ClinicalEvidence

Burning mouth syndrome

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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 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 November 2009 (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 15 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 one 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.

  Complete spontaneous remission occurs in only a small percentage of people, and up to 30% will note moderate improvement with or without treatment.

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

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

  Dietary supplements may be no more effective than placebo at reducing symptoms of burning mouth.

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. [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 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%). [5] Many studies of people with symptoms of burning mouth do not distinguish those with BMS (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 BMS.

INCIDENCE/ PREVALENCE

BMS mainly affects women, [11] [12] [13] particularly after the menopause, when its prevalence may be 18% to 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 to 69 years. [5] Reported prevalence in general populations varies from 1% to 15%. [11] However, there may several aetiological factors behind BMS. One oral clinical examination survey in the general adult population in Finland found that 14.8% of the individuals surveyed had experienced BMS. However, when people with mucosal lesions, oral candidiasis, or both were excluded, the frequency decreased to 7.9%. Less than 1% (0.7%) of people reported continuous BMS complaints. [11] Incidence and prevalence vary according to diagnostic criteria, [4] and many studies have included people with the symptom of burning mouth, rather than with BMS 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 cause comes from studies that have shown altered sensory and pain thresholds in people with BMS. [18] Two studies using blink reflex and thermal quantitative sensory tests have demonstrated signs of neuropathy in most people with BMS. [19] [20]

PROGNOSIS

We found no prospective cohort studies describing the natural history of BMS. [21] 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. [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

Clinical Evidence search and appraisal November 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2009, Embase 1980 to November 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs 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. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. 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 reviews as required. To aid readability of the numerical data in our reviews, 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). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table). 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 *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 treatments for burning mouth syndrome?

OPTION COGNITIVE BEHAVIOURAL THERAPY

Symptom relief
Compared with no CBT CBT may be more effective 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 9 .

Benefits: We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which identified the same RCT. The reviews found one small RCT comparing CBT (12–15 sessions of 1 hour/week) versus a control group who received no CBT, but otherwise similar attention (see comment below). [25] 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. [25]

Comment: The trial was small, and individual characteristics of the two groups were not described; therefore, the groups may not have been comparable. [25] 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 (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 9 .

Benefits: We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which both 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 daily) for 14 days. [26] 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).

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 greater than 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). [26] 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. [27]

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 8 weeks in people with burning mouth syndrome (moderate-quality evidence).

Selective serotonin reuptake inhibitors compared with each other The SSRIs sertraline, paroxetine, and amisulpride may all be equally effective 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 9 .**

Benefits:

Antidepressants versus placebo:
We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which both identified one RCT that met *Clinical Evidence* inclusion criteria. [28] The double-blind RCT compared trazodone 200 mg daily versus 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).

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). [29] 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 reviews found that 7/18 (39%) people taking trazodone and 2/19 (10%) taking placebo withdrew from the trial owing to adverse effects. [28] A significantly greater proportion of 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. [29] 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:

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. [28] In the RCT comparing SSRIs versus each other, 34 people had a concurrent psychiatric diagnosis. [29] The widespread use of antidepressants in burning mouth syndrome may be because of their effects on neuropathic pain, [30] and the association of burning mouth syndrome with generalised anxiety disorder, depression, and adverse life events. [31]

OPTION BENZYDAMINE HYDROCHLORIDE

Symptom relief
Compared with placebo Benzydamine hydrochloride may be no more effective 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 9 .**

Benefits:

We found two systematic reviews (search dates 2004 [23] and 2005 [24]). Both reviews identified 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. [32] 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. [32]

Harms: None of the participants in the RCT reported adverse effects. [32]

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 alphalipoic acid may be no more effective at improving symptoms in people with burning mouth syndrome (very low-quality evidence).

Compared with HRT The dietary supplement oryzanol plus vitamin E may be less effective than tibolone at improving symptoms at 6 months in postmenopausal women with burning mouth syndrome (very low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 9 .

Benefits:

Dietary supplements versus placebo:
We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which both identified the same three RCTs. [33] [34] [35] Neither review performed a meta-analysis. We found two subsequent RCTs. [36] [37]

The three RCTs identified by the reviews evaluated outcomes on a 5-point scale (symptoms "worsening", "unchanged", "slight improvement", "decided improvement", or "resolution"). The first RCT identified by the review compared alphalipoic acid (600 mg/day for 20 days, followed by 200 mg/day for 10 days) versus placebo. [33] 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 less than 0.0001). [34]

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. [35] 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).

The first subsequent RCT (38 people, median age 62.9 years) compared alphalipoic acid (200 mg 3 times daily) versus placebo in a crossover design involving two treatment cycles of 30 days, with a 20-day washout period between treatments. [36] 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. [36]

The second subsequent RCT (66 people) compared three interventions: alphalipoic acid (400 mg twice daily), alphalipoic acid plus multivitamins, and placebo. [37] 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). Loss to follow-up in the study was high, with 10 people withdrawing because of non-compliance and four people because of lack of effect. [37]

Dietary supplements versus hormone-replacement therapy (HRT):
See benefits of HRT in postmenopausal women, p 6 .

Harms:

Dietary supplements versus placebo:
The first and second RCTs [33] [34] identified by the reviews [23] [24] did not report adverse effects. In the third RCT identified by the reviews, four people in the alphalipoic acid arm reported heartburn, which settled with ranitidine. [35] Four people taking bethanecol experienced adverse events, including nausea, dizziness, cold perspiration, or abdominal pain. In the first subsequent RCT, mild adverse effects such 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). [36] Four people discontinued treatment because of adverse effects; two with alphalipoic acid and two with placebo. The second subsequent RCT did not report adverse effects. [37]

Dietary supplements versus HRT:
See harms of HRT in postmenopausal women, p 6 .

Comment:

Dietary supplements versus placebo:
The three RCTs of alphalipoic acid identified by the reviews were performed by the same group at overlapping time periods. [33] [34] [35] 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. [36] [37] 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. [37]

Dietary supplements versus HRT:
See comment of HRT in postmenopausal women, p 6 .

OPTION HORMONE-REPLACEMENT THERAPY IN POSTMENOPAUSAL WOMEN

Symptom relief
Compared with dietary supplements Tibolone may be more effective at 6 months than the dietary supplement oryzanol plus vitamin E at improving symptoms in postmenopausal women with burning mouth syndrome (very low-quality evidence).

For GRADE evaluation of burning mouth syndrome, see table, p 9 .

Benefits:

HRT versus placebo:
We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which identified no RCTs of sufficient quality comparing HRT versus placebo.

HRT versus dietary supplements:
We found one additional RCT, which compared oral tibolone 2.5 mg daily versus oryzanol (30 mg 3 times daily; see comment below) plus vitamin E (100 mg 3 times daily). [38] The study's methods were flawed in several ways (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: 85% with tibolone *v* 13% with oryzanol plus vitamin E; P less than 0.005; AR for improvement at 6 months: 88% with tibolone *v* 17% with oryzanol plus vitamin E; P less than 0.005).

Harms:

Adverse effects of HRT are well documented, including increased risk of breast cancer recurrence with tibolone (see oestrogens in the review on menopausal symptoms).

Comment:

We found three non-randomised intervention studies with no clear diagnostic criteria or outcome measures. [39] [40] [41] The additional RCT (which was reported in Chinese) had several design weaknesses, which suggests that the results need to be interpreted with caution. [38] 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 from RCTs 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 9 .**

Benefits: We found two systematic reviews (search dates 2004 [23] and 2005 [24]), which identified no RCTs of comparing local anaesthetics versus placebo.

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.

SUBSTANTIVE CHANGES

Anaesthetics (local) One new systematic review added, [24] which identified no RCTs comparing local anaesthetics versus placebo. Categorisation unchanged (Unknown effectiveness).

Antidepressants One new systematic review added, [24] which identified one already included RCT. Categorisation unchanged (Unknown effectiveness).

Benzodiazepines One new systematic review added, [24] which identified one already included RCT. Categorisation unchanged (Trade-off between benefits and harms).

Benzydamine hydrochloride One new systematic review added, [24] which identified one already included RCT. Categorisation unchanged (Unknown effectiveness).

CBT One new systematic review added, [24] which identified one already included RCT. Categorisation unchanged (Likely to be beneficial).

Dietary supplements One systematic review added, [24] which identified three already included RCTs. Two subsequent RCTs added, [36] [37] which both found no significant difference in symptoms between alphalipoic acid and placebo. Despite conflicting results with the earlier RCTs which found some benefit with dietary supplements, categorisation changed from Unknown effectiveness to Unlikely to be beneficial as the subsequent RCTs finding no benefit were larger and of higher quality.

HRT in postmenopausal women One new systematic review added, [24] which identified one already included RCT. Categorisation unchanged (Unknown effectiveness).

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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 treatments for burning mouth syndrome?									
1 (30) [25]	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) [26]	Symptom relief	Benzodiazepines *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (37) [28]	Symptom relief	Antidepressants *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (76) [29]	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) [32]	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
5 (286) [33] [34] [35] [36] [37]	Symptom relief	Dietary supplements *v* each other	4	–4	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, blinding flaws, and poor follow-up. Directness point deducted for range of outcomes
1 (56) [38]	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.