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Title	Allergen immunotherapy for the treatment of allergic rhinitis and/or asthma: an overview of systematic reviews
Authors	Jesse Elliott, Shannon Kelly, Amy Johnston, Becky Skidmore, Tara Gomes, George Wells
Reviewer 1	Dr. Pia Pace-Asciak
Institution	St. Paul's Hospital, Division Otolaryngology, BC Rotary Hearing and Balance Centre
General comments (author response in bold)	MAJOR: 1) Such a comprehensive review can be very valuable to allergists as well as otolaryngologist, I would recommend extending the dates to include more than 5 years. Additionally, the study should be updated to reflect the latest literature in 2016. There is mention on line 214 of an earlier review from 2003-2008, but a 2 year gap exists between your review and the previous review. Your hard work can be very valuable to clinicians especially if it is comprehensive. **As requested by the reviewer and editors, we have updated the literature search to capture studies published up to November 20, 2016. As well, we have added additional text to more fully describe the rapid review methodology. Please see our response to the editor's first and second question for more details about our search strategy.** MINOR: 2) The clinical question seems to focus on harms and benefits of immunotherapy, however the authors also discuss efficacy of SIT without any mention in the introduction of the known success rates of SIT in the literature and does it differ between SCIT and SLIT. There is a statement in the intro about how SIT is underused, however in reality/clinically it is used for patients who can't avoid the allergen with a rough efficacy of 70%. **In our review, we sought to summarize the literature base for allergen specific-immunotherapy (SIT) to provide high-quality evidence to policy-makers to inform reimbursement decisions. We intended to address exactly the issue raised by this reviewer, namely whether there are differences in efficacy (and harms) between SCIT and SLIT. While SCIT is generally believed to be the gold-standard for immunotherapy, practical considerations and concerns around the risk of adverse events may limit its use in clinical practice. We have added an additional statement to the introduction to address this reviewer's comment.** 3) The outcome measures for benefits are not defined clearly. The lay reader does not have a sense of these outcome measures and ie. total combined symptom-medication score. Are these measures standardized across studies? Were these defined by the authors to assess quality? The harm outcomes are more straightforward but could also be defined better to describe what local vs systemic reactions are present at the earlier part of the paper. **We have added a subheading in the methods section called "Outcomes" and have more fully described the outcomes of interest. We assessed all outcomes based on the definitions applied in the systematic reviews. In terms of local and systemic reactions, we did not a priori define which ones would be eligible; instead, we collected all data available and report a narrative summary in our report.** 4) For exclusion criteria, were reviews about pregnancy excluded? This can be an important compounding factor in rhinitis. **We agree with Reviewer 1 that pregnancy can be an important compounding factor in rhinitis. Based on stakeholder consultation prior to initiation of the research, rhinitis during pregnancy was considered to be outside the scope of the review. As such, we excluded systematic reviews that aimed to include participants with rhinitis in pregnancy. We have added rhinitis in pregnancy to the list of excluded conditions in the methods section.** 5) What is rush updosing for SCIT? line 135. Maybe in the appendix there should be an explanation of terms. **Rush updosing is an accelerated injection schedule for SCIT. We have added this explanation following use of the term "rush updosing" in the manuscript.** 6) In the interpretation, adherence is not discussed and this is a major factor in patient not completing SIT. This may also be the reason for varying rates of success of SIT. Maybe a comment on why this is the case (ie. 5 year compliance for treatment). Does this differ for SCIT vs SLIT? I imagine it does. **We agree with Reviewer 1 that medication adherence is an important issue. Although we aimed to compare adherence rates between SCIT and SLIT, only two of the included systematic reviews assessed medication adherence or discontinuation among patients receiving SCIT or SLIT compared with placebo. Compared with placebo, discontinuation was significantly higher for both SCIT and SLIT among patients with allergic rhinitis. Of the included reviews, none compared, via direct or indirect comparison methods, discontinuation with SCIT relative to discontinuation with SLIT, therefore we cannot comment on whether discontinuation is higher with one form of SIT product over another.** 7) Children are more likely to be treated with SLIT instead of SCIT. Did the authors find this in their results? **Whether children were more likely to be treated with SLIT or SCIT was beyond the scope of this review, as such we cannot comment on the frequency of either treatment in a pediatric population. We did find, however, that few reviews assessed outcomes of SCIT or SLIT in pediatric populations.**
Reviewer 2	Mr. Lawrence Mbuagbaw
Institution	McMaster University, Department of Clinical Epidemiology and Biostatistics
General comments (author response in bold)	This is a well conducted and documented overview of systematic reviews on the benefits and harms of allergen immunotherapy in the treatment of allergic rhinitis. I have a few comments: 1. The background is a bit short and is missing a justification of methods and context of work. It will be important for readers to know if this was a commissioned and time-sensitive piece of work. **We thank reviewer 2 for this helpful suggestion. We have updated the background section in the manuscript to better capture the context of our review. Please see our response to the editor's comment 1 and 2 for a more detailed explanation of our changes.** 2. That would explain the rapid review approach. Moreso, no information is given to warrant an overview e.g conflicting systematic reviews etc.

	As discussed in our responses to the editors and reviewer 1, we have updated the introduction section in the manuscript to reflect this issue. 3. The search was conducted 17 months ago. It should be updated. **We have updated the search as suggested by Reviewer 2 and the editors. The updated search was performed on November 20, 2016, and the results of the updated search have been incorporated into the review.** 4. Please provide a reference for AMSTAR and spell it out in full at first use. **We have added a reference to the original development of AMSTAR (Shea 2007) and its validation (Shea 2009), and have spelled out the abbreviation.** 5. Please comment on the degree of overlap between included systematic reviews and how it was handled. It is likely that one or more primary studies appeared in more than one systematic review. **Due to the level of study detail reported in the systematic reviews, we were unable to assess in depth the degree of overlap among the included systematic reviews for each outcome. As shown in Table 1, the number of RCTs included in the systematic reviews ranged from 7 to 140. However, there was also heterogeneity in the type of included allergen. For example, the review by Lu 2015 included 7 RCTs involving patients with allergic asthma induced by house dust mite. In contrast, the review by Abramson 2010 included 88 RCTs involving patients with allergic asthma induced by house dust mites, pollen, animal dander, mould, or latex. Thus, although there may be overlap among some of the systematic reviews, it is not expected to be extensive due to the number of studies and the allergens included.**
Reviewer 3	Dr. Nishant Mishra
Institution	University of Glasgow, Medicine
General comments (author response in bold)	This is a well written review article. But this is also an unusual review article. It studied the systematic reviews and not the research papers included therein. The articles were limited for a period between 2010 and 2015. The objective was to assess the safety and efficacy from subcutaneous and sublingual immunotherapy in patients with allergic rhinitis or asthma. The authors did not pool data from individual research papers to provide an estimate of safety or efficacy. The findings are inconclusive and I am not sure if these will have an impact on policy/guidelines. 1. What is the rationale for selecting papers for only last 5 years, why not all papers till today? Why meta analytic methods were not adopted? i.e., why the data from research studies were not pooled together to obtain a pooled estimate of benefit/harm? **We thank reviewer 3 for the questions and suggestions. We have addressed the date-limitations in a previous response to the editors above (see response 1 and 2)** **In our umbrella review, we did not use meta-analytic methods because obtaining a precise effect estimate across studies was not prioritized by the health-care decision-makers who were the end-users of this review. Following consultation with end-users, as well as with the rest of the research team and clinical experts, we came to the decision that the descriptions of relative benefits and harms were sufficient. In addition, because of the limitations in the reporting among the included systematic reviews, and heterogeneity in the approach, inclusion criteria, interventions and outcomes, meta-synthesis of data from the reviews would likely have been not technically feasible or advisable.** 2. The regulatory bodies tend to separately analyses data from their jurisdiction, in your case Canada. Perhaps, it will be useful to look at the data from Northern America. **Although jurisdictional analyses are often of interest, this was not of interest for our knowledge users. Based on consultation with the stakeholders before the start of the project, it was decided that an umbrella review of reviews from all jurisdictions would best met their needs.** 3. "rapid review" : what is that? **We have updated the manuscript background and methods to provide a justification for, and description of, the rapid review approach.** 4. Authors themselves state that most of the articles could not be assessed for quality. This article does not appear to contribute newer information that will impact practice. **Our review aims to systematically review the evidence base and to provide a comprehensive summary for clinicians and policy makers. We did assess the quality of each included systematic review via use of the AMSTAR checklist. As reported in our results section, most had poor compliance with AMSTAR, which does make it difficult to speak to their quality. For interested readers, we have included our AMSTAR assessment of each review in the web supplement.** 5. Table 5: Last two columns on death appear to have overlapping information. Third column on anaphylaxis suggests that the articles were not consistent in reporting various adverse effects, and therefore a reliable estimate cannot be calculated. **To address reviewer 2's concerns, we have simplified table 5 to include one column each for anaphylaxis and death.** **We agree that the included systematic reviews were not consistent in their reporting of adverse events; however, we did not aim to calculate a summary effect estimate. Our intent, as a priori established via stakeholder consultation, was to provide a description of the relative benefits and harms associated with SCIT and SLIT. As well, because of limitations in the reporting among the included systematic reviews and clinical and methodological heterogeneity, meta-synthesis of data from the reviews would likely have been not technically feasible or advisable.** **References:** **Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Methodology for JBI Mixed Methods Systematic Reviews 2014. http://joannabriggs.org/assets/docs/sumari/ReviewersManual-Methodology-JBI_Umbrella Reviews-2014.pdf (accessed15 Aug 2016).** **Di Bona D, Plaia A, Leto-Barone MS, Piana SL, Lorenzo GD. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med. 2015;175:1301.** **Ganann R, Cilska D, Thomas H. Expediting systematic reviews: methods and implications of rapid reviews. Implementation Science 2010;5:56.**

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