Interventions for the treatment of Frey's syndrome (Protocol)

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[Intervention Protocol]

Interventions for the treatment of Frey's syndrome

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of different methods for the treatment of Frey's syndrome.

BACKGROUND

Description of the condition

Frey's syndrome, or gustatory sweating, is named after Łucja Frey, who first described the syndrome as 'auriculotemporal syndrome' in 1923 (Frey 1923). It is a sequela of parotidectomy, submaxillary gland surgery, radical neck dissection, inflammatory infection and traumatic injury in the parotid region, and is probably caused by the aberrant regrowth of facial autonomic nerve fibres (Bonanno 1992; O'Neill 2008). The clinical symptoms of Frey's syndrome include sweating, flushing and warming over the preauricular and temporal areas after gustatory stimulus (de Bree 2007). This unpleasant phenomenon may occur three to six months or even 14 years after surgery on the parotid gland (Bakke 2006; Wenzel 2004). The incidence of Frey's syndrome varies distinctively (O'Neill 2008). A survey has reported patients' self reported incidence of Frey's syndrome to be 23%, while a positive Minor's iodine starch test was observed in 62% of cases (Neumann 2011). In a questionnaire evaluation of patients who had undergone any type of parotidectomy for benign salivary diseases, Frey's syndrome was identified as the most serious self perceived sequela and was of greatest concern, resulting in discomfort which worsened with time, even at more than five years postoperatively (Baek 2009).

Description of the intervention

Several treatments have been proposed for this syndrome. Current options include topical application of anticholinergics, antiperspirant and intradermal injections of botulinum toxin (Clayman 2006). As reported, 2% diphemanil methylsulfate (an anticholinergic agent) topically applied showed partial relief in 33.3% (5/15) of patients and total relief in 40% (6/15) after a 10-day period, with the side effect of mouth dryness (Laccourreye 1990). Black et al reported that topical application of aluminium chloride hexahydrate, with intervals varying from one to 50 days, had successfully controlled gustatory sweating in nine patients (Black 1990). Another study suggested that the subjective effect was excellent (no sweating after eating hot spicy food) in 10 patients

(77%) and fair (clearly reduced sweating) in three patients (23%) after the application of topical glycopyrrolate as a treatment for Frey's syndrome, with a mildly dry mouth and a sore throat in two patients (2% glycopyrrolate) and a light headache in one patient (1.5% glycopyrrolate) (Kim 2003).

Botulinum toxin has been recognised as the first-line treatment for Frey's syndrome. Patients injected intradermally with botulinum toxin type A showed improvement after four to seven days (Pomprasit 2007), flushing regressed (Tugnoli 2002) and gustatory sweating decreased (Beerens 2002). Botulinum toxin A could also significantly improve patients' functional quality of life, according to the results of a questionnaire survey (Hartl 2008). However, the effect of the intracutaneous injection of botulinum toxin type A in patients with gustatory sweating does regress, and the one, two and three-year actuarial estimate for symptomatic recurrent gustatory sweating was 27%, 63% and 92%, respectively (Laccourreye 1999). However, recurrence of Frey's syndrome could still be amenable to reinjection with botulinum toxin type A, and investigators have shown that repeated injections are safe, decrease the size of the affected area and increase the duration of the recurrence-free period (Beerens 2002; de Bree 2009; Laskawi 1998).

Botulinum toxin type A is the most commonly used treatment for Frey's syndrome but some patients may become resistant, while botulinum toxin type B has been shown effective and can be considered as a potential alternative to botulinum toxin type A when treatment with type A fails (Cantarella 2010). However, dry mouth is reported as a side effect when applying botulinum injections (Martos 2008)

How the intervention might work

It is well accepted that Frey's syndrome is the result of aberrant regeneration of cut postganglionic parasympathetic fibres between the otic ganglion and subcutaneous vessels when injury to branches of auriculotemporal nerve occurs (de Bree 2007). Due to this abnormal communication, the skin glands and vessels are stimulated when eating and masticating (Singh 2011). In response to such nerve impulses, acetylcholine (ACh) is released from the presynaptic nerve endings to postsynaptic cholinergic receptors, which results in sweating and flushing. As sweating is controlled by sympathetic cholinergic pathways, treatments have traditionally involved anticholinergics (Watkins 1973). Topical glycopyrrolate, an antimuscarinic agent, does not cross the blood-brain barrier and penetrates biological membranes slowly, and thus has few side effects compared to systemic use (Hays 1978; May 1989). Topical application of aluminium chloride hexahydrate directly acts on the sweat glands. Aluminium salt blocks the distal acrosyringium, which leads to functional and structural degeneration of the eccrine acini. However, it may also damage the sweat duct epithelium and cause inflammation (Hölzle 1984). Botulinum toxin is a polypeptide produced by the bacterium *Clostridium botulinum*. Seven serological types exist, classified from A to G, with similar structure and distinct antigenic specificity and therapeutic profiles. Injection of botulinum toxin has the effect of an anticholinergic (Khoo 2006), blocks acetylcholine release at the neuromuscular junction of striated muscles and hence produces chemical denervation and paralysis of the muscles, which is effective both for striated muscle and eccrine glands (Kreyden 2004; Tugnoli 2002).

Why it is important to do this review

Although the different treatments for Frey's syndrome mentioned above are understood to be effective, they all have drawbacks. Adverse effects occur and currently recurrence of the phenomenon is unavoidable. Dosage of agents has been a focus of attention (Bakke 2006; Guntinas-Lichius 2002). At the same time, outcomes such as the duration of freedom from symptoms, degree of clinical phenomenon regression, incidence of recurrence and seriousness of the crises should be carefully discussed. There is still a lot of work that needs to be done to determine the best evidence for the treatment of Frey's syndrome. Such efforts would help to improve quality of life for patients suffered from gustatory sweating.

OBJECTIVES

To assess the efficacy and safety of different methods for the treatment of Frey's syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Participants diagnosed with Frey's syndrome according to clinical criteria (such as presentation with typical symptoms and proven by Minor's starch-iodine test, iodine-sublimated paper histogram method, blotting paper technique).

Types of interventions

The intervention group should receive any possibly effective intervention (such as antiperspirants, anticholinergic agents, alcohol injections, tympanic neurectomy, etc.) aiming to treat Frey's

syndrome, either alone or combined with other active treatment. The comparison (control group) should receive no treatment (observation) or an alternative method of treating Frey's syndrome, with or without a second active treatment.

Types of outcome measures

The primary outcomes are defined as those that we will use to draw the main conclusion and we will use the secondary outcomes to support the primary outcomes in our conclusions.

Primary outcomes

- Success rate assessed clinically (Minor's starch-iodine test, the iodine-sublimated paper histogram method, blotting paper technique etc.)
- Adverse events

Secondary outcomes

- Success rate assessed by participants (disappearance or improvement of symptoms)

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

We will identify published, unpublished and ongoing studies by searching the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; ISRCTN; ClinicalTrials.gov; ICTRP; OpenSigle; Sciencepaper Online; CNKI; CBM; VIP and Google

We will model subject strategies for databases on the search strategy designed for CENTRAL (Appendix 1). Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. We will search PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register. We will handsearch the following journals: *Head and Neck* (1978 to present); *Otolaryngology - Head and Neck Surgery* (2006 to present); *Chinese Journal of Stomatology* (2000 to present); *West China Journal of Stomatology* (2000 to present); *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology* (1995 to present); *Journal of Dental Research* (1970 to present) and *International Journal of Oral Science* (2009 to present).

Reference lists and contacts

We will screen the references of the included articles for studies. We will contact authors and experts in the field to identify unpublished RCTs.

Data collection and analysis

Two review authors (Chunjie Li and Qi Zhang) will carry out the selection of studies, data extraction and management, and assessment of risk of bias in the included studies. We will resolve any disagreement by discussion or by sending to an arbiter (Longjiang Li).

Selection of studies

We will use two steps in the selection of studies. First, we will screen titles and abstracts of the search results in order to find any studies that need further assessment. We will retrieve the full text of those possibly eligible studies and assess them to judge whether they meet the inclusion criteria. We will classify studies into three categories: included, excluded and awaiting classification (if one study is considered as unclear in some specific items of the inclusion criteria, we will judge it to be a study awaiting classification). For studies awaiting classification, we will send letters to the original authors to get any useful information for judgement. We will also classify these studies into the previous three categories (if there is no reply or unclear reply, we will judge the studies as awaiting classification). We will record reasons for the exclusion of full texts.

Data extraction and management

For data extraction and management, we will extract and record all the following data using a data extraction form which we will pilot test using three included studies before the formal data extraction.

- **Source**: study ID; review author ID; citation and contact details.
- **Eligibility**: reasons for inclusion or exclusion.
- **Methods of the study**: centres and their location; study duration; inclusion and exclusion criteria for participants; study design, sequence generation, allocation concealment, blinding and statistical methods.
- **Participants**: total number; age and sex; characteristics of participants in each group, etc.
- **Interventions**: number of intervention groups; intervention details of the treatment; control treatment and other active treatment; time, frequency, dose and usage if drugs administered.
- **Outcomes**: definition of outcome measures and units of the measurements; time points of measurement; measurement methods; sample size calculation; number of participants allocated to each group; number of lost follow-up and the reasons; detailed summary data for each group.
- **Miscellaneous**: funding; key conclusions of each article; correspondence required and miscellaneous comments from review authors.

Assessment of risk of bias in included studies

CJ Li and Q Zhang will carry out assessment of the risk of bias of the included trials independently with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective reporting (reporting bias);
7. other bias which is not covered by the first six such as confounding bias, co-intervention and contamination.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.1 (RevMan 2011), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.
We will further classify the risk of bias in the included studies as 'high risk of bias', 'unclear risk of bias' or 'low risk of bias' according to the criteria presented in Table 1.
The 'Risk of bias' assessment of the outcome will be based on the key domains. For each outcome, there will be a series of key domains derived from the seven domains listed above. The key domains for success rate assessed by clinical assessment are domain 1, 2, 4, 5, 6 and 7; the key domains for adverse events and success rate assessed by participants are domains 1, 2, 3, 5, 6 and 7. We will also classify the risk of bias of the outcome into 'high risk of bias', 'unclear risk of bias' or 'low risk of bias' according to the criteria presented in Table 1.

Measures of treatment effect

The measures of treatment effect differ according to data type and the outcome variables. We will treat success rate (either assessed clinically or by the participants) as dichotomous data. Adverse events can be ordinal or dichotomous data. However, ordinal data can also be treated as dichotomous data. We will express all the dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs).
There will be no continuous data, considering the nature of the outcomes.

Unit of analysis issues

The unit of analysis will be participants. It is not possible that cross-over or cluster-randomised controlled trials could be designed to study treatments for Frey's syndrome.

Studies with multiple treatment groups

As each meta-analysis addresses only a single pair-wise comparison, we will consider two approaches. For those trials with multiple treatment groups, we will first try to combine groups to create a single pair-wise comparison (groups will be combined in one outcome and they may not be combined in another outcome), or if this fails we will select the most related pair of interventions.

Dealing with missing data

We will try to obtain any missing data from the original study authors. If we receive no replies regarding missing data or replies are unclear, we will try to calculate the missing data. If these methods fail, we will only describe the outcomes qualitatively in this systematic review.

Assessment of heterogeneity

Clinical heterogeneity may be due to different participant types (participants with different kinds of surgery or trauma, etc), or different interventions and comparisons.
For statistical heterogeneity, we will use the I^2 statistic to determine the range as follows:

- 0% to 40% slight heterogeneity
- 30% to 60% moderate heterogeneity
- 50% to 90% substantial heterogeneity
- 75% to 100% considerable heterogeneity

If there is considerable heterogeneity in one outcome, we will not carry out the meta-analysis.

Assessment of reporting biases

We will try to assess any reporting bias for each outcome if there are more than 10 studies per outcome. We will draw funnel plots initially. Asymmetric funnel plots will indicate that there might be reporting bias. We will then conduct statistical analysis. We will test the asymmetry of the funnel plot using the methods introduced by Begg 1994 (using STATA 11.0) at the level of α = 0.10.

Data synthesis

We will consider two types of analysis model. We will adopt a random-effects model if the I^2 statistic > 50%, P $\leq$ 0.10. If not, we will choose a fixed-effect model. The exact statistical methods for the meta-analysis will be the Mantel-Haenszel (M-H) method for dichotomous data and the inverse variance (IV) method for continuous data. Statistical significance for the hypothesis test will be set at P < 0.05 (two-tailed z tests).

Subgroup analysis and investigation of heterogeneity

We will adopt subgroup analysis according to the different interventions and types of participants. Such methods are mainly adopted to reduce the clinical heterogeneity in each outcome.

Sensitivity analysis

We will carry out sensitivity analysis in order to test the stability of each outcome. There are two ways to conduct the sensitivity analysis:

- including high-quality studies only; and
- intention-to-treat (ITT) analysis ('worst-case scenario' analysis versus 'best-case scenario' analysis).

We will report the results of sensitivity analysis and analyse the stability of the outcome.

'Summary of findings' tables

To provide suggestions and recommendations for clinicians, we will assess the quality of the body of evidence. The quality of the combined data may be decreased for several reasons including study limitations (risk of bias at study level), directness of the evidence, heterogeneity, precision of effect estimates and risk of publication bias (see Assessment of reporting biases). To achieve this, we will adopt the GRADE system for evaluating the quality of the evidence (Atkins 2004; Guyatt 2008; Handbook 2011) using the software GRADEprofiler. We will classify the quality of the body of evidence into four categories: high, moderate, low and very low. The strength of recommendations will derive from the evidence quality and will be considered as strong and weak (Guyatt 2008). We will produce a 'Summary of findings' table for each of the primary outcomes of this review.

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REFERENCES

Additional references

Atkins 2004
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al.Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490–4.

Baek 2009
Baek CH, Chung MK, Jeong HS, Son YI, Jung SC, Jeon HK, et al.Questionnaire evaluation of sequelae over 5 years after parotidectomy for benign diseases. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 2009;**62**(5):633–8.

Bakke 2006
Bakke M, Max Thorsen N, Bardow A, Dalager T, Eckhart Thomsen C, Regeur L. Treatment of gustatory sweating with low-dose botulinum toxin A: a case report. *Acta Odontologica Scandinavica* 2006;**64**(3):129–33.

Beerens 2002
Beerens AJ, Snow GB. Botulinum toxin A in the treatment of patients with Frey syndrome. *British Journal of Surgery* 2002;**89**(1):116–9.

Begg 1994
Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**(4):1088–101.

Black 1990
Black MJ, Gunn A. The management of Frey's syndrome with aluminium chloride hexahydrate antiperspirant. *Annals of the Royal College of Surgeons of England* 1990;**72**(1):49–52.

Bonanno 1992
Bonanno PC, Casson PR. Frey's syndrome: a preventable phenomenon. *Plastic and Reconstructive Surgery* 1992;**89**(3):452-6; discussion 457-8.

Cantarella 2010
Cantarella G, Berlusconi A, Mele V, Cogiamanian F, Barbieri S. Treatment of Frey's syndrome with botulinum toxin type B. *Otolaryngology - Head and Neck Surgery* 2010; **143**(2):214–8.

Clayman 2006
Clayman MA, Clayman SM, Seagle MB. A review of the surgical and medical treatment of Frey syndrome. *Annals of Plastic Surgery* 2006;**57**(5):581–4.

de Bree 2007
de Bree R, van der Waal I, Leemans CR. Management of Frey syndrome. *Head and Neck* 2007;**29**(8):773–8.

de Bree 2009
de Bree R, Duyndam JE, Kuik DJ, Leemans CR. Repeated botulinum toxin type A injections to treat patients with Frey syndrome. *Archives of Otolaryngology - Head and Neck Surgery* 2009;**135**(3):287–90.

Frey 1923
Frey L. Le syndrome du nerf auriculo-temporal. *Revue Neurologique* 1923;**2**:92–104.

Guntinas-Lichius 2002
Guntinas-Lichius O. Increased botulinum toxin type A dosage is more effective in patients with Frey's syndrome. *Laryngoscope* 2002;**112**(4):746–9.

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6.

Handbook 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hartl 2008
Hartl DM, Julieron M, LeRidant AM, Janot F, Marandas P, Travagli JP. Botulinum toxin A for quality of life improvement in post-parotidectomy gustatory sweating (Frey's syndrome) . *Journal of Laryngology and Otology* 2008; **122**(10):1100–4.

Hays 1978
Hays LL. The Frey syndrome: a review and double blind evaluation of the topical use of a new anti-cholinergic agent. *Laryngoscope* 1978;**88**(11):1796–824.

Hölzle 1984
Hölzle E, Braun-Falco O. Structural changes in axillary eccrine glands following long-term treatment with aluminium chloride hexahydrate solution. *British Journal of Dermatology* 1984;**110**(4):399–403.

Khoo 2006
Khoo SG, Keogh IJ, Timon C. The use of botulinum toxin in Frey's syndrome. *Irish Medical Journal* 2006;**99**(5): 136–7.

Kim 2003
Kim WO, Kil HK, Yoon DM, Cho MJ. Treatment of compensatory gustatory hyperhidrosis with topical glycopyrrolate. *Yonsei Medical Journal* 2003;**44**(4):579–82.

Kreyden 2004
Kreyden OP, Scheidegger EP. Anatomy of the sweat glands, pharmacology of botulinum toxin, and distinctive syndromes associated with hyperhidrosis. *Clinics in Dermatology* 2004;**22**(1):40–4.

Laccourreye 1990
Laccourreye O, Bonan B, Brasnu D, Laccourreye H. Treatment of Frey's syndrome with topical 2% diphemanil methylsulfate (Prantal): a double-blind evaluation of 15 patients. *Laryngoscope* 1990;**100**(6):651–3.

Laccourreye 1999
Laccourreye O, Akl E, Gutierrez-Fonseca R, Garcia D, Brasnu D, Bonan B. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin type A: incidence, management, and outcome. *Archives of Otolaryngology - Head and Neck Surgery* 1999; **125**(3):283–6.

Laskawi 1998
Laskawi R, Drobik C, Schönebeck C. Up-to-date report of botulinum toxin A treatment in patients with gustatory sweating (Frey's syndrome). *Laryngoscope* 1998;**108**(3): 361–84.

Martos 2008
Martos Díaz P, Bances del Castillo R, Mancha de la Plata M, Naval Gías L, Martínez Nieto C, Lee GY, et al.Clinical results in the management of Frey's syndrome with injections of botulinum toxin. *Medicina Oral, Patología Oral y Cirugía Bucal* 2008;**13**(4):E248–52.

May 1989
May JS, McGuirt WF. Frey's syndrome: treatment with topical glycopyrrolate. *Head and Neck* 1989;**11**(1):85–9.

Neumann 2011
Neumann A, Rosenberger D, Vorsprach O, Dazert S. The incidence of Frey syndrome following parotidectomy: results of a survey and follow-up. *HNO* 2011;**59**(2):173–8.

O'Neill 2008
O'Neill JP, Condron C, Curran A, Walsh A. Lucja Frey--historical relevance and syndrome review. *Surgeon* 2008;**6** (3):178–81.

Pomprasit 2007
Pomprasit M, Chintrakarn C. Treatment of Frey's syndrome with botulinum toxin. *Journal of the Medical Association of Thailand* 2007;**90**(11):2397–402.

RevMan 2011
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Singh 2011
Singh N, Kohli M, Kohli H. Innovative technique to reduce incidence of Frey's syndrome after parotid surgery. *The American Surgeon* 2011;**77**(3):351–4.

Tugnoli 2002
Tugnoli V, Marchese Ragona R, Eleopra R, Quatrale R, Capone JG, et al.The role of gustatory flushing in Frey's syndrome and its treatment with botulinum toxin type A. *Clinical Autonomic Research* 2002;**12**(3):174–8.

Watkins 1973
Watkins PJ. Facial sweating after food: a new sign of diabetic autonomic neuropathy. *British Medical Journal* 1973;**1**(5853):583-7.

Wenzel 2004
Wenzel GI, Draf W. Unusually long latency before the appearance of Frey's syndrome after parotidectomy. *HNO* 2004;**52**(6):554–6.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Criteria for summary 'Risk of bias' assessment

Risk of bias	Interpretation	In outcome	In included studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

APPENDICES

Appendix 1. CENTRAL search strategy

#1 frey* AND syndrome
#2 MeSH descriptor "Sweating, Gustatory" explode all trees
#3 MeSH descriptor "Facial Nerve Injuries" explode all trees
#4 MeSH descriptor "Taste" explode all trees
#5 MeSH descriptor "Taste Disorders" explode all trees
#6 gustatory
#7 #3 OR #4 OR #5 OR #6
#8 MeSH descriptor "Sweat" explode all trees
#9 MeSH descriptor "Sweat Glands" explode all trees
#10 MeSH descriptor "Sweating" explode all trees

#11 MeSH descriptor “Hyperhidrosis” explode all trees

#12 sweat* OR hyperhidrosis

#13 #8 OR #9 OR #10 OR #11 OR #12
#14 #7 AND #13
#15 #1 OR #2 OR #14

HISTORY

Protocol first published: Issue 7, 2012

CONTRIBUTIONS OF AUTHORS

- Chunjie Li proposed the title, registered the review and participated in the writing of the protocol.
- Qi Zhang participated in the writing of the protocol.
- Longjiang Li proposed the title, registered the review, provided advice on the clinical and policy perspective for the review and revised the text.
- Zongdao Shi provided advice on the methodological perspective for the review, guided and revised the text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- West China School of Stomatology, Sichuan University, China.
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External sources

- UK Cochrane Centre, UK.
- Cochrane Ear, Nose and Throat Disorders Group, UK.

NOTES

None.