

Interventions for the management of dry mouth: non-pharmacological interventions (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	9
Figure 1.	10
Figure 2.	13
Figure 3.	14
ADDITIONAL SUMMARY OF FINDINGS	16
DISCUSSION	17
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	19
REFERENCES	19
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	36
Analysis 1.1. Comparison 1 Acupuncture versus placebo, Outcome 1 Mouth dryness.	37
Analysis 1.2. Comparison 1 Acupuncture versus placebo, Outcome 2 Unstimulated whole saliva (end of treatment).	38
Analysis 1.3. Comparison 1 Acupuncture versus placebo, Outcome 3 Stimulated whole saliva (end of treatment).	39
Analysis 1.4. Comparison 1 Acupuncture versus placebo, Outcome 4 Unstimulated whole saliva (12 months).	40
Analysis 1.5. Comparison 1 Acupuncture versus placebo, Outcome 5 Stimulated whole saliva (12 months).	40
Analysis 2.1. Comparison 2 Electrical stimulation versus placebo, Outcome 1 Unstimulated whole saliva (end of treatment).	41
Analysis 2.2. Comparison 2 Electrical stimulation versus placebo, Outcome 2 Stimulated whole saliva (end of treatment).	42
Analysis 3.1. Comparison 3 Powered versus manual toothbrush, Outcome 1 Unstimulated whole saliva (45 minutes after brushing).	42
Analysis 3.2. Comparison 3 Powered versus manual toothbrush, Outcome 2 Stimulated whole saliva (5 minutes after brushing).	43
ADDITIONAL TABLES	43
APPENDICES	43
WHAT'S NEW	47
CONTRIBUTIONS OF AUTHORS	47
DECLARATIONS OF INTEREST	48
SOURCES OF SUPPORT	48
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	48

[Intervention Review]

Interventions for the management of dry mouth: non-pharmacological interventions

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ABSTRACT

Background

Xerostomia is the subjective sensation of dry mouth. Common causes of xerostomia include adverse effects of many commonly prescribed medications, disease (e.g. Sjogren's Syndrome) and radiotherapy treatment for head and neck cancers. Non-pharmacological techniques such as acupuncture or mild electrostimulation may be used to improve symptoms.

Objectives

To assess the effects of non-pharmacological interventions administered to stimulate saliva production for the relief of dry mouth.

Search methods

We searched the Cochrane Oral Health Group's Trials Register (to 16th April 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 3), MEDLINE via OVID (1948 to 16th April 2013), EMBASE via OVID (1980 to 16th April 2013), AMED via OVID (1985 to 16th April 2013), CINAHL via EBSCO (1981 to 16th April 2013), and CANCERLIT via PubMed (1950 to 16th April 2013). The *meta*Register of Controlled Clinical Trials (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) were also searched to identify ongoing and completed trials. References lists of included studies and relevant reviews were also searched. There were no restrictions on the language of publication or publication status.

Selection criteria

We included parallel group randomised controlled trials of non-pharmacological interventions to treat dry mouth, where participants had dry mouth symptoms at baseline.

Data collection and analysis

At least two review authors assessed each of the included studies to confirm eligibility, assess risk of bias and extract data using a piloted data extraction form. We calculated mean difference (MD) and 95% confidence intervals (CI) for continuous outcomes or where different scales were used to assess an outcome, we calculated standardised mean differences (SMD) together with 95% CIs. We attempted to extract data on adverse effects of interventions. Where data were missing or unclear we attempted to contact study authors to obtain further information.

Main results

There were nine studies (total 366 participants randomised) included in this review of non-pharmacological interventions for dry mouth which were divided into three comparisons. Eight studies were assessed at high risk of bias in at least one domain and the remaining study was at unclear risk of bias.

Five small studies (total 153 participants, with dry mouth following radiotherapy treatment) compared acupuncture with placebo. Four were assessed at high risk and one at unclear risk of bias. Two trials reported outcome data for dry mouth in a form suitable for meta-analysis. The pooled estimate of these two trials (70 participants, low quality evidence) showed no difference between acupuncture and control in dry mouth symptoms (SMD -0.34, 95% CI -0.81 to 0.14, P value 0.17, $I^2 = 39%$) with the confidence intervals including both a possible reduction or a possible increase in dry mouth symptoms. Acupuncture was associated with more adverse effects (tiny bruises and tiredness which were mild and temporary). There was a very small increase in unstimulated whole saliva (UWS) at the end of 4 to 6 weeks of treatment (three trials, 71 participants, low quality evidence) (MD 0.02 ml/minute, 95% CI 0 to 0.04, P value 0.04, $I^2 = 57%$), and this benefit persisted at the 12-month follow-up evaluation (two trials, 54 participants, low quality evidence) (UWS, MD 0.06 ml/minute, 95% CI 0.01 to 0.11, P value 0.03, $I^2 = 10%$). For the outcome of stimulated whole saliva (SWS, three trials, 71 participants, low quality evidence) there was a benefit favouring acupuncture (MD 0.19 ml/minute, 95% CI 0.07 to 0.31, P value 0.002, $I^2 = 1%$) an effect which also persisted at the 12-month follow-up evaluation (SWS MD 0.28 ml/minute, 95% CI 0.09 to 0.47, P value 0.004, $I^2 = 0%$) (two trials, 54 participants, low quality evidence).

Two small studies, both at high risk of bias, compared the use of an electrostimulation device with a placebo device in participants with Sjögren's Syndrome (total 101 participants). A further study, also at high risk of bias, compared acupuncture-like electrostimulation of different sets of points in participants who had previously been treated with radiotherapy. None of these studies reported the outcome of dry mouth. There was no difference between electrostimulation and placebo in the outcomes of UWS or SWS at the end of the 4-week treatment period in the one study (very low that provided data for these outcomes. No adverse effects were reported.

A single study at high risk of bias, compared the stimulatory effect of powered versus manual toothbrushing and found no difference for the outcomes of UWS or SWS.

Authors' conclusions

There is low quality evidence that acupuncture is no different from placebo acupuncture with regard to dry mouth symptoms, which is the most important outcome. This may be because there were insufficient participants included in the two trials to show a possible effect or it may be that there was some benefit due to 'placebo' acupuncture which could have biased the effect to the null. There is insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms. It is well known that dry mouth symptoms may be problematic even when saliva production is increased, yet only two of the trials that evaluated acupuncture reported dry mouth symptoms, a worrying reporting bias. There is some low quality evidence that acupuncture results in a small increase in saliva production in patients with dry mouth following radiotherapy.

There is insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms or saliva production in patients with Sjögren's Syndrome. Reported adverse effects of acupuncture are mild and of short duration, and there were no reported adverse effects from electrostimulation.

PLAIN LANGUAGE SUMMARY

Non-drug treatments for dry mouth symptoms

Review question

This review, carried out by authors of the Cochrane Oral Health Group, has been produced to assess the effects of non-drug treatments used to stimulate saliva production for the relief of dry mouth (xerostomia) symptoms.

Background

Dry mouth is a common problem with an estimated incidence of between 10% and 26% in men and between 10% and 33% in women, which may or may not be due to reduced saliva secretion. Common causes of dry mouth include the side effects of many commonly prescribed medications, diseases (such as Sjögren's syndrome where the immune system destroys tissues in the glands which produce saliva) and radiotherapy treatments for head and neck cancers.

Saliva moistens the skin in the mouth and helps to maintain oral health. The presence of saliva facilitates speech, acts to wash away food residue from around the teeth, neutralises potentially damaging food and bacterial acids, enhances a person's ability to taste the food, and generally lubricates the mouth. Saliva also acts to soften food, making it easier to chew and swallow. Enzymes in saliva start the digestion of starch and fats, and other substances in saliva, such as epidermal growth factors, promote tissue growth, differentiation and wound healing. The antibacterial, antifungal and antiviral agents in saliva balance the oral flora and help to prevent oral infections, while the minerals in saliva help to maintain tooth enamel.

Non-drug treatments such as acupuncture, mild electrical stimulation, lasers, tooth brushing and other stimulation techniques are used to improve dry mouth symptoms.

Study characteristics

The evidence on which this review is based was up-to-date as of 16 April 2013.

Nine studies were included in this review. A total of 366 adult participants took part in these trials, with an average of 40 participants per trial, and an age range from 12 to 77 years. The causes of dry mouth were radiotherapy for oral cancers in four trials, Sjögren's syndrome in three trials, medication-related in one trial, and in the remaining trial participants had a range of causes of dry mouth.

The included studies were divided into three groups, according to the interventions evaluated.

1. Five small studies with a total 153 participants evaluated acupuncture.
2. Three studies evaluated electrostimulation devices.
3. One study evaluated a power toothbrush.

Key results

The five studies evaluating the effects of acupuncture in people who had dry mouth were generally of poor quality. There was no evidence of a difference in dry mouth symptoms, but there was some evidence of a small increase in saliva production which persisted for a year after the end of the acupuncture treatment. There may not have been enough people included in the trials to show a difference in dry mouth, or it may have been that both the real acupuncture and the 'placebo' acupuncture had some beneficial effect. Acupuncture was associated with more adverse effects (tiny bruises and tiredness which were mild and temporary).

The studies evaluating the effects of electrostimulation devices were poorly conducted and reported, and provided insufficient evidence to determine the effects of these devices on either dry mouth or saliva production.

The single small study of a powered versus a manual toothbrush also found no difference for either dry mouth or saliva production.

None of the included studies reported the outcomes of duration of effectiveness, quality of life, patient satisfaction, or oral health assessment.

Quality of the evidence

These studies were generally of poor quality (low and very low).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Acupuncture compared with placebo for dry mouth symptoms				
Patient or population: People with dry mouth due to either radiotherapy or Sjögren's Syndrome Settings: Outpatients Intervention: Acupuncture Comparison: Placebo (sham acupuncture)				
Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Mouth dryness Different scales (at the end of treatment 4-6 weeks)	SMD -0.34 (-0.81 to 0.14)	70 (2 RCTs*)	⊕⊕○○ low ¹	*Participants had dry mouth following radiotherapy treatment for head and neck cancers
Unstimulated whole saliva millilitres/minute (end of treatment)	MD 0.02 (0 to 0.04)	71 (3 RCTs**)	⊕⊕○○ low ²	**Most of the participants in these trials had dry mouth following radiotherapy treatment
Stimulated whole saliva (end of treatment) millilitres/minute (end of treatment)	MD 0.19 (0.07 to 0.31)	71 (3 RCTs**)	⊕⊕○○ low ²	**Most of the participants in these trials had dry mouth following radiotherapy treatment
Unstimulated whole saliva (12 months) millilitres/minute (1 year follow-up)	MD 0.06 (0.01 to 0.11)	54 (2 RCTs**)	⊕⊕○○ low ³	**Most of the participants in these trials had dry mouth following radiotherapy treatment
Stimulated whole saliva (12 months) millilitres/minute (1 year follow-up)	MD 0.28 (0.09 to 0.47)	54 (2 RCTs**)	⊕⊕○○ low ³	**Most of the participants in these trials had dry mouth following radiotherapy treatment

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; SMD: standardised mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: 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: We are very uncertain about the estimate

¹ Quality of the body of evidence is downgraded due to risk of bias (2 very small RCTs at high risk of bias), and also because three trials which evaluated this comparison did not report the outcome of dry mouth

² Quality of the body of evidence is downgraded due to high risk of bias (2 studies at high risk of bias and 1 unclear), and heterogeneity ($I^2 = 57\%$)

³Quality of the body of evidence is downgraded due to risk of bias (1 high, 1 unclear risk of bias) and small number of participants

BACKGROUND

Description of the condition

Xerostomia is the subjective sensation of a dry mouth (Napenas 2009; Visvanathan 2010), which can have a number of different causes. Dry mouth may be an objective finding with a reduction in the quantity of saliva produced, or a change in the composition of the saliva (Napenas 2009; Visvanathan 2010), or it may be a subjective sensation of dry mouth, found in patients with normal salivary gland function.

In a healthy individual, saliva production ranges from 0.5 to 1.5 litres per day (Mese 2007; Porter 2004). Approximately 90% of this saliva is produced by three pairs of major glands (the parotid, submandibular and sublingual salivary glands), with the remaining 10% of saliva produced by the minor salivary glands which are distributed around the mouth (in the labial, buccal, lingual and palatal mucosa) (Mese 2007; Napenas 2009). Secretion of saliva from the salivary glands is controlled by the brain via the saliva reflex arch. The taste, smell and/or chewing of food stimulates the salivary centre in the medulla of the brain, which then stimulates the nerves to the salivary glands which produce saliva (Proctor 2007). Saliva moistens the oral mucosa and helps to maintain oral health. The presence of saliva facilitates speech, acts to wash away food residue from around the teeth, neutralises potentially damaging food and bacterial acids, enhances a person's ability to taste the food, and generally lubricates the mouth (Hopcraft 2010; Mese 2007). Saliva also acts to soften food, making it easier to chew and swallow. Enzymes in saliva start the digestion of starch and fats, and other substances in saliva, such as epidermal growth factors, promote tissue growth, differentiation and wound healing. The antibacterial, antifungal and antiviral agents in saliva balance the oral flora and help to prevent oral infections, while the minerals in saliva help to maintain tooth enamel.

Dry mouth is a very common symptom, with an estimated incidence of between 10% and 26% in men and between 10% and 33% in women (Hopcraft 2010). Sufferers may complain of their mouth feeling dry or sticky in texture, report difficulty with chewing and swallowing food, and describe a decreased sensation of taste. Irritation when wearing dentures has also been reported (Visvanathan 2010).

The causes of xerostomia can be separated into two groups: salivary and non-salivary (Napenas 2009). Non-salivary causes of dry mouth include: mouth breathing, anxiety, neurological dysfunction and dehydration (Napenas 2009). Salivary causes of dry mouth symptoms can be further subdivided into those associated

with salivary gland pathology such as Sjögren's Syndrome, sarcoidosis, diabetes mellitus and hepatitis C virus. There is some potential overlap between these groups as Sjögren's Syndrome is not only associated with direct salivary gland damage but is also associated with neuropathy (Tobón 2012) which could result in neurologically mediated salivary dysfunction. In addition, there are over 500 medications reported to cause oral dryness through various proposed mechanisms (Femiano 2008; Porter 2004). It is reported that drugs can inhibit salivation via effects on central and peripheral receptors (Proctor 2007; Scully 2004). The medications known to cause oral dryness are wide ranging and often very commonly prescribed preparations such as those used to treat depression, epilepsy and hypertension. Moreover, xerostomia is a recognised side effect of both radiotherapy (Shiboski 2007) and chemotherapy (Porter 2004) used to treat cancer.

Xerostomia is especially common among the elderly. While salivary glands certainly undergo changes due to age, the impact of changes due to aging on salivary gland function is contentious (Mese 2007). It has been suggested that subjective complaints of dry mouth in the elderly population can mostly be attributed to causes other than age-related changes to the tissues in the salivary glands (Mese 2007); notably the increased prevalence of chronic conditions in this population, and resultant 'polypharmacy' (Femiano 2008; Porter 2004).

The experience of having a dry mouth can have a detrimental effect on a sufferer's quality of life, and can force them to modify their daily behaviour in order to cope with their symptoms (Hopcraft 2010). Dry mouth can be associated with a number of negative consequences which include: difficulty with speaking, chewing, swallowing and tasting food; soreness of the gums and oral mucosa, making the wearing of dentures uncomfortable or impossible; impaired sleep; psychological and social disability; increased risk of caries; oral candidiasis and salivary gland infections (Enger 2011; Fedele 2008; Hackett 2012; Porter 2010; Visvanathan 2010; Wolff 2012). Effective management of this condition is therefore important to improve the quality of life of sufferers. In addition, from both a public health and patient perspective it is important to manage dry mouth symptoms in order to minimise possible sequelae such as dental decay and oral infections.

Because dry mouth is a subjective symptom it is assessed by questioning individuals. A series of questions targeting different aspects of dry mouth may provide more information regarding the aspects which have greatest impact on an individual's quality of life. There are numerous such tools used to assess dry mouth symptoms, including various quality of life scales and some specific tools such as the Xerostomia Questionnaire (XQ) and the Xerostomia In-

ventory (XI). The Xerostomia Inventory is an 11-item summated rating scale which has been validated as both a discriminative measure of the severity of dry mouth symptoms, and as a responsive measure of the effects of interventions for dry mouth (Thomson 2007). The range of possible XI scores is from 11 to 55 (Appendix 1) and a change in XI score of six points is likely to be clinically meaningful (Thomson 2007).

In some patients it may be possible to manage the problems associated with a dry mouth through optimal management of the underlying condition(s); for example through better management of diabetes. Smoking cessation and a reduction in alcohol consumption may also be of some benefit, as both these factors may exacerbate symptoms of dry mouth (Mese 2007). For individuals with mild symptoms, sucking ice chips or frequent sips of cold water may provide sufficient relief (Hopcraft 2010).

Topical application of salivary substitutes may provide short-term relief during waking hours (Femiano 2008). Salivary stimulation by means of either systemic or topical medications, or chewing gum, may be appropriate for use by patients with some degree of salivary gland function (Porter 2004). However, while the use of some systemic pharmacotherapies, such as pilocarpine, to stimulate saliva production are effective (Davies 2007), these drugs have associated adverse effects and may be contraindicated in patients with existing chronic respiratory, cardiovascular and renal disease (Fedele 2008).

Description of the intervention

Non-pharmacological interventions, such as electrostimulation of the salivary glands, acupuncture or the application of low level laser therapy, have the potential to increase saliva production. In electrostimulation, a hand-held battery-operated device may be used to administer an electrical stimulus to the tongue or hard palate. Alternatively, a transcutaneous electrical nerve stimulation (TENS) machine may be used and electrodes connected to the skin. Electrostimulation may be administered in the patient's home or at a medical facility. In acupuncture, needles are inserted by a professional into pre-determined acupuncture points on the body. In low level laser therapy, a laser beam is applied by a professional to the salivary glands of patients with xerostomia. For patients with some residual salivary gland function, and co-morbidities or contraindications to pharmacological therapies, identifying effective alternative means for stimulating saliva production, could provide a useful management strategy.

How the intervention might work

Acupuncture and electrostimulation have been reported to have both biological and clinical plausibility with regards to the treatment of dry mouth (O'Sullivan 2010; Wolff 2012; Zhuang 2013). It is proposed that application of electrical impulses to one or more

arms of the salivary reflex arch may increase salivation (Fedele 2008). Electrostimulation of the efferent trigeminal fibres of the lingual nerve may promote the submandibular and sublingual glands to increase saliva secretion (Wolff 2012). Acupuncture is suggested to produce physiological effects such as stimulation of the autonomic nervous system and increased peripheral blood flow which may in turn stimulate saliva production (O'Sullivan 2010). The mechanism of action for low level laser therapy is complex and is also poorly understood, however laser therapy is thought to increase salivary secretion through the stimulation of mitotic activity in salivary gland epithelial tissue (Lone ar 2011).

Why it is important to do this review

The number of people living with dry mouth symptoms is expected to rise as life expectancy increases, and treatment for chronic diseases becomes more effective (Mese 2007; Porter 2004). Dry mouth conditions can have considerable negative impact on the quality of life of patients (Enger 2011; Hackett 2012; Porter 2010). Effective treatments for patients unable to use systemic pharmacotherapies would not only improve the quality of life for these patients, but would also help maintain oral health, avoiding further potentially painful, debilitating and costly oral disease and tooth loss.

This review complements other existing Cochrane reviews of treatments for dry mouth.

- Pharmacological interventions for preventing salivary gland dysfunction following radiotherapy (Tavender 2004).
- Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy (Davies 2007).
- Amifostine for salivary glands in high dose radioactive iodine treated differentiated thyroid cancer (Ma 2009).
- Interventions for the management of dry mouth: topical therapies (Furness 2011) which includes the use of saliva substitutes and saliva stimulants such as pastilles and chewing gum.

OBJECTIVES

To assess the effects of non-pharmacological interventions administered to stimulate saliva production for the relief of dry mouth.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing techniques designed or used to stimulate saliva production (such as acupuncture, laser or electrostimulation) with either placebo or with another treatment. Trials were included irrespective of language or publication status.

We excluded cross-over studies from this review due to the potential for non-pharmacological therapies, such as acupuncture, laser therapy and electrostimulation, to exert a prolonged effect that could carry-over to subsequent periods of the trial (Higgins 2011).

Types of participants

Trials where participants were seeking treatment for the symptoms of dry mouth (xerostomia) due to any cause. Participants must have had xerostomia at baseline. Causes of xerostomia may have included haemodialysis, hormonal disorders (diabetes), autoimmune conditions (Sjögren's Syndrome, systemic lupus erythematosus and rheumatoid arthritis) and immune disorders (such as AIDS and graft versus host disease). This review also included patients currently undergoing, or who have previously received, radiotherapy; and patients seeking treatment for xerostomia due to current use of medications to control chronic or neoplastic conditions.

Types of interventions

Non-pharmacological interventions, such as acupuncture, electrostimulation or low level laser therapy, for the management of xerostomia. Active interventions were compared with either placebo, no treatment or another active non-systemic treatment, such as topical salivary stimulants. Trials which compared a non-pharmacological intervention with systemic treatments such as oral pilocarpine or oral cevimeline were excluded. Systemic pharmacological treatments are effective, but may be contraindicated in some patients with co-morbidities or concomitant medications and it is this group who may benefit from non-pharmacological interventions. Trials which compared different frequencies of treatment were included.

Types of outcome measures

Primary outcomes

Xerostomia both short term (4 weeks after start of treatment) and longer term (3 months after end of treatment). Dry mouth may have been measured using a visual analogue scale (VAS) or been subjectively assessed as improved, no change or worse compared to baseline. Dry mouth symptoms may also have been measured using a validated questionnaire such as the Xerostomia Questionnaire (XQ).

Secondary outcomes

- Duration of effectiveness.
- Quality of life: assessed using a standard quality of life instrument, or a specific instrument such as head and neck quality of life (HNQOL), or similar.
- Patient satisfaction with the treatment(s).
- Adverse events.
- Salivary flow: a clinically measured objective outcome such as unstimulated whole saliva (UWS) or stimulated whole saliva (SWS).
- Oral health assessment.

Search methods for identification of studies

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE (Appendix 2) but appropriately revised for each database to take account of differences in syntax rules and controlled vocabulary. This subject strategy was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (as published in box 6.4.c in the *Cochrane Handbook for Systematic Reviews of Interventions*, Higgins 2011).

Electronic searches

We searched the following databases:

- The Cochrane Oral Health Group's Trials Register (to 16th April 2013) (Appendix 3)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 3) (Appendix 4)
- MEDLINE via OVID (1948 to 16th April 2013) (Appendix 2)
- EMBASE via OVID (1980 to 16th April 2013) (Appendix 5)
- AMED via OVID (1985 to 16th April 2013) (Appendix 6)
- CINAHL via EBSCO (1981 to 16th April 2013) (Appendix 7)
- CANCERLIT via PubMed (1950 to 16th April 2013) (Appendix 8).

Only handsearching carried out as part of The Cochrane Collaboration's handsearching programme was included in the search, where these references have been incorporated into the CENTRAL database (see the Cochrane [Master List](#) of journals which have been handsearched).

The *metaRegister* of Controlled Clinical Trials (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) were also searched to identify ongoing and completed trials and to contact trialists for further information. There were no restrictions on the language of publication or publication status.

Searching other resources

The reference lists of related review articles and all articles obtained were checked for further trials.

Data collection and analysis

Selection of studies

At least two review authors screened the results of the searches to identify possible included studies. Paper copies were obtained of all trials which appeared to meet the inclusion criteria or where there was insufficient information in the title or abstract or both to make a clear decision about eligibility. At least two review authors assessed each of these papers to determine which met the inclusion criteria for this review. Any disagreements were resolved by discussion. Papers not in English were translated by members of The Cochrane Collaboration as required.

Data extraction and management

All randomised controlled trials which appeared to meet the inclusion criteria for this review were assessed by at least two review authors to confirm eligibility, assess risk of bias and extract data using a piloted data extraction form. Disagreements were resolved by discussion. The following data were recorded.

- Study design, location, funding, number of centres.
- Inclusion and exclusion criteria, number of patients recruited, number of patients randomised to each group, number of patients withdrawn, numbers evaluated.
- Intervention(s), comparator, dose, frequency, duration of treatment, concomitant medications.
- Primary and secondary outcomes, times measured, numbers of patients included in the outcome evaluation.
- Whether a sample size calculation was performed.

Information was entered into the table of characteristics of included studies and additionally into an Excel spreadsheet from which a summary of the characteristics of the studies was made. Where the published paper was unclear concerning aspects of trial design, attempts were made to contact the study authors for clarification or more information or both.

Assessment of risk of bias in included studies

This was conducted using the recommended approach for assessing the risk of bias in studies included in Cochrane reviews (Higgins 2011). We used the two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other bias'). Each domain included one or more specific entries in a 'Risk of bias' table. Within each study, the first

part of the tool involved describing what was reported to have happened in the study. The second part of the tool involved assigning a judgement relating to the risk of bias for that entry. This was achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of 'low' indicated low risk of bias, 'high' indicated high risk of bias, and 'unclear' indicated unclear or unknown risk of bias.

The domains of sequence generation, allocation concealment, incomplete outcome data and selective outcome reporting are each addressed in the tool by a single entry for each study. For blinding two entries were used because assessments needed to be made separately for a) patients and b) outcome assessor. Where the patients self assessed the outcomes to the trial, this was noted. The final domain ('other sources of bias') was assessed as a single entry for studies as a whole.

The risk of bias assessment was undertaken independently and in duplicate by two review authors as part of the data extraction process.

After taking into account the additional information provided by the authors of the trials, studies were grouped into the following categories.

- Low risk of bias (plausible bias unlikely to seriously alter the results) for all key domains.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more key domains were assessed as unclear.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more key domains were assessed to be at high risk of bias.

A 'Risk of bias' table was completed for each included study. The results were also presented graphically.

Measures of treatment effect

For dichotomous outcomes (e.g. xerostomia improved or not), the estimate of treatment effect of an intervention would have been expressed as risk ratios (RR) (xerostomia improved/not) together with 95% confidence intervals (CIs). For continuous outcomes (such as mean VAS scores), mean differences and standard deviation were used to summarise the data for each trial.

Dealing with missing data

Where data were missing from the published report of a trial, we attempted to contact the author(s) to obtain the data and clarify any uncertainty. The analysis generally included only the available data (ignoring missing data), however, methods for estimating missing standard deviations in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) would have been used if appropriate. Otherwise we did not undertake any imputations or use any statistical methods to impute missing data.

Assessment of heterogeneity

Heterogeneity was assessed by inspection of the point estimates and confidence intervals on the forest plots. The variation in treatment effects was assessed by means of Cochran's test for heterogeneity and quantified by the I^2 statistic. Heterogeneity was considered statistically significant if P value was < 0.1 . A rough guide to the interpretation of the I^2 statistic given in the *Cochrane Handbook for Systematic Reviews of Interventions* is: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

If there had been sufficient numbers of trials (more than 10) in any meta-analysis, publication bias would have been assessed according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry were identified we would have examined possible causes.

Data synthesis

A meta-analysis was only conducted if there were studies of similar comparisons reporting the same outcome measures. We would have combined risk ratios for dichotomous data, and we combined mean differences for continuous data, using fixed-effect models. If there were more than three studies included in any meta-analysis, we would have used random-effects models.

Subgroup analysis and investigation of heterogeneity

We planned to investigate clinical heterogeneity by examining the different causes of xerostomia. If there had been sufficient studies of each intervention and outcome, we planned, a priori, to conduct

subgroup analyses for different causes of xerostomia (type of drug or type of condition causing xerostomia).

Sensitivity analysis

If there had been sufficient studies for each outcome and intervention, we would have undertaken sensitivity analysis based on the overall risk of bias.

Presentation of main results

A summary of findings table was developed for the main outcomes of this review using GRADEPro software. The quality of the body of evidence was assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, the risk of publication bias and the magnitude of the effect. The quality of the body of evidence of each of the main outcomes was categorised as high, moderate, low or very low.

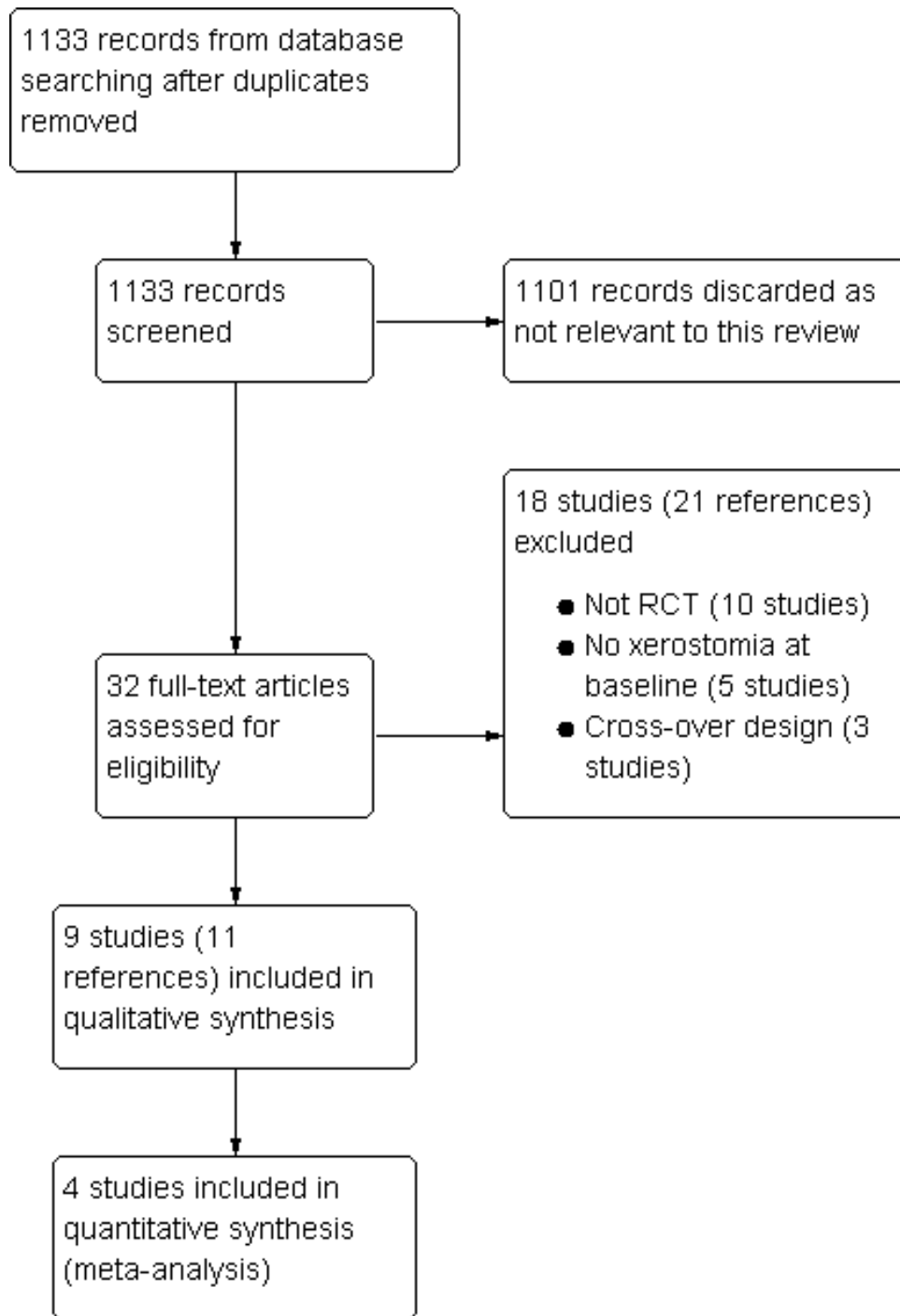
RESULTS

Description of studies

Results of the search

After de-duplication a total of 1133 references were identified from the electronic searches. Titles and abstracts were screened by two review authors and 1101 were discarded as being not relevant to this systematic review. Thirty-two references were retrieved in full text and of these, 11 references to nine RCTs met the inclusion criteria for this review and 21 references to 18 studies were listed as excluded (Figure 1).

Figure 1. Study flow diagram.



Included studies

Characteristics of the trial designs and settings

Nine RCTs met the inclusion criteria and were included in this review ([Characteristics of included studies](#)). All were parallel group trials and all except one ([Wong 2003](#)) had two arms comparing an experimental arm with a control arm. Four trials were conducted in the USA ([Papas 2006](#); [Pfister 2010](#); [Steller 1988](#); [Talal 1992](#)), three in Sweden ([Blom 1992](#); [Blom 1996](#); [List 1998](#)) and one in each of Canada ([Wong 2003](#)) and Korea ([Cho 2008](#)). Two studies were described as either a pilot study ([Cho 2008](#)) or a Phase I/II study ([Wong 2003](#)), and there were no sample size calculations reported for any of the included studies. Eight of the included studies took place in a single centre but [Talal 1992](#) was a three-centre study. Three studies had some support from companies who supplied the products being evaluated ([Papas 2006](#); [Talal 1992](#); [Wong 2003](#)), four were funded solely by research grants from publicly funded bodies ([Blom 1996](#); [Cho 2008](#); [List 1998](#); [Pfister 2010](#)), and the remaining two ([Blom 1992](#); [Steller 1988](#)) did not state the sources of funding for the studies.

Characteristics of the participants

A total of 366 participants took part in these trials with a mean of 40 participants per trial and a range of 12 to 77. All participants were adults. The causes of xerostomia were radiotherapy for oral cancers in four trials ([Blom 1996](#); [Cho 2008](#); [Pfister 2010](#); [Wong 2003](#)), Sjögren's Syndrome in three trials ([List 1998](#); [Steller 1988](#); [Talal 1992](#)), medication-related in one trial ([Papas 2006](#)) and in the remaining trial ([Blom 1992](#)) participants had a range of causes of xerostomia.

Characteristics of the interventions

We divided the included studies into three groups, according to the interventions evaluated. Five trials evaluated acupuncture ([Blom 1992](#); [Blom 1996](#); [Cho 2008](#); [List 1998](#); [Pfister 2010](#)), three evaluated electrostimulation devices ([Steller 1988](#); [Talal 1992](#); [Wong 2003](#)) and one evaluated a powered toothbrush in participants with dry mouth ([Papas 2006](#)).

1. Acupuncture

Three trials ([Blom 1992](#); [Blom 1996](#); [Cho 2008](#)) compared acupuncture to a sham acupuncture (placebo) control group, one trial ([List 1998](#)) compared acupuncture with both manual and electrical stimulation of the needles to acupuncture with manual stimulation only, and [Pfister 2010](#) compared acupuncture to

'usual care'. The duration of treatment varied between these studies. The study by [Cho 2008](#) used a 6-week treatment period, in [Pfister 2010](#) treatment was over 4 weeks and in the study by [List 1998](#) participants had a 10-week course of treatment. In both the other trials ([Blom 1992](#); [Blom 1996](#)) treatment was two courses of 6 weeks separated by a 2-week rest period.

2. Electrostimulation

Two trials ([Steller 1988](#); [Talal 1992](#)) of electrostimulation devices compared a device with a placebo (sham device). Participants received training in the use of the devices, initially under the supervision of the researchers, and then used the devices at home three times daily. In the three-arm trial ([Wong 2003](#)) a comparison was made between transcutaneous electrostimulation of three different sets of acupuncture points.

3. Powered toothbrush

The final trial in this review ([Papas 2006](#)) compared the salivary stimulation achieved by brushing teeth, gums and tongue with a powered toothbrush, with that resulting from a similar brushing pattern with a manual toothbrush.

Characteristics of the outcomes

The primary outcome of our review was mouth dryness and three of the five included trials which evaluated acupuncture treatments stated that they collected data on this outcome. [Cho 2008](#) used a Xerostomia Questionnaire to assess dry mouth and [List 1998](#) stated that they used a VAS scale to measure mouth dryness. [Pfister 2010](#) evaluated the effect of acupuncture primarily on pain due to radiotherapy but this trial reported mouth dryness as measured by Xerostomia Inventory as a secondary outcome. Neither [Blom 1992](#) nor [Blom 1996](#) reported the outcome of dry mouth symptoms.

In the electrostimulation group, both [Wong 2003](#) and [Talal 1992](#) described collecting data on dry mouth symptoms but did not report outcome data for each randomised group. The trial by [Steller 1988](#) did not report dry mouth symptoms.

The powered versus manual toothbrush study ([Papas 2006](#)) stated that they used a VAS scale to measure mouth dryness as an outcome but this trial did not report dry mouth outcome data.

None of the included studies reported the outcomes of duration of effectiveness, quality of life, patient satisfaction, or oral health assessment.

Measures of stimulated salivary flow (SWS) were reported by eight trials ([Blom 1992](#); [Blom 1996](#); [Cho 2008](#); [List 1998](#); [Papas 2006](#); [Steller 1988](#); [Talal 1992](#); [Wong 2003](#)) and seven of these also reported the outcome of unstimulated salivary flow (UWS) ([Blom](#)

1992; Blom 1996; Cho 2008; List 1998; Papas 2006; Steller 1988; Wong 2003).

Excluded studies

After at least two review authors had assessed the full-text study report, 21 references to a total of 18 studies were excluded from this review. Ten studies were found not to be randomised controlled trials (Blom 2000; Cheville 2006; Fontanesi 1991; Garcia 2009; Loncar 2011; Niemtzow 2007; Schiff 2009; Simcock 2009; Weiss 1986; Wong 2012), five studies were of interventions to prevent dry mouth where participants did not have dry mouth symptoms at baseline (Braga 2011; Deng 2008; Meng 2012; Simoes 2010; Wong 2010) and three studies used a cross-over design which was an explicit exclusion criteria for this review (Simcock 2013; Strietzel 2007; Strietzel 2011). See [Characteristics of excluded studies](#) for further details.

Risk of bias in included studies

Allocation

We judged three studies (33.3%) to have adequate sequence generation (Pfister 2010; Steller 1988; Talal 1992) and two of these (Pfister 2010; Talal 1992) also described adequate allocation concealment, and therefore these trials were assessed as at low risk of selection bias.

The trial by Steller 1988 did not report sufficient information to determine whether allocation concealment was done. The remaining six trials (Blom 1992; Blom 1996; Cho 2008; List 1998; Papas 2006; Wong 2003) reported insufficient information for us to make a judgement. These seven trials were assessed at unclear risk of selection bias.

Blinding

Blinding of participants to the allocated treatment by use of a placebo was done in five of the included studies (Blom 1992; Blom 1996; Cho 2008; Steller 1988; Talal 1992) and these trials were assessed at low risk of performance bias. The other four trials did not blind participants to the allocated treatment and were therefore assessed at high risk of performance bias.

Outcome assessors were blinded to allocated treatment in four trials (Blom 1992; Blom 1996; Steller 1988; Talal 1992) and these trials were assessed at low risk of detection bias. One trial (Wong 2003) did not use blinded outcome assessment and was judged at high risk of detection bias. The remaining four trials did not report sufficient information concerning outcome evaluation and were assessed at unclear risk of detection bias.

Incomplete outcome data

Incomplete outcome data were a problem in two trials (Steller 1988; Wong 2003) where 17% and 20% of trial participants respectively, were excluded from the outcome evaluation, and the numbers lost were not similar in each arm of these trials. These two trials were assessed at high risk of attrition bias.

Two trials (Blom 1996; Talal 1992) did not report the number of participants included in the outcome evaluation and these trials were assessed at unclear risk of attrition bias. The remaining five trials were assessed at low risk of attrition bias.

Selective reporting

We found selective reporting in three trials in this review (Papas 2006; Talal 1992; Wong 2003) and these trials were assessed at high risk of reporting bias. Talal 1992 and Wong 2003 stated in the methods that they were collecting data on dry mouth symptoms but neither of these trials reported these data for the allocated treatment groups. Papas 2006 described in the methods that VAS scores for mouth dryness would be collected but these were not reported, and participant satisfaction was only reported for the powered toothbrush.

Reporting bias was unclear in Blom 1992; Blom 1996 as neither of these trials reported a dry mouth outcome.

In the remaining four trials there was a low risk of reporting bias.

Other potential sources of bias

Three of the included trials were assessed at high risk of other bias (Blom 1996; Cho 2008; Papas 2006). The authors of Blom 1996 acknowledged in the discussion of this trial report that the placebo intervention of superficial needling appears to have some effect on dry mouth and so use of this placebo may have reduced the relative benefit of acupuncture treatment. In Cho 2008 at baseline, the two trial arms were not balanced with regard to saliva flow rates, although the groups were so small that differences were not statistically significant. In the Papas 2006 trial powered toothbrushes were given to all participants and this may have introduced some bias into the assessment of participant satisfaction.

The remaining six trials were assessed at low risk of other bias.

Overall risk of bias

All of the trials included in this review had at least one domain where risk of bias was either unclear or high. Consequently eight trials were assessed at high risk of bias and the remaining one (Blom 1992) at unclear risk of bias (Figure 2; Figure 3). For further details see [Characteristics of included studies](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

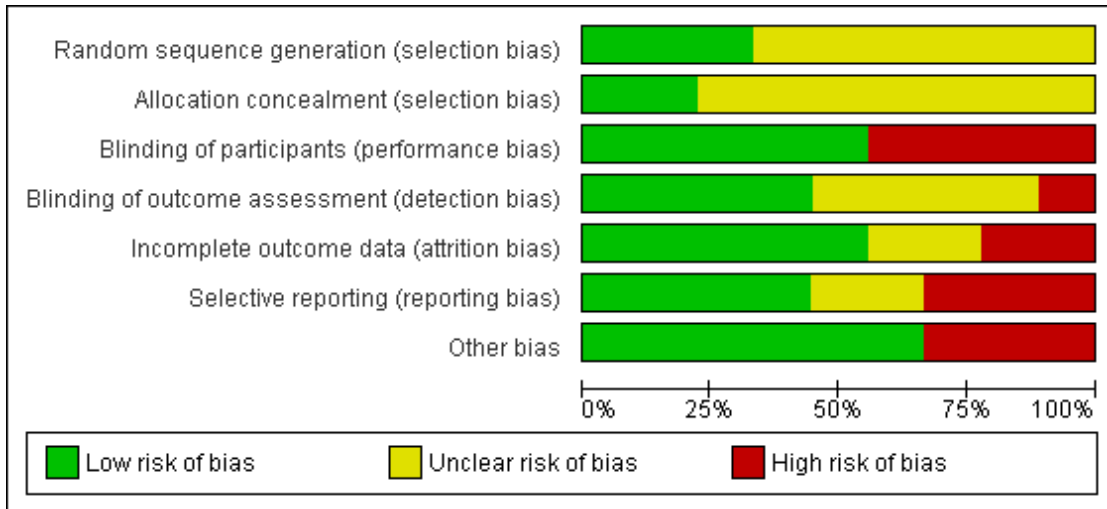


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blom 1992	?	?	+	+	+	?	+
Blom 1996	?	?	+	+	?	?	-
Cho 2008	?	?	+	?	+	+	-
List 1998	?	?	-	?	+	+	+
Papas 2006	?	?	-	?	+	-	-
Pfister 2010	+	+	-	?	+	+	+
Steller 1988	+	?	+	+	-	+	+
Talal 1992	+	+	+	+	?	-	+
Wong 2003	?	?	-	-	-	-	+

Effects of interventions

See: [Summary of findings for the main comparison Acupuncture versus placebo](#); [Summary of findings 2 Electrostimulation versus placebo](#)

Acupuncture versus placebo

Dry mouth

The primary outcome of this review was the effect of the interventions on dry mouth. According to their methods sections, this outcome was planned to be recorded in three of the six (Cho 2008; List 1998; Pfister 2010) included acupuncture trials, but only Cho 2008 and Pfister 2010 reported dry mouth outcome data suitable for inclusion in a meta-analysis. Each of these trials compared acupuncture (either a 4-week or a 6-week course of treatment) with placebo and each measured dry mouth using a different scale, so these data were combined using a standardised mean difference (SMD). The pooled estimate (SMD -0.34, 95% confidence interval (CI) -0.81 to 0.14, P value 0.17, $I^2 = 39%$) (Analysis 1.1) showed no evidence of a difference between acupuncture and placebo, but the combined trials included only 70 participants. An SMD of 0.3 is generally considered to be a small to moderate effect (Cohen 1988), but the confidence interval ranges between a large decrease in mouth dryness and a very small increase. The heterogeneity in this estimate ($I^2 = 39%$) is likely to have been due to the different causes of dry mouth in the participants in these trials. There may have been insufficient participants and statistical power to show a difference (Type 1 error) if indeed a difference exists, or as the authors of the trials suggest, the 'placebo' acupuncture may have had some benefit, thus biasing the effect towards the null.

A third study (List 1998) compared acupuncture with both electrical and manual stimulation to acupuncture with manual stimulation (placebo) in patients with Sjögren's Syndrome and reported a statistically significant reduction in the outcome of dry mouth ($P < 0.05$). However, data from this study (medians and ranges Additional Table 1) could not be used in the meta-analysis.

Adverse effects

In the trials evaluating acupuncture, both Blom 1992 and Blom 1996 noted that tiny bruises appeared at acupuncture sites in some participants and there was tiredness after treatments and List 1998 noted that "significant discomfort in the eyes was registered in the acupuncture group". Pfister 2010 reported that no serious adverse effects were noted but "participants reported temporary increases

in pain, minor bruising or bleeding and constitutional symptoms" associated with acupuncture. The study by Cho 2008 did not mention adverse effects.

Unstimulated whole saliva

Three trials, two at high risk of bias and one unclear, reported data for this outcome at the end of treatment. In two studies (Blom 1992; Blom 1996) participants had 6 weeks of either acupuncture or sham acupuncture treatment, followed by a 2-week 'rest' and then a second course of 6 weeks of treatment. The study by Cho 2008 reported outcomes at the end of a 6-week course of treatment. A fourth study (List 1998) reported this outcome and found no difference, but data from this study (medians and ranges in each group, Additional Table 1) could not be included in the meta-analysis.

Meta-analysis of unstimulated whole saliva data from these three trials shows a very small effect favouring acupuncture which is unlikely to be clinically important (mean difference (MD) 0.02 ml/minute, 95% CI 0 to 0.04, P value 0.04, $I^2 = 57%$) (Analysis 1.2). Heterogeneity is likely to be due to the different reasons for dry mouth in participants in these trials.

Likewise after 12 months follow-up there is a very small benefit associated with acupuncture (MD 0.06 ml/minute, 95% CI 0.01 to 0.11, P value 0.03, $I^2 = 10%$) which may or may not be associated with a clinically meaningful improvement (Analysis 1.4).

Stimulated whole saliva

At the end of the treatment period the meta-analysis of three trials of acupuncture reported data which showed an increase in stimulated whole saliva production favouring the acupuncture groups (MD 0.19 ml/minute, 95% CI 0.07 to 0.31, P value 0.002, $I^2 = 1%$) (Analysis 1.3). The difference favouring acupuncture persisted at 12 months of follow-up (MD 0.28 ml/minute, 95% CI 0.09 to 0.47, P value 0.004, $I^2 = 0%$) (Analysis 1.5). A fourth study (List 1998) reported this outcome and found no difference but data from this study (medians and ranges in each group) could not be included in the meta-analysis. The clinical importance of this finding is unclear. It may indicate a small increase in saliva production, but the effect of increased saliva production on the symptom of dry mouth is not evaluated.

Electrostimulation

Dry mouth

Two small studies compared the use of an electrostimulation device with a placebo device in patients with Sjögren's Syndrome.

Neither of these trials reported outcome data for dry mouth. One trial (Talal 1992) reported that data on dry mouth were collected, but these data were not reported and we have not been able to obtain them from the trial authors. The only information available from this study is that “patients using the active device experienced relief from six of the most common symptoms of xerostomia secondary to Sjögren’s Syndrome, with two of these symptoms being statistically significantly improved compared to patient’s using the placebo device”. No other data were reported to support this statement (Additional Table 1).

The outcome of dry mouth was not mentioned by Steller 1988. A further study (Wong 2003) compared acupuncture-like electrostimulation of different sets of points in patients who had been treated with radiotherapy. There was no control group in this study which did not report outcomes by randomised group.

Adverse effects

Wong 2003 stated that “no adverse effects were caused by Code-tron” in their Phase I-II study of different treatment points. Neither of the other two reports (Steller 1988; Talal 1992) mentioned whether or not adverse effects occurred during the trial.

Unstimulated whole saliva

Steller 1988 reported no difference in unstimulated whole saliva between electrostimulation and control at the end of 4 weeks of treatment (MD 0.02 grams/2 minutes, 95% CI -0.12 to 0.16) (Analysis 2.1).

Stimulated whole saliva

Two included trials of electrostimulation (Steller 1988; Talal 1992) reported the outcome of stimulated whole saliva, but Talal 1992 reported no estimate of variance in each group so we were unable to use the data from this trial (Additional Table 1).

Steller 1988 found no difference between the active and placebo groups (MD 0.16 grams/2 minutes, 95% CI -0.05 to 0.37)

(Analysis 2.2). The study by Talal 1992 reported that saliva secretion increased more in the active electrostimulation group compared to those receiving placebo at each of the weekly treatment sessions, but this increase in saliva production did not appear to persist as the pre-treatment mean saliva secretion was similar prior to each treatment in both groups.

Powered versus manual toothbrush

Unstimulated whole saliva

The single trial by Papas 2006 which compared powered and manual toothbrushes in participants with dry mouth found no difference between the groups in the volume of saliva produced 45 minutes after brushing (MD -0.07, 95% CI -0.74 to 0.60) (Analysis 3.1).

Stimulated whole saliva

There was no difference between the groups in the volume of saliva produced 5 minutes after brushing, assuming that brushing may have stimulated saliva production (MD -0.13, 95% CI -1.92 to 1.66) (Analysis 3.2).

Duration of effectiveness, quality of life, participant satisfaction, oral health assessment

These outcomes were not reported by any of the trials included in this review.

Sensitivity analyses

Planned sensitivity analyses were not conducted because there were insufficient trials included in this review.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Electrostimulation compared with placebo for dry mouth symptoms				
Patient or population: People with dry mouth due to Sjögren's Syndrome Settings: Outpatients Intervention: Electrostimulation Comparison: Placebo				
Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Unstimulated whole saliva millilitres/minute (end of treatment)	MD 0.02 grams/2 minutes (95% CI -0.12 to 0.16)	24 (1 RCT*)	⊕○○○ very low ¹	*Participants had Sjögren's Syndrome
Stimulated whole saliva millilitres/minute (end of treatment)	MD 0.16 grams/2 minutes (95% CI -0.05 to 0.37)	24 (1 RCT*)	⊕○○○ very low ¹	*Participants had Sjögren's Syndrome

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: 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: We are very uncertain about the estimate

¹ Quality of the body of evidence downgraded due to high risk of bias, imprecision (confidence intervals include both a potential benefit and a potential negative effect on saliva production), and estimate based on a single small study. This study did not report the primary outcome of this review

DISCUSSION

Summary of main results

The nine studies included in this review of non-pharmacological interventions for dry mouth were divided into three comparisons. Five small studies (total 153 participants, with dry mouth following radiotherapy treatment) compared acupuncture with placebo and two trials reported outcome data for dry mouth in a form suitable for meta-analysis. The pooled estimate for dry mouth showed no difference between acupuncture and control in these two trials (SMD -0.34, 95% CI -0.81 to 0.14, P value 0.17, I² = 39%)

with the confidence intervals including both a possible reduction or a possible increase in dry mouth symptoms. Acupuncture was associated with more adverse effects (tiny bruises and tiredness which were mild and temporary). There was a very small increase in unstimulated whole saliva (UWS) at the end of treatment (three trials) (MD 0.02 ml/minute, 95% CI 0 to 0.04, P value 0.04, I² = 57%), and this benefit persisted at the 12-month follow-up evaluation (UWS, MD 0.06 ml/minute, 95% CI 0.01 to 0.11, P value 0.03, I² = 10%). For stimulated whole saliva (SWS) there was a benefit favouring acupuncture (MD 0.19 ml/minute, 95% CI 0.07 to 0.31, P value 0.002, I² = 1%) an effect which also remained at the 12-month follow-up evaluation (SWS MD 0.28 ml/

minute, 95% CI 0.09 to 0.47, P value 0.004, $I^2 = 0\%$) ([Summary of findings for the main comparison](#)). It is unclear whether this small increase in saliva production is associated with a clinically important benefit because dry mouth symptoms were not assessed in all of the studies that measured saliva production.

Two small studies compared the use of an electrostimulation device with a placebo device (total 101 patients with Sjögren's Syndrome). A further study compared acupuncture-like electrostimulation of different sets of points in participants who had previously been treated with radiotherapy. None of these studies reported the outcome of dry mouth. There was no difference between electrostimulation and placebo in the outcomes of UWS or SWS at the end of the 4-week treatment period in the one study that provided data for these outcomes. No adverse effects were reported ([Summary of findings 2](#)).

A single study compared the stimulatory effect of powered versus manual toothbrushing and found no difference for the outcomes of UWS or SWS.

Overall completeness and applicability of evidence

We have included nine trials which randomised a total of 366 participants. However, the total number included in the outcome assessment is unclear as this information was not stated in one study ([Talal 1992](#)) and our attempts to contact the authors were not successful. Only two of the nine trials included in this review reported the primary outcome of this review: dry mouth. We pooled the data using standardised mean difference because each of the trials used a different scale to measure dry mouth. The confidence intervals of the pooled estimate cross the line of no effect, suggesting that there is no difference between acupuncture and placebo, although the point estimate SMD 0.34 could be interpreted as showing a small benefit in favour of acupuncture. It could be that the number of participants included in this meta-analysis is too small to detect a statistically significant effect, and further RCTs evaluating acupuncture are required to determine whether this is the case. There is also a suggestion from the authors of these trials that the placebo ('sham' acupuncture) may actually have a beneficial effect on dry mouth. If there is a beneficial effect from the placebo treatment this would make it less likely to show a difference between the two arms of these trials. Consideration should be given to designing a different control intervention.

In the published protocol, we decided a priori to exclude trials with cross-over designs from this review. The reason for this decision is that there is some suggestion that acupuncture may have a sustained effect on dry mouth. With regard to electrostimulation and laser therapies, there is little information available concerning the duration of effects.

Electrostimulation devices have undergone development over recent years and it is likely that the trials included in this review which were published between 1988 and 2003 evaluate 'first-gen-

eration' devices which may be considered obsolete. Newer 'second generation' devices which employ electrodes embedded within a removable oral splint are now available ([Fedele 2008](#)). A recent trial of a 'second generation' electrostimulation device ([Strietzel 2011](#)) has been excluded from this review due to the use of a cross-over design in this study. This trial reported a "cumulative positive effect" from the electrostimulation device. It is hoped that further research with this or similar electrostimulation devices will be undertaken using a double-blind parallel-group design.

Another consideration is the variation between the participants in these trials. Three trials included participants with Sjögren's Syndrome, four included patients who had previously undergone radiotherapy for head and neck cancer and two trials included participants with a range of cause of dry mouth symptoms. The nature and extent of salivary gland disease is likely to vary between these participants with resultant variations in residual gland function, disease natural history and prognosis amongst participants. Meta-analysis of the acupuncture trials showed some evidence of a benefit due to acupuncture on the outcomes of both unstimulated and stimulated saliva production. It is not known whether or not this small average benefit, translated to an improvement in the symptoms of dry mouth or the (oral health related) quality of life for these trial participants because this information was not reported. From the literature we know that increased saliva production may or may not reduce dry mouth symptoms.

However, while there is little effect as measured by the mean differences between the randomised groups in these four trials, in both trials some individuals did appear to benefit from the active intervention.

Quality of the evidence

None of the trials included in this review are at low risk of bias. All are small (range of 12 to 77 participants per trial), none reported sample size calculations and all are likely to lack statistical power to detect a difference between the arms of the trial should such a difference exist. Few reported important outcomes such as dry mouth symptoms, quantifiable adverse effects or (oral health related) quality of life. There is evidence of reporting bias, whereby important patient-centred outcomes are either not measured and/or not reported, and this is a major limitation on the findings of this review. The quality of the body of evidence for all the main outcomes of this review has been assessed as low or very low.

Potential biases in the review process

We conducted a broad search of several databases and placed no restrictions on the language of publication when searching the electronic databases or reviewing reference lists of included studies. However, it is likely that there are other studies, which may or may not be RCTs, published in the Chinese language literature

which we have not identified for this review. However a similar published review prepared by a team of authors based in China (Zhuang 2013) identified the same three RCTs for treatment of radiotherapy-induced xerostomia that we included in this review. We decided to exclude cross-over studies from this review because we were unable to determine empirically the duration of any potential effect of either acupuncture or electrostimulation techniques on dry mouth symptoms. It seemed likely that the potential effects of these interventions could extend for weeks or months after the end of the treatment phase. In this case the use of a cross-over study design to evaluate these interventions would be inappropriate.

Agreements and disagreements with other studies or reviews

Our findings are broadly in agreement with those of other published systematic reviews (Garcia 2013; O'Sullivan 2010; Zhuang 2013) which focused on participants with post-radiotherapy xerostomia and found evidence of some increase in saliva production but no difference in dry mouth symptoms. A review of treatment approaches for patients with xerostomia due to Sjögren's Syndrome (Wolff 2012) refers to one of the studies included in our Cochrane review (Talal 1992) and reports that electrostimulation is effective in stimulating saliva secretion. This review goes on to describe initial testing in a cross-over trial of a small intraoral electrostimulation device, which is activated by a remote control. Early results appear promising for patients and further research is ongoing and may be included in future updates of this Cochrane review.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine the effects of any of the interventions included in this review on dry mouth symptoms. There is some evidence that acupuncture increases saliva

production in patients with dry mouth following radiotherapy. There is insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms or saliva production in patients with Sjögren's Syndrome. Reported adverse effects of both acupuncture and electrostimulation are mild and transient. The use of relatively non-invasive techniques with favourable side-effect profiles, such as electrostimulation and acupuncture are certainly desirable in dry mouth patients. Some patients with dry mouth symptoms may benefit from one of these treatments, but in the absence of good evidence of their effectiveness, neither acupuncture nor electrostimulation treatments are likely to be funded by healthcare providers, and therefore any cost is likely to be borne by the patient. However, due to the paucity of data in relation to quality of life outcomes, patient satisfaction and longevity of clinical benefit, the clinical effectiveness of such treatments remains obscured. The use of such treatments outside of the clinical trial setting remains difficult to justify at present.

Implications for research

Both acupuncture and electrostimulation show some indications of possible benefit in some patients with dry mouth symptoms. Further well-designed and conducted double-blind trials with sufficient numbers of participants are required to determine the benefits of these interventions. Trials should be designed and conducted according to SPIRIT 2013 guidelines and reported according to CONSORT 2010 guidelines. Trials should include outcomes which are important to people with dry mouth such as dry mouth symptoms, quality of life, together with duration of effectiveness and satisfaction with the intervention.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blom 1992

Methods	Location: Sweden Number of centres: 1 Recruitment period: Not stated Funding source: Not stated Trial design: Parallel group RCT
Participants	Inclusion criteria: Severe xerostomia “mostly associated with systemic diseases”. 12 (57%) had either primary or secondary Sjögren’s Syndrome, 9 (43%) hypothyroidism, and remainder xerostomia following radiation therapy or of unknown aetiology Exclusion criteria: Not stated Age range: 33-72 Number randomised: 21 Number evaluated: 20
Interventions	Comparison: Acupuncture versus placebo (superficial acupuncture) Group A (n = 11): Acupuncture twice weekly for 6 weeks then 2 week break and further 6 weeks treatment Group B (n = 10): Superficial acupuncture (designed to act as placebo) Duration of follow-up: 12 months
Outcomes	Stimulated and unstimulated salivary flow rates (median and range reported), mean and SD calculable at 7 weeks, minor adverse effects noted
Notes	Sample size calculation: Not reported

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “randomly assigned” Comment: No method of sequence generation described
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	Low risk	Quote: “Neither the person who evaluated salivary flow nor the patients themselves knew whether they received acupuncture or superficial needling” Comment: Probably done

Blom 1992 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Neither the person who evaluated salivary flow nor the patients themselves knew whether they received acupuncture or superficial needling” Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1/21 lost to follow-up after 3 months. This was judged unlikely to have introduced a bias
Selective reporting (reporting bias)	Unclear risk	Comment: No patient-reported symptoms included. Outcome measure is objective salivary flow
Other bias	Low risk	Comment: No other sources of bias identified

Blom 1996

Methods	Location: Sweden Number of centres: 1 Recruitment period: Not stated Funding source: 3 grants. Swedish Patent Revenue Research Fund, Swedish Dental Society and King Gustav V Research Fund Trial design: Parallel group RCT	
Participants	Inclusion criteria: Xerostomia following radiation therapy Exclusion criteria: None stated Number randomised: 41 Number evaluated: Between 32 and 38 depending on outcome	
Interventions	Comparison: Acupuncture versus placebo (superficial acupuncture) Group A (n = 21): Classical acupuncture, 12 x 20-minute treatments during which 5-8 points were stimulated manually until the appearance of a needling reaction (Q1). 2 sessions per week for 6 weeks, then 2-week break then further 6 weeks of treatment Group B (n = 20): Superficial acupuncture delivered to 5-8 points on same schedule as above Duration of follow-up: 12 months	
Outcomes	Stimulated and unstimulated salivary flow rates (median and range reported), mean and SD calculable at 8 weeks, minor adverse effects noted	
Notes	Sample size calculation: Not reported	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Blom 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: “randomly assigned” Comment: No method of sequence generation described
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	Low risk	Quote: “double blind” Comment: Patients and outcome assessors. Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blind” Comment: Patients and outcome assessors. Probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 41 patients randomised 38 patients evaluated and 1/20 and 4/18 patients lost to follow-up in acupuncture and placebo groups respectively. No reasons for drop-out/withdrawal described
Selective reporting (reporting bias)	Unclear risk	Comment: No patient-evaluated outcomes of xerostomia reported
Other bias	High risk	Comment: In the discussion section study authors suggest that superficial needling is not reliable as placebo because it has some activity in some people

Cho 2008

Methods	Location: South Korea Number of centres: Unclear. Konyang University Hospital, Daejeon and Dunsan Oriental Hospital of Daejeon University both approved study Recruitment period: Not stated Funding source: Acupuncture, Moxibustion and Meridian Research Project (K06070) of Korean Institute of Oriental medicine R&D Project (B050018) Ministry of Health and Welfare, Republic of Korea Trial design: Parallel group pilot study
Participants	Inclusion criteria: Patients with xerostomia with history of radiation therapy (minimum dose 38 Gy and at least 50% of parotid gland exposed to radiation) Exclusion criteria: Patients with distant metastases, and inflammatory disease or ECOG scores > 2 Number randomised: 12 Number evaluated: 12

Cho 2008 (Continued)

Interventions	Comparison: Acupuncture versus placebo (sham acupuncture) Group A (n = 6): Acupuncture delivered to 4 points in 2 sessions per week for 6 weeks Group B (n = 6): Sham acupuncture delivered to 4 points at least 2 cm away from 'real' acupoints, in 2 sessions per week for 6 weeks Duration of follow-up: 6 weeks	
Outcomes	Xerostomia Questionnaire, stimulated and unstimulated salivary flow rates at end of treatment	
Notes	Sample size calculation: Pilot study	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "allocated using block randomization" Comment: Random component not described
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	Low risk	Comment: Patients likely to be blinded because placebo acupuncture used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information to determine 'yes' or 'no'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants included in outcome evaluations
Selective reporting (reporting bias)	Low risk	Comment: Xerostomia questionnaire (patient-evaluated measure) and UWS, SWS reported
Other bias	High risk	Groups very unbalanced at baseline

List 1998

Methods	Location: Sweden Number of centres: 1 Recruitment period: Not stated Funding source: Swedish National Social Insurance Board Trial design: Parallel group RCT
Participants	Inclusion criteria: Patients diagnosed with primary Sjögren's Syndrome Exclusion criteria: None stated Age range: 44-78 years (mean 65 years) Number randomised: 21 Number evaluated: 20
Interventions	Comparison: Acupuncture versus placebo (manual stimulation only) Group A (n = 10): 30-minute session twice weekly with both electrical and manual stimulation for a total of 10 weeks Group B (n = 10): No treatment during the first 10 weeks and then acupuncture as above weeks 11-20 Duration of follow-up: 20 weeks
Outcomes	UWS, SWS, median mouth dryness (10-point VAS scale), adverse effects
Notes	Sample size calculation: Not reported Email sent to author 29 April 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized into 2 groups" Comment: Random component not described
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	High risk	Comment: Blinding not possible. Manual versus electrical stimulation. Electrical stimulation evoked visible muscle contractions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The evaluation was performed by one person, treatment by another" Comment: Unclear if person evaluating patients was blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1/21 patients excluded from evaluation

List 1998 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: UWS, SWS, VAS scores (patient-evaluated outcome) reported
Other bias	Low risk	Comment: No other sources of bias identified

Papas 2006

Methods	Location: Boston, USA Number of centres: 1 Recruitment period: Not stated Funding source: Philips Oral Healthcare provided the Sonicare Advance Toothbrushes Trial design: Parallel group with control group crossing over to powered toothbrush after 9 weeks
Participants	Inclusion criteria: Participants aged 40-80 years, on a medication (list reported) of medications likely to result in dry mouth, > 10 natural teeth, UWS < 0.3 ml/min Exclusion criteria: Advanced periodontitis, infection, wasting diseases requiring premedication, participation in another clinical trial, on a chronic antibiotic regimen Number randomised: 61 Number evaluated: 58
Interventions	Comparison: Powered versus manual toothbrush Group A (n = 29): Sonicare Advance Toothbrush used according to directions given by investigators. Daily diaries to record toothbrushing, flossing and type of dentifrice used Group B (n = 29): Manual toothbrush (Oral B) used according to directions given by investigators. Daily diaries to record toothbrushing, flossing and type of dentifrice used
Outcomes	UWS, SWS, patient's preference, microbiology of oral cavity, changes in VAS for responders and non-responders
Notes	Sample size calculation: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized to each of the treatment groups" Comment: Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'
Blinding of participants (performance bias)	High risk	Comment: Blinding not possible

Papas 2006 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3 participants lost to follow-up
Selective reporting (reporting bias)	High risk	VAS for responders and non-responders planned as an outcome but not reported
Other bias	High risk	Study funded by Philips who provided the toothbrushes. Unclear whether participants were aware that they would all be given a Sonicare electric toothbrush at the end of the research

Pfister 2010

Methods	Location: New York, USA Number of centres: 1 Recruitment period: 2004-2007 Funding source: NIH grant CA098792 Trial design: Parallel group RCT	
Participants	Inclusion criteria: Patients who had undergone neck dissection for cancer, with pain and dysfunction likely to be attributable to neck dissection, at least 3 months post neck dissection and radiation, with moderate to severe pain on Constant-Murley score \leq 70 Exclusion criteria: Those who had received acupuncture in previous 6 weeks Cause of xerostomia: Radiation treatment for cancer Number randomised: 58 Number evaluated: 58	
Interventions	Comparison: Acupuncture versus usual care Group A (n = 28): Acupuncture once a week for 4 weeks. Needles were placed at both standard and customised points to "optimise efficacy while facilitating reproducibility". Additional 5th treatment was added to improve compliance with assessment visit after 4th treatment Group B (n = 30): Usual care - antiinflammatory and analgesic medication Duration of follow-up: 4 weeks	
Outcomes	Pain on constant Murley scale, pain (numerical rating scale), Xerostomia Inventory, adverse effects	
Notes	Sample size calculation: Not reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Pfister 2010 (Continued)

Random sequence generation (selection bias)	Low risk	"...random assignment was stratified by neck (surgical) procedure type (selective, modified or radical), and baseline Constant-Murley score, using blocks of random length"
Allocation concealment (selection bias)	Low risk	"..random assignment was implemented via a secure computerised database, ensuring full allocation concealment"
Blinding of participants (performance bias)	High risk	Open trial, no placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patients self assessed main outcomes but attempts were made to use blinded clinical assessment of objective components of Constant-Murley scale
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 58 randomised participants are included in the outcome assessment
Selective reporting (reporting bias)	Low risk	Planned primary and secondary outcomes are reported
Other bias	Low risk	No other sources of bias identified

Steller 1988

Methods	Location: USA Number of centres: 1 Recruitment period: Not stated Funding source: Not stated Trial design: Parallel group RCT
Participants	Inclusion criteria: Participants aged > 18 years with dry mouth, focal sialoadenitis in labial salivary gland biopsy specimen Exclusion criteria: On medication known to affect saliva production, presence of pacemaker, pregnancy, UWS < 0.2 gram/minute Cause of xerostomia: Sjögren's Syndrome Number randomised: 29 Number evaluated: 24
Interventions	Comparison: Electrical stimulation versus placebo Group A (n = 14): Electrical stimulation used for 3 minutes under supervision, then at home 3 times daily for 4 weeks Group B (n = 15): Placebo electrical stimulation used under supervision for 3 minutes then at home 3 times daily for 4 weeks The electronic stimulation device consisted of a hand held probe, tipped with 2 electrodes, and a control console box which housed the battery and controls

Steller 1988 (Continued)

	Duration of follow-up: 4 weeks	
Outcomes	Mean UWS and SWS	
Notes	Sample size calculation: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a table of random numbers" Comment: Random number table. Probably done
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	Low risk	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 5/29 patients withdrew (1 per intervention arm, 4 per control arm) (17%)
Selective reporting (reporting bias)	Low risk	Comment: SWS, visual examination, patient evaluation of any increase in saliva
Other bias	Low risk	Comment: No other sources of bias identified

Talal 1992

Methods	Location: USA Number of centres: 3 Recruitment period: Not stated Funding source: Biosonics Trial design: Parallel group RCT
Participants	Inclusion criteria: Participants aged > 18 years with Sjögren's Syndrome plus 1 other rheumatic condition (from specified list) and maximum saliva production of 0.4 g saliva/ 2 minutes Exclusion criteria: None stated Cause of xerostomia: Sjögren's Syndrome Number randomised: 77 Number evaluated: Unclear

Interventions	Comparison: Active electrostimulation device versus sham device Group A (n = 40): Active electrostimulation device Group B (n = 37): Sham electrostimulation device System comprised a control module plus a hand held stimulus probe with 2 electrodes, to be placed between the tongue and the roof of the mouth. Patients were instructed on the use of the system, supervised and then instructed to use it at home 3 times daily for 4 weeks Duration of follow-up: 4 weeks	
Outcomes	SWS, symptom relief	
Notes	Sample size calculation: Not reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...assignment was performed according to a statistical table of random numbers" Comment: Random number table
Allocation concealment (selection bias)	Low risk	Quote: "...neither the technician nor the physician/investigator were provided with the code for active and placebo devices" Comment: Probably done
Blinding of participants (performance bias)	Low risk	Quote: "double blind" Comment: Probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Comment: Probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Numbers of participants included in outcome evaluations unclear
Selective reporting (reporting bias)	High risk	Comment: Salivary output data reported per group but no estimates of variance and data for symptom improvement not provided
Other bias	Low risk	Groups similar at baseline with regard to salivary output

Wong 2003

Methods	Location: Canada Number of centres: 1 Recruitment period: Not stated Funding source: Hamilton Health Sciences Corporation Foundation and equipment provision by EHM Rehabilitation Technologies Inc Trial design: Parallel (3 groups) RCT
Participants	Inclusion criteria: Patients treated with radiotherapy for head and neck cancer who had symptoms of xerostomia. Those who had no response to pilocarpine were also included after a 1 month washout period Exclusion criteria: Patients taking medications that may induce xerostomia, those with unstable cardiac disease, with a pacemaker, those taking pilocarpine Cause of xerostomia: Radiotherapy Number randomised: 46 Number evaluated: 37
Interventions	Comparison: Transcutaneous nerve stimulation to different acupuncture points Group A (n = 13): Sp6, St36, L14 (active electrode) and CV 24 (indifferent electrode) Group B (n = 10): Sp6, St36, P6 (active electrode) and CV 24 (indifferent electrode) Group C (n = 14): Sp6, St 5 and 6, P6 (active electrode) and CV 24 (indifferent electrode) All 3 groups had twice weekly stimulation sessions to the prespecified points for 6 weeks, followed by a 2-week break and then a second 6-week phase of treatment Duration of treatment: 14 weeks Follow-up: At 3, 6 and 12 months after the end of treatment
Outcomes	Total xerostomia symptom score, patient-reported improvement in tongue dryness, speech, swallowing and overall mouth comfort. UWS, SWS, adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized into 3 groups" Comment: Random component not described
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to determine
Blinding of participants (performance bias)	High risk	Comment: Not described
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 9 (9/46) of those randomised did not complete the trial. No information

Wong 2003 (Continued)

		as to which groups they were from. 13, 10 and 14 described in groups A, B and C respectively
Selective reporting (reporting bias)	High risk	Comment: Results reported as means and SDs for the whole cohort only, or on graphs for VAS scores - unclear whether the randomisation to different groups had any effect
Other bias	Low risk	No other sources of bias identified

ECOG = Eastern Cooperative Oncology Group; Gy = gray; RCT = randomised controlled trial; SD = standard deviation; SWS = stimulated whole saliva; UWS = unstimulated whole saliva; VAS = visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Blom 2000	Retrospective study
Braga 2011	Participants did not have xerostomia at baseline
Cheville 2006	Not randomised. No control group
Deng 2008	Participants did not have xerostomia at baseline
Fontanesi 1991	Not randomised. No control group. 6 patients received hyperbaric oxygen therapy in a non-randomised, non-controlled pilot study. The authors also report the results of a retrospective uncontrolled study in 5 patients
Garcia 2009	Not RCT
Loncar 2011	Not RCT
Meng 2012	Participants did not have xerostomia at baseline
Niemtzow 2007	Not RCT
Schiff 2009	Not RCT
Simcock 2009	Not RCT
Simcock 2013	Cross-over study

(Continued)

Simoes 2010	Participants did not have xerostomia at baseline
Strietzel 2007	Cross-over study with 158 different treatment sessions tested on 20 patients with only 90 minutes between treatments
Strietzel 2011	Cross-over study where participants experienced both active (mechanical and electrical stimulation) and sham (mechanical only) device effects for 1 month in a random order. A carry-over effect cannot be discounted
Weiss 1986	Not RCT
Wong 2010	Participants did not have xerostomia at baseline
Wong 2012	Non-randomised phase II feasibility trial of acupuncture-like transcutaneous electrical nerve stimulation (AL-TENS)

RCT = randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

NCT01141231

Trial name or title	Acupuncture in treating dry mouth caused by radiation therapy in patients with head and neck cancer
Methods	Randomised controlled trial
Participants	Patients with grade 2 or 3 xerostomia following radiotherapy for head and neck cancer. No prior use of acupuncture and at least 9 months after last radiotherapy treatment
Interventions	Acupuncture twice weekly for 4 weeks (2 regimens) versus standard oral hygiene care
Outcomes	Xerostomia, saliva production
Starting date	November 2012
Contact information	Dr Lorenzo Cohen (lcohen@mdanderson.org)
Notes	

DATA AND ANALYSES

Comparison 1. Acupuncture versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mouth dryness	2	70	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.81, 0.14]
1.1 Xerostomia Inventory	1	58	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.72, 0.31]
1.2 Xerostomia Questionnaire (change)	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-1.09 [-2.34, 0.16]
2 Unstimulated whole saliva (end of treatment)	3	71	Mean Difference (IV, Fixed, 95% CI)	0.02 [0.00, 0.04]
3 Stimulated whole saliva (end of treatment)	3	71	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.07, 0.31]
4 Unstimulated whole saliva (12 months)	2	54	Mean Difference (IV, Fixed, 95% CI)	0.06 [0.01, 0.11]
5 Stimulated whole saliva (12 months)	2	54	Mean Difference (IV, Fixed, 95% CI)	0.28 [0.09, 0.47]

Comparison 2. Electrical stimulation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Unstimulated whole saliva (end of treatment)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Stimulated whole saliva (end of treatment)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 3. Powered versus manual toothbrush

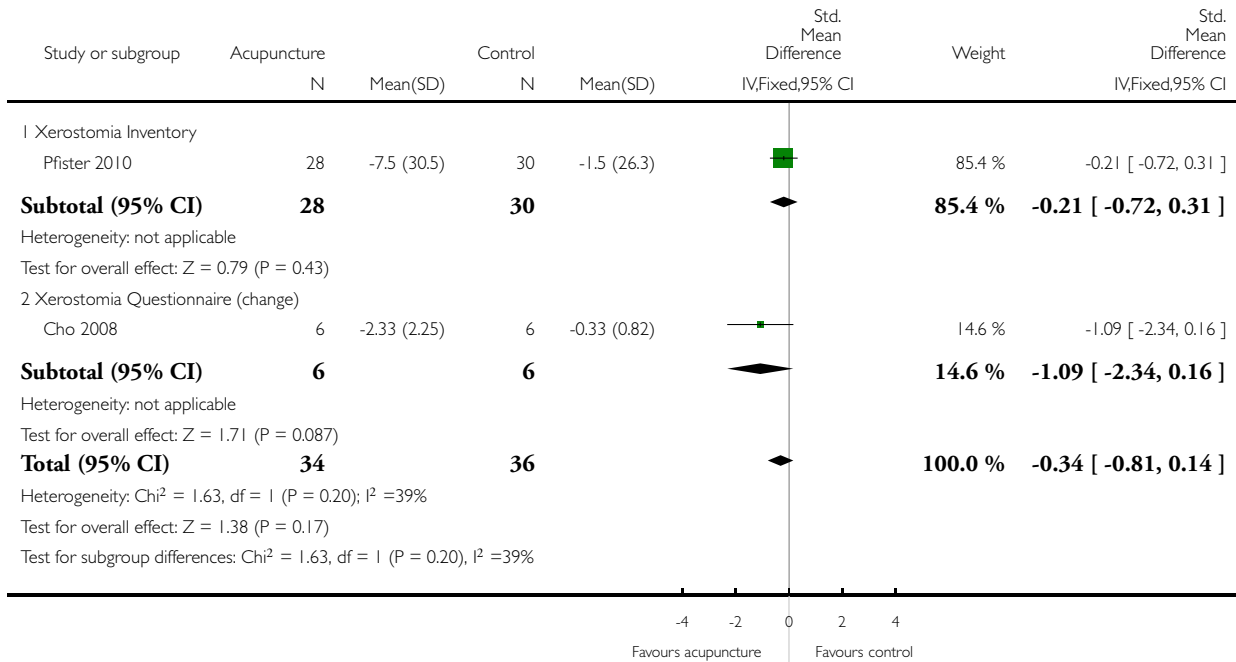
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Unstimulated whole saliva (45 minutes after brushing)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Stimulated whole saliva (5 minutes after brushing)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Acupuncture versus placebo, Outcome 1 Mouth dryness.

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 1 Acupuncture versus placebo

Outcome: 1 Mouth dryness

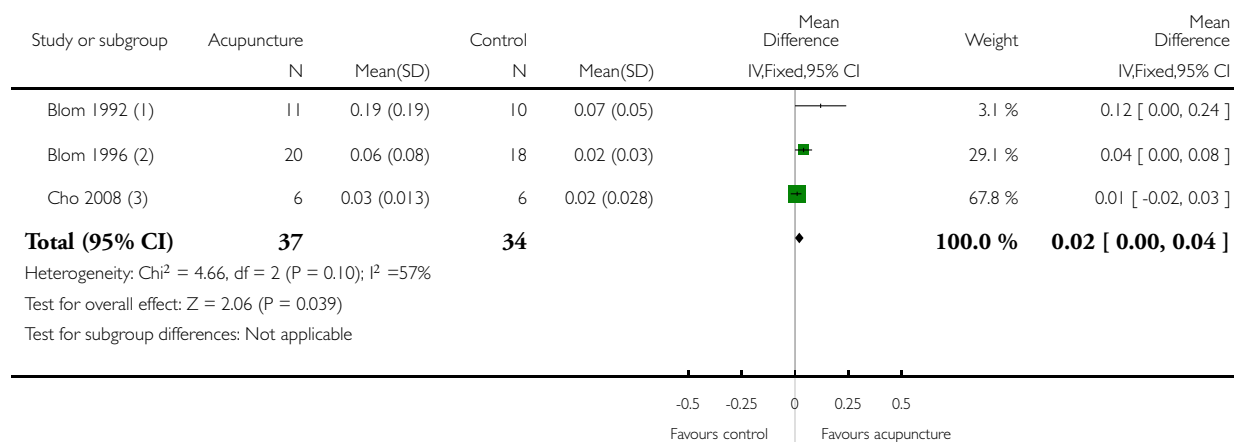


Analysis 1.2. Comparison 1 Acupuncture versus placebo, Outcome 2 Unstimulated whole saliva (end of treatment).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 1 Acupuncture versus placebo

Outcome: 2 Unstimulated whole saliva (end of treatment)



(1) 14 week treatment period with no treatment in weeks 7&8

(2) 14 week treatment period with no treatment in weeks 7&8

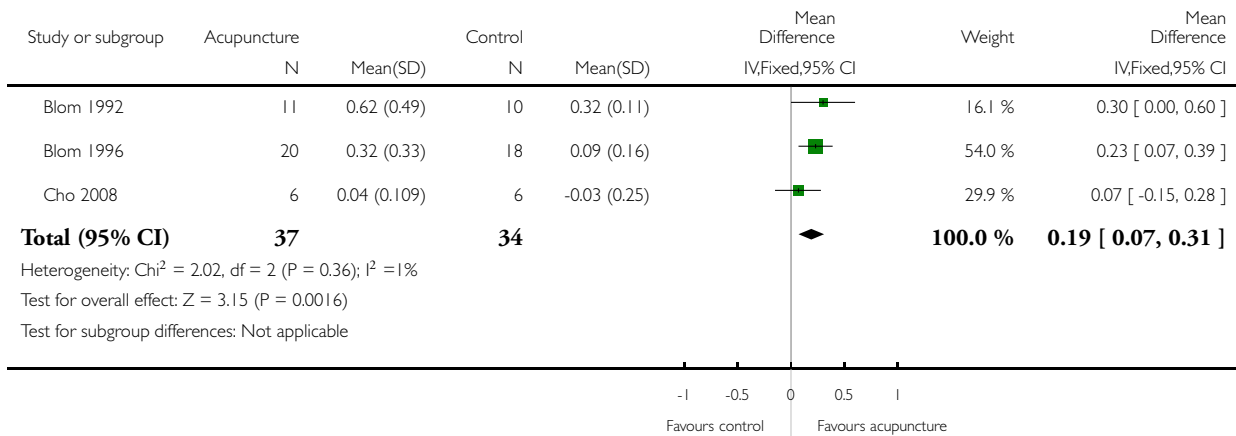
(3) 6 week treatment period

Analysis 1.3. Comparison 1 Acupuncture versus placebo, Outcome 3 Stimulated whole saliva (end of treatment).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 1 Acupuncture versus placebo

Outcome: 3 Stimulated whole saliva (end of treatment)

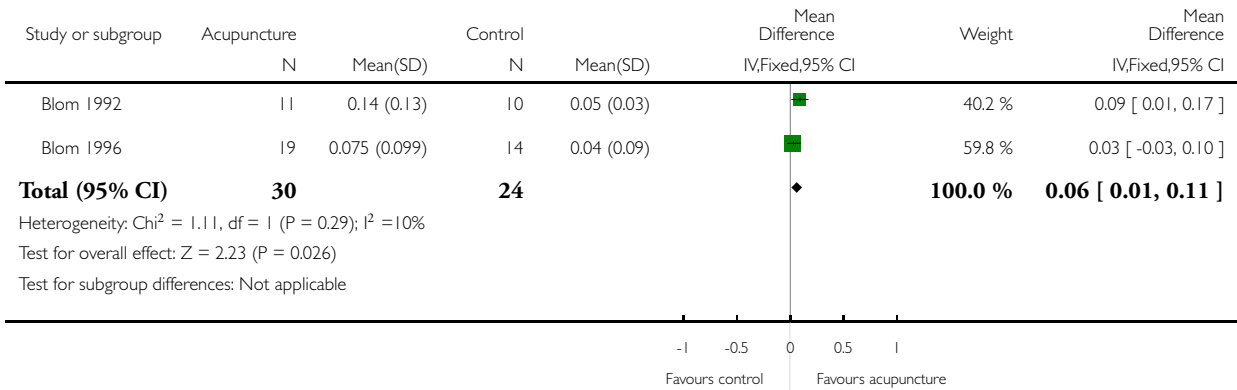


Analysis 1.4. Comparison 1 Acupuncture versus placebo, Outcome 4 Unstimulated whole saliva (12 months).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 1 Acupuncture versus placebo

Outcome: 4 Unstimulated whole saliva (12 months)

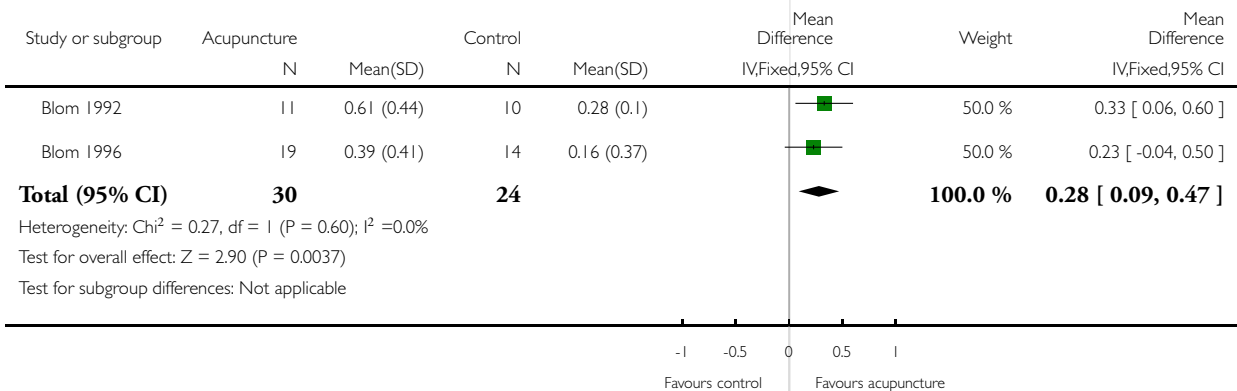


Analysis 1.5. Comparison 1 Acupuncture versus placebo, Outcome 5 Stimulated whole saliva (12 months).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 1 Acupuncture versus placebo

Outcome: 5 Stimulated whole saliva (12 months)

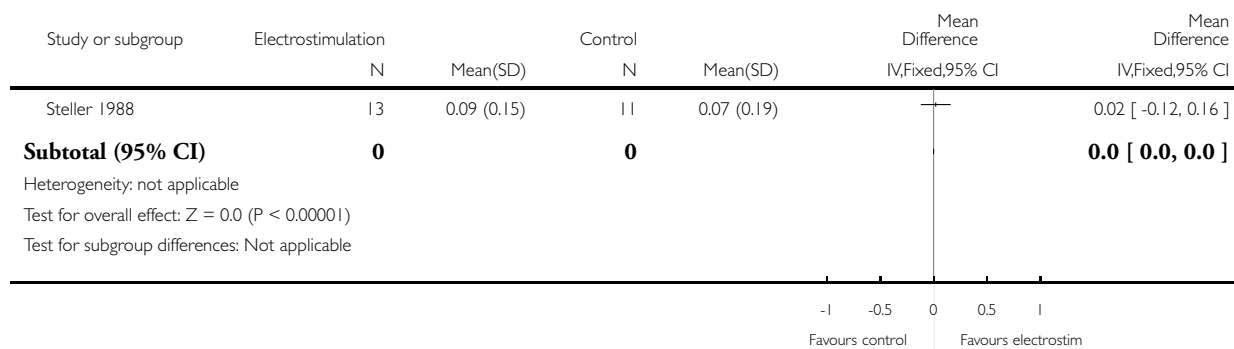


Analysis 2.1. Comparison 2 Electrical stimulation versus placebo, Outcome 1 Unstimulated whole saliva (end of treatment).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 2 Electrical stimulation versus placebo

Outcome: 1 Unstimulated whole saliva (end of treatment)

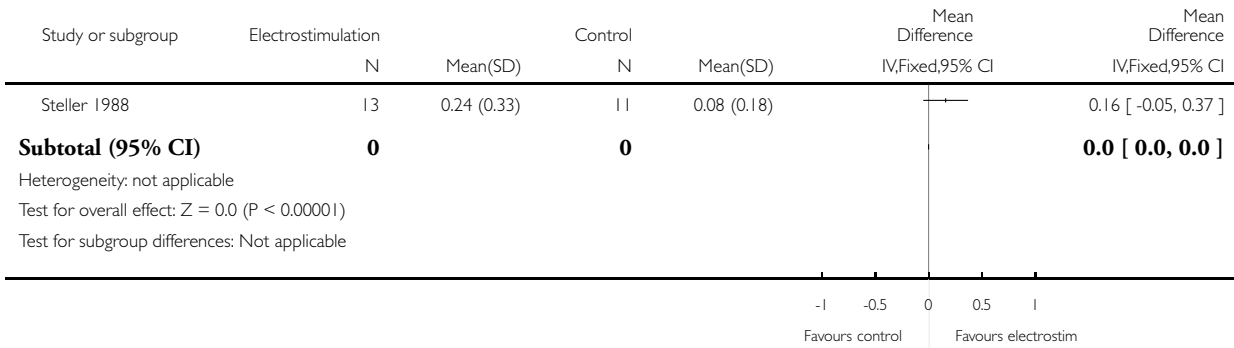


Analysis 2.2. Comparison 2 Electrical stimulation versus placebo, Outcome 2 Stimulated whole saliva (end of treatment).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 2 Electrical stimulation versus placebo

Outcome: 2 Stimulated whole saliva (end of treatment)

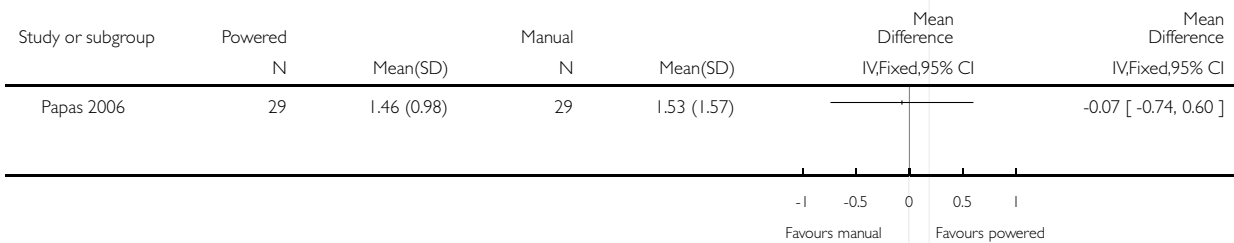


Analysis 3.1. Comparison 3 Powered versus manual toothbrush, Outcome 1 Unstimulated whole saliva (45 minutes after brushing).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 3 Powered versus manual toothbrush

Outcome: 1 Unstimulated whole saliva (45 minutes after brushing)

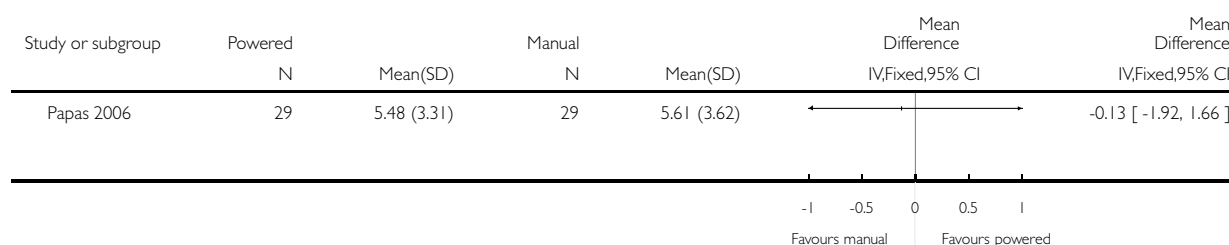


Analysis 3.2. Comparison 3 Powered versus manual toothbrush, Outcome 2 Stimulated whole saliva (5 minutes after brushing).

Review: Interventions for the management of dry mouth: non-pharmacological interventions

Comparison: 3 Powered versus manual toothbrush

Outcome: 2 Stimulated whole saliva (5 minutes after brushing)



ADDITIONAL TABLES

Table 1. Additional outcome data from included studies

Study ID	Outcome	Intervention group	N	Control group	N
List 1998 Acupuncture versus placebo	Mouth dryness 10-point VAS	Median 5.5 (Range 3.2 to 10)	10	Median 6.8 (Range 0 to 9.5)	11
	UWS (ml/15 minutes)	Median 0.0 (Range 0.0 to 0.6)	10	Median 0.0 (Range 0 to 0.2)	11
	SWS (ml/5 minutes)	Median 1.2 (Range 0.05 to 2.6)	10	Median 0.6 (Range 0.1 to 2.5)	11
Talal 1992 Electrostimulation versus placebo	SWS (ml/min)	Mean 0.385	40	Mean 0.196	37

SWS = stimulated whole saliva; UWS = unstimulated whole saliva; VAS = visual analogue scale

APPENDICES

Appendix I. Xerostomia Inventory

Individuals are asked to choose a response to the following 11 questions. Each response is assigned a score between 1 and 5 and the combined total score (a number between 11 and 55) is calculated, which represents the severity of the underlying xerostomia (score of 11 represents very mild xerostomia and 55 represents severe xerostomia) (Thomson 2005).

1. My mouth feels dry
2. I have difficulty in eating dry foods
3. I get up at night to drink
4. My mouth feels dry when eating a meal
5. I sip liquids to aid in swallowing food
6. I suck sweets or cough lollies to relieve dry mouth
7. I have difficulties swallowing certain foods
8. The skin of my face feels dry
9. My eyes feel dry
10. My lips feel dry
11. The inside of my nose feels dry

Response to each question	Score
Never	1
Hardly ever	2
Occasionally	3
Fairly often	4
Very often	5

Appendix 2. MEDLINE via OVID search strategy

1. Xerostomia/
2. xerostomia.mp.
3. (dry\$ adj2 (oral or mouth\$)).mp.
4. (asialia or "salivary gland hypofunction" or hyposalivat\$).mp.
5. (radioxerostomia or radio-xerostomia).mp.
6. or/1-5
7. Electrical Stimulation/
8. ((electric\$ adj3 stimulat\$) or neuroelectrostimulation or "masticatory stimulation").mp.
9. Lasers/
10. laser\$.mp.
11. "intra-oral device\$".mp.
12. Acupuncture/
13. acupuncture.mp.
14. Hypnosis/
15. (hypnosis or hypnotism or "autogenic train\$" or autosuggestion or auto-suggestion).mp.
16. or/7-15
17. 6 and 16

Appendix 3. Cochrane Oral Health Group's Trials Register search strategy

((xerostomia or "dry mouth*" or asialia or "salivary gland hypofunction" or hyposaliva*) AND (neuroelectrostimulation or "masticatory stimulation" or (electro and stimulat*) or "intra-oral device*" or acupuncture* or hypnosis or hypnotism or "autogenic* train*" or autosuggest* or auto-suggest* or laser*))

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor Xerostomia this term only

#2 xerostomia in All Text

#3 ((dry* in All Text near/2 oral in All Text) or (dry in All Text near/2 mouth* in All Text))

#4 (asialia in All Text or "salivary gland hypofunction" in All Text or hyposalivat* in All Text)

#5 (radioxerostomia in All Text or radio-xerostomia in All Text)

#6 (#1 or #2 or #3 or #4 or #5)

#7 MeSH descriptor Electric Stimulation this term only

#8 ((electric* in All Text near/3 stimulat* in All Text) or neuroelectrostimulation in All Text or "masticatory stimulation" in All Text)

#9 MeSH descriptor Lasers this term only

#10 laser* in All Text

#11 "intra-oral device*" in All Text

#12 MeSH descriptor Acupuncture this term only

#13 acupuncture in All Text

#14 MeSH descriptor hypnosis this term only

#15 (hypnosis in All Text or hypnotism in All Text or "autogenic train*" in All Text or autosuggestion in All Text or auto-suggestion in All Text)

#16 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)

#17 (#6 and #16)

Appendix 5. EMBASE via OVID search strategy

1. Xerostomia/

2. xerostomia.mp.

3. (dry\$ adj2 (oral or mouth\$)).mp.

4. (asialia or "salivary gland hypofunction" or hyposalivat\$).mp.

5. (radioxerostomia or radio-xerostomia).mp.

6. or/1-5

7. Electrostimulation/

8. ((electric\$ adj3 stimulat\$) or neuroelectrostimulation or "masticatory stimulation").mp.

9. Lasers/

10. laser\$.mp.

11. "intra-oral device\$".mp.

12. Acupuncture/

13. acupuncture.mp.

14. Hypnosis/

15. (hypnosis or hypnotism or "autogenic train\$" or autosuggestion or auto-suggestion).mp.

16. or/7-15

17. 6 and 16

The above subject search was linked to the following Filter for EMBASE via OVID:

1. random\$.ti,ab.

2. factorial\$.ti,ab.

3. (crossover\$ or cross over\$ or cross-over\$).ti,ab.

4. placebo\$.ti,ab.

5. (doubl\$ adj blind\$).ti,ab.

6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

Appendix 6. AMED via OVID search strategy

1. xerostomia.mp.
2. (dry\$ adj2 (oral or mouth\$)).mp.
3. (asialia or "salivary gland hypofunction" or hyposalivat\$).mp.
4. (radioxerostomia or radio-xerostomia).mp.
5. or/1-4
6. laser\$.mp.
7. ((electric\$ adj3 stimulat\$) or neuroelectrostimulation or "masticatory stimulation").mp.
8. "intra-oral device\$".mp.
9. acupuncture.mp.
10. (hypnosis or hypnotism or "autogenic train\$" or autosuggestion or auto-suggestion).mp.
11. or/6-10
12. 5 and 11

Appendix 7. CINAHL via EBSCO search strategy

- S1 MH Xerostomia
- S2 xerostomia
- S3 ((dry* N2 oral) or (dry* N2 mouth*))
- S4 (asialia or "salivary gland hypofunction" or hyposalivat*)
- S5 (radioxerostomia or radio-xerostomia)
- S6 S1 or S2 or S3 or S4 or S5
- S7 MH "Electric Stimulation"
- S8 ((electric* N3 stimulat*) or neuroelectrostimulation or "masticatory stimulation")
- S9 "intra-oral device*"
- S10 MH Acupuncture
- S11 acupuncture
- S12 MH Hypnosis
- S13 (hypnosis or hypnotism or "autogenic train*" or autosuggestion or auto-suggestion)
- S14 MH Lasers
- S15 laser*
- S16 S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15
- S17 S6 and S16

Appendix 8. CANCERLIT via PubMed search strategy

- #1 Search Xerostomia [mh:noexp]
- #2 Search xerostomia
- #3 Search (dry* and (oral or mouth*))
- #4 Search (asialia or “salivary gland hypofunction” or hyposalivat*)
- #5 Search radioxerostomia or radio-xerostomia
- #6 Search #1 or #2 or #3 or #4 or #5
- #7 Search Electrical Stimulation [mh:noexp]
- #8 Search ((electric* and stimulat*) or neuroelectrostimulation or “masticatory stimulation”)
- #9 Search “intra-oral device*”
- #10 Search Acupuncture [mh:noexp]
- #11 Search acupuncture
- #12 Search Hypnosis [mh:noexp]
- #13 Search hypnosis or hypnotism or “autogenic train*” or autosuggestion or auto-suggestion
- #14 Laser [mh:noexp]
- #15 laser*
- #16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
- #17 #6 and #16

Appendix 9. Search strategy for Clinicaltrials.gov

- 1. xerostomia and laser
- 2. xerostomia and acupuncture
- 3. xerostomia and electrostimulation
- 4. or/1-3

WHAT'S NEW

Last assessed as up-to-date: 16 April 2013.

Date	Event	Description
4 September 2013	Amended	Changes to external sources of support
4 September 2013	New citation required but conclusions have not changed	Authorship change

CONTRIBUTIONS OF AUTHORS

Gemma Bryan (GB), Sue Furness (SF) and Helen Worthington (HW) wrote the protocol. Roddy McMillan (RM) and Sarah Birchenough (SB) provided a clinical perspective on xerostomia and treatments for dry mouth.

The search results were screened against the inclusion criteria for this review by GB and SF. Full-text copies of papers appearing to meet the inclusion criteria were then evaluated by at least two authors (GB, SF or HW) independently, and any disagreements were resolved by discussion, following clinical input as required from RM.

Risk of bias assessment and data extraction were conducted by GB, SF and HW, with at least two authors independently evaluating each included study. Data entry and analysis were conducted by SF.

The text of the review was drafted by SF and reviewed by all the other authors.

DECLARATIONS OF INTEREST

Gemma Bryan: no interests to declare.

Sue Furness: no interests to declare.

Helen Worthington: no interests to declare.

Roddy McMillan: no interests to declare.

Sarah Birchenough: no interests to declare.

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Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was amended to clarify that participants in included studies must have dry mouth symptoms at baseline.