LETTER

Letter to the Editor: Questionable validity of the systematic review and meta-analysis by Lovelace et al on management of radiotherapy-induced salivary hypofunction and xerostomia in patients with oral or head and neck cancer.

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Sir,

We have read with great interest the recently published paper "*Management of radiotherapy-induced salivary hypofunction and consequent xerostomia in patients with oral or head and neck cancer: meta-analysis and literature review" by Lovelace et al* (1). We certainly agree with the authors that there is little evidence-based guidance for clinicians as regards the efficacy of available treatments for hyposalivation and xerostomia associated with head and neck radiotherapy. We also share their concerns regarding the limited number of available randomized controlled trials and the great variability in the definition and measurements of hyposalivation and xerostomia, as well as the lack of quality of life data. This can affect robustness of available evidence and hinder comparison and pooling of data from different studies. Therefore we applaud their attempt to perform a much needed systematic review and meta-analysis on the topic.

However, systematic review and meta-analyses require rigorous research methods in order to limit bias and provide a more reliable and enhanced precision of effect estimate than those achieved in individual studies. Strict rules apply so to synthesize the results of multiple primary investigations and generate the necessary, validated high levels of evidence that can guide clinical decision making and support practice guidelines (2, 3). When methodological rigor is not diligently applied, systematic review and meta-analyses can be subject to bias and can be flawed (3), with several examples being reported where serious errors have been identified (4, 5). Systematic

reviews of questionable validity can be misleading and have the potential for an adverse impact on clinical practice.
We have identified a number of methodological issues in the work of Lovelace et al that carry a significant risk of affecting validity of their results.

1. Authors searched only one electronic database (Pubmed/MEDLINE) for studies reporting on treatment options for radiation-induced xerostomia in patients with head and neck cancer. Most systematic reviews search multiple databases (MEDLINE, EMBASE, CENTRAL) in order to increase coverage and maximize the number of studies to be considered (6, 7). Cochrane's and other guidelines clearly point out that a search of MEDLINE database alone is not adequate (8). Indeed it has been reported that the average sensitivity of Medline searching can be as low as 51% when all known trials are considered as gold standard, and not higher than 77% even when only trials published in journals available in Medline are used as gold standard (9).
2. Restricting the search to electronic databases carries a significant risk of excluding relevant studies (8, 10) and having an incorrect effect estimate because of exclusion of grey literature (11). Current guidelines recommend the use of supplementary approaches to maximize the chances of identifying all relevant studies (8, 10, 12). Lovelace et al did search references from identified studies; however they do not seem to have performed any of the other recommended supplementary search methods including hand searching of key journals, conference proceedings, as well as search of trials registries or regulatory agency websites.
3. Current guidelines on performing and reporting systematic reviews (Cochrane Handbook and PRISMA statement) (8, 12), clearly state that authors should report the start and end dates for the search of each database, so to allow readers to assess the recency of the review. Considerable delays between search and publication are not uncommon, with a relatively recent analysis of 100 systematic reviews suggesting that 7% of them were already out of date on the day of publication (13).
4. Publication language was limited to English, although it is well reported that reviews exclusively based upon English-language reports are at higher risk of bias (14, 15). We wonder why authors did not mention the potential importance of language bias among the limitations of their meta-analysis.
5. The authors included a prospective controlled study (16), which however is a review of two randomized, placebo-controlled, multicenter trials previously published and already included in the systematic review (17, 18). The inclusion of duplicated data is a well recognised cause of bias and may lead to overestimate intervention effects (19).
6. The authors selected and included a prospective controlled study that addressed treatment of hyposalivation/xerostomia with hyperbaric oxygen therapy (20). In this paper Teguh *et al* recruited patients who were due to have radiotherapy, which is in clear contrast with inclusion criteria stated by Lovelace et al "agent or procedure initiated after radiation therapy". These individuals were not complaining of xerostomia and did not present with hyposalivation at the time of recruitment and randomization. Also, this trial was stopped prematurely, with only 19 patients having been recruited out of 132 needed as per protocol and

sample size calculation (20). We wonder whether inclusion of this paper is appropriate.

7. The authors also included a placebo-controlled randomized trial of topical pilocarpine dose escalation by Hamlar et al (21). However this study presents a number of serious methodological issues, including unclear study design and lack of randomization in allocating participants to dose escalation, and we suggest that should have not been included into a systematic review. Indeed this very same paper was excluded from a previous systematic review on the management of dry mouth with topical therapies (22).
8. The authors assessed the risk of bias in the selected studies using the Jadad 5-point questionnaire but reported only summary data (''*eleven of the fourteen studies included in the review received a score of 4 or 5"*), therefore failing to inform readers about the actual studies that had a particular methodological shortcoming. A more informative approach is recommended in order to report explicitly the methodological features evaluated for each study. It is often advised to provide these data in a tabular format or graphs (8, 12).
9. PRISMA guidelines clearly recommend that authors identify their work as a systematic review in the title (12). The terms ''literature review'' do not describe whether the review was systematic or narrative, which would confuse readers and potentially affect indexing and identification.

We feel that the above points raise significant doubts about the accuracy and the validity of the meta-analysis.

References

1. Lovelace TL, Fox NF, Sood AJ, Nguyen SA, Day TA. Management of radiotherapy-induced salivary hypofunction and consequent xerostomia in patients with oral or head and neck cancer: meta-analysis and literature review. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2014.
2. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: Synthesis of best evidence for clinical decisions. Annals of Internal Medicine. 1997;126(5):376-80.
3. Yuan Y, Hunt RH. Systematic reviews: The good, the bad, and the ugly. American Journal of Gastroenterology. 2009;104(5):1086-92.
4. Holmdahl L. A misleading meta-analysis of Seprafilm. World Journal of Surgery. 2008;32(8):1888-9.
5. Tobin MJ, Jubran A. Meta-analysis under the spotlight: Focused on a meta-analysis of ventilator weaning. Critical Care Medicine. 2008;36(1):1-7.
6. Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: Rapid versus exhaustive searches. International Journal of Technology Assessment in Health Care. 2003;19(4):591-603.
7. Stevinson C, Lawlor DA. Searching multiple databases for systematic reviews: Added value or diminishing returns? Complementary Therapies in Medicine. 2004;12(4):228-32.
8. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series2008. 1-649 p.
9. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. British Medical Journal. 1994;309(6964):1286-91.

10. Systematic Reviews. CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination UoY, 2009.
11. Hopewell S, McDonald S, Clarke MJ, Egger M. Grey literature in meta-analyses of randomized trials of health care interventions. Cochrane Database of Systematic Reviews. 2007(2).
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Annals of Internal Medicine. 2009;151(4):W-65-W-94.
13. Ünalp A, Tonascia S, Meinert CL. Presentation in relation to publication of results from clinical trials. Contemporary Clinical Trials. 2007;28(4):358-69.
14. Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: Is there a Tower of Babel bias? Journal of Clinical Epidemiology. 1995;48(1):159-63.
15. Moher D, Fortin P, Jadad AR, Jüni P, Klassen T, Le Lorier J, et al. Completeness of reporting of trials published in languages other than English: Implications for conduct and reporting of systematic reviews. Lancet. 1996;347(8998):363-6.
16. Rieke JW, Hafermann MD, Johnson JT, LeVeque FG, Iwamoto R, Steiger BW, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two prospective randomized clinical trials. International journal of radiation oncology, biology, physics [Internet]. 1995; (3):[661-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/363/CN-00110363/frame.html.
17. Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. The New England journal of medicine [Internet]. 1993; (6):[390-5 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/368/CN-00094368/frame.html.
18. LeVeque FG, Montgomery M, Potter D, Zimmer MB, Rieke JW, Steiger BW, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology [Internet]. 1993; (6):[1124-31 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/488/CN-00093488/frame.html.
19. Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: A case study. British Medical Journal. 1997;315(7109):635-40.
20. Teguh DN, Levendag PC, Noever I, Voet P, Est H, Rooij P, et al. Early hyperbaric oxygen therapy for reducing radiotherapy side effects: early results of a randomized trial in oropharyngeal and nasopharyngeal cancer. International journal of radiation oncology, biology, physics [Internet]. 2009; (3):[711-6 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/585/CN-00720585/frame.html.
21. Hamlar DD, Schuller DE, Gahbauer RA, Buerki RA, Staubus AE, Hall J, et al. Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. The Laryngoscope [Internet]. 1996;

(8):[972-6 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/849/CN-00127849/frame.html.
22. Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database of Systematic Reviews. 2011(12).