Mouthrinses for the treatment of halitosis (Review)

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[Intervention Review]

Mouthrinses for the treatment of halitosis

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ABSTRACT

Background

Halitosis is an unpleasant odour emanating from the oral cavity. Mouthwashes, which are commonly used for dealing with oral malodour, can be generally divided into those that neutralize and those that mask the odour.

Objectives

To investigate the effects of mouthrinses in controlling halitosis.

Search strategy

We searched the following databases: Cochrane Oral Health Group Trials Register (to August 2008); the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 3); MEDLINE (1950 to August 2008); EMBASE (1980 to August 2008); and CINAHL (1982 to August 2008). There were no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) comparing mouthrinses to placebo in adults over the age of 18 with halitosis and without significant other comorbidities or health conditions.

The primary outcomes considered were self expressed and organoleptic (human nose) assessments of halitosis, and the secondary outcomes included assessment of halitosis as measured by a halimeter, portable sulphide monitor or by gas chromatography coupled with flame-photometric detection.

Data collection and analysis

Two independent review authors screened and extracted information from, and independently assessed the risk of bias in the included trials.

Main results

Five RCTs, involving 293 participants who were randomised to mouthrinses or placebo, were included in this review.

In view of the clinical heterogeneity between the trials, pooling of the results and meta-analysis of the extracted data was not feasible and therefore only a descriptive summary of the results of the included trials is provided.

0.05% chlorhexidine + 0.05% cetylpyridinium chloride + 0.14% zinc lactate mouthrinse significantly reduced the mean change (standard deviation (SD)) of organoleptic scores from baseline compared to placebo (-1.13 (1.1) P < 0.005 versus -0.2 (0.7)) and also caused a more significant reduction in the mean change (SD) in peak level of volatile sulphur compounds (VSC) (-120 (92) parts per billion (ppb) versus 8 (145) ppb in placebo). The chlorhexidine cetylpyridinium chloride zinc lactate mouthrinse showed significantly more tongue (P < 0.001) and tooth (P < 0.002) staining compared to placebo.

However, in view of the incomplete reporting of results in three of the trials and the sole use of the halimeter for assessment of VSC levels as outcomes in two further trials, caution should be exercised in interpreting these results.

Authors' conclusions

Mouthrinses containing antibacterial agents such as chlorhexidine and cetylpyridinium chloride may play an important role in reducing the levels of halitosis-producing bacteria on the tongue, and chlorine dioxide and zinc containing mouthrinses can be effective in neutralisation of odouriferous sulphur compounds.

Well designed randomised controlled trials with a larger sample size, a longer intervention and follow-up period are still needed.

PLAIN LANGUAGE SUMMARY

Mouthrinses for the treatment of halitosis

Halitosis is an unpleasant odour that originates from the mouth and can be serious enough to cause personal embarrassment. Up to half of the population in the USA and between 50% and 60% of the population in France claim to suffer from bad breath. Accumulation of halitosis-causing bacteria and food residues at the back and in the furrows of the tongue which are then broken down into volatile sulphur compounds (VSC) and other volatile compounds are considered to be the major causes of bad breath.

A wide range of mouthrinses, which can neutralize or mask bad breath, are available over the counter.

This review, which included five trials (293 participants), found that there is some evidence that mouthrinses containing antibacterial agents such as chlorhexidine and cetylpyridinium chloride or those containing chlorine dioxide and zinc can to some extent reduce the unpleasant odour but the use of mouthrinses containing chlorhexidine resulted in noticeable but temporary staining of the tongue and teeth.

Future research should aim to provide reliable evidence for people to make informed decisions about whether these treatments are effective in reducing and eliminating halitosis.

BACKGROUND

Halitosis is an unpleasant odour that emanates from the oral cavity and can be serious enough to cause personal embarrassment. Mouthwashes are a generally well accepted and popular way of dealing with oral malodour.

Classification of halitosis

Although this classification has not been universally accepted by all experts in the field there is general agreement that halitosis can be categorised as genuine halitosis, pseudo-halitosis and halitophobia (Yaegaki 2000). Genuine halitosis has been further subclassified as physiologic halitosis in which there is no readily apparent disease

or pathological condition, or pathologic halitosis which occurs as a result of an infective process of the oral tissues. Pseudo-halitosis is a condition in which there is absence of halitosis but the patient believes that they have oral malodour. Halitophobia can occur when there is no physical or social evidence to suggest that halitosis is present and which can persist after treatment for either genuine halitosis or as pseudo-halitosis.

Aetiology and prevalence

The reliability of epidemiological data has been questioned, but the prevalence of halitosis has been reported to be as high as 50% (Yaegaki 2000). In a study in Japan 24% of patients complained of oral malodour (Miyazaki 1995) while in France it was reported that between 50% and 60% of the population suffer from chronic halitosis (Meningaud 1999).

It is now fairly widely accepted that halitosis originates from the oral cavity (Ayers 1998; Delanghe 1997). Accumulation of bacteria and food residues at the posterior part and in the furrows of the tongue (van Steenberghe 1997) is considered the major cause (Scully 1997). Interdental plaque and gingivitis may also play a contributory role, and although periodontal pockets may produce putrid odours, their contribution to oral malodour is still unclear (Morita 2001).

Halitosis-causing bacteria are the primary sources of volatile sulphur compounds (VSC); the chief components of which are hydrogen sulphide and methyl mercaptans (Kleinberg 1990; Tonzetich 1977). Volatile sulphur compounds and other additional odours such as indole, skatole, putrescine and cadaverine (Kleinberg 1995) are produced through the bacterial metabolic degradation of food debris, desquamated cells, saliva proteins, dental plaque and microbial putrefaction (Ratcliff 1999). The periodontal pocket also provides an ideal environment for VSC production thus explaining why patients with periodontal disease often complain of oral malodour (Morita 2001). The intensity of clinical bad breath has been shown to be significantly associated with the amount of intraoral VSC level and to be correlated directly with periodontal health status (Bosy 1994; Replogle 1996; Stamou 2005).

Treatment options

The success of any halitosis intervention appears to hinge on the reduction of VSC levels and other foul volatiles and consequently the majority focus on mechanical and chemical options.

Mechanical interventions (i.e. brushing, flossing and tongue scraping) aim to reduce the numbers of VSC-producing bacteria, residual food matter and cellular debris from the gingivae and tongue. In a recent review of the effectiveness of tongue scraping for treating halitosis, the review authors found that mechanical tongue cleaning with tongue scrapers appeared to have very limited and short acting benefits in controlling halitosis (Outhouse 2006).

The limitations of mechanical methods to effectively reach and remove VSC-producing bacteria from all oral ecological sites are acknowledged. The possibility that mouthrinses may be more effective in reaching the less accessible parts of the oral cavity, their greater social acceptance and ease of use has led to the development of a large number and range of over the counter mouthrinses (Ayers 1998; Richter 1996).

A number of mouthrinses contain antibacterial agents in addition to flavouring agents and have been generally categorised into those that neutralize and those that mask the odour. Components which neutralize can further be divided into those that affect the bacteria directly or the chemical compounds they produce and include chlorhexidine, phenol, Triclosan, chlorine dioxide, alcohol and metal ions, the most common of which is zinc (Carvalho 2004; Farrell 2006). Some of the odour-masking agents, consist of essential oils, which can also provide a competing and purely temporary smell that is capable of disguising the unfavourable malodour.

Organoleptic measurement by trained breath judges is considered to be the gold standard and the most reliable way of evaluating malodour (Rosenberg 1995), but this has been contested by studies showing that measurements with the halimeter appear to be more reproducible albeit possibly less reliable than organoleptic methods (Silwood 2001).

Measurement of VSC levels can be carried out by a variety of methods: organoleptic which are considered subjective by some investigators but are the ones of most relevance to patients (Tsunoda 1981), and the more complex gas chromatography techniques (Solis-Gaffar 1975). Portable computerized VSC monitors or halimeters are available, they are compact, easy to use and relatively inexpensive (Pedrazzi 2004) but have their limitations in that they have a high sensitivity for hydrogen sulphide, but low sensitivity for one of the other sources of malodour, methyl mercaptan (Rosenberg 1991).

Rationale for a systematic review

Controversy exists as to which is the most effective method of oral malodour control with the most popular being chemical which attempts to destroy odour-forming bacteria in addition to disguising the smell through the use of various odour-masking agents. The simplicity in use and social acceptability of mouthrinses appear to support their popularity but we are unaware of any other systematic reviews that have been conducted to assess their effectiveness in controlling halitosis.

OBJECTIVES

To investigate the effects of mouthrinses in controlling halitosis.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered in this review.

Types of participants

Only studies which had recruited adult participants over the age of 18 who presented with a clinical or self assessed diagnosis of halitosis, with no significant comorbidity or health condition that might lead to increased halitosis (e.g. diabetes) were considered. We excluded studies which had been conducted on participants with refractory and severe chronic periodontal diseases.

Types of interventions

The following interventions and controls were considered: mouthrinses compared to placebo, or against each other.
The active interventions or controls would have been administered over a minimum of 1 week and with no upper time limit.
We considered all mouthrinses which are either available over the counter or those which have been prescribed by a clinician for the treatment of halitosis. Studies which included single use mouthwashes were not considered for this review.

Types of outcome measures

Primary outcomes

For the primary outcomes in this review we considered self expressed (perceived) (Greenman 2004) and organoleptic (human nose) assessments of halitosis using any validated malodour intensity scale.

Secondary outcomes

We considered the assessment of halitosis as measured by a halimeter, portable sulphide monitor or gas chromatography coupled with flame-photometric detection.
Additional outcomes which were considered included determination of peak and steady-state volatile sulphur compound levels using a sulphide monitor, prior to and at several time-points after mouthrinsing.

Adverse events

We reported on any specific adverse effects related to any clinically diagnosed hypersensitivity or other reactions to the mouthrinses.

Search methods for identification of studies

Electronic searches

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 but revised appropriately for each database.
For the MEDLINE search, the subject search was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (updated February 2008) (Higgins 2008) and amended by the Cochrane Oral Health Group to include research design terms particular to oral health trials.

Databases searched

Cochrane Oral Health Group Trials Register (to August 2008)
Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 3)
MEDLINE (1950 to August 2008)
EMBASE (1980 to August 2008)
CINAHL (1982 to August 2008).
For the detailed search strategies applied to each of the databases *see* Appendix 1; Appendix 2; Appendix 3; Appendix 4 and Appendix 5.
Date of the last search: 11 August 2008.

Handsearches

We did not conduct handsearching of any journals but searched the reference lists of relevant articles and contacted investigators of included studies by electronic mail to ask for details of additional published and unpublished trials.

Language

There were no language restrictions on included studies and we arranged to translate any relevant non-English papers.

Data collection and analysis

Assessment of search results

Two review authors (Zbys Fedorowicz (ZF) and Trent Outhouse (TO)) independently and in duplicate assessed the abstracts of studies resulting from the searches. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, were obtained. The full text papers were assessed independently and in duplicate by two review authors and any disagreement on the eligibility of included studies was resolved through discussion and consensus or if necessary through a third party (Mona Nasser (MN)). All irrelevant records were excluded and details of the studies and the reasons for their exclusion were noted in the Characteristics of excluded studies table in RevMan 5 (RevMan 2008).

Data collection

Study details were entered into the Characteristics of included studies table. The review authors (ZF and Hamad Aljufairi (HA)) independently and in duplicate extracted data using a pre-determined form designed for this purpose. Any disagreements were resolved by consulting with a third review author (MN).
The following details were extracted.
(1) Trial methods:
(a) method of allocation
(b) masking of participants, trialists and outcomes
(c) exclusion of participants after randomisation and proportion of losses at follow up.
(2) Participants:
(a) country of origin
(b) sample size
(c) age
(d) sex
(e) inclusion and exclusion criteria.
(3) Intervention:
(a) type and dose
(b) duration and length of time in follow up.
(4) Control:
(a) type and dose
(b) duration and length of time in follow up.
(5) Outcomes:
(a) primary and secondary outcomes mentioned in the outcome measures section of this review.
Any sources of funding declared by the investigators were recorded.
The review authors used this information to help them assess heterogeneity and the external validity of the trials.

Assessment of methodological quality

Each review author then graded the selected studies and every study reporting a randomised controlled trial (RCT) was assessed following the criterion grading system described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (updated February 2008) (Higgins 2008). The gradings were compared and any inconsistencies between the review authors were discussed and resolved.
The following parameters of methodological quality were assessed and used to help us assess the risk of bias within the included studies.
(1) Sequence generation.
The review authors graded this criterion as adequate (A), unclear (B), inadequate (C). Adequate (A) included any one of the following methods of randomisation: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. Inadequate (C) methods of randomisation were those utilising any of the following: case record number, date of birth or alternate numbers.
(2) Allocation concealment.
Grading of this criterion was according to the following categories: adequate (A), unclear (B), inadequate (C). Adequate (A) methods of allocation concealment included either central randomisation or sequentially numbered sealed opaque envelopes. The review authors considered this criterion inadequate (C) if there was an open allocation sequence and the participants and trialists could foresee the upcoming assignment.
(3) Blinding.
We assessed blinding using the following criteria (detection and performance bias):
(a) blinding of participants (yes/no/unclear);
(b) blinding of researcher (yes/no/unclear);
(c) blinding of outcome assessment (yes/no/unclear).
(4) Handling of withdrawals and losses.
This criterion was graded as yes (A), unclear (B) and no (C) according to whether there was a clear description given of the difference between the two groups of losses to follow up (attrition bias).
Risk of bias in the included studies was categorized according to the following.
(A) Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
(B) Moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met.
(C) High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (Higgins 2008).

Data synthesis

Results of clinically and statistically homogeneous trials were to be pooled to provide estimates of the efficacy of the interventions only if the included studies had similar interventions received by similar participants. Extracted data were to be analysed by two review authors (ZF and Vinicius Pedrazzi (VP)) follow-

ing Cochrane Collaboration statistical guidelines and reported according to Cochrane Collaboration criteria. We intended presenting risk ratios for beneficial outcomes, and odds ratios for adverse effect outcomes. Number needed to treat to benefit (NNTB) and number needed to treat to harm (NNTH) were to be calculated for the whole pooled estimates.

For the synthesis and meta-analysis of any quantitative data we intended using the fixed-effect or random-effects models as appropriate. In the event of significant statistical heterogeneity between the studies the random-effects model, with studies grouped by action, was to be used.

If sufficient studies were included we had planned to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment, unclear or inadequate blinding of outcomes assessment and completeness of follow up. The paucity of included trials did not permit planned attempts to assess publication bias through the use of a funnel plot (Egger 1997).

Clinical homogeneity between the included trials was assessed by examining the characteristics of the participants, the types of intervention and the outcomes reported. However, in view of heterogeneity between the trials, pooling of the results and meta-analysis of the extracted data were not feasible and therefore this review provides a descriptive summary of the results of the included trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Finding the trials

The search strategy retrieved 555 (149 Cochrane Oral Health Group Trials Register, 140 CENTRAL, 151 MEDLINE, 97 EMBASE, 18 CINAHL) references, of which 273 remained after de-duplication. After examination of the titles and abstracts of these references all but 15, which included six citations (Borden 2001; Kozak 1994; Nachnani 1998; Ono 2002; Pitts 1981; Witt 1998) to papers and poster presentations from conference proceedings, were eliminated and excluded from further review. Full text copies of nine of the studies (Borden 2002; Carvalho 2004; Codipilly 2004; Kozlovsky 1996; Peruzzo 2007; Quirynen 2002; Rassameemasmaung 2007; van Steenberghe 2001; Winkel 2003) were obtained and subjected to further evaluation. The abstracts of the six papers from conference proceedings were also acquired for more detailed examination, and two (Pitts 1981; Witt 1998) of which were subsequently eliminated and the reasons for their exclusion noted (*see* Characteristics of excluded studies). The lack of trial details in the remaining four abstracts did not permit their further evaluation and these await a more complete assessment whilst attempts are made to contact the investigators.

Of the nine remaining studies, five (Borden 2002; Codipilly 2004; Kozlovsky 1996; Rassameemasmaung 2007; Winkel 2003) were parallel group and four (Carvalho 2004; Peruzzo 2007; Quirynen 2002; van Steenberghe 2001) were cross-over trials. Examination of the bibliographical references of their full text reports did not provide any further citations to potentially eligible studies.

Following discussion with the Cochrane Oral Health Group editorial team it was agreed that although two (Carvalho 2004; Peruzzo 2007) of the trials met most of our inclusion criteria, because the intervention periods did not match our stipulated criterion of a minimum of 1 week (*see* Criteria for considering studies for this review) these should be excluded.

A further two studies (Quirynen 2002; van Steenberghe 2001), investigated the effects of mouthrinses on morning breath odour in volunteers with a healthy periodontium and low organoleptic scores and volatile sulphur compounds (VSC) ratings. As routine oral hygiene procedures were prohibited during all of the experimental periods in these studies it could be inferred that halitosis had been induced, and consequently these were also excluded from this review.

Organoleptic scores of ≥ 3 which correspond to VSC levels in excess of 75 parts per billion (ppb) are generally accepted as diagnostic indicators of halitosis and were the minimum acceptable characteristics of participants enrolled in any of the studies to be considered eligible for inclusion in this review.

After discussion between the review authors any remaining uncertainties on the eligibility of any of the studies were resolved by consensus, and subsequently five trials involving 293 participants were included in this review.

Characteristics of the trial setting and investigators

One of the trials was conducted in Thailand (Rassameemasmaung 2007), one in Israel (Kozlovsky 1996), one was a multicentre trial in Holland and Spain (Winkel 2003) and a further two were conducted in the USA (Borden 2002; Codipilly 2004). Two trials were supported by government or scientific foundation funding and three acknowledged assistance from pharmaceutical or oral care products manufacturers.

The providers and assessors of the treatments, with the exception of one trial (Borden 2002) in which the researchers were from a consumer products testing division of a private research organisation, were mainly university research staff.

Characteristics of the participants

Only adults were recruited for these trials which excluded participants with significant periodontal disease, extensive dental caries

or chronic oral neglect in addition to those wearing any form of dentures. All but one of the trials (Winkel 2003) excluded smokers but participants in this trial were prohibited from smoking for 12 hours prior to any assessment. Participants were also excluded if they had taken systemic antibiotics before the study period, or had any systemic disease likely to have an influence on the outcome of the trial.

One study (Winkel 2003) only enrolled participants with a VSC score of > 170 ppb who had been referred to a halitosis clinic, and Borden 2002 screened out participants with organoleptic ratings of < 3 (scale 0 to 5). A further study (Codipilly 2004) screened potential participants, only enrolled those with mean halimeter assessed VSC levels of > 80 ppb and further grouped them into three categories based on ranges of VSC levels (i.e. 80 to 90 ppb, 91 to 135 ppb or > 135 ppb). In Rassameemasmaung 2007, the mean (standard deviation (SD)) VSC levels of participants at baseline were 248.35 (172.30) ppb in the intervention and 237.45 (114.15) ppb in the placebo groups.

Characteristics of the interventions

The interventions included herbal as well as several over the counter mouthrinses: two-phase oil and water/cetylpyridinium chloride; a chlorhexidine with cetylpyridinium chloride and zinc lactate formulation; an essential oil; and a chlorine dioxide based product. All of the mouthrinses were used twice daily with intervention periods ranging from 2 to 6 weeks and there were no restrictions on routine oral hygiene measures during the course of these studies. Assessment of participants' compliance and usage of the mouthrinses were reported in all of the studies with the exception of Kozlovsky 1996.

Treatment of halitosis:

- essential oils (Listerine ®); cetylpyridinium chloride + essential oils + chlorine dioxide + zinc (Breath Rx ®); chlorine dioxide + zinc (Oxygene ®) mouthrinses versus placebo (Borden 2002);
- zinc chloride + sodium chlorite (TriOral ®); zinc chloride minus sodium chlorite (Breath Rx ® containing cetylpyridinium chloride) mouthrinses versus control containing neither zinc chloride nor sodium chlorite (Codipilly 2004);
- two-phase oil-water (0.05% cetylpyridinium chloride) mouthrinse versus control referred to as "a mouthrinse which has been previously shown to be effective in reducing levels of odour related organisms" i.e. Listerine ® (Kozlovsky 1996);
- pericarp extract of Garcinia mangostana L mouthrinse versus placebo (Rassameemasmaung 2007);
- 0.05% chlorhexidine + 0.05% cetylpyridinium chloride + 0.14% zinc lactate mouthrinse versus placebo (Winkel 2003).

Characteristics of outcome measures

Treatment of halitosis

Three of the studies assessed halitosis organoleptically as well as by halimeter/portable sulphide monitor. The investigators in Rassameemasmaung 2007 relied solely on halimeter assessed VSC levels while Codipilly 2004 undertook indirect surrogate salivary organoleptic assessments in addition to recording halimeter scores. Organoleptic assessments of mouth odour (scale 0 to 5 with 5 as most severe) were conducted according to standard and internationally recognised procedures which involved two trained and independent organoleptic odour judges. Identical portable sulphide monitors, the Halimeter ® Interscan Corporation Chatsworth Ca, were used in all of the studies. In all of the studies, with the exception of one (Kozlovsky 1996) in which the assessments were conducted in the late afternoon (< 8 hours after rinsing), VSC levels and organoleptic scores were recorded in the morning after rinsing. In two of the studies (Borden 2002; Kozlovsky 1996) in which an alcohol-containing mouthrinse was used, the investigators ensured that halimeter recordings were conducted at least 2 hours after rinsing. Restrictions on eating, drinking and toothbrushing prior to assessment varied between trials and ranged from 2 hours (Rassameemasmaung 2007; Winkel 2003), to 12 hours (Codipilly 2004). Although the actual measurement periods varied between studies any data collected were used to calculate mean organoleptic ratings and halimeter scores, and if appropriate the percentage changes of VSC from baseline for each study. Peak VSC values were recorded in all of the studies but at differing times throughout the experimental periods. No self assessments of halitosis were reported but participants in one trial (Winkel 2003) completed post-treatment questionnaires. There were no outcomes reported in which gas chromatography coupled with flame-photometric detection was used to assess halitosis.

Adverse events

Two of the five studies took note of adverse events but only one reported any side effects.

For further details *see* the Characteristics of included studies table.

Risk of bias in included studies

Details of the quality assessment for each study are given in Additional Table 1.

Table 1. Quality assessment table

Study ID	Randomisation	Concealment	Blinding	Attrition
Borden 2002	unclear (B)	adequate (A)	(a) blinding of participants (yes) (b) blinding of researcher (yes) (c) blinding of outcome assessment (unclear)	unclear (B): missing participants: week 4 assessment: essential oils (Listerine) 4/25; cetylpyridinium chloride (Breath Rx) nil; placebo 1/25; chlorine dioxide-Zn (Oxygene) 4/22
Codipilly 2004	unclear (B)	unclear (B)	(a) blinding of participants (yes) (b) blinding of researcher (unclear) (c) blinding of outcome assessment (unclear)	no (C) 2 unaccounted for
Kozlovsky 1996	unclear (B)	unclear (B)	(a) blinding of participants (unclear) (b) blinding of researcher (unclear) (c) blinding of outcome assessment (unclear)	yes (A)
Rassameemasmaung 2007	adequate (A)	adequate (A)	(a) blinding of participants (yes) (b) blinding of researcher (yes) (c) blinding of outcome assessment (yes)	yes (A)
Winkel 2003	adequate (A)	unclear (B)	(a) blinding of participants (yes) (b) blinding of researcher (yes) (c) blinding of outcome assessment (yes)	yes (A)

The methods used to randomise participants were only clearly described in one study (Winkel 2003), and the method of randomisation in a further study (Rassameemasmaung 2007) was only confirmed after e-mail contact with the investigators.

Concealment of the allocation sequence was adequate (A) in only two of the five trials, unclear (B) for the remaining three but in no trials was it considered inadequate (C). Methods used to blind participants to the interventions were clearly described in four of the five trials. Blinding of outcomes assessment was reported in only two of the trials (Rassameemasmaung 2007; Winkel 2003).

There were several withdrawals in the included trials; four participants in Borden 2002 of which three with low organoleptic scores were subsequently excluded and one dropped out in the first week of the study. Additionally in this trial, with the exception of the cetylpyridinium chloride (Breath Rx ®) mouthrinse group, several participants failed to attend for the last assessment at week 4 (Additional Table 1). Two participants dropped out in one trial (Codipilly 2004) and no reasons were given. Attempts were made to contact several of the investigators by e-mail to seek clarification of missing trial details and only one reply was received (Rassameemasmaung 2007), which enabled a change in the assessment of concealed randomisation from unclear to adequate to be made for this study.

The validity of each study was assessed as at low, moderate or high risk of bias. Two of the studies were rated as at low risk of bias (A) (Rassameemasmaung 2007; Winkel 2003), and the remaining three studies (Borden 2002; Codipilly 2004; Kozlovsky 1996) as at moderate risk of bias (B). This assessment is based solely on the details as reported and will be amended if further information is

made available from the investigators in these three trials.

Effects of interventions

The electronic searches identified 555 titles and abstracts which provided 15 relevant full reports. After evaluation against the inclusion criteria for this review only five trials were considered eligible. In these trials 293 participants were randomised to mouthrinse or placebo and provided data for this review. There were 16 to 30 participants per treatment or control group in the trials. Three of the trials (Borden 2002; Kozlovsky 1996; Winkel 2003), which included 185 participants, provided data for the primary outcome of changes in organoleptic ratings in addition to one of the secondary outcomes of halimeter assessed volatile sulphur compounds (VSC) scores. One of the trials (Codipilly 2004) provided indirect surrogate salivary organoleptic scores as well as halimeter assessed VSC levels, and only halimeter assessed scores were reported in (Rassameemasmaung 2007). The only self assessed outcomes reported were related to any adverse effects experienced with the mouthrinses during the intervention periods.

Clinical heterogeneity between the studies in terms of the participants at baseline, the range in formulation of mouthrinses and controls used and the diversity in outcomes assessments did not permit any meaningful pooling of data. We were unable to obtain adequate data from one of the trials (Codipilly 2004) and therefore the outcomes data of only four of the trials are presented. (*See* additional tables Table 2; Table 3; Table 4; Table 5).

Table 2. (Borden 2002) Change in organoleptic & halimeter ratings: baseline to week 2 & 4

Mouthrinse (n = 95)	**Mean change 2 weeks**			**Mean change 4 weeks**		
(n = 22-25 per intervention group)	Organoleptic	Halimeter ppb	% reduction	Organoleptic	Halimeter ppb	% reduction
Listerine (essential oil)	0.02	-43.22	48.54	0	-68.90	77.39
Breath Rx (cetylpyridinium chloride)	-0.52	-66.84	67.65	-0.41	-77.87	78.82
Placebo	0.23	-39.86	45.25	0.16	-36.77	41.75
Oxygene (chlorine dioxide + zinc)	0	-47.63	64.97	0.06	-53.28	72.67

ppb = parts per billion

Table 3. (Kozlovsky 1996) Organoleptic ratings and peak VSC levels: week 0 to 6

Mouthrinse (n = 50)	**Baseline (Mean ± SD)**		**Week 1 (Mean ± SD)**		**Week 3 (Mean ± SD)**		**Week 6 (Mean ± SD)**	
(Organoleptic scale 0 to 5)	Organoleptic	Peak VSC ppb	Organoleptic	Peak VSC ppb	Organoleptic	Peak VSC ppb	Organoleptic	Peak VSC ppb
2-phase oil-water (0.05%	2.14 ± 0.88	94 ± 36	0.85 ± 0.83	58 ± 14	0.69 ± 0.69	52 ± 11	0.42 ± 0.55	56 ± 10

Table 3. (Kozlovsky 1996) Organoleptic ratings and peak VSC levels: week 0 to 6 (*Continued*)

cetylpyridinium chloride) n = 26								
Control: essential oils (Listerine) n = 24	2.40 ± 1.00	79 ± 40	1.38 ± 0.84	69 ± 33	1.29 ± 0.78	58 ± 16	0.71 ± 0.64	56 ± 16

ppb = parts per billion
SD = standard deviation
VSC = volatile sulphur compounds

Table 4. (Rassameemasmaung 2007) VSC levels at baseline & day 15

Mouthrinse	Baseline (Mean ± SD)	Day 15 (Mean ± SD)	Change from baseline
Herbal (Garcinia mangostana L) n = 30	248.35 ± 172.30	100.54 ± 69.37	59.68%
Placebo n = 30	237.45 ± 114.15	176.83 ± 123.6	25.74%

SD = standard deviation
VSC = volatile sulphur compounds

Table 5. (Winkel 2003) Organoleptic and VSC scores: baseline & week 2

Mouthrinse	Organoleptic score			Peak VSC ppb		
(Organoleptic scale 0 to 5)	Baseline	Day 14	Mean change (SD)	Baseline	Day 14	Mean change (SD)
0.05% chlorhexidine + 0.05% cetylpyridinium chloride + 0.14% zinc lactate n = 20	2.8 (0.5)	1.5 (1.0)	-1.3 (1.1) P < 0.005	292 (141)	172 (104)	-120 (92) P < 0.005
Placebo n = 20	2.7 (0.8)	2.5 (1.1)	-0.2 (0.7)	352 (161)	360 (254)	8 (145)

SD = standard deviation

Treatment of halitosis

Borden 2002

At the end of this 4-week trial the cetylpyridinium chloride + essential oils + chlorine dioxide + zinc (Breath Rx ®) mouthrinse produced a larger reduction in mean organoleptic score of -0.41 from baseline when compared with essential oils (Listerine ®) 0; chlorine dioxide + zinc (Oxygene ®) 0.06; and placebo 0.16 mouthrinses, results which were supported by a reduction in halimeter assessed mean VSC readings of -77.87, -68.90, -53.28 and -36.77 respectively (Additional Table 2).

Codipilly 2004

Unfortunately, the outcomes presented as graphplots in the 4-week comparison of zinc chloride plus sodium chlorite (TriOral ®); zinc chloride minus sodium chlorite (Breath Rx ® containing cetylpyridinium chloride) versus control mouthrinses did not permit the extraction of precise data from the report. In addition the organoleptic ratings reported were of indirect surrogate salivary organoleptic scores and not organoleptic breath scores and it was also not possible to make any accurate deductions from the absolute results which were presented as halimeter VSC ratings. The investigators did however report that VSC reductions from baseline at 2 weeks were: 55% ($P < 0.01$) in the zinc chloride plus sodium chlorite (TriOral ®), and 38% ($P < 0.05$) in the zinc chloride minus sodium chlorite (Breath Rx ® containing cetylpyridinium chloride) mouthrinses, and that at 4 weeks the TriOral ® mouthrinse achieved a VSC reduction of 60% ($P < 0.01$).

Kozlovsky 1996

In this 6-week comparison, the two-phase oil-water (0.05% cetylpyridinium chloride) mouthrinse achieved a reduction in mean baseline organoleptic scores of 80% (2.14 ± 0.88 to 0.42 ± 0.55) and peak VSC levels of < 40% versus Listerine ® with a reduction in organoleptic scores of 2.40 ± 1.00 to 0.71 ± 0.64 and a mean VSC reduction of 29% (Additional Table 3).

Rassameemasmaung 2007

The extract of Garcinia mangostana L mouthrinse reduced VSC levels by 59.68% from baseline 248.35 ± 172.30 to 100.54 ± 69.37 at 15 days ($P < 0.05$), compared with 25.74% (237.45 ± 114.15 to 176.83 ± 123.6, $P < 0.05$) in placebo (Additional Table 4).

Winkel 2003

In this 2-week comparison of 0.05% chlorhexidine + 0.05% cetylpyridinium chloride + 0.14% zinc lactate mouthrinse versus placebo, the mean change (standard deviation (SD)) of organoleptic scores from baseline was -1.13 (1.1) $P < 0.005$ with the chlorhexidine cetylpyridinium chloride zinc lactate mouthrinse versus -0.2 (0.7) in the placebo group. The mean change (SD) in peak level of VSC was -120 (92) parts per billion (ppb) in the mouthrinse group versus 8 (145) ppb in the placebo group (Additional Table 5).

Adverse events

There were 13 adverse events reported in one of the trials (Borden 2002) but the investigators concluded that none were likely to be related to product usage. In one trial (Winkel 2003) significantly more tongue ($P < 0.001$) and tooth ($P < 0.002$) staining was noted with the chlorhexidine cetylpyridinium chloride zinc lactate mouthrinse rather than placebo. There were no reported adverse effects in the herbal mouthrinse study (Rassameemasmaung 2007) or in either of the two other studies.

DISCUSSION

A range of over the counter mouthrinses for controlling mouth odour have been available for some time and although there have been a large number of studies conducted over the last 30 years, it was somewhat surprising to find so few high quality randomised controlled trials comparing the effectiveness of some of these mouthrinses.

Although this review provided some evidence for the comparative effectiveness of several different mouthrinses the results must be weighed carefully against the diversity in baseline characteristics of the participants included in these studies as well as the methods used to assess their outcomes. Clinical heterogeneity between the studies was illustrated by the inclusion of participants with low organoleptic and baseline volatile sulphur compounds (VSC) scores in addition to those with significantly higher scores who had been referred to halitosis clinics. Whilst the 'gold standard' for evaluation of mouth odour is organoleptic assessment, the comparative ease of use and convenience of the halimeter must be offset against its poor sensitivity to significant malodourants other than hydrogen sulphide and therefore its limitations in only being able to assess surrogate outcomes. All of the included trials conducted halimeter assessments of VSC levels, but because no additional organoleptic breath odour assessments were conducted in two of the trials (Codipilly 2004; Rassameemasmaung 2007), caution must be exercised in interpreting relevant outcomes in these trials and specifically in comparisons showing substantial reductions in VSC levels.

Chlorhexidine-containing mouthrinses have been shown to be successful in reducing antibacterial activity in supragingival plaque as well as the bacterial load on the tongue and thus are seen as potentially effective agents in controlling halitosis. The clinical effectiveness of a mouthrinse combining 0.05% chlorhexidine with cetylpyridinium chloride and zinc lactate was demonstrated in one of the included studies (Winkel 2003). In this mouthrinse, the antibacterial properties of chlorhexidine and cetylpyridinium chloride (i.e. in reducing the number of VSC-producing bacteria), are combined with the ability of zinc ions to transform volatile sulphur compounds into non-odiferous breakdown products. Unfortunately chlorhexidine, as was noted in this trial, also has some dis-

advantages principally with the increased tooth and tongue staining, bad taste and some reduction in taste sensation.

The effectiveness of a two-phase oil-water mouthrinse containing 0.05% cetylpyridinium chloride was illustrated by favourable reductions of organoleptically assessed mouth odour scores in three of the trials included in this systematic review. In one of the trials, as the principal constituent of Breath Rx, it was the only mouthrinse that reduced organoleptic scores at both 2 and 4 weeks. Organoleptic scores were significantly reduced in a further comparison of this mouthrinse with an essential oil mouthrinse at the end of a 6-week trial. A combination of this mouthrinse with chlorhexidine in a 2-week study of participants with moderate to severe halitosis also achieved a reduction of 50% in mean organoleptic scores.

Albeit the herbal extract of Garcinia mangostana has shown some effectiveness in reducing salivary mutans streptococci, this appears to be the first such study of this extract as a mouthrinse to combat halitosis, and whilst the lack of organoleptic mouth odour assessments may be an important oversight this study did nevertheless show significant reduction in halimeter assessed mean VSC levels and little or no reported adverse effects over a 2-week period.

Chlorine dioxide based mouthrinse formulations were examined in two trials, one mouthrinse (TriOral ®) delivered VSC reductions of up to 60% at 4 weeks which were said to be consistent with surrogate organoleptically assessed salivary odour scores, but conversely in the second trial daily use of a similar mouthrinse (Oxygene ®) did not appear to reduce organoleptic scores from baseline over a 4-week period although the reduction in halimeter assessed VSC levels was reportedly similar (72%).

AUTHORS' CONCLUSIONS

Implications for practice

The reduction of bacterial levels in sites such as the tongue that might serve as reservoirs for odour-producing bacteria is of paramount importance in controlling halitosis and whilst it was noted in this review that mouthrinses containing antibacterial agents such as chlorhexidine and cetylpyridinium chloride play an important role, the effectiveness of chlorine dioxide and zinc containing mouthrinses in neutralisation of odoriferous sulphur compounds should not be underestimated and there would therefore appear to be a place in the management strategy of halitosis for formulations which include and combine some of these constituents.

Implications for research

Although there are long standing concerns about the variability and somewhat subjective nature of organoleptic assessment it nevertheless remains the 'gold standard' principally because direct assessment of breath malodour is a reflection of what the breath recipient actually encounters and is therefore of the most relevance to the haltosis sufferer. The results from the included studies have reinforced the well held belief that discrepancies can occur between organoleptic and halimeter breath odour assessment and consequently investigators should ensure that organoleptic assessments are routinely conducted for this research question. In addition to including a larger sample, a longer intervention and follow-up period, further studies should also be well designed randomised controlled trials and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Borden 2002

Methods	Randomised, double blind, parallel group trial (4 weeks) in the USA. Random assignment (method not specified).
Participants	99 enrolled, 3 (organoleptic score < 2) disqualified, 1 withdrawal at week 1. n = 95 (29 males, 66 females age 19 to 65 years). Inclusion criteria: good general health, organoleptic score > 4 (0 to 5 scale), > 16 teeth. Exclusion criteria: smokers, systemic antibiotics, periodontal disease with pocket depth > 4 mm.
Interventions	Mouthrinses coded and identical packaging by study sponsor: Product: 1 (Listerine), 2 (Breath Rx-cetylpyridinium chloride), 3 placebo, 4 (Oxygene-chlorine dioxide + zinc). 22-25 participants/intervention group. Twice daily mouthrinsing for 4 weeks. Toothbrush use permitted.
Outcomes	At day 0. Week 2 & 4: baseline organoleptic ratings (0-5) and halimeter scores, followed by mouthrinse and organoleptic rating at 15 min, 2 h, 4 h and halimeter score at 2 h, 4 h. Some missing participants at week 4 assessment. Adverse events noted.
Notes	Consumer Products Testing Division, Hill Top Research, Inc., Cincinnati, Ohio. Study sponsor: Discus Dental Inc. manufacturer of rinse (2) (Breath Rx -cetylpyridinium chloride).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Codipilly 2004

Methods	Randomised, parallel group trial (4 weeks) in the USA. Random assignment (method not specified).
Participants	n = 48 (20 males, 28 females, age 21 to 69, mean 40 years). Inclusion criteria: good oral health, VSC > 80 ppb. Exclusion criteria: denture wearers, periodontitis. Divided into 3 groups: 80-90 ppb, 91-135 ppb, > 135 ppb.
Interventions	Mouthrinses as 2 separate components mixed prior to use and dispensed similarly. Group 1: control (no active ingredients) 20 ml. Group 2: zinc chloride minus sodium chlorite 20 ml. Group 3: zinc chloride plus sodium chlorite (TriOral) 20 ml. Twice daily mouthrinsing for 4 weeks. Routine oral hygiene measures permitted.

Codipilly 2004 (*Continued*)

Outcomes	At day 0. Week 2 & 4: halimeter scores. (Included indirect surrogate salivary organoleptic measurement).
Notes	Sponsored by Triumph Pharmaceuticals, Inc. the license holder Tri Oral technology.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kozlovsky 1996

Methods	Randomised parallel group trial (6 weeks) in Israel. Method of randomisation not specified.
Participants	n = 50 (13 males, 37 females, mean age 24 years). Exclusion criteria: smokers, denture wearers.
Interventions	2-phase oil-water (0.05% cetylpyridinium chloride) n = 26 versus essential oils (Listerine) n = 24. Twice daily mouthrinsing for 6 weeks. Routine oral hygiene measures permitted.
Outcomes	At day 0. Week 1, 3, 6: organoleptic ratings (0-5 scale) and halimeter assessed VSC scores.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rassameemasmaung 2007

Methods	2-part study including 2-week randomised parallel group trial in Thailand. Randomisation by numbers table.
Participants	n = 60 (12 male, 48 female, age 17 to 37 mean 26.15 years). Inclusion criteria: mild to moderate chronic gingivitis, > 80 ppb VSC. Exclusion criteria: smokers, denture wearers, recent systemic antibiotics.
Interventions	Participants and mouthrinse coded, independent allocation by minimisation according to VSC levels. Sequence concealed in envelope disclosed after data collection. Herbal mouthrinse pericarp extract of Garcinia mangostana L versus placebo mouthwash (unspecified) (15 ml each). Twice daily mouthrinse for 2 weeks.

Rassameemasmaung 2007 (*Continued*)

	Routine oral hygiene measures permitted.
Outcomes	At baseline & day 15: halimeter assessed VSC scores.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Winkel 2003

Methods	Randomised, double blind, parallel group placebo (2 weeks) controlled trial. Dual centre (Holland and Spain). Randomisation by computer generated list.
Participants	n = 40 (all referrals with diagnosis of halitosis; n = 20 Amsterdam, n = 20 Madrid). (21males,19 females, age 21 to 84 mean 43.8 years). 8/40 smokers. Inclusion criteria: halitosis, organoleptic rating > 1 (0-5 scale), halimeter score VSC > 170 ppb, pocket depth < 4 mm. Exclusion criteria: systemic disease, systemic antibiotics.
Interventions	15 ml 0.05% chlorhexidine + 0.05% cetylpyridinium chloride + 0.14% zinc lactate mouthrinse versus placebo. Twice daily mouthrinse for 2 weeks. Routine oral hygiene measures permitted.
Outcomes	At baseline, day 0 & 14: organoleptic rating (0-5 scale), halimeter VSC scores, tooth staining.
Notes	Supported by Dentaid SL Barcelona.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ppb = parts per billion
VSC = volatile sulphur compounds

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carvalho 2004	4-day intervention period. Intervention to test suppression of intentionally induced morning breath.
Peruzzo 2007	4-day intervention period. Intervention to test suppression of intentionally induced morning breath.
Pitts 1981	Single rinse mouthwash.
Quirynen 2002	Participants with healthy periodontium and not assessed as having halitosis.
van Steenberghe 2001	Participants with healthy periodontium and not assessed as having halitosis. Intervention to test suppression of morning breath.
Witt 1998	No control or placebo.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Cochrane Oral Health Group Trials Register search strategy

halitosis or halitose* or "oral malodour*" or "oral malodor*" or (breath AND odor*) or "bad breath" or (breath AND odour*) or (breath and smell*) or (breath AND offensive) or (mouth AND odor*) or (mouth AND odor*) or (mouth AND malodor*) or (mouth AND malodour*) or "volatile sulphur compound*" or "volatile sulfur compound*" or "fetor oris" or "foetor oris" or "fetor ex ore" or "foetor ex ore" or "foul breath" or "fetid breath" or "putrid breath"

Appendix 2. CENTRAL search strategy

#1. HALITOSIS/
#2. halitosis or halitose*
#3. "oral malodour*" or "oral malodor*"
#4. ((breath near/3 odor*) or "bad breath*" or (breath NEAR/4 odour*") or (breath NEAR/4 smell*) or (breath NEAR/4 offensive) or (mouth NEAR/4 odour*) or ("mouth odor*) or (mouth NEAR/4 malodour*) or (mouth NEAR/4 malodor*))
#5. ("volatile sulphur compound*" or "volatile sulfur compound*"
#6. "fetor oris" or "foetor oris" or "fetor ex ore" or "foetor ex ore" or "foul breath" or "fetid breath" or "putrid breath"
#7 OR/1-6

Appendix 3. MEDLINE (OVID) search strategy

1. Halitosis/
2. (halitosis or halitose$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. ((oral adj malodour$) or (oral adj malodor$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. ((breath adj3 odor$) or (bad adj breath) or (breath adj4 odour$) or (breath adj4 smell$) or (breath adj4 offensive) or (mouth adj4 odour$) or (mouth adj odor$) or (mouth adj4 malodour$) or (mouth adj4 malodor$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. (volatile sulphur compound$ or volatile sulfur compound$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. (fetor oris or foetor oris or fetor ex ore or foetor ex ore or foul breath or fetid breath or putrid breath).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. or/1-6
Cochrane/Oral Health Group search filter for MEDLINE via OVID:
1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE BLIND METHOD.sh.
7. CROSS-OVER STUDIES.sh.
8. MULTICENTER STUDIES.sh.
9. ("multicentre stud$" or "multicentre trial$" or "multicenter stud$" or "multicenter trial$" or "multi-centre stud$" or "multi-centre trial$" or "multi-center stud$" or "multi-center trial$" or "multi-site trial$" or "multi-site stud$").ti,ab.
10. MULTICENTER STUDY.pt.
11. latin square.ti,ab.

12. (crossover or cross-over).ti,ab.
13. (split adj (mouth or plot)).ti,ab.
14. or/1-13
15. (ANIMALS not HUMANS).sh.
16. 14 not 15
17. CLINICAL TRIAL.pt.
18. exp CLINICAL TRIALS/
19. (clin$ adj25 trial$).ti,ab.
20. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
21. PLACEBOS.sh.
22. placebo$.ti,ab.
23. random$.ti,ab.
24. RESEARCH DESIGN.sh.
25. or/17-24
26. 25 not 15
27. 16 or 26

Appendix 4. EMBASE (OVID) search strategy

1. Halitosis/
2. (halitosis or halitose$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. ((oral adj malodour$) or (oral adj malodor$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((breath adj3 odor$) or (bad adj breath) or (breath adj4 odour$) or (breath adj4 smell$) or (breath adj4 offensive) or (mouth adj4 odour$) or (mouth adj odor$) or (mouth adj4 malodour$) or (mouth adj4 malodor$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
5. (volatile sulphur compound$ or volatile sulfur compound$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (fetor oris or foetor oris or fetor ex ore or foetor ex ore or foul breath or fetid breath or putrid breath).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. or/1-6

EMBASE filter:

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 5. CINAHL (OVID) search strategy

1. Halitosis/
2. (halitosis or halitose$).mp. [mp=title, subject heading word, abstract, instrumentation]
3. ((oral adj malodour$) or (oral adj malodor$)).mp. [mp=title, subject heading word, abstract, instrumentation]
4. ((breath adj3 odor$) or (bad adj breath) or (breath adj4 odour$) or (breath adj4 smell$) or (breath adj4 offensive) or (mouth adj4 odour$) or (mouth adj odor$) or (mouth adj4 malodour$) or (mouth adj4 malodor$)).mp. [mp=title, subject heading word, abstract, instrumentation]
5. (volatile sulphur compound$ or volatile sulfur compound$).mp. [mp=title, subject heading word, abstract, instrumentation]
6. (fetor oris or foetor oris or fetor ex ore or foetor ex ore or foul breath or fetid breath or putrid breath).mp. [mp=title, subject heading word, abstract, instrumentation]

CINAHL filter:

1. Random Assignment/
2. single-blind studies/
3. Double-Blind Studies/
4. Triple-Blind Studies/
5. Crossover Design/
6. Factorial Design/
7. (multicentre study or multicenter study or multi-centre study or multi-center study).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
8. random$.ti,ab.
9. latin square.ti,ab.
10. cross-over.mp. or crossover.ti,ab. [mp=title, cinahl subject headings, abstract, instrumentation]
11. Placebos/
12. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
13. placebo$.mp. [mp=title, cinahl subject headings, abstract, instrumentation]
14. Clinical Trials/
15. (clin$ adj25 trial$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
16. or/1-15

WHAT'S NEW

Last assessed as up-to-date: 10 August 2008.

Date	Event	Description
11 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Zbys Fedorowicz (ZF), Trent Outhouse (TO), Hamad Aljufairi (HA) and Mona Nasser (MN) were responsible for: organising the retrieval of papers, writing to authors of papers for additional information, screening search results, screening retrieved papers against inclusion criteria, appraising the quality of papers, data collection for the review, extracting data from papers, obtaining and screening data on unpublished studies.

ZF and HA entered the data into RevMan.

Vinicius Pedrazzi (VP) was responsible for analysis and interpretation of the data.

All review authors contributed to writing of the review.

ZF, TO and MN were responsible for: designing and co-ordinating the review, data management for the review.

TO and ZF conceived the idea for the review and are the guarantors for the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Halitosis [*drug therapy]; Mouthwashes [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans