Aphthous ulcers (recurrent)

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QUESTIONS

What are the effects of treatments for recurrent aphthous ulcers?. 2

INTERVENTIONS

TREATMENT

Likely to be beneficial

Chlorhexidine and similar agents 2

Unknown effectiveness

Analgesics (Local) New 5

Carbenoxolone mouthwash New 3

Corticosteroids (topical). 4

Tetracycline antibiotic mouthwash New 5

To be covered in future updates

Barrier techniques

Laser

Low intensity ultrasound

Novel toothpastes

Other drug treatments

Key Points

- Most people with recurrent aphthous ulcers develop a few ulcers less than 1 cm in diameter, that heal after 5–14 days without scarring.

  The causes are unknown, but risks of recurrence may decrease if the person gives up smoking.

  Local physical trauma may trigger ulcers in susceptible people.

  In 10% of sufferers, lesions are more than 1 cm in diameter and can cause scarring.
- Chlorhexidine mouth rinses may reduce the severity and pain of ulceration, although studies have reported inconclusive results about whether the incidence of new ulcers is reduced.
- We don't know whether topical corticosteroids reduce the number of new ulcers, but they may reduce pain and increase healing of ulcers without causing notable adverse effects.
- We don't know whether carbenoxolone gel or mouthwash, local analgesics , or tetracycline mouthwash work, as few well planned studies were found

DEFINITION

Recurrent aphthous ulcers are superficial, rounded, painful mouth ulcers usually occurring in recurrent bouts at intervals of a few days to a few months in otherwise well people. [1]

INCIDENCE/ PREVALENCE

The point prevalence of recurrent aphthous ulcers in Swedish adults has been reported as 2%. [1] Prevalence may be 5–10% in some groups of children. Up to 66% of young adults give a history consistent with recurrent aphthous ulceration.

AETIOLOGY/ RISK FACTORS

The cause of aphthous ulcers remains unknown. Associations with haematinic deficiency, infections, gluten sensitive enteropathy, food sensitivities, and psychological stress have rarely been confirmed. Similar ulcers are seen in Behçet's syndrome. Local physical trauma may initiate ulcers in susceptible people. Recurrent aphthous ulcers are uncommon on keratinised oral mucosal surfaces, and the frequency of recurrent aphthous ulcers may fall if people cease any tobacco smoking habit.

PROGNOSIS

About 80% of people with recurrent aphthous ulcers develop a few ulcers smaller than 1 cm in diameter that heal within 5–14 days without scarring (the pattern known as minor aphthous ulceration). The episodes recur typically after an interval of 1–4 months. One in 10 people with recurrent ulceration may have multiple minute ulcers (herpetiform ulceration). Likewise, one in 10 sufferers has a more severe form (major aphthous ulceration), with lesions larger than 1 cm that may recur after a shorter interval, which and can cause scarring. Most of the trials in this review have focused on the treatment of minor aphthous ulceration.

AIMS OF INTERVENTION

To reduce the severity of the episode and the incidence, duration, and pain of ulceration with minimal adverse effects.

OUTCOMES

Ulcer day index: The sum of the number of ulcers each day over a period, usually 4–8 weeks, which indicates the severity of the episode and reflects the mean prevalence and duration of ulcers; number of ulcer free days during a specified period; **incidence of new ulcers:** number of new ulcers appearing within a specified period, usually 4–8 weeks; **duration of ulceration:** mean duration of individual ulcers (difficult to determine because of uncertainty in detecting the point of complete resolution); **severity of pain:** symptom score based on subjective pain severity recorded in categories on a questionnaire (e.g. from 0 to 3, ranging from no pain to severe pain) or on a 10 cm visual analogue scale; **user preference:** preference of people for one treatment over another. The **diameter of lesions** is a proxy measure of the clinical severity of an episode of ulceration.

METHODS

BMJ Clinical Evidence search and appraisal August 2006. The following databases were used to identify studies for this review: Medline 1966 to August 2006, Embase 1980 to August 2006, and The Cochrane Library, Issue 3, 2006. 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 National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review 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. 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. In addition, the authors augmented studies with their own search, through attendance at conferences, and through regular contact with experts in the field. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 9).

QUESTION What are the effects of treatments for recurrent aphthous ulcers?

OPTION CHLORHEXIDINE AND SIMILAR AGENTS

Ulcer incidence

Chlorhexidine compared with placebo Chlorhexidine mouthwash may be more effective at reducing the severity of ulceration, and chlorhexidine gel may be more effective at reducing the incidence or duration of ulceration, compared with placebo (very low-quality evidence).

Hexetidine compared with placebo Hexetidine may be no more effective at reducing the severity, duration, or incidence of ulcers in people with recurrent aphthous ulceration compared with placebo (very low-quality evidence).

Proprietary antibacterial rinse compared with control A proprietary antibacterial rinse may be no more effective at reducing the severity, pain, duration, or incidence of ulcers in people with recurrent aphthous ulceration compared with a hydroalcoholic control (very low-quality evidence).

Pain relief

Chlorhexidine compared with placebo Chlorhexidine gel may be more effective at reducing pain in people with recurrent aphthous ulceration compared with placebo (very low-quality evidence).

Hexetidine compared with placebo Hexetidine may be no more effective at reducing pain in people with recurrent aphthous ulceration compared with placebo (very low-quality evidence).

For GRADE evaluation of interventions for aphthous ulcers, see table, p 9 .

Benefits:

We found no systematic review but found five RCTs (203 people with recurrent aphthous ulceration) comparing chlorhexidine gluconate or similar preparations versus inactive control preparations (see table 1, p 7). [2] [3] [4] [5] [6] Four of the RCTs used a crossover design with a randomised sequence comparing a control preparation versus 1% chlorhexidine gel, [2] 0.2% chlorhexidine gel, [3] 0.2% chlorhexidine mouthwash, [4] or 0.1% hexetidine mouthwash. [5] A fifth RCT compared a proprietary antibacterial rinse with a hydroalcoholic control. [6]

Ulcer days index:

Three RCTs reported the ulcer days index. [3] [4] [5] Two RCTs found that chlorhexidine significantly reduced the ulcer day index compared with a control preparation. [3] [4] One of these RCTs found that chlorhexidine significantly increased the number of ulcer free days per 6 weeks of treatment compared with an inert preparation. [4] A third RCT found that hexitidine had no significant effect on the ulcer day index compared with a control preparation. [5]

Incidence of ulceration:
All five RCTs reported the number of ulcers, defined as either the total number of ulcers or the number of new ulcers with each treatment per week. [2] [3] [4] [5] [6] Only one RCT, using 0.2% chlorhexidine gel, found that active treatment significantly reduced the number of new ulcers (see comment below). [3]

Duration of ulceration:
The mean duration of individual ulcers was reported in four of the RCTs. [2] [4] [5] [6] The mean duration of individual ulcers was reduced by active treatment in all four RCTs, but the difference was significant in only one RCT, using 1% chlorhexidine gel, [2] and the mean difference was less than 1 day in the others. Three RCTs found that the number of ulcers fell during the course of the study, irrespective of the treatment received (see comment below). [4] [5] [6]

Severity of pain:
All five RCTs reported on pain severity scores. [2] [3] [4] [5] [6] Two RCTs found that chlorhexidine significantly reduced the mean severity of pain compared with an inert preparation. [2] [3] One RCT which compared a proprietary antibacterial mouthwash versus the alcohol-containing control preparation found no significant difference in pain severity between the treatment groups, but found a large improvement in clinical outcomes in both groups compared with baseline levels (see comment below). [6]

User preference:
One crossover RCT found no significant difference in user preference between 0.1% hexetidine mouthwash and control mouthwash, but found that many more people preferred the treatment received second. [5]

Harms: One RCT found that chlorhexidine had a bitter taste and was associated with brown staining of teeth and tongue, and with nausea. [3] In one RCT, one person reported a severe inflammation of the gums during the treatment with 0.1% hexitidine mouthwash. [5] Three RCTs gave no information on adverse events. [2] [4] [6]

Comment: Four of the RCTs used a crossover design and reported high withdrawal rates. A consistent observation was that outcomes improved during the course of the trials irrespective of the treatment received. One of the crossover studies did not make it clear if reported results took account of the effect of confounding factors, such as inadequate washout period, and different loss to follow up in the two treatment periods (data were available from only 12/26 people who were recruited). [3] The parallel group trial had fewer withdrawals: 106 people with recurrent aphthous ulceration were recruited, and 96 completed the study. [6] Analysis was not by intention to treat, and the method of randomisation was not reported. People recruited to the trials might not be typical of the average person with recurrent aphthous ulceration.

OPTION CARBENOXOLONE GEL OR MOUTHWASH New

Ulcer incidence
Compared with placebo Carbenoxolone mouthwash may be more effective at reducing the number of ulcers in people with recurrent aphthous ulceration compared with placebo (very low-quality evidence).

Pain relief
Compared with placebo Carbenoxolone mouthwash may be more effective at reducing pain in people with recurrent aphthous ulceration compared with placebo (very low-quality evidence).

For GRADE evaluation of interventions for aphthous ulcers, **see table, p 9** .

Benefits: We found no systemic review, but identified one small double blind crossover RCT (30 people) of carbenoxolone sodium mouthwash compared with placebo in people with recurrent aphthous ulceration (see table 1, p 7). [7]

Ulcer incidence:
Carbenoxolone sodium mouthwash significantly reduced the average number of ulcers per day, increased the mean number of ulcer free days, and reduced new ulcer formation. [7]

Ulcer pain:
Carbenoxolone sodium mouthwash significantly reduced the mean daily pain score associated with aphthous ulceration. [7] Of 30 people initially randomised in the RCT, the results were based on 24 (80%) or 23 (76%) people who completed the protocol. It did not present an intention to treat analysis. One person with a low serum folate level was excluded from the analysis. The method of randomisation was not described.

Harms: The RCT reported that "no adverse effects were shown following the use of the mouthwash". [7]

Comment: While the RCT found a significant reduction in the number of ulcers per day, and a significant increase in number of ulcer free days, the small number of examined people and the lack of any further relevant studies indicate that the evidence of efficacy is weak. There remains insufficient evidence that carbenoxolone sodium is of consistent benefit in the treatment of aphthous ulceration.

OPTION CORTICOSTEROIDS (TOPICAL)

Incidence of ulcers
Compared with placebo We don't know whether topical corticosteroids may be more effective at reducing the incidence of new ulcers, or the duration of ulceration in people with recurrent aphthous ulcers, compared with placebo (very low-quality evidence).

Pain relief
Compared with placebo Topical corticosteroids may be more effective at hastening pain relief, and at reducing the duration and pain of ulcers in people with recurrent aphthous ulcers, without causing notable local or systemic adverse effects, compared with placebo (very low-quality evidence).

For GRADE evaluation of interventions for aphthous ulcers, **see table, p 9 .**

Benefits: We found no systematic review, but found nine RCTs that reported clinical outcomes in people with recurrent aphthous ulcers (see table 1, p 7 . [8] [9] [10] [11] [12] [13] [14] [15] Overall, one RCT found larger effect sizes than the others. [8]

Ulcer days index:
We found four RCTs reporting data on the number of ulcer days. [8] [10] [11] [13] They found that topical corticosteroids reduced the number of ulcer days compared with control, although the reduction was significant in only two of the RCTs.

Incidence of new ulcers:
Five crossover RCTs (102 people) reported inconsistent effects on the incidence of new ulcers. [8] [10] [11] [14] One RCT found no effect on reducing frequency of ulcer recurrence during follow up in either treatment or control groups. [14]

Duration of ulceration:
We found six RCTs reporting data on ulcer duration, three of which had a crossover design. [9] [10] [12] [13] [14] [15] Four RCTs reported the mean duration of ulcers with topical corticosteroids compared with control preparations, but found no evidence of a consistent effect. [9] [10] [13] [15] One RCT found that topical corticosteroids significantly increased the proportion of people who had mean ulcer duration of 6 days or less compared with control preparations. [12] One RCT found that topical corticosteroids significantly reduced the total number of ulcer days compared with control preparations. [14]

Severity of pain:
Four RCTs, three of which had a crossover design, reported on severity of pain with topical corticosteroids compared with control, but all presented their results in different ways. [12] [13] [14] [15] One RCT found that topical corticosteroids significantly increased the proportion of people with pain relief compared with a control preparation. [12] The first crossover RCT found that topical corticosteroids reduced symptom scores compared with a control preparation, but the difference was not significant. [13] The second crossover RCT found that topical corticosteroids significantly increased the proportion of people with reduced pain severity compared with a control preparation. [14] The third crossover RCT found that the pain score fell with time in both treatment and control groups (see comment below), but the rate of fall was significantly faster when using topical corticosteroids ($P < 0.0001$). [15]

User preference:
Three crossover RCTs found that more users preferred topical corticosteroids than control preparations; however, no significance data was presented. [10] [12] [13]

Harms: In five of the nine RCTs, no adverse effects were found. [8] [9] [12] [13] [14] One RCT reported adrenal suppression in one person using betamethasone disodium phosphate. [11] However, limited studies of adrenal function found no evidence that 0.05% fluocinonide in adhesive paste and betamethasone-17-valerate mouth rinse caused adrenal suppression. [14] [16] Two RCTs gave no information on adverse effects. [10] [15]

Comment: The trials differed in many ways: selection of people, type of topical corticosteroid and formulation used, control preparation used (although this was usually a base without topical steroid), duration of treatment, reported outcomes, and design (double or single blind, parallel group or crossover, presence and length of washout period). In one crossover RCT, the pain score fell during the course of the trial irrespective of the treatment received. [15] The study did not make clear if the effect of crossover sequence had been allowed for. Withdrawal rates were high. Most people in the trials had more severe ulceration than the average person with recurrent aphthous ulceration.

OPTION ANALGESICS (LOCAL) New

Ulcer incidence
Benzydamine hydrochloride mouthwash compared with placebo Benzydamine hydrochloride mouthwash may be no more effective at reducing the number of new ulcers compared with placebo (low-quality evidence).

Pain relief
Benzydamine hydrochloride mouthwash compared with placebo Benzydamine may be no more effective at reducing pain in people with mouth ulcers compared with placebo, but may be preferred because of its transient topical analgesic effect (low-quality evidence).

For GRADE evaluation of interventions for aphthous ulcers, see table, p 9 .

Benefits: We found no systematic review but identified one small crossover RCT (18 people) comparing benzydamine hydrochloride mouthwash, chlorhexidine, and placebo (see table 1, p 7). [17]

Ulcer incidence:
The RCT found that benzydamine hydrochloride mouthwash did not significantly reduce the number of new ulcers compared with placebo, or mean ulcer size.

Ulcer pain:
The RCT found that benzydamine hydrochloride did not significantly reduce pain intensity score compared with placebo. [17]

User preference:
The RCT found that 8/18 (44%) people stated a preference of benzydamine hydrochloride because of its transient topical analgesic effect. [17]

Harms: The RCT reported that stinging was reported with nine people with benzydamine hydrochloride mouthwash and nine people with placebo. [17]

Comment: We found no other good studies of the efficacy of local analgesic agents for the treatment of aphthous ulceration.

OPTION TETRACYCLINE ANTIBIOTIC MOUTHWASH New

Pain relief
Compared with placebo Tetracycline antibiotic mouthwash may be more effective at reducing pain in people with aphthous stomatitis compared with placebo (very low-quality evidence).

For GRADE evaluation of interventions for aphthous ulcers, see table, p 9 .

Benefits: We found no systematic review, but found two small RCTs (61 people in total with aphthous stomatitis) comparing different topical tetracycline preparations versus inactive control preparations (see table 1, p 7). [18] [19]

Ulcer days index:
The ulcer index was significantly reduced in one RCT. [19]

Severity of pain:
The main pain score was reported to be significantly reduced in both studies. [18] [19] One RCT (31 people) was single blind and quasi-randomised. [18] Allocation was made by alternate allocation, with every second subject being in the experimental group and all others being in the control group. In addition, the application of treatment or control was made by a clinician using a spatula, and was made only once during the aphthous ulcer episode. In the other small RCT (30 people), the method of randomisation was not described, and outcomes were assessed by people being asked to record, on pretyped forms, days when pain and/or ulcers were present (further details of forms and timing of final assessment not reported). [19]

Harms: One RCT did not report on adverse effects. [18] The other RCT reported that "no side effects were encountered". [19]

Comment: One RCT was a multiarm trial. [19] We have only reported data from it regarding our comparison of interest. There is limited evidence that topical tetracyclines lessen the signs or symptoms of aphthous ulceration.

GLOSSARY

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

SUBSTANTIVE CHANGES

New option added Carbenoxolone gel or mouthwash
New option added Analgesics (Local)
New option added Tetracycline antibiotic mouthwash
Chlorhexidine and similar agents Evidence on hexetidine re-evaluated. Categorisation of hexetidine as Unlikely to be beneficial withdrawn. Categorisation of "chlorhexidine and similar agents" unchanged (Likely to be beneficial).

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TABLE 1 **Effects of treatments on different outcomes: results of RCTs (see text).**

Outcomes	Ref	Participants	Treatment duration (weeks)	Results: Treatment	Results: Control	Effect* (significance)
Topical antibacterial versus inert preparations						
Severity of episode						
Ulcer day index (definition see below)	[3]	12	5	9.5	17.0	P < 0.05
	[4]	38	6	42.8	52.3	P < 0.05
	[5]	37	6	79.7	65.7	NS
Number of ulcer free days	[4]	38	6	22.9	17.5	P < 0.02
Incidence of ulceration						
Number of new ulcers/week	[2]	20	5	1.04	1.4	NS
	[3]	12	5	0.60	1.02	P < 0.05
	[4]	38	6	1.26	1.38	NS
	[5]	37		1.48	1.39	NS
	[6]	96		0.09	0.13	NS
Duration of ulceration						
Mean number of days of ulcer duration	[2]	20	5	4.8	7.80	P < 0.01
	[4]	38	6	5.02	5.78	NS
	[5]	37		6.64	6.80	NS
Median fall in days of ulcer duration from start to end of trial	[6]	96	24	2.19	1.94	NS
Severity of pain						
Mean pain severity score	[2]	20	5	0.93	1.22	P < 0.05
Mean total pain severity score	[3]	12	5	About 24 (graph)	About 49 (graph)	P < 0.05
	[4]	38	6	16.31	16.35	NS
	[5]	37	6	16.9	17.8	NS
Adverse effects	[3]	12	5	Bitter taste, tooth staining	Not given	Not given
	[5]	37	6	1/37***	0/37	Not given
Carbenoxolone sodium mouthwash versus placebo						
Average number of ulcers per day	[7]	23	4	Given pre-crossover 1.54; given post-crossover 1.09	Given pre-crossover 1.94; given post-crossover 1.71	P < 0.05
New ulcer formation	[7]	23	4	Given pre-crossover 3.3; given post-crossover 4.07	Given pre-crossover 8.46; given post-crossover 4.7	P < 0.05
Mean daily pain score	[7]	24	4	Given pre-crossover 1.72; given post-crossover 1.09	Given pre-crossover 1.98; given post-crossover 1.77	P < 0.05
Mean number of ulcer free days	[7]	24	4	Given pre-crossover 6.72; given post-crossover 15.77	Given pre-crossover 6.38; given post-crossover 6.36	P < 0.05
Topical corticosteroids versus inert preparations						
Ulcer day index (definition see below)	[8]	17	8	26.3	65.9	–60%; P < 0.01
	[10]	26	8	58.3	71.3	–18%; NS
	[11] main	25	4	24.0	30.7	–22%; NS
	[13]	20	6	48.3	70.6	–32%; P < 0.05
Incidence of new ulcers	[8]	17	8	0.51	1.15	–55%; P < 0.05
	[10]	26	8	0.84	0.94	–11%; NS
Number of new ulcers/week	[11] pilot	8	4	2.07	1.85	+12%; NS
	[11] main	31†	4	0.73	0.82	–11%; NS

Outcomes	Ref	Participants	Treatment duration (weeks)	Results		
				Treatment	Control	Effect* (significance)
	[11]	20	6	1.27	1.92	+6%; NS
Effect on reducing frequency of ulcer recurrence during follow up	[14]	15	26	No effect	No effect	Not given
Duration of ulceration						
Mean number of days of ulcer duration	[9]	50	UCH	6.00	6.00	0%; NS
	[10]	26	8	8.07	8.94	–10%; NS
	[13]	20	6	4.93	7.83	–37%; P < 0.001
	[15]	19	12	5.93	5.92	0%; NS
Proportion of people with ulcer duration < 6 days	[12]	63	UCH	23/33	14/30	P < 0.05
Proportion of people with the total number of ulcer days reduced by preparation	[14]	15	4	13/15	Not given	P < 0.001
Severity of Pain						
Proportion of people with pain relief	[12]	63	UCH	29/33	18/30	P < 0.01
Average pain severity score during ulcer days	[13]	20	6	2.77	3.54	NS
Proportion of people with reduced pain severity	[14]	15	4	11/15	Not given	P < 0.05
User preference						
Proportion of people receiving both forms of treatment preferring active treatment	[10]	26	8	13/26		N/A
	[12]	17	UCH	10/13		N/A
	[13]	20	6	18/20		N/A
Adverse effects	[8]	17	8	None found	None found	
	[11]	31	4	1**	Not given	
	[12]	63	UCH	None found	None found	
	[13]	20	6	None found	None found	
	[14]	15	4	None found	None found	
Benzydamine mouthwash versus placebo						
Mean ulcer size	[17]	18	12	Absolute numbers not reported	Absolute numbers not reported	NS
Pain intensity score	[17]	18	12	Absolute numbers not reported	Absolute numbers not reported	NS
Number of ulcers	[17]	18	12	Absolute numbers not reported	Absolute numbers not reported	NS
Topical tetracycline versus control						
Ulcer days	[19]	30	4 days	Absolute numbers not reported	Absolute numbers not reported	P < 0.05
Mean pain	[18]	31	One single application by clinician	Results presented graphically	Results presented graphically	P < 0.05
Mean pain	[19]	30	4 days	Absolute numbers not reported	Absolute numbers not reported	P < 0.05

*Defined as difference between outcome measures for control and treatment, expressed as a fraction of the control. **One case adrenal suppression in one person using betamethasone disodium phosphate. *** One case of severe gum inflammation in one person using 0.1% hexitidine mouthwash. †Each participant received one treatment for 4 weeks, a blank month, then another treatment with another drug. The trial compared an inert base, two local steroids and two other preparations. The figures given here are those during treatment with local steroids and with the inert base. N/A Not applicable; NS, not significant; ref, reference; UCH, until complete healing.

TABLE **GRADE evaluation of interventions for aphthous ulcers**

Important outcomes	**Symptom relief, recurrence, incidence and duration of ulcers, 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 recurrent aphthous ulcers?									
3 (70) [2] [3] [4]	Ulcer incidence	Chlorhexidine mouthwash *v* placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about benefit of treatment
1 (37) [5]	Ulcer incidence	Hexetidine mouthwash *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results. Directness point deducted for uncertainty about benefit of treatment
1 (96) [6]	Ulcer incidence	Proprietary antibacterial mouthwash *v* control	4	–3	0	–2	0	Very low	Quality points deducted for poor follow-up, incomplete reporting of results, no intention-to-treat analysis, and uncertainty about method of randomisation. Directness point deducted for uncertainty about disease severity in population and benefit from treatment
3 (70) [2] [3] [4]	Pain relief	Chlorhexidine mouthwash *v* placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about benefit of treatment
1 (37) [5]	Pain relief	Hexetidine mouthwash *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results. Directness point deducted for uncertainty about benefit of treatment
1 (23) [7]	Ulcer incidence	Carbenoxolone *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no intention-to-treat analysis, and uncertainty about method of randomisation
1 (24) [7]	Pain relief	Carbenoxolone *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no intention-to-treat analysis, and uncertainty about method of randomisation
11 (295) [8] [9] [10] [11] [12] [13] [14] [15]	Ulcer incidence	Topical corticosteroids *v* placebo	4	–3	–1	–3	0	Very low	Quality points deducted for incomplete reporting of results, uncertainty about methodology, and duration of treatment. Consistency point deducted for conflicting results. Directness points deducted for uncertainty about population, comparators, or outcomes
3 (98) [12] [13] [14]	Pain relief	Topical corticosteroids *v* placebo	4	–3	–1	–3	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, uncertainty about methodology and duration of treatment. Consistency point deducted for conflicting results. Directness points deducted for inconsistency in reporting outcomes, uncertainty about population, and comparators
1 (18) [17]	Ulcer incidence	Benzydamine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (18) [17]	Pain relief	Benzydamine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (61) [18] [19]	Pain relief	Tetracycline mouthwash *v* placebo	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about randomisation in one RCT. Directness points deducted for uncertainty of reporting outcomes and single application of treatment

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