placebo; P = 0.46; proportion of people with 'slight improvement', 'decided improvement', or 'resolution' after second cycle: 8/14 [57%] with alphalipoic acid *v* 12/17 [71%] with placebo; P = 0.62). The RCT reported that, 60 days after the completion of the trial, only one person maintained resolution of symptoms. [38]

The seventh RCT was a four-armed RCT (120 people) evaluating alphalipoic acid 600 mg per day (20 people), gabapentin 300 mg (20 people), and a combination of the two treatments (20 people) versus placebo (60 people) for a period of 8 weeks. [41] The RCT evaluated change in burning sensation by area afflicted using a 5-point VAS, ranging from 0 (absence of burning) to 4 (burning spread throughout the mouth). People were categorised as having a positive change if they had a change in burning sensation by one point or more. The RCT found that a significantly larger proportion of people in the alphalipoic acid group experienced a positive change at 8 weeks compared with people in the placebo group (11/20 [55%] with alphalipoic acid *v* 9/60 [15%] with placebo; P <0.001), but there was a larger change in the group using alphalipoic acid in combination with gabapentin.

Harms:

Alphalipoic acid versus placebo:
The first and second RCTs [35] [36] identified by the review [34] did not report adverse effects. In the third RCT identified by the review, four people in the alphalipoic acid arm reported heartburn, which settled with ranitidine. [37] In the fourth RCT, mild adverse effects such as gastric complaints and headache were more frequent with alphalipoic acid compared with placebo, although this did not reach significance (gastric complaints: 6 events with alphalipoic acid *v* 2 events with placebo; P = 0.29; headache: 4 events with alphalipoic acid *v* 0 events with placebo; P = 0.13). [38] Four people discontinued treatment because of adverse effects; two with alphalipoic acid and two with placebo. The final three RCTs did not report adverse effects. [39] [40] [41]

Comment:

Alphalipoic acid versus placebo:
One of the RCTs used boric acid as a control intervention, which the authors suggested was a much lower dose than reported in any therapeutic studies. [40]

The three RCTs of alphalipoic acid identified by the review were performed by the same group at overlapping time periods. [35] [36] [37] Therefore, it is possible that duplicate data may have been reported. Two of the trials were not clearly reported as being blinded. Unblinded assessment of subjective outcomes should be interpreted with caution. The subsequent RCTs reported using the CONSORT guidelines. [38] [39] They were better designed and had more robust outcome measures. Taken together, both studies indicated that alphalipoic acid either on its own or in combination with vitamins was no more efficacious than placebo. No adverse effects were reported in the second subsequent RCT, which could be related to the practice of taking the medication 30 minutes after food. [39] The dose of gabapentin was very small, and in neuropathic recommendations doses of 1800 mg to 3600 mg daily are used. [42]

Clinical guide
Alphalipoic acid, in varying combinations, can be bought from health food shops and could be recommended to those patients who do not want to take prescribed medications.

OPTION BENZODIAZEPINES (CLONAZEPAM)

Symptom relief
Clonazepam compared with placebo Clonazepam (topical or oral) may be more effective than placebo at reducing pain at up to 6 months in people with burning mouth syndrome. However, we don't know if clonazepam (oral) is more effective than placebo at improving symptoms of depression at up to 9 weeks in people with burning mouth syndrome (low-quality evidence).

Adverse effects
Topical clonazepam may be absorbed systemically, and both oral and topical formulations could lead to benzodiazepine dependence if used in the long term.

For GRADE evaluation of burning mouth syndrome, **see table, p 11 .**

Benefits:

We found one systematic review (search date 2012), [34] which identified two RCTs evaluating the use of benzodiazepines in the treatment of burning mouth syndrome. [43] [44] We also found one additional RCT. [45]

The first RCT identified by the review compared topical clonazepam with placebo (1 mg tablet of clonazepam or placebo sucked and held in the mouth for 3 minutes and then expectorated, 3 times daily) for 14 days. [43] The RCT found that clonazepam decreased pain compared with placebo after 2 weeks' treatment (48 people; pain measured on a numerical scale of 0 = no pain to 10 = worst pain imaginable; mean decrease in pain score from baseline [intention-to-treat analysis]: 2.2 with clonazepam *v* 0.6 with placebo; P = 0.03).

The second RCT identified by the review also compared clonazepam with placebo (0.5 mg of clonazepam or placebo, taken orally as a capsule once daily with water for 9 weeks). [44] The RCT found that clonazepam significantly decreased pain compared with placebo at 9 weeks (20 people; pain measured on a numerical scale where 0 = no pain to 10 = maximum possible pain; mean change in score from baseline: from 7.4 to 4.5 with clonazepam *v* from 6.0 to 4.5 with placebo; P = 0.011). The RCT found no significant difference between groups in the severity of depression (measured using the Beck Depression Inventory scale; mean change in BDI score from baseline: from 0.5 to 0.6 with clonazepam *v* from 0.6 to 0.8 with placebo; P = 0.56).

The additional RCT also compared clonazepam with placebo (0.5 mg of clonazepam [maximum 4 tablets per day] or lactose tablets held in the mouth for 3 minutes and then expectorated) over a treatment period of 6 months. [45] The RCT found that clonazepam significantly improved symptoms of burning mouth syndrome at 1 month compared with placebo (proportion of people with >50% reduction in symptoms; 23/33 [69%] with clonazepam *v* 4/33 [12%] with placebo, P <0.05). The effectiveness of clonazepam was maintained in the longer term, with the difference between clonazepam and placebo in the proportion of people achieving more than 50% reduction in burning sensation remaining statistically significant at 6 months (23/33 [69%] with clonazepam *v* 2/33 [6%] with placebo, P <0.05).

Harms:

The first RCT found no significant difference between clonazepam and placebo in the frequency of adverse events (9/24 [38%] with clonazepam *v* 6/24 [25%] with placebo; P >0.05). The adverse events experienced included drowsiness, increased burning sensation, dry mouth, spasmophilia, and euphoria (drowsiness: 4/24 [17%] with clonazepam *v* 3/24 [13%] with placebo; increased burning sensation: 2/24 [8%] in both groups; dry mouth: 1/24 [4%] with clonazepam *v* 0/24 [0%] with placebo; spasmophilia: 1/24 [4%] with clonazepam *v* 0/24 [0%] with placebo; euphoria: 1/24 [4%] with clonazepam *v* 0/24 [0%] with placebo; statistical assessments not performed for individual adverse effects). [43] Two participants (2/24 [8%]) in the clonazepam group and one participant (1/24 [4%]) in the placebo group withdrew from the trial because of adverse events (statistical assessment not performed). Five participants using topical clonazepam were assessed for systemic absorption after the 14-week treatment period. While the blood concentration of clonazepam did not reach therapeutic ranges (defined as 20 micrograms/L or more), there was evidence of some systemic absorption, with blood concentrations of clonazepam reaching about 8 micrograms/L after sucking one tablet, and about 12 micrograms/L after swallowing one tablet. Systemic use of benzodiazepines such as clonazepam can lead to dependence. [46]

The second RCT [44] identified by the review gave no information on adverse effects.

The only side effect reported by the additional RCT was some degree of sleepiness in five patients in the clonazepam group. This did not require the suspension of treatment. [45]

Comment:

In view of the possibility of systemic absorption and concerns about benzodiazepine dependence, the use of clonazepam in the management of burning mouth syndrome should be limited, and people should be made aware of the potential consequences of clonazepam use.

Clinical guide
Topical clonazepam does get absorbed, and in some countries the tablets are so small that they are inadvertently swallowed.

OPTION BENZYDAMINE HYDROCHLORIDE

Symptom relief
Benzydamine hydrochloride compared with placebo Benzydamine hydrochloride may be no more effective than placebo at reducing symptoms in people with burning mouth syndrome at 4 weeks (very low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 11 .

Benefits: We found one systematic review (search date 2012) [34] that identified one small RCT. [47] The RCT compared benzydamine hydrochloride oral rinse, placebo, and no treatment. [47] It found no significant difference in symptoms among groups at 4 weeks (30 people with burning mouth syndrome; AR for improvement: 10% with benzydamine hydrochloride *v* 20% with placebo *v* 10% with no treatment; P value not reported). However, the trial was too small to detect a clinically important difference. [47]

Harms: None of the participants in the RCT reported adverse effects. [47]

Comment: Inclusion criteria were well defined. The trial was incompletely blinded because the third group received no treatment.

Clinical guide
Many patients will buy benzydamine over the counter, either as an oral rinse (green colour) or as a spray, but it has very limited effect, inducing a numb feeling to the tongue.

OPTION COGNITIVE BEHAVIOURAL THERAPY

Symptom relief
CBT compared with no CBT CBT may be more effective than no CBT at reducing the intensity of symptoms at 6 months in people with resistant burning mouth syndrome (very low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 11 .

Benefits: We found two systematic reviews (search dates 2004; [48] and 2005 [49]), which identified the same RCT. The reviews found one small RCT comparing CBT (12–15 sessions of 1 hour/week) with a control group who received no CBT, but otherwise similar attention (see Comment section). [29] The RCT found that CBT significantly reduced the intensity of symptoms at 6 months (30 people with resistant burning mouth syndrome; pain measured on a visual analogue scale ranging from 1 = endurable to 7 = unendurable; mean pre-treatment score: 5.0 with CBT *v* 4.3 with placebo; mean score change at 6 months: –3.6 with CBT *v* +0.4 with placebo; P <0.001; AR for being symptom free at 6 months: 4/15 [27%] with CBT *v* 0/15 [0%] with placebo; significance not reported).

Harms: The RCT gave no information on adverse effects. [29]

Comment: The RCT [29] was small, and individual characteristics of the two groups were not described; therefore, the groups may not have been comparable. The visual analogue scale for assessing oral burning was not validated.

A small open-label study in 24 women, providing two sessions at 6-month intervals, reported a reduction in pain intensity and anxiety. [50] A consistent finding in the pain management literature, which includes CBT, is that the designs of the trials are complex and not well developed. It has also been noted that patients vary substantially in their response to treatments; this may be due to the dynamics of the session and the intervention being more affected by the deliverer of the intervention than in drug trials. [33] [51] Overall, in chronic pain, CBT has been shown to be effective, especially in improving mood. [52] A Cochrane systematic review of psychological therapies in orofacial pain showed that these methods were potentially effective; due to high risk of bias, the study came to the conclusion that there was weak evidence, but it recommended their use in preference to more invasive treatments. [53]

Clinical guide
CBT in chronic pain has been shown to have impact on mood and improves coping strategies more than pain intensity. Combined with its non-invasive nature, it is a valuable intervention, but it may need to be done either on a one-to-one basis or in groups with other BMS sufferers.

OPTION SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS New

SSRIs compared with each other We don't know if the SSRIs sertraline and paroxetine differ in their effectiveness at reducing pain at 8 weeks in people with burning mouth syndrome (very low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 11 .

Benefits:

SSRIs versus placebo:
We found one systematic review (search date 2012), [34] which identified no RCTs evaluating SSRIs versus placebo in the treatment of burning mouth syndrome.

SSRIs versus each other:
We found one small RCT, which found similar reduction in pain score (pain assessed by 10-point visual analogue scale, higher scores indicating more-severe pain) with sertraline, paroxetine, and amisulpride at 8 weeks (76 people; mean score reduction: 4.4 with sertraline *v* 3.7 with paroxetine *v* 4.0 with amisulpride; P values not reported). [54] However, the study may have lacked power to detect clinically important differences among treatments, and lacked a placebo comparison.

Harms:

The adverse effects of antidepressants in other populations are well documented.

SSRIs versus placebo:
We found no RCTs.

SSRIs versus each other:
The RCT reported no serious adverse effects in any treatment group. [54] In 2005, the US Food and Drug Administration and the UK Medicines and Healthcare Products Regulatory Agency issued warnings that observational studies have found that the use of paroxetine by women in the first trimester of pregnancy may increase the risk of congenital malformations. Antidepressants used in the treatment of burning mouth syndrome are used in relatively low doses, and women with burning mouth syndrome are usually over child-bearing age. People with clinical depression and burning mouth syndrome should be assessed by psychiatrists. Antidepressants should only be prescribed by suitably experienced and qualified practitioners who can assess the relative benefits and risks of antidepressant use for the individual.

Comment:

In the RCT comparing SSRIs with each other, 34 people had a concurrent psychiatric diagnosis. [54] The widespread use of antidepressants in burning mouth syndrome may be because of their effects on neuropathic pain, [42] and the association of burning mouth syndrome with generalised anxiety disorder, depression, and adverse life events. [55] See Comment in the option on Tricyclic antidepressants, p 8 for information on the antidepressant trazodone.

Clinical guide
In recommendations for management of neuropathic pain, the only serotonin-noradrenaline re-uptake inhibitor suggested is duloxetine, specifically for diabetic neuropathy. [56]

OPTION TRICYCLIC ANTIDEPRESSANTS New

We found no direct information from RCTs about the effects of tricyclic antidepressants in people with burning mouth syndrome.

For GRADE evaluation of burning mouth syndrome, see table, p 11 .

Benefits:

We found one systematic review (search date 2012), [34] which identified no RCTs evaluating tricyclic antidepressants in the treatment of burning mouth syndrome.

Harms:

We found no RCTs.

Comment:

One RCT [57] included paroxetine, amitriptyline, amilsulpride, and placebo, but it had a 79% attrition (19/24), so no meaningful data extraction was possible. One double-blind RCT, included in two systematic reviews (search dates 2004; [48] and 2005 [49]) compared trazodone with placebo. It found no significant difference in pain or related symptoms between trazodone and placebo measured on a visual analogue scale (0 mm = best score and 100 mm = worst score) at 8 weeks (37 women with burning mouth syndrome; mean difference in pain reduction between the groups at 8 weeks: –4.8 mm, 95% CI –20.3 mm to +10.7 mm).

Clinical guide
If we are to consider BMS a possible neuropathic pain, then tricyclic antidepressants, such as amitriptyline or nortriptyline, may be helpful as found in other types of neuropathic pain. [42]

GLOSSARY

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of 4 statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13 to 80 years. Scores of more than 12 or 13 indicate the presence of depression.

Hamilton Anxiety Scale (HAM-A) The HAM-A is a validated instrument consisting of 14 items scored on a 5-point scale, ranging from 0 (not present) to 4 (severe), to give a total score of between 0 and 56.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Short Form-36 [SF-36] Health Survey Includes one multi-item scale that assesses eight health concepts: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and wellbeing), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions. The survey was constructed for self-administration by people aged 14 years or older, and for administration by a trained interviewer in person or by telephone.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Alphalipoic acid New option. One systematic review [34] and seven RCTs [35] [36] [37] [38] [39] [40] [41] added. Categorised as 'unknown effectiveness'.

Selective serotonin re-uptake inhibitors New option. One systematic review added. [34] Categorised as 'unknown effectiveness'.

Tricyclic antidepressants New option. One systematic review added. [34] Categorised as 'unknown effectiveness'.

Benzodiazepines (clonazepam) One systematic review [34] and one RCT added. [44] One further RCT also added. [45] Categorisation unchanged (trade-off between benefits and harms).

Benzydamine hydrochloride One systematic review added. [34] Categorisation unchanged (unknown effectiveness).

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Joanna Zakrzewska
Consultant/ Honorary Professor, Facial pain consultant
Division of Diagnostic
Surgical and Medical Sciences, Eastman Dental Hospital, UCLH NHS Foundation
London
UK

John A. G. Buchanan
Clinical Senior Lecturer/Honorary Consultant in Oral Medicine
Barts and The London School of Medicine and Dentistry
Dental Institute, Royal London Hospital
London
UK

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Disclaimer

TABLE **GRADE evaluation of interventions for burning mouth syndrome**

Important outcomes					Symptom relief, adverse effects				
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of selected treatments for burning mouth syndrome?									
1 (30) [29]	Symptom relief	CBT *v* control	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about methods of validation of outcomes; directness point deducted for uncertainty about comparisons between the groups
3 (134) [43] [44] [45]	Symptom relief	Benzodiazepines *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for differences in regimens and duration of treatment and follow-up across studies
1 (76) [54]	Symptom relief	SSRIs *v* each other	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for differences in disease state
1 (30) [47]	Symptom relief	Benzydamine hydrochloride *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and blinding flaws
7 (340) [35] [36] [37] [38] [39] [40] [41]	Symptom relief	Alphalipoic acid *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for methodological flaws (incomplete reporting of results, imbalance in numbers of people in groups in some RCTs, and lack of statistical assessment of between-group difference in some RCTs); directness point deducted for variation in doses of alphalipoic acid used across studies and variation in outcome assessment

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generaliseability of population or outcomes.
Effect size: based on relative risk or odds ratio.