

# BMJ Open Acupuncture for patients with cancer-induced xerostomia: a systematic review protocol

Xixiu Ni <sup>1</sup>, Yang Yu,<sup>1</sup> Tian Tian,<sup>1</sup> Lu Liu,<sup>1</sup> Xiao Li,<sup>1</sup> Fengmei Li,<sup>1</sup> Yue Xu,<sup>2</sup> Ling Zhao<sup>1</sup>

**To cite:** Ni X, Yu Y, Tian T, *et al.* Acupuncture for patients with cancer-induced xerostomia: a systematic review protocol. *BMJ Open* 2019;9:e031892. doi:10.1136/bmjopen-2019-031892

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-031892>).

XN and YY contributed equally.

Received 24 May 2019

Revised 12 November 2019

Accepted 12 November 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Acupuncture and Tuina School, Chengdu University of TCM, Chengdu, Sichuan, China

<sup>2</sup>Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu University of TCM, Chengdu, Sichuan, China

## Correspondence to

Professor Ling Zhao;  
zhaoling@cdutcm.edu.cn

## ABSTRACT

**Introduction** Xerostomia is a common symptom in patients with cancer. Currently available methods to manage xerostomia include stringent oral hygiene using fluoride agents and antimicrobials, saliva substitutes and sialagogic agents, but side effects such as headache, dizziness and sweating can occur with these therapies. Clinical trials have shown that acupuncture may be effective in treating xerostomia. The objective of this systematic review is to assess the effectiveness and safety of acupuncture treatment for xerostomia caused by cancer.

**Methods and analysis** This systematic review will incorporate articles identified by electronically searching the following databases: PubMed, MEDLINE, the Cochrane Library, AMED, Embase, WorldSciNet, Nature, Science Online, China National Knowledge Infrastructure, the Chongqing VIP Chinese Science and Technology Periodical Database, the Wanfang Database and China Biology Medicine Disc from inception to 1 December 2019. Other sources including conference proceedings and reference lists of identified publications and existing systematic reviews will also be searched. Two reviewers will independently search the databases, perform data extraction and assess the quality of studies. Data will be synthesised using either a fixed-effects model or a random-effects model, according to heterogeneity testing. Patient-reported change in the Visual Analogue Scale or the Xerostomia Inventory will be assessed as the primary outcome. Saliva collection, whole saliva production and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 will be evaluated as secondary outcomes. RevMan V. 5.3 will be employed for data analysis. The results will be expressed as risk ratios for dichotomous data and mean differences for continuous data.

**Ethics and dissemination** This protocol will not evaluate individual patient information or affect patient rights and therefore does not require ethical approval. Results from this review will be disseminated through peer-reviewed journals and conference reports.

**Trial registration number** CRD42019129069.

## INTRODUCTION

Xerostomia is typically considered to be a subjective sensation of dry mouth and is associated with a decrease in salivary production, one of the most common symptoms in

## Strengths and limitations of this study

- Although systematic reviews of acupuncture for radiation-induced xerostomia in patients with head and neck cancer have been previously conducted, the present study will update the evidence base by including multiple clinical trials of the past 10 years.
- The study design adheres to all relevant guidelines for systematic reviews and meta-analyses.
- Given that some clinical results have been used in published trials, it may not be possible to aggregate all included studies; however, subgroup analyses will be performed based on various outcomes.
- Variations in study design and patient characteristics among the studies included in this systematic review will likely lead to high heterogeneity that may limit the quality of the evidence.

cancer patients, with a reported prevalence of up to 77% of hospice admissions.<sup>1</sup> Cancer-induced xerostomia is caused by multiple factors including the consequences of cancer itself, dehydration, the effect of cancer treatment, especially radiotherapy<sup>2–7</sup> and chemotherapy<sup>8</sup>, the use of opioids, antimuscarinic agents and diuretics and pre-existing comorbidities such as Sjogren's syndrome.<sup>9</sup> The current diagnosis is based on the primary complaint reported by the patient.<sup>10</sup> A previous study<sup>11</sup> found that patients with cancer reported different degrees of dry mouth, reduced drinking and eating and waking up at night due to dry mouth and that the risk of progression to oral ulcers was higher among this patient population and could significantly affect the quality of life.

Xerostomia can also interfere with patient compliance and may lead to treatment delays resulting in inadequate tumour control<sup>12</sup>; therefore, effective management is a priority. Current available methods to manage xerostomia include stringent oral hygiene with fluoride agents and antimicrobials, saliva substitutes, sialagogic agents<sup>13–21</sup> and cytoprotective agents such as amifostine. Currently,

the main treatment for xerostomia is medication such as pilocarpine and cevimeline which are approved by the US Food and Drug Administration and are effective in promoting salivation and treating dry mouth. However, these strategies are associated with side effects such as headache, dizziness and sweating.<sup>19–21</sup> A systematic review of xerostomia in patients with advanced cancer showed that there was low-quality evidence to support the use of salivary substitutes and stimulants for the treatment of xerostomia symptoms.<sup>22</sup>

Acupuncture is an important component of complementary medicine and has recently gained popularity as a valid palliative intervention modality.<sup>23</sup> Emerging reports also suggest that acupuncture may be effective in treating xerostomia.<sup>24</sup> Acupuncture has been shown to increase salivary flow in healthy volunteers,<sup>25 26</sup> in patients with Sjogren's syndrome<sup>27</sup> and in patients with radiation-induced salivary gland injury.<sup>24 28 29</sup> Some studies have shown that acupuncture can alleviate the symptoms of dry mouth caused by cancer<sup>30 31</sup> and radiotherapy.<sup>29 32</sup> Acupuncture is commonly used in China as a safe treatment for xerostomia in cancer patients with few adverse effects.

In traditional Chinese medicine theory, acupuncture is considered to regulate qi and blood by stimulating acupuncture points and subsequently improving physiological functions. Although the mechanism of acupuncture remains unclear, some studies have shown that the levels of at least two neuropeptides (vasoactive intestinal peptide and calcitonin gene-related peptide) are increased in the saliva following acupuncture treatment.<sup>33 34</sup> Because these substances can stimulate salivary secretion, the production of neuropeptides may be the cause of increased salivary secretion.

Although two systematic reviews of acupuncture for radiation-induced xerostomia in patients with head and neck cancer have been published,<sup>35 36</sup> the present study will update the evidence base by including multiple clinical trials published over the past 10 years and will systematically evaluate the effectiveness and safety of acupuncture in treating patients with cancer-related xerostomia caused by various factors. Hence, a comprehensive review of acupuncture treatment of xerostomia caused by cancer may be beneficial to patients, practitioners and health policy makers. Therefore, the objective of this systematic review is to evaluate the effectiveness and safety of acupuncture treatment for xerostomia caused by cancer.

## METHODS AND ANALYSIS

### Review design

This protocol report is structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines.<sup>37</sup> The review will be implemented in accordance with the PRISMA statement guidelines.<sup>38</sup>

## Inclusion criteria for study selection

### Type of study

All randomised controlled trials (RCTs) of acupuncture therapy for cancer-induced xerostomia will be included in the review. The language is limited to English and Chinese. Non-RCTs, quasi-RCTs, case series, reviews and animal studies will be excluded.

### Type of participant

Patients diagnosed with cancer and symptoms of dry mouth will be included. There will be no restrictions on gender, education, ethnicity or tumour stage.

### Type of intervention

#### Experimental interventions

Patients who have undergone acupuncture treatment such as body acupuncture, manual acupuncture and electroacupuncture will be included in the experimental group, along with patients who have received acupuncture alongside other treatments. Studies that evaluated laser acupuncture, transcutaneous electrical nerve stimulation, dry needling, moxibustion or cupping will be excluded. The duration and frequency of treatment are not limited.

#### Control interventions

The control group will include patients treated with control interventions such as placebo acupuncture, sham acupuncture, herbs, western medicine, no treatment (waiting list control), routine care or conventional therapy.

### Outcome measures

#### Primary outcomes

The primary outcomes will be changes in the Visual Analogue Scale and Xerostomia Inventory.<sup>39</sup>

#### Secondary outcomes

Secondary outcomes are saliva collection, whole saliva production and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.<sup>40</sup>

## Search methods for identification of studies

### Data sources

The following databases will be searched: PubMed, MEDLINE, the Cochrane Library, AMED, EMBASE, World-SciNet, Nature, Science Online, China National Knowledge Infrastructure, the Chongqing VIP Chinese Science and Technology Periodical Database, the Wanfang Database and China Biology Medicine Disc. The temporal interval will be the time from database creation to 1 December 2019. The WHO International Clinical Trials Registration Platform and ClinicalTrials.gov will also be searched for ongoing experimental and Chinese RCTs related to the disease.

### Other search resources

A reference list of potential, qualified studies and related system reviews will be manually retrieved and reviewed to

determine the location of other RCTs. For ongoing RCTs, the trial author will be contacted for the most up-to-date clinical data. Furthermore, relevant conference proceedings will be evaluated to identify studies related to this review.

### Search strategy

The search terms will include acupuncture (eg, “acupuncture” or “acupuncture points” or “body acupuncture” or “manual acupuncture” or “electroacupuncture”), cancer (eg, “cancer” or “tumor” or “neoplasms” or “carcinoma”), xerostomia (eg, “xerostomia” or “dry mouth” or “salivary gland dysfunction” or “hyposalivation” or “hyposiali” or “salivary gland hypofunction”) and randomized controlled trial (eg, “randomized controlled trial” or “controlled clinical trial” or “random allocation” or “randomized” or “randomly” or “double-blind method” or “single-blind method” or “clinical trial”). The following terms will be used in the Chinese database searches: “Zhenjiu”, “Zhenci”, “Dianzhen”, “Kougan”, “Kouqiang-ganzao”, “Tuoyejianshao”, “Tuoyequafa”, “Ai”, “Aizheng”, “Liu”, “Zhongliu” and “Suijiduizhao”. The search strategy for the PubMed database is shown in [table 1](#); this strategy will be modified appropriately for other databases.

### Data collection and analysis

#### Selection of studies

Two trained reviewers will independently screen the title and abstract of search results to identify all applicable RCTs. After eliminating duplicate records and ineligible studies, the full text of eligible studies will be reviewed to determine whether they meet the predefined inclusion criteria. Where the researchers are unable to reach a consensus, a third reviewer will make the final judgement.

#### Data extraction and management

Two investigators will independently extract information from the included literature and enter the relevant data into a unified data statistics table, including the reference ID, first author, publication year, type of cancer, patient age, type of intervention, type of control intervention, sample size of each intervention group, intervention time, randomisation, allocation concealment and blinding methods, outcome measures, primary outcomes and adverse events, duration of follow-up, type and source of financial support and a list of the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA). Where the reported data are insufficient, the study author will be contacted for further information. Where a consensus on data extraction cannot be obtained through negotiation, a third investigator will make the final judgement.

#### Assessment of risk of bias and reporting of study quality

The Cochrane collaboration risk-of-bias assessment method will be used independently by the two researchers to assess the quality of included literature and complete the STRICTA checklist.<sup>41</sup> The assessments include random sequence generation, allocation

**Table 1** Search strategy for the PubMed database

Number	Search terms
1	Acupuncture. Mesh.
2	Acupuncture. ti, ab
3	Acupuncture therapy. Mesh
4	Acupuncture therapy. ti, ab
5	(acupuncture) and (therapy). ti, ab
6	Acupuncture points. Mesh.
7	Acupuncture points. ti, ab
8	Acupuncture*
9	Body acupuncture. ti, ab
10	(body) and (acupuncture). ti, ab
11	Manual acupuncture. ti, ab
12	(manual) and (acupuncture). ti, ab
13	Electroacupuncture. ti, ab
14	(electro) and (acupuncture). ti, ab
15	1 or 2–14
16	Neoplasms. Mesh.
17	Neoplasms. ti, ab.
18	Tumor. Mesh.
19	Tumor. ti, ab.
20	Cancer. Mesh.
21	Cancer. ti, ab.
22	Carcinoma. Mesh.
23	Carcinoma. ti, ab.
24	16 or 17–23
25	Xerostomia. Mesh.
26	Xerostomia. ti, ab.
27	Dry mouth. ti, ab.
28	Salivary gland dysfunction, ti, ab.
29	Hyposalivation. ti, ab.
30	Hyposiali. ti, ab.
31	Salivary gland hypofunction. ti, ab.
32	25 or 26–31
33	randomized controlled trial. pt
34	controlled clinical trial. pt
35	randomized controlled trials. Mesh.
36	random allocation. Mesh.
37	randomized. ti, ab
38	randomly. ti, ab
39	double-blind method. Mesh
40	single-blind method. Mesh
41	clinical trial. pt
42	33 or 34–41
43	15 and 24 and 32 and 42

concealment, blinding, incomplete outcome data, selective reporting and other possible biases. According to the relevant standards in the Cochrane Intervention



System Assessment Manual, risk of bias will be classified as low, high and unclear risk. Discrepancies will be resolved through discussions and consensus will be arrived at with a third investigator, who will make the final judgement where a consensus on risk assessment cannot be reached through discussion.

### Measures of treatment effect

The effect size will be calculated for each study and combined to generate an overall effect size. For results measured on the same scale, the mean difference and 95% CI will be used for effect evaluation, while the standard mean difference (SMD) will be used for results measured on different scales. Dichotomous data will be recorded as risk ratio (RR).

### Unit of analysis issues

Data from patients in RCTs will be used. Where more than one acupuncture group is used in an RCT, separate multiple meta-analyses will be performed for each treatment arm. For trials with a crossover design, data from the first sequence will be used. Where multiple non-acupuncture controls are included, results for all controls will be summarised to analyse the control and intervention groups.

### Handling of missing data

For missing data identified during screening and data extraction, the cause of the loss will be determined, and if this is unsuccessful, the missing data will be requested from the study author. If the missing data cannot be obtained, this will be documented and the available data will be extracted and analysed.

### Assessment of heterogeneity

A random-effects or fixed-effects model will be used for meta-analysis. According to the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity can be assessed by a visual check of the forest plot, a heterogeneity  $\chi^2$  test, and Higgins'  $I^2$  statistic.<sup>42 43</sup> If the p value is  $>0.10$  and the  $I^2$  value is  $<50\%$ , a fixed-effects model will be used to pool the data. Otherwise, a random-effects model will be used. If there is significant heterogeneity between a set of studies, causes of heterogeneity such as patient characteristics and degree of variation in interventions will be explored. Sensitivity analysis or subgroup analysis will be used to evaluate heterogeneity if applicable.

### Assessment of reporting bias

If more than 10 trials are included in the meta-analysis, a funnel plot will be used to assess the reporting biases. Begg and Egger tests will be used to evaluate the asymmetry of the funnel plot and values of  $p < 0.05$  will be considered to represent significant publication bias.<sup>44</sup>

### Data synthesis

RevMan 5 software (V. 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) will be used for data analysis. The use of a fixed-effects

or random-effects model will be determined based on the level of heterogeneity. For the two categorical variables, RR or odds ratio (OR) and 95% CI will be used. For continuous variables, weighted mean difference or SMD and 95% CI will be used. If there is meaningful heterogeneity that cannot be explained by any assessment (such as a subgroup analysis), no meta-analysis will be performed. If necessary, each subgroup will be carefully considered for subgroup analysis.

### Subgroup analysis

Subgroup analyses will be performed based on the heterogeneity of the acupuncture type (including body acupuncture, manual acupuncture and electroacupuncture), control type (including no acupuncture, placebo acupuncture, sham acupuncture, medication or conventional therapy), acupuncture points and clinical differences.

### Sensitivity analysis

To test the robustness of the review conclusions, a sensitivity analysis will be performed for the primary outcome according to the following criteria: sample size, heterogeneity quality and statistical model (random-effects or fixed-effects model).

### Grading of evidence quality

The Grading of Recommendations Assessment approach will be used to describe the quality of the evidence for the results obtained.<sup>45</sup> The assessment includes risk of bias, heterogeneity, indirectness, imprecision and publication bias. The quality of the results will be divided into high, moderate, low and very low.

## DISCUSSION

Xerostomia is one of the most common side effects reported during cancer treatment. According to traditional Chinese medicine theory, cancer-induced dry mouth is caused by the cancer itself and the treatment process, resulting in the loss of moisture and nourishment. Patients with tumours have yin deficiency; alternatively, the cancer may readily consume the qi and yin of the body, breaking the balance of qi and blood. Eventually, this imbalance can lead to disordered production and metabolism of body fluid, resulting in dry mouth, which may have serious consequences for patient treatment. Although western medicine is commonly used to treat xerostomia,<sup>13–21</sup> shortcomings such as per-cycle administration (daily use), headache, dizziness, sweating and other adverse events, and the high cost of antineoplastic agents render it somewhat inconvenient and limit its clinical application. Acupuncture can regulate qi and blood to improve physiological functions by stimulating acupoints. Previous studies<sup>29–32</sup> have reported that acupuncture can prevent the occurrence of dry mouth and increase the secretion of saliva and can therefore be

used as adjunctive and even alternative therapy alongside drugs, with fewer side effects and at relatively low cost.

Although multiple RCTs of acupuncture as a treatment for dry mouth caused by cancer have been reported to date, the cumulative evidence for its efficacy has not been systematically evaluated. This study will be the first systematic review of the efficacy of acupuncture in patients with cancer-induced xerostomia. The review will be divided into four sections: identification, study inclusion, data extraction and data synthesis. The resulting evidence may provide important information that will benefit patients, practitioners, health policy makers and acupuncturists.

**Acknowledgements** We thank Clare Cox, PhD, from Liwen Bianji, Edanz Editing China ([www.liwenbianji.cn/ac](http://www.liwenbianji.cn/ac)) for editing the English text of a draft of this manuscript.

**Contributors** XN and YY contributed equally to this work and designed the study. TT developed the search strategy. LL and XL will search the databases and screen the eligibility of the retrieved studies. YX and FL will extract information from the eligible studies and prepare the information for data analysis. XN and TT will perform the data analysis. XN and LZ wrote the first draft of the protocol. In practice, LZ will monitor each procedure of the review and is responsible for quality control. All authors read the article and approved it for publication.

**Funding** The review is supported by the National Natural Science Foundation of China (Grant No.81722050, 81973962) and the Interdisciplinary Program of Chengdu University of Traditional Chinese Medicine (Grant No.CZYJC1901). Funders and sponsors have no role in the design of this protocol.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iD

Xixiu Ni <http://orcid.org/0000-0001-7359-6173>

## REFERENCES

- Guggenheimer J, Moore PA, Yin XM. Xerostomia: etiology, recognition and treatment. *J Am Dent Assoc* 2003;134:61–9.
- Chen AM, Farwell DG, Lau DH, et al. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? *Int J Radiat Oncol Biol Phys* 2011;81:346–52.
- Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109–22.
- Franzén L, Funegård U, Ericson T, et al. Parotid gland function during and following radiotherapy of malignancies in the head and neck: a consecutive study of salivary flow and patient discomfort. *Eur J Cancer* 1992;28:457–62.
- Wijers OB, Levendag PC, Braaksma MMJ, et al. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck* 2002;24:737–47.
- Eisbruch A, Ten Haken RK, Kim HM, et al. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1999;45:577–87.
- Wynn RL, Meiller TF. Artificial saliva products and drugs to treat xerostomia. *Gen Dent* 2000;48:630–6.
- Yin XM, Feng LX, Feng LN, et al. Study on the intervention effect of traditional Chinese medicine prescription on dry mouth symptoms caused by chemotherapy chemotherapy. *J Nurs Train* 2018;33:1712–3.
- Twycross R, Wilcock A, Toller C. Alimentary symptoms. In: Twycross R, Wilcock A, Toller C, eds. *Symptom management in advanced cancer*. 4th edition. 4th edn. Oxford: Palliativedrugs.com Ltd, 2009: 62–5.
- YQ W, Fu J, Song W, et al. The etiology and treatment progress of xerostomia. *Journal of Clinical Medicine and Pharmacy* 2015;31:762–4.
- Feng LN, Feng LX. Investigation of symptom groups in patients with lymphoma chemotherapy. *Journal of Practical Nursing* 2017;33:2130–3.
- Van den Bogaert W, Van der Leest A, Rijnders A, et al. Does tumor control decrease by prolonging overall treatment time or interrupting treatment in laryngeal cancer? *Radiother Oncol* 1995;36:177–82.
- Jellema AP, Langendijk H, Bergenhenegouwen L, et al. The efficacy of Xialine in patients with xerostomia resulting from radiotherapy for head and neck cancer: a pilot-study. *Radiother Oncol* 2001;59:157–60.
- Momm F, Volegova-Neher NJ, Schulte-Mönting J, et al. Different saliva substitutes for treatment of xerostomia following radiotherapy. *Strahlenther Onkol* 2005;181:231–6.
- Epstein JB, Loh R, Stevenson-Moore P, et al. Chlorhexidine rinse in prevention of dental caries in patients following radiation therapy. *Oral Surg Oral Med Oral Pathol* 1989;68:401–5.
- Epstein JB, McBride BC, Stevenson-Moore P, et al. The efficacy of chlorhexidine gel in reduction of Streptococcus mutans and Lactobacillus species in patients treated with radiation therapy. *Oral Surg Oral Med Oral Pathology* 1991;71:172–8.
- Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390–5.
- Chambers MS, Posner M, Jones CU, et al. Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007;68:1102–9.
- Simcock R, Shields P. Management of radiation induced xerostomia in the UK. *Clin Oncol* 2011;23:S53.
- Davies AN, Daniels C, Pugh R, et al. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. *Palliat Med* 1998;12:105–11.
- Mercadante S, Calderone L, Villari P, et al. The use of pilocarpine in opioid-induced xerostomia. *Palliat Med* 2000;14:529–31.
- Hanchanale S, Adkinson L, Daniel S, et al. Systematic literature review: xerostomia in advanced cancer patients. *Support Care Cancer* 2015;23:881–8.
- Lu W, Rosenthal DS. Recent advances in oncology acupuncture and safety considerations in practice. *Curr Treat Options Oncol* 2010;11:141–6.
- Blom M, Lundberg T. Long-Term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.
- Davidson I, Blom M, Lundberg T, et al. The influence of acupuncture on salivary flow rates in healthy subjects. *J Oral Rehabil* 1997;24:204–8.
- Deng G, Hou BL, Holodny AI, et al. Functional magnetic resonance imaging (fMRI) changes and saliva production associated with acupuncture at LI-2 acupuncture point: a randomized controlled study. *BMC Complement Altern Med* 2008;8:37.
- List T, Lundberg T, Lundström I, et al. The effect of acupuncture in the treatment of patients with primary Sjögren's syndrome: a controlled study. *Acta Odontol Scand* 1998;56:95–9.
- Johnstone PAS, Peng YP, May BC, et al. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50:353–7.
- Wong RKW, Jones GW, Sagar SM, et al. A phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:472–80.
- Rydholm M, Strang P. Acupuncture for patients in hospital-based home care suffering from xerostomia. *J Palliat Care* 1999;15:20–3.
- Meidell L, Holritz Rasmussen B. Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study. *Int J Palliat Nurs* 2009;15:12–20.
- Braga FdoPF, Lemos Junior CA, Alves FA, et al. Acupuncture for the prevention of radiation-induced xerostomia in patients with head and neck cancer. *Braz Oral Res* 2011;25:180–5.
- Davidson I, Angmar-Månsson B, Blom M, et al. Sensory stimulation (acupuncture) increases the release of vasoactive intestinal polypeptide in the saliva of xerostomia sufferers. *Neuropeptides* 1998;32:543–8.
- Davidson I, Angmar-Månsson B, Blom M, et al. Sensory stimulation (acupuncture) increases the release of calcitonin gene-related peptide in the saliva of xerostomia sufferers. *Neuropeptides* 1999;33:244–50.

- 35 Zhuang L, Yang Z, Zeng X, *et al.* The preventive and therapeutic effect of acupuncture for radiation-induced xerostomia in patients with head and neck cancer. *Integr Cancer Ther* 2013;12:197–205.
- 36 O'Sullivan EM, Higginson IJ. Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review. *Acupunct Med* 2010;28:191–9.
- 37 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- 38 Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
- 39 Thomson WM, Chalmers JM, Spencer AJ, *et al.* The xerostomia inventory: a multi-item approach to measuring dry mouth. *Community Dent Health* 1999;16:12–17.
- 40 Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
- 41 Higgins JPT, Altman DG, Higgins JPT. Assessing risk of bias in included studies. In: *Cochrane Handbook for systematic reviews of interventions*. Cochrane book series. Wiley, Chichester, 2008: 187–241.
- 42 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- 43 Deeks JJ, Higgins JPT, Altman DG. Chapter 9: analyzing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane Handbook for systematic reviews of interventions version 5.1.0*. The Cochrane Collaboration, 2011.
- 44 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- 45 Guyatt GH, Oxman AD, Vist GE, *et al.* Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.