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Burning mouth syndrome

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John Buchanan and Joanna Zakrzewska

ABSTRACT

INTRODUCTION: Burning mouth syndrome mainly affects women, particularly after the menopause, when its prevalence may be 18–33%. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for burning mouth syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 12 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anaesthetics (local), antidepressants, benzodiazepines (topical clonazepam), benzydamine hydrochloride, cognitive behavioural therapy (CBT), dietary supplements, and hormone replacement therapy (HRT) in postmenopausal women.

QUESTIONS

INTERVENTIONS

Key Points

- Burning mouth syndrome is characterised by discomfort or pain of the mouth, with no known medical or dental cause. It may affect up to a third of postmenopausal women and up to 15% of adults overall.

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

  Psychogenic factors may be involved in some people, such as anxiety, depression, or personality disorders.

  People with burning mouth syndrome may show altered sensory and pain thresholds, or other signs of neuropathy.

  Long-term outcomes are unknown, but half of people may have spontaneous resolution of their symptoms over 6–7 years.

- CBT may improve symptom intensity compared with placebo, although no good-quality studies have been found.
- Topical clonazepam may reduce pain compared with placebo, but may be absorbed systemically, with increased risk of dependence over time.

  We don't know whether antidepressants, benzydamine hydrochloride, dietary supplements, or HRT in postmenopausal women can improve symptoms of burning mouth, as few studies have been found.

DEFINITION

Burning mouth syndrome is an idiopathic burning discomfort or pain affecting people with clinically normal oral mucosa, in whom a medical or dental cause has been excluded. [1] [2] [3] Terms previously used to describe what is now called burning mouth syndrome include glossodynia, glossopyrosis, stomatodynia, stomatopyrosis, sore tongue, and oral dysaesthesia. [4] A survey of 669 men and 758 women randomly selected from 48,500 people aged 20–69 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%). [5] Many studies of people with symptoms of burning mouth do not distinguish those with burning mouth syndrome (i.e. idiopathic disease) from those with other conditions (such as vitamin B deficiency), making results unreliable. Local and systemic factors (such as infections, allergies, ill-fitting dentures, [6] hypersensitivity reactions, [7] and hormone and vitamin deficiencies [8] [9] [10]) may cause the symptom of burning mouth, and should be excluded before diagnosing burning mouth syndrome. This review deals only with idiopathic burning mouth syndrome.

INCIDENCE/ PREVALENCE

Burning mouth syndrome mainly affects women, [11] [12] [13] particularly after the menopause, when its prevalence may be 18–33%. [14] 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 60–69 years. [5] Reported prevalence in general populations varies from 1% [14] to 15%. [11] Incidence and prevalence vary according to diagnostic criteria, [4] and many studies included people with the symptom of burning mouth, rather than with burning mouth syndrome as defined above.

AETIOLOGY/ RISK FACTORS

The cause is unknown, and we found no good aetiological studies. Possible causal factors include hormonal disturbances associated with the menopause, [12] [13] [14] psychogenic factors (including anxiety, depression, stress, life events, personality disorders, and phobia of cancer), [6] [15] [16] and neuropathy in so-called supertasters . [17] Support for a neuropathic aetiology comes from studies that have shown altered sensory and pain thresholds in people with burning mouth syndrome. [18] Two studies using blink reflex and thermal quantitative sensory tests have demonstrated signs of neuropathy in most people with burning mouth syndrome. [19] [20]

PROGNOSIS

We found no prospective cohort studies describing the natural history of burning mouth syndrome. [21] We found anecdotal reports of at least partial spontaneous remission in about 50% of people with burning mouth syndrome within 6–7 years. [15] However, a recent retrospective study assessing 53 people with burning mouth syndrome (48 women and 5 men, mean duration of burning mouth syndrome 5.5 years, mean follow-up 56 months) found a complete spontaneous resolution of oral symptoms in 11% of people (2/19) who received no treatment. Overall, 30% of people (15/53) experienced a moderate improvement, with or without treatment. [22]

AIMS OF INTERVENTION

To alleviate symptoms, with minimal adverse effects.

OUTCOMES

Self-reported relief of symptoms (burning mouth, altered taste, dry mouth); incidence and severity of anxiety and depression; quality of life using a validated ordinal scale.

METHODS

BMJ Clinical Evidence search and appraisal February 2007. The following databases were used to identify studies for this review: Medline 1966 to February 2007, Embase 1980 to February 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 1. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this reveiw were: published systematic reviews and RCTs in any language, 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 required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 7).

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

OPTION CBT

Symptom relief

Compared with control CBT may be more effective at reducing the intensity of symptoms at six months in people with resistant burning mouth syndrome compared with control (very low quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits:

We found one systematic review (search date 2004). [23] The review identified one small RCT which compared CBT (12–15 sessions of 1 hour/week) versus a control group who received similar attention but without the CBT sessions (see comment below). [24] 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 pretreatment 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 less than 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. [24]

Comment: The trial was small, and individual characteristics of the two groups were not described; therefore, the groups may not have been comparable. [24] The visual analogue scale for assessing oral burning was not validated.

OPTION BENZODIAZEPINES

Symptom relief
Clonazepam compared with placebo Topical clonazepam is more effective at reducing pain at 14 days in people with burning mouth syndrome compared with placebo (moderate quality evidence).

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

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits: We found one systematic review, [23] which identified one small, short-term RCT comparing topical clonazepam versus placebo (1 mg tablet of clonazepam or placebo sucked and held in the mouth for 3 minutes and then expectorated, 3 times/day) for 14 days. [25] 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 = 0.027).

Harms: The 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 more than 0.05). The adverse events experienced included 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), and euphoria (1/24 [4%] with clonazepam *v* 0/24 [0%] with placebo; statistical assessments not performed for individual adverse effects). 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 µg/L or more), there was evidence of some systemic absorption, with blood concentrations of clonazepam reaching about 8 µg/L after sucking one tablet, and about 12 µg/L after swallowing one tablet. Systemic use of benzodiazepines such as clonazepam can lead to dependence. [26]

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.

OPTION ANTIDEPRESSANTS

Symptom relief
Trazodone compared with placebo Trazodone is no more effective at reducing pain at eight weeks in people with burning mouth syndrome than placebo (moderate quality evidence).

SSRIs compared with each other The SSRIs sertraline, paroxetine, and amisulpride may all be equally effective at reducing pain at eight weeks in people with burning mouth syndrome (very low quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits: **Antidepressants versus placebo:**
We found one systematic review (search date 2004) which identified one RCT that met *BMJ Clinical Evidence* inclusion criteria. [23] The double blind RCT compared trazodone 200 mg daily versus placebo. [27] 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).

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 50 mg daily, paroxetine 20 mg daily, and amisulpride 50 mg daily 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). [28] 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, see review on depression in adults: drug and other physical treatments.

Antidepressants versus placebo:
The RCT identified by the review found that adverse effects caused 7/18 (39%) people taking trazodone to withdraw from the trial compared with 2/19 (10%) taking placebo. [23] [27] Significantly more people given trazodone experienced dizziness and drowsiness compared with placebo (dizziness: 11/18 [61%] with trazodone *v* 1/19 [5%] with placebo; P less than 0.001; drowsiness: 9/18 [50%] with trazodone *v* 2/19 [11%] with placebo; P less than 0.05).

SSRIs versus each other:
The RCT reported no serious adverse effects in any treatment group. [28] In 2005, the US Food and Drug Administration and the UK Medicines and Healthcare Products Regulatory Agency issued warnings that recent 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: Although the RCT comparing trazodone versus placebo was well conducted and used several pertinent outcome measures, including psychological ones, it was also too small and brief to detect clinically important effects. [23] [27] In the RCT comparing SSRIs versus each other, 34 people had a concurrent psychiatric diagnosis. [28] The widespread use of antidepressants in burning mouth syndrome may be because of their effects on neuropathic pain, [29] and the association of burning mouth syndrome with generalised anxiety disorder, depression, and adverse life events. [30]

OPTION BENZYDAMINE HYDROCHLORIDE

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

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits: We found one systematic review (search date 2004). [23] It found one small RCT comparing benzydamine hydrochloride oral rinse (15 mL of 0.15% for 1 minute 3 times daily for 4 weeks), placebo, and no treatment. 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. [23]

Harms: None of the participants in the RCT reported adverse effects. [23]

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

OPTION DIETARY SUPPLEMENTS

Symptom relief
Compared with placebo The dietary supplement alphalioic acid may be more effective at improving symptoms in people with burning mouth syndrome compared with placebo (very low quality evidence).

Compared with HRT The dietary supplement oryzanol plus vitamin E may be less effective than tibolone at improving symptoms in postmenopausal women with burning mouth syndrome at six months (very low quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits:

Dietary supplements versus placebo:
We found one systematic review (search date 2004, 3 RCTs). [23] All three RCTs identified by the review evaluated outcomes on a 5-point scale (symptoms "worsening", "unchanged", "slight improvement", "decided improvement", or "resolution"). The first RCT included in the review compared alphalipoic acid (600 mg/day for 20 days, followed by 200 mg/day for 10 days) versus placebo. [31] It found that alphalipoic acid significantly improved symptoms compared with placebo (42 people; AR for "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 included in the review found that alphalipoic acid (200 mg 3 times/day) significantly improved symptoms after 2 months compared with placebo (60 people; AR for "slight improvement", "decided improvement", or "resolution": 29/30 [97%] with alphalipoic acid *v* 12/30 [40%] with placebo; P less than 0.0001). [32] The third RCT included in the review compared alphalipoic acid (200 mg 3 times/day), lactoperoxidase mouth rinse (5–6 times/day), bethanecol (5 mg 3 times/day), and placebo. [33] 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 what comparison the reported P less than 0.0001 refers).

Dietary supplements versus HRT:
See benefits of HRT in postmenopausal women, p 5 .

Harms:

Dietary supplements versus placebo:
In the third RCT identified by the review, four people in the alphalipoic acid arm reported heartburn, which settled with ranitidine. [33] Four people taking bethanecol experienced adverse events, including nausea, dizziness, cold perspiration, or abdominal pain.

Dietary supplements versus HRT:
See harms of HRT in postmenopausal women, p 5 .

Comment:

Dietary supplements versus placebo:
The three RCTs of alphalipoic acid were performed by the same group at overlapping time periods. [31] [32] [33] 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.

Dietary supplements versus HRT:
See comment of HRT in postmenopausal women, p 5 .

OPTION HRT IN POSTMENOPAUSAL WOMEN

Symptom relief
Compared with dietary supplements Tibolone may be more effective at improving symptoms in postmenopausal women with burning mouth syndrome at six months than the dietary supplement oryzanol plus vitamin E (very low quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 7 .

Benefits:

We found one systematic review (search date 2004), which identified no RCTs of sufficient quality comparing HRT versus placebo. [23] We found one additional RCT which compared oral tibolone 2.5 mg daily versus oryzanol (30 mg 3 times/day; see comment below) plus vitamin E (100 mg 3 times/day). [34] The study had several flaws in its methods (see comment below). It found that tibolone significantly improved symptoms compared with oryzanol plus vitamin E at 3 and 6 months (56 postmenopausal women; AR for improvement at 3 months: 84.6% with tibolone *v* 13.3% with oryzanol plus vitamin E; P less than 0.005; AR for improvement at 6 months: 88.5% with tibolone *v* 16.7% with oryzanol plus vitamin E; P less than 0.005).

Harms:

Adverse effects of HRT are well documented (See oestrogens under menopausal symptoms).
Drug safety alert:
A drug safety alert has been issued on the increased risk of breast cancer recurrence associated with tibolone (http://www.mhra.gov.uk).

Comment:

We found three non-randomised intervention studies with no clear diagnostic criteria or outcome measures. [35] [36] [37] The additional RCT (which was reported in Chinese) had several design weaknesses, which suggests that the results need to be interpreted with caution. [34] The study gave no clear definition of burning mouth syndrome; it did not specify the method of randomisation; the study was not blinded; the scale used for assessing improvement of symptoms was not validated;

and there were important differences between the groups at baseline. Oryzanol is a product mainly derived from rice bran oil and is used as a food supplement.

OPTION ANAESTHETICS (LOCAL)

We found no direct information assessing the effects of local anaesthetics in the treatment of people with burning mouth syndrome.

For GRADE evaluation of burning mouth syndrome, **see table, p 7 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

GLOSSARY

Supertaster People who have the highest density of fungiform papillae, which are responsible for taste, on the anterior tongue and taste 6-n-propylthiouracil as intensely bitter.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

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John AG 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

Burning mouth syndrome

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

Competing interests: JB and JZ declare that they have no competing interests.

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 treatments for burning mouth syndrome?									
1 (30) [24]	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
1 (48) [25]	Symptom relief	Benzodiazepines v placebo	4	-1	0	0	0	Moderate	Quality point deducted for sparse data
1 (37) [27]	Symptom relief	Antidepressants v placebo	4	-1	0	0	0	0	Quality point deducted for sparse data
1 (76) [28]	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) [23]	Symptom relief	Benzydamine hydrochloride v palcebo	4	-3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results and blinding flaws
3 (182) [31] [32] [33]	Symptom relief	Dietary supplements v each other	4	-3	0	-1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results and blinding flaws. Directness point deducted for range of outcomes
1 (56) [34]	Symptom relief	HRT v dietary supplements	4	-3	0	-1	0	Very low	Quality points deducted for sparse data, baseline differences and methodological flaws (blinding flaws, uncertainty about randomisation and scale used for assessment of symptom improvement). Directness point deducted for uncertainty about diagnosis in one study

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.

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