Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Treatments for Seasonal Allergic Rhinitis

Draft review available for public comment from August 2, 2012 to August 30, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The target populations are broad but appropriate. Good key questions and good patient outcomes used.	Thank you for the comment.
Peer Reviewer #1	Introduction	About the right length	No response required.
Peer Reviewer #1	Methods	Methods exemplary	Thank you for the comment.
Peer Reviewer #1	Results	While rather detailed and tedious, the detail was appropriate and necessary.	No response required.
Peer Reviewer #1	Discussion/ Conclusion	Again, all well done.	Thank you for the comment.
Peer Reviewer #1	Clarity/ Usability	I would have broken this up into at least two separate reports; one for non-pregnant adults and the other for children and pregnant women.	Key Questions (KQs) were defined with input from Key Informants and included these populations.
Peer Reviewer #4	General	The design of the study, key questions, and goals are appropriate and meaningful. The target population is also well-defined. Unfortunately, the deficiencies in published research design, defined severity of SAR symptoms, MCID, and representation of all drugs within a pharmaceutical class, makes the interpretation of the findings very difficult. The overall conclusions do not really help the practicing physician or the patient that much.	Methods, Results, and Discussion, of ES and Full Report, and Conclusions of Full Report, revised to emphasize more the limitations to forming conclusions.
Peer Reviewer #4	General	I would have like to have seen olopatadine included in the studies.	One trial compared intranasal corticosteroid to nasal olopatadine. This has been corrected in the “Description of Included Studies” for this comparison, in Table 10 (Drugs studied in included trials), and throughout the report.
Peer Reviewer #4	Executive Summary (Page 15 of 345 of PDF), line 21-26	These findings and symptoms are not limited to children but would apply to adolescents and adults as well. I would add and “word and/or school performance” to line 26.	Text revised in Background sections of Executive Summary (ES) and Full Report; new reference added.
Peer Reviewer #4	Executive Summary Page 21 of 345 in PDF, line 53-54	It seems that using just two experts to define a meaningful change in TNSS is too arbitrary. At least a panel should have been used.	Input from the entire TEP was sought.

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Peer Reviewer #4	Executive Summary Page 28 or 345 in PDF, line 26	I think that this is best shown in line 11 of Table B instead of D if we are only talking about eye symptoms.	Corrected in ES and Full Report.
Peer Reviewer #4	Executive Summary Page 28, line 27	The reference to #2 in the list above seems to be an inappropriate reference. Needs to be clarified	Corrected in ES and Full Report.
Peer Reviewer #4	Introduction Page V (page 5 of 345 in PDF) line 45	It's indicated that the insomnia is a moderate strength evidence for adverse effect of using a decongestant. Line 49-51 would seem to say that that there is low strength evidence to suggest oral selective antihistamine over a decongestant to avoid adverse effect of insomnia. This seems to be contradictory- one says moderate and one says low. This needs to be clarified.	Two different comparisons are described: In comparison to combination oral selective antihistamine plus oral decongestant, evidence to avoid insomnia is moderate strength. In comparison to oral decongestant monotherapy, evidence to avoid insomnia is low strength. Paragraph has been rewritten for greater clarity.
Peer Reviewer #4	Methods	All are appropriate and I see no need for improvement.	No response required.
Peer Reviewer #4	Results	Details presented are appropriate, characteristics of studies are clearly stated, figures, tables, and appendices are adequate and descriptive. I do not know of any omissions in terms of studies.	No response required.
Peer Reviewer #4	Discussion	I would like to see more practical advice for the clinician and patient. Maybe this could be placed in a table. For example: 1) If you do not mind the bitter taste, combined INCS and nasal AH are more efficacious for nasal allergy symptoms 2) If decongestants to not interfere with your sleep, they may be more effective for congestion, especially when combined with a selective antihistamine	Our charge was to present the state of the evidence rather than to make recommendations.

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Peer Reviewer #4	Clarity and Usability	The conclusions are really too vague to provide much guidance to clinicians, patients, or policy makers. When you conclude that that is no single product for SAR that is clearly both more effective and safer than another, it does not give much guidance to anyone. And for the groups of people that are most difficult to treat, children and pregnant females, we are given no guidance. I doubt that many clinicians or policy makers will want to read 345 pages to find out that there are no significant recommendations. I understand that this is not the fault of the authors but that the quality of the research is overall of low quality. It seems to say to me that it will ultimately have to be the patient that decides what works the best and that this will often vary from person to person. It does indicate that combination medications do play a role and for some people are more effective. Hopefully this will allow policy makers to permit the use of more expensive medications (INCS + nasal AH) or combination of medications instead of refusing to cover or setting these medications at an extremely high formulary tier which results in it being unaffordable for the patient.	Our charge was to present the state of the evidence rather than to make recommendations. Methods, Results, and Discussion, of ES and Full Report, and Conclusions of Full Report, revised to emphasize more the limitations to forming conclusions.
Peer Reviewer #5	General	The goal of this CER for treatment of seasonal allergic rhinitis (SAR) was to advise policy makers, patients, and health system leaders regarding pharmacologic treatments based on studies of at least 2 weeks duration from the 39 FDA labeled medications. It was hoped that there would be sufficiently rigorous studies to inform regarding direct comparisons of treatments for SAR in adolescents, adults, pregnant women, and children (< 12 yrs of age). The methodology is described in detail and the report demonstrates a truly major effort to explore many key questions. In the conclusion on p 197 of the draft report, there were 6 informative findings regarding direct comparisons between groups of medications such as that nasal symptoms were more effectively reduced by the combination of an intranasal corticosteroid + intranasal antihistamine compared to an intranasal corticosteroid itself. The draft report considers limitations of this CER. The target populations and audiences are defined. The key questions are identified clearly	No response required.
Peer Reviewer #5	Executive Summary ES1 line 14	Molds also cause SAR	The search strategy focused on seasonal allergic rhinitis and did not identify molds in association with SAR. However, our clinical content expert provided evidence for seasonal fluctuation in allergy-causing molds. We have added this information to the report.

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Peer Reviewer #5	Executive Summary Line 26	Reduction of productivity at work should be added	Done.
Peer Reviewer #5	Executive Summary Line 56	Re safety….. seemingly excessively negative when the intranasal corticosteroids have literature not causing HPA impairment or interference with ultimate linear height in children. If this sentence remains, would insert citations, otherwise modify.	Text revised as follows: "Intranasal corticosteroids do not appear to cause adverse events associated with systemic absorption (e.g., adrenal suppression, bone fracture among the elderly, and reduced bone growth and height in children)."
Peer Reviewer #5	Executive Summary Page 2, line 27	Mast cell stabilizer can be effective with a single pre-treatment administration…would clarify this point or refer to the 2 week study requirement	Text added to Background of ES and Full Report: "As-needed use also has been described and may be of benefit."
Peer Reviewer #5	Executive Summary Lines 40-44	Literature exists re safety in pregnancy at least for orally inhaled cromolyn	Sentence revised to list Pregnancy Category B drugs: "Preferred treatments are Pregnancy Category B drugs (nasal cromolyn, budesonide, and ipratropium; several oral selective and nonselective antihistamines; and the oral leukotriene receptor antagonist, montelukast) commencing in the second trimester, after organogenesis."
Peer Reviewer #5	Executive Summary ES-10 line 32	Spelling for antihistamine	Corrected.
Peer Reviewer #5	Introduction	Although allergen immunotherapy is discussed, it should be noted that this is the only immunomodulator that can alter the natural history of SAR. Patients become frustrated with the lack of resolution of the SAR or as presented in this review, the lack of sufficient benefit of one class of treatments over another.	We refer the interested reader to the AHRQ CER of allergen-specific immunotherapy for more information on this treatment modality.
Peer Reviewer #5	Introduction	Many patients don't take medications for 2 straight weeks for SAR; they use intermittent therapy. Thus, because of early onset of action (not really discussed in this draft document because the therapeutic approach was focused on at least 2 weeks of directly comparable treatment) the extrapolation to formulary decisions may be limited. Indeed, intranasal corticosteroids begin reducing symptoms in 9-12 hours; such a point should be incorporated in this document.	In the Limitations of Review sections in the ES and Full Report, we state: "Our minimum 2-week duration excluded examination of other treatment features which may be important to patients, e.g., onset of action."
Peer Reviewer #5	Methods	Completely so.	No response required.
Peer Reviewer #5	Results, p. 2, lines 23-25	Histamine is preformed but leukotrienes are "newly synthesized"…kinins are preformed and dilate vessels. Note that "in the park" studies show onset of action of intranasal corticosteroids in 9-12 hours	Leukotrienes deleted from this sentence in ES and Full Report.

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Peer Reviewer #5	Results, p. 4, lines 13-14	Mast cell stability doesn't take several weeks of pre-treatment to be effective; inhibition of LTD4 blocks this potent mediator that increases vascular permeability; wouldn't label the leukotriene antagonists as anti-inflammatory	Text added to Background of ES and Full Report: "As-needed use also has been described and may be of benefit." References describing the anti-inflammatory action of leukotriene receptor antagonists in asthma added. Clinical content expert advises that LRA mechanism of action is the same in asthma and SAR.
Peer Reviewer #5	Results, p. 5	Intranasal corticosteroids…comment re harms such as growth retardation and HPA suppression without any citations…should state that the highly topical intranasal corticosteroids haven't been shown to have these theoretical harms in recommended dosages.	The excerpt referenced is in the Background section of the report. Text revised to state: "Potential adverse events resulting from systemic absorption, such as impaired bone growth, reduced height, suppression of the adrenal axis, hyperglycemia, and weight gain, have not been definitively demonstrated."
Peer Reviewer #5	Results	Table 75…should comment on relevance to intranasal corticosteroids in pregnancy. These well-known physiologic changes may not contribute to lack of benefit of pharmacologic treatments (especially intranasal) or contribute to harms. Would give an example of how this information is important and a basis for studies in pregnant women with SAR.	In the absence of evidence to address KQ3, we supply an overview of the physiologic changes of pregnancy to demonstrate the difficulty of predicting drug effects in pregnant women based on findings in non-pregnant women. Additional analysis is beyond the scope of the report.
Peer Reviewer #5	Results	Beclomethasone should be beclomethasone dipropionate throughout as there are differences in potency of the 2 chemicals	In tables, we use the corticosteroid salt name, but in text we use the abbreviated name for greater readability. Only beclomethasone dipropionate is FDA-approved.
Peer Reviewer #5	Discussion/ Conclusion	Yes they are in 6 bullet points for the direct comparisons and then for the research gaps as well (of which there are many). Would also add that studies of CER of onset of action should be undertaken.	We are unable to identify this as a research gap because we did not search for studies that would assess onset of action. This limitation of the review is identified.
Peer Reviewer #5	Clarity and Usability	The literature review, organization and tone of writing are excellent. Research gaps for needed rigorous investigation are listed.	Thank you for the comment.
Peer Reviewer #5	General	The conclusions should be stated again that they are based on as rigorous studies as can be located and with the 2 week study requirement. Would also re-emphasize that the direct comparisons within a class such as intranasal corticosteroids or intranasal antihistamines are limited but such information would be informative for policy makers.	Study eligibility criteria are stated clearly in the Methods chapter and their consequences in the Limitations of Review.

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Peer Reviewer #6	General	Thank you for the opportunity to review this manuscript. I hope the comments and suggestions will be helpful. I have one general question about the concept of a review that also relates to the criteria for the inclusion of the studies. I assumed that this systematic review was performed to inform clinical practice and healthcare decision making. In this context, restricting a review only to direct comparisons of active treatments and dismissing indirect comparisons (e.g. several treatment options against placebo or non-FDA-approved medications) seems to reduce its clinical usefulness. Long lists of outcomes for which evidence is judged "insufficient" seem not helpful for clinicians.	The review was designed to assess the evidence provided by direct comparisons only. Based on our findings, subsequent reviews may include indirect comparisons.
Peer Reviewer #6	General	The authors themselves admit that the "absence of placebo arms particularly limited our assessment of harms, in which event reporting by patients receiving blinded placebo can be especially informative" (p.). The Authors provided a rationale for this choice stating that "this was a necessary decision given the volume of placebo-controlled trials and timelines for the project" (p. 228, l. 11-13). As much as it is hard to dispute with the limitations of resources to perform the review, lack of sufficient resources seems to be a questionable justification for compromising the usefulness of the work. Did the Authors consider a possibility of focusing on fewer comparisons but performing a thorough review of those selected ones? It might be beneficial if the Authors could explain their choice and provide some rationale for intentionally limiting the usefulness of their review for decision making. I understand the concept of comparative effectiveness but it's literary application here seems to have reduced the usefulness of the final product.	KQs were defined with input from Key Informants. Examination of the evidence for multiple treatment comparisons in several populations was desired rather than a narrower scope.
Peer Reviewer #6	General	Key questions of this review are important but are very broad. Not specifying a priori the real world clinical questions that the review intended to answer (i.e. those questions that are real choices that clinicians face in their daily practice) creates a risk of providing data-driven (or availability-of-studies-driven) answers and focusing on irrelevant comparisons. It seems to be beneficial if the Authors could specify which of the specific questions (specific comparisons within specific populations) were the most important from the point of view of current clinical practice.	We aimed to address a topic of importance to decision-makers within the constraints of a feasible project. As stated in the Methods section, "We sought expert guidance to identify drug class comparisons most relevant for treatment decision making." The treatment comparisons selected reflect input received from Key Informants, the TEP, and our Clinical Content Expert.

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Peer Reviewer #6	Methods Page 20, line 16-17 + page 43	"Articles were limited to those published in the English language, based on technical expert advice that the majority of the literature on this topic is published in English." Figure 3 shows 12 studies were excluded as not published in English. It might be beneficial if the Authors commented whether their results differed from the English language publications? As the studies with "negative" or less interesting results tend to be published in languages other than English, it might be beneficial if the Authors commented on the possibility of introducing language bias (see Cochrane Handbook chapter 10.2.2.4). It is generally considered that no language restrictions should be included in the search strategy (see Cochrane Handbook chapter 6.4.9). However, on page 242 line 41 the Authors reported restricting search to English language. It might be beneficial if the Authors reported if they screened titles and abstracts without language restrictions or after excluding non-English publications during the electronic search process.	Our Technical Expert Panel and Clinical Content Expert asserted that, in the field of allergic rhinitis research, the majority of the literature is published in English; thus, we reasoned that the potential risk of bias introduced by English language restriction would be minimal. Although it is possible that we could miss some important studies due to this restriction, in situations such as this, the amount of information gained by translating non-English language studies is generally not warranted by the effort required to do so.
Peer Reviewer #6	Methods Page 20, line 25-30	"Head-to-head randomized controlled trials (RCTs) were preferred, due to potential bias introduced in uncontrolled studies by the subjective reporting of both efficacy outcomes and harms in SAR research. For comparisons with sparse data from RCTs, we sought comparative observational studies that controlled confounders and were blinded." It might be beneficial if the Authors used a consistent terminology throughout the review. I am not sure what the Authors meant by "uncontrolled studies" in this context. Did they refer to observational studies without an independent control group (case series and case reports) or to non-randomized studies or some other study design? From the following sections of the document it seems they might have referred to observational studies in general but it is not clear. The above statement seems not consistent with the statement on page 46, line 28-30: "For the treatment comparisons, only head-to-head RCTs were selected; uncontrolled studies are prone to increased risk of bias due to the subjective reporting of both efficacy outcomes and adverse events in SAR research." It might be beneficial if the Authors clarified whether they "preferred" RCTs to observational studies or excluded observational studies.	Text revised to state: "For comparisons with sparse data from RCTs, we sought nonrandomized trials and comparative observational studies that controlled confounders and were blinded." Text revised to state: "Head-to-head RCTs were preferred; uncontrolled or noncomparative studies are prone to increased risk of bias due to the subjective reporting of both efficacy outcomes and adverse events in SAR research." A list of included study designs appears on page 13 and in Table 3 of the full report.

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Peer Reviewer #6	Methods Page 20, line 52-56 + Table 3 + page 53 + page 46	"Particular care was taken to ascertain whether patients were properly blinded to treatment, because all outcomes of interest were patient-reported. Open label trials and trials in which patient blinding was deemed inadequate received a quality rating of poor." Blinding of participants and care providers in a randomized trial seems to mostly serve the purpose of avoiding co-interventions and contamination rather than "objectifying" patient-reported outcomes. Blinding of outcome assessors seems more important when interpreting patient-reported outcomes. Lack of blinding may not introduce important bias and this should be assessed on an outcome level (as opposed to study level). It might be beneficial if the Authors reevaluated their ratings of risk of bias due to lack of blinding of patients in single studies.	We agree that "[b]linding of outcome assessors seems more important when interpreting patient-reported outcomes." In the *AHRQ Methods Guide*,[1] assessor blinding "especially with subjective outcome assessments" is emphasized for the avoidance of detection bias. Because patients are the assessors in patient-reported outcomes, we concluded that proper blinding of patients was highly important.
Peer Reviewer #6	Methods Page 46, lines 40-54	The Authors stated that "controlling for confounders, such as baseline comorbidities, baseline symptom severity, and pollen counts, was necessary" and "detection bias was addressed through blinding of outcome assessors or clinicians to drug exposure". The Authors listed those conditions as inclusion criteria. Does that mean that studies not fulfilling those criteria were excluded from the review? If so, it might be beneficial if the Authors provided the number of studies excluded based on, for instance, no control for baseline pollen counts. I am also not sure if blinding was a necessary inclusion criterion, was just "addressed" (how?) or was only the criterion when assessing the risk of bias in the studies. It might be beneficial if the Authors could consistently clarify it throughout the document since this issue has been described differently in different sections.	These features of observational study designs were never assessed because no observational studies were identified from our literature search despite the use of a very comprehensive search strategy for these studies. This has been stated more clearly in the Results of Literature Searches section. Text has been revised for greater clarity: The statement, "Trials were assessed for blinding of patients and assessors" has been removed from the discussion of inclusion and exclusion criteria.
Peer Reviewer #6	Methods Page 21, line 20-23 + page 54, lines 46-48	"Quantitative pooling of results (meta-analysis) was considered if three or more clinically and methodologically similar studies reported on a given outcome, and if each study reported variance estimates for group-level treatment effects." It might be beneficial if the Authors could provide rationale for their choice to pool only 3 or more studies. Why did they choose not to combine results when only 2 studies were available?	We added the following statement to the ES and the Full Report to clarify our rationale: "Meta-analyses based on very small numbers of studies tend to produce unstable effect estimates."

[1] Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov.

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Peer Reviewer #6	Methods Page 22, line 24-31 + page 56	"The strength of the body of evidence was determined in accordance with the AHRQ Methods Guide and is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Two reviewers independently evaluated the strength of evidence; agreement was reached through discussion and consensus when necessary. Four main domains were assessed: risk of bias, consistency, directness, and precision. The body of evidence was evaluated separately for each treatment comparison and each outcome of interest, to derive a single GRADE of high, moderate, low, or insufficient evidence." It might be beneficial if the Authors could clarify whether they assessed risk of publication bias, magnitude of effects, dose-response and influence of residual confounding in observational studies. Those are the other 4 criteria to be considered wen grading the quality of the body of evidence in the GRADE approach. If the Authors did not assess those they might want to clarify that they did not actually follow the GRADE approach but rather just selected criteria. If so, it might be beneficial to provide rationale for not evaluating the remaining criteria.	As stated in the *AHRQ Methods Guide*:[2] "The AHRQ EPC (Evidence-based Practice Center) approach is conceptually similar to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of evidence rating. • It requires assessment of four domains: risk of bias, consistency, directness, and precision. • Additional domains to be used when appropriate include dose-response association, presence of confounders that would diminish an observed effect, strength of association, and publication bias." Criteria included in the *Guide* for invoking publication bias concerns were not met. After this review was completed, an updated *Guide* was published that required assessment of reporting bias, defined as publication, outcome and selective analysis reporting bias.[3]
Peer Reviewer #6	Methods	A grade of "insufficient evidence" is not included in the GRADE approach and it might be reasonable to admit that the grading used here was a modification of the GRADE approach.	The report states: "The strength of the body of evidence was determined in accordance with the *AHRQ Methods Guide* and is based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system." The reference cited in the report states, "Strength of evidence receives a single grade: high, moderate, low, or insufficient."[4]
Peer Reviewer #6	Methods	Minor semantic comment: until now in the GRADE approach one assesses "quality of evidence" rather than "strength of evidence" to distinguish it clearly from "strength of recommendations".	Agree that the differences in terminology are largely semantic and that the AHRQ "strength of evidence" is conceptually similar to the GRADE "quality of evidence."

[2] Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews [posted July 2009]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.

[3] AHRQ Methods Guide Chapter, June 26, 2012. Grading the strength of a body of evidence when assessing health care interventions: an update. Available online at: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1163. Accessed September 2012.

[4] Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. March 2012. AHRQ Publication No. 12-EHC047-EF. Available at: www.effectivehealthcare.ahrq.gov.

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Peer Reviewer #6	Methods Page 44	"Antihistamines were classified into nonselective and selective subclasses." I wonder if the Authors could comment on the criteria they used to classify antihistamines into selective and nonselective. How did they determine that a given medication belonged to particular subgroup? How the groups were defined? To my knowledge there is no one agreed on and consistent classification of antihistamines.	As stated in the Background section: "Antihistamines used to treat allergic rhinitis bind the H1 histamine receptor selectively or nonselectively. By binding other receptor types, nonselective antihistamines can potentially cause adverse effects...In contrast, selective antihistamines may have reduced incidence of adverse effects." Text in the Methods section of ES and Full Report has been revised for greater clarity: "Selective and nonselective antihistamine (based on specificity for peripheral H1 receptors) were considered different classes."
Peer Reviewer #6	Methods Page 46, line 30-33	"Trials of less than 2-weeks duration were excluded as the most informative (highest quality) RCTs have a minimum treatment exposure of that duration, but minimum followup time was not required." Studies of at least 2 weeks duration are considered the "appropriate" design to assess treatments in SAR but studies of shorter duration may provide indirect evidence of the effects, especially when no studies of at least 2 weeks duration are available for a given comparison. I wonder if the Authors could provide rationale for excluding studies of less than 2 weeks duration and provide the number of studies excluded based on this criterion.	The rationale for the two-week minimum trial duration was explored in discussion with the TEP, and TEP agreed. The report is applicable to those who use SAR treatments for two weeks continuously and less so to those who use SAR treatments for shorter durations. This limitation of the review is noted in the Discussion section.
Peer Reviewer #6	Methods Page 47-48, table 3	I wonder if the Authors could provide information whether the outcomes of interest were selected a priori or based on what has been reported in the studies? This information seems to be important for readers as frequently different outcomes are needed for decision making than those that were measured in the studies.	Outcomes of interest were identified in the Protocol which was written with input from both Key Informants and the TEP.
Peer Reviewer #6	Methods Page 60, Figure 3.	15 studies were excluded as "mixed adult/children populations". This has not been stated to be an exclusion criterion and the questions asked in this review concerned both adults and children. It might be beneficial if the Authors explained why they excluded those studies despite that was not listed as exclusion criterion? I assume those studies did not report results separately for adults and children. Did the Authors consider including those studies if their results were consistent with results of studies done in adults and/or children separately?	Inclusion criteria for KQ4 are listed in the Full Report and state: "Inclusion criteria for RCTs, observational studies, systematic reviews, and meta-analyses were those outlined in Table 3 [for KQ1], with the exception that the study population was younger than 12 years old. For comparisons with sparse bodies of evidence, we considered inclusion of studies that mixed results for adults and children together."

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Peer Reviewer #6	Methods Page 65, line 49-52	"When meta-analysis was not possible, comparison of treatment effect magnitude among studies that used different symptom assessment tools was not feasible. In this situation, statistical significance of results was compared…". I wonder if the Authors could clarify what criteria determined whether meta-analysis was possible or not. I am not sure if I understand that sentence at all – would comparison of treatment effects be feasible if the symptoms were assessed with the same tool?	Criteria for pooling are provided in the Methods section and include the following statement: "[T]rials that used both different symptom rating scales and different calculations for treatment effects could not be pooled." Across studies that could not be pooled (e.g., due to lack of reported variance estimates for group-level treatment effects), comparison of treatment effects was feasible if symptoms were assessed with the same tool.
Peer Reviewer #6	Methods	I wonder if the authors could provide rationale for "vote counting" (comparing statistical significance) when meta-analysis was not done. This seems to be a particularly problematic approach that may provide misleading results (see Cochrane Handbook, Chapter 9.4.11).	For trials that could not be pooled, we sought a qualitative impression of whether results were precise.
Peer Reviewer #6	Methods Page 65, line 52-53	"Most trials could not be pooled due to inconsistent reporting of variance associated with group-level treatment effects" I am not sure if I understand what the Authors meant by "inconsistent reporting of variance". Does that mean that variance was not reported at all or that it was reported in different ways (e.g. as SD, SE and/or confidence interval)? This distinction seems important since in the former case one cannot pool the results (without imputing variance making assumptions about it) whereas in the latter one can pool converting SE or CI into SD. It might be beneficial if the Authors could clarify that in the manuscript.	Text revised: "Most trials could not be pooled due to lack of reporting of variance associated with group-level treatment effects."
Peer Reviewer #6	Methods	I was unable to find whether the Authors assessed the risk of publication bias and, if so, what was their judgment about that risk for all comparisons.	The ES states, "Four main domains were assessed: risk of bias, consistency, directness, and precision." The Full Report adds, "Additional domains (dose-response association, strength of association, and publication bias) were considered for assessment but deemed not relevant."
Peer Reviewer #6	Results	Given the questions about the methods I have not reviewed the results section.	No response required.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion/ Conclusion Page 227, line 22	"We did not find strong evidence for effectiveness or adverse effects in any treatment comparison." It might be beneficial if the Authors reworded this sentence. It may be read as if they did not find evidence for effectiveness or harm of the reviewed management options when they only did not find high quality evidence about superiority of one option over another (since the Authors did not look at comparisons vs placebo). It might also be beneficial if the authors defined what they meant by "strong" evidence. This has not been explained anywhere in the text.	Text revised to state: "We did not find high strength of evidence for differences in effectiveness or adverse effects in any treatment comparison."
Peer Reviewer #6	Discussion/ Conclusion	"Given the lack of high strength evidence for superior effectiveness of one treatment over the other, differential costs of treatments may not be warranted." Please see the comment above about the unclear meaning of "high strength" evidence. I wonder if whether this statement is justified. First, lack of evidence of superiority is not equal to evidence of no superiority and second, I am not sure whether costs of treatments should be determined only by their effectiveness. It might be beneficial if the Authors reconsidered their conclusion and, if they choose to communicate it unchanged, provided rationale for their judgment.	The statements have been changed to: "This evidence may be insufficient for policy decisionmaking. For example, although conclusions of comparable effectiveness may suggest that differential costs of treatments are unwarranted, lack of evidence to evaluate comparative harms of these treatments prohibits full assessment of their risk-benefit profiles."
Peer Reviewer #6	Discussion/ Conclusion Page 227, line 31-35	"Given the lack of high strength evidence for reduced harms with one treatment compared to the other, differential dispensing (over the counter or prescription only) may not be warranted". Similarly to the statement about efficacy above lack of evidence of increased harm is not equal to evidence of no increased harm. I am particularly not sure whether this conclusion is justified since 1) the Authors admitted that this "is tricky, however, because adverse events that are innocuous in most may be dangerous in some", 2) the Authors admitted that the review restricted to comparisons of active treatments may not be sufficient to assess adverse effects – they actually write in the conclusions [p. 230] that "evidence was insufficient regarding harms" – and 3) mode of dispensing of medications (over the counter or prescription only) seems to depend on many other factors, for instance, severity of potential overdose. Those and other factors have not been investigated in the reviewed studies. As above, it might be beneficial if the Authors reconsidered their conclusion.	The Discussion of Key Question 2 has been substantially revised for greater clarity. The cited statements have been deleted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion/ Conclusion Page 230, line 35-46	The Authors make several statements about potential superiority of some treatments based on their effect on single outcomes. The conclusions about superiority (as well as non-inferiority, equivalence etc.) of one treatment over another should be made based on consideration of all patient-important outcomes together. It seems clinically not useful to compare treatment based on their impact on single symptoms/outcomes. It might be beneficial if the Authors considered rephrasing this part of the conclusions as well.	AHRQ Methods Guide states:[5] "EPCs should grade strength of evidence separately for each major outcome and, for Comparative Effectiveness Reviews, all major comparisons."
Peer Reviewer #6	Clarity and Usability	It might be beneficial if the Authors reviewed the document for consistency of the description of methods (see comments above).	Report reviewed as suggested.
Peer Reviewer #7	General	The report is clinically relevant and is consistent with clinical practice and the findings of other expert panel reports. It points to an edge for intranasal steroids alone or in combination with selective antihistamines which is my clinical experience. The section on research gaps points clearly to important areas that need further work.	No response required.
Peer Reviewer #7	Introduction	The Executive Summary is excellent and clearly presents the wealth of data presented in this review.	Thank you for the comment.
Peer Reviewer #7	Methods	The methods seem state of the art and the selection of studies for inclusion unbiased.	Thank you for the comment.
Peer Reviewer #7	Methods	I did not find the comparison tables with the blacked out areas clear or helpful.	Report authors and AHRQ agreed upon table format after discussion.
Peer Reviewer #7	Results	There seems to be a misstatement in the Results section: However, to avoid a bitter aftertaste there is low strength evidence that nasal antihistamine alone is preferred. Should nasal read oral? It is the nasal antihistamines that give the bitter aftertaste.	The statement is from the Structured Abstract and is made in comparison to combination intranasal corticosteroid plus nasal antihistamine.
Peer Reviewer #7	Results	The results are well summarized by the Tables.	No response required.

[5] Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews [posted July 2009]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion/ Conclusion	The discussion is excellent and clearly lays out the major findings as well as the limitations of the studies and areas for further research.	Thank you for the comment.
Peer Reviewer #7	Clarity and Usability	The structure is excellent and allows the reader to move from the general to the detailed specifics of the study-to drill down to the information supporting the study report conclusions.	Thank you for the comment.
Peer Reviewer #7	Clarity and Usability	For practice it informs us on the treatment modalities that have solid scientific support and a caution that the impact of our drug therapies may not be as effective as we believe. The findings on decongestants are revealing in this regard.	No response required.
TEP #2	General	I felt the report to be useful and having meaningful value. It was disappointing to find the research was found to be done as poorly as it was and to have as many gaps in it. I was hoping more definitive guidance would be revealed. Report clearly shows why those gaps exist. Audience is well defined. I feel the key questions are clearly defined and appropriate. Report is clearly written and consistent in format, making it easier to read through	Methods, Results, and Discussion, of ES and Full Report, and Conclusions of Full Report, revised to emphasize more the limitations to forming conclusions.
TEP #2	Introduction	Clearly defines the category of SAR, its pathophys, treatment and impact. The planned scope of this report is plainly laid out as well as the rational for the key questions. Very succinct.	Thank you for the comment.
TEP #2	Methods	Criteria were laid out clearly and all were appropriate. I am not a statistician so these parts of the methods are beyond me being able to give any meaningful input. From a non-statistician's viewpoint, I found the parts of Risk of Bias and quality to be somewhat confusing. That may well be my lack of personal understanding of these areas, although I suspect I am pretty typical of most practicing doctors. Similar thoughts apply to heterogenecity and clinical diversity measures. The section on MCID was quite clear to me. SMD seemed to be arbitrarily defined. How this was determined and exactly what it represented was unclear to me.	Translation of USPSTF quality ratings of individual trials to GRADE risk of bias assessments is clarified in the following revised text: "Risk of bias was based on USPSTF quality ratings of trials that reported on a given outcome, weighted by sample size using a semi-quantitative method. For example, if less than half of patients were in good quality studies, the risk of bias was considered medium." For heterogeneity and clinical diversity, the following text was added: "We explored statistical heterogeneity (defined as variability in observed treatment effects due to clinical and/or methodological diversity, biases, or chance) and clinical diversity (defined as variability in study population characteristics, interventions, and outcome assessments) by performing subgroup analysis, sensitivity analysis, and meta-regression if possible." After revising our method of data synthesis (as described in the revised Methods section), SMD was no longer used to compare effect sizes across studies.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	Results presented in a very thorough and consistent manner. The lack of good studies for all the comparisons is made very evident. Funding by industry is referenced in many comparisons but not all. Do I assume that if not mentioned, it is unknown or that it is not funded by industry? Maybe a column or section putting into one of 3 groups re industry funded - yes, no, unknown.	In the Results section, funding is reported in the narrative description of the evidence for each comparison in KQ1 and KQ4. Appendix Table C lists funding for each included trial by comparison.
TEP #2	Results	I never got a good handle despite reading the methods and the Appendix E re level of bias - or at least got comfortable in my understanding of it. Not always addressed in the body of the report or in the tables.	USPSTF quality assessment tables for each comparison are shown in Appendix C. The translation of USPSTF quality ratings of individual trials to GRADE risk of bias assessments is clarified in the following revised text: "Risk of bias was based on USPSTF quality ratings of trials that reported on a given outcome, weighted by sample size using a semi-quantitative method. For example, if less than half of patients were in good quality studies, the risk of bias was considered medium." In Results for KQ1, risk of bias is described in the Key Points, Strength of Evidence table, and Synthesis and Strength of Evidence text for each outcome that had sufficient evidence to form a conclusion.
TEP #2	Results	In the adverse effects (Key Question #2), risk of bias is more consistently addressed.	No response required.
TEP #2	Results	Key Questions 3 & 4 laid out the limitations well. Thus, not much to discuss.	No response required.
TEP #2	Discussion	The lack of validated MCIDs was very well written and clearly addressed the impact on this report.	Thank you for the comment.
TEP #2	Discussion/ Conclusions	Limitations are well delineated, including the lack of many direct comparisons. Research Gap section details the multiple holes that need to be filled. Fertile ground for residencies looking to do research. Description of PICOTS was nicely done and a new term for me, one who spends the day seeing patients. Sections on limitations of evidence process and evidence base are clearly stated and understandable, even to a non-academician.	No response required.
TEP #2	Clarity and Usability	Because of the multiple of comparisons, parts of the results seem to be repetitive although they are not. Format is clear and maintained throughout the report, making it easier to find the same information for one comparison to another. This can guide a formulary committee to make a few general decisions re sequencing therapeutic decisions but not for the actual drug itself. Patient preference and tolerance rise to top of considerations based on this report.	No response required.
TEP #3	General	This is a comprehensive review of the literature pertaining to treatment of seasonal allergic rhinitis.	No response required.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Executive Summary	The Executive Summary is excellent.	Thank you for the comment.
TEP #3	Introduction	The Introduction outlines the rationale for the Key Questions.	No response required.
TEP #3	Methods	The Methods clearly define the process of study selection and evidence grading.	No response required.
TEP #3	Results	The studies are adequately described & the tables are user friendly.	Thank you for the comment.
TEP #3	Discussion/ Conclusion	The Research Gaps section articulates the need for methodologic rigor in future trial design & inclusion of populations such as minorities, the elderly, children & pregnant women. However, because they involve vulnerable populations, inclusion of children & pregnant women in rigorously designed studies of pharmacologic treatment is ethically problematic.	The following text was added to Research Gaps: "Ethical considerations limit the inclusion of children and pregnant women in well-designed studies of pharmacologic interventions."
TEP #3	Clarity and Usability	The report is well organized and emphasizes the paucity of high level evidence informing the treatment of SAR in various populations.	Thank you for the comment.
TEP #8	General	Would suggest mentioning intracocular pressure as a safety concern with nasal steroids	Increased intraocular pressure is listed among adverse effects of interest for intranasal corticosteroids.
TEP #8	Executive Summary, page ES-1, line 23	Shiners are not limited to children, not even sure the salute is limited either	Text revised in Background sections of ES and Full Report.
TEP #8	Executive Summary, page ES-1, line 30	Avoidance is always the preferred treatment but in this case it may not be feasible-think that wording would be better	Text revised in Background sections of ES and Full Report
TEP #8	Executive Summary, page ES-1, line 56	Also a concern about increased eye pressure in adults	Text revised in Background sections of ES and Full Report: "Adverse local effects may include increased intraocular pressure, nosebleeds, stinging, burning, and dryness."
TEP #8	Introduction, page 3, line 20	and increased intraocular pressure J Allergy Clin Immunol. 2005 Nov;116(5):1042-7. Epub 2005 Oct 3. **Discontinuing nasal steroids might lower intraocular pressure in glaucoma.**	Text revised in Background sections of ES and Full Report: "Adverse local effects may include increased intraocular pressure, nosebleeds, stinging, burning, and dryness."
TEP #8	Introduction, page 3, line 35	I don't they are 'often' prescribed before	Text revised: "Intranasal decongestants (e.g., oxymetazoline) may be administered before an intranasal corticosteroid or an intranasal antihistamine to increase delivery of these drugs."

Commentator & Affiliation	Section	Comment	Response
TEP #8	Methods, page 21, line 51	The World Allergy Association recommends 20% over placebo Consequently the minimal clinically relevant efficacy should be at least 20% higher than placebo (34) Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007;62(3):317-24.	The recommendation of the World Allergy Association (WAA) is based on a systematic review that "considered a difference of 10% in nasal score…to be clinically relevant."[6] Because of this inconsistency, the WAA was not cited.
TEP #9	General	This is an excellent review of existing evidence regarding the relative effectiveness of treatments for allergic rhinitis. The methodology, review of procedures, approach, background, and conclusions are appropriate, useful, and well written. As a clinician I will make use of this report in my own daily work and I am confident that other primary care providers will feel the same. The executive summary did an excellent job of laying out the work clearly and the full report then provided the additional resources needed for the reader who desires more details. I believe the executive summary will generally be the document used by clinicians - as it should be.	Thank you for the comment.
TEP #9	Introduction	The introduction to this report was very well written and logical. There was a clear review of the need for the report and the basis for the methodologic approach taken. The structured approach to breaking down these distinct components is critical to laying out the importance and utility of the report. The background section was appropriate and sufficiently detailed. The Burden of Disease and Pathophysiology sections also provided helpful frameworks for reviewing the content. The Treatment review was very helpful for laying out the approaches taken by clinicians currently - without focus on the evidence for particular approaches. The detail of the treatment approaches was sufficiently detailed. Figure 1 , the analytic framework, was very helpful for halping guide the reader through the key questions and analysis.	Thank you for the comment.

[6] Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med. 2004 Mar 1;116(5):338-44.

Commentator & Affiliation	Section	Comment	Response
TEP #9	Methods	The inclusion and exclusion criteria used for the report are very clear and fully justifiable. The approach to searching studies is fully within the methodologic standards used for studies such as these. The definitions and disgnostic criteria for outcomes are fully appropriate and well within the standard used by clinicians for this disorder and the treatments used for them. The statistical methods are also fully appropriate.	Thank you for the comment.
TEP #9	Results	The detail provided in the results sections of the report (in the exec summ and full report) are adequately detailed to support the use of the guide. The characteristics of the studies reviewed are adequately described and also referenced so that if a reader needed additional information they could look up the study in question. In my own experience the majority of users of this report will be clinicians and educators and this level of detail is sufficient. More detail would be unnecessary and distracting. I am not aware of additional studies that were not included in the review. I do not believe that any unnecessary studies were included that should be excluded.	No response required.
TEP #9	Discussion/ Conclusion	The implications for the major findings are clear and the need for additional studies - as well as the areas that are needed are also well defined.	No response required.
TEP #9	Clarity and Usability	Yes the study is extremely well structured and organized. The authors should be commended for their work on this review. The conclusions can be directly used to inform health care policy as well as the work of individual providers.	Thank you for the comment.
TEP #10	General	The terms “chromones”, “mast cell stabilizers” and “cromolyn” are used interchangeably throughout the text. Since the only “chromone” used of SAR in the US is cromolyn, it may be better from the perspective of consistency to use only that term with an explanatory statement early on in the text. Similarly, the terms “oral leukotriene inhibitors” and “leukotriene receptor antagonists” are used interchangeably. The latter is more accurate since 5-LO inhibitors (the other group of leukotriene inhibitors) have not been used for SAR.	Changes made as suggested.
TEP #10	Executive Summary, page ES-1	What’s described for children are “signs”, not “symptoms”	Change made in background of both ES and Full Report

Commentator & Affiliation	Section	Comment	Response
TEP #10	Executive Summary, page ES-1	Since comparisons between selective and non-selective antihistamines were sought, and since this distinction permeates the report, it is important to provide a Table in this section with "selective" and "non-selective" antihistamines that were identified in articles that were used in the review (similar to Table 1 of the main section of the report)	Distinction is described clearly in text in the ES.
TEP #10	Executive Summary, page ES-1	I think that, for sedation, it is not a matter of a different receptor, but a matter of crossing the blood-brain barrier	Text revised as suggested.
TEP #10	Executive Summary, Figure A	Would add insomnia here	Text revised as suggested.
TEP #10	Executive Summary, Table B	Which item on the Table does this refer to?	Superscript added to table.
TEP #10	Executive Summary, page ES-13	My concern with the term "insufficient evidence" is that it suggests that there is no evidence to draw ANY conclusion (too few studies, statistical power issues) and not that there is no evidence of a difference between two treatments. You need to clarify this repetitively, to avoid confusion.	The specific sentence cited has been modified to state: "…evidence was insufficient to draw any conclusion about effectiveness between treatments."Similar revisions have been made throughout the ES and Full Report.
TEP #10	Executive Summary, page ES-13	Is it a "problem" of decongestants or is it that antihistamines do show some effectiveness against this symptom that appears to be as close as that of decongestants? That's an important distinction to make.	Text in ES and Full Report revised for greater clarity: "This calls into question what is perhaps accepted wisdom about the greater efficacy of oral decongestants over oral selective antihistamines for nasal congestion."
TEP #10	Executive Summary, page ES-14	Isn't this finding negated by the fact that there was low strength evidence that INCS have stronger effects than oral S-AH in nasal symptoms, when directly compared (item 4bi)? This issue should be commented upon	The following sentence has been added: "This is consistent with the finding of low strength evidence for the comparative effectiveness of intranasal corticosteroid over oral selective antihistamine for the relief of nasal symptoms."
TEP #10	Executive Summary, page ES-14	As per an earlier comment, better refer to this as cromolyn as there are minimal to no studies with the only other chromone, nedocromil.	Text revised as suggested.
TEP #10	Executive Summary, page ES-16	With the exception of some onset of action trials, the vast majority of trials of SAR are of at least 2 weeks duration; your point about "onset of action" is correct, but there is no evidence that you would have caught effects on people with milder disease if you were to examine trials of shorter duration	Text in the ES and Full Report has been modified as suggested.
TEP #10	Executive Summary, page ES-16	It is worth mentioning here, however, that very rarely are such symptoms assessed	Text revised to state: "Symptoms potentially important to patients but seldom assessed (e.g., post-nasal drip, and ear and palate itching) were not included in this review."

Commentator & Affiliation	Section	Comment	Response
TEP #10	Executive Summary, page ES-16	Another gap that you may want to consider is the lack of appropriate clinical trial designs that can test more efficiently the concept of "two meds vs one". By that, I mean that when one wants to know whether adding an antihistamine to a nasal steroid is of any help, the correct design is to place everybody on a steroid and only enter in the second phase of the trial those people who did not get adequate relief by the steroid.	Text added to the Discussion of ES and Full Report: "Study designs that can more efficiently assess the effects of additive therapies also are lacking. That is, studies in which all patients are treated with one component of a combination (e.g., intranasal corticosteroid) and only those who are resistant receive the second component may more efficiently isolate the additive effect of the second component."
TEP #10	Executive Summary, page ES-16	Another clinical trial design that may be important for the evaluation of SAR medications, but is relatively absent in the literature is the preventive design in which people with SAR are started on treatment PRIOR to the development of rhinitis symptoms.	The trial design proposed addresses the prevention rather than treatment of SAR symptoms, which is beyond the scope of the review.
TEP #10	Introduction, page 2	Not aware that LTs can stimulate cholinergic nerve fibers. The effect of LTs on glands is most probably due to direct activation of LT receptors on glandular epithelial cells.	Correction made.
TEP #10	Introduction, page 2	Add basophils	Added.
TEP #10	Introduction, page 3	These maybe theoretical concerns, but, given that no evidence has emerged with SAR treatment, I think you should state that here; otherwise, the text may be misleading. On the other hand, the local side effects are very real.	Text revised as follows: "Intranasal corticosteroids do not appear to cause adverse events associated with systemic absorption (e.g., adrenal suppression, bone fracture among the elderly, and reduced bone growth and height in children)."
TEP #10	Introduction, page 3	Not often; they are only used this way if the patient has very severe nasal airway obstruction	Text revised: "Intranasal decongestants (e.g., oxymetazoline) may be administered before an intranasal corticosteroid or an intranasal antihistamine to increase delivery of these drugs."
TEP #10	Introduction, page 6	Is there evidence to support any of these or are these theoretical risks? If the latter, it needs to be stated.	Text revised as follows: "Potential adverse events resulting from systemic absorption, such as impaired bone growth, reduced height, suppression of the adrenal axis, hyperglycemia, and weight gain, have not been definitively demonstrated."
TEP #10	Results, page 32	Was a TNSS minus congestion outcome where the analysis failed to find a difference between these two classes? If that is the case, the finding is biased by the fact that the only symptom oral decongestants are supposed to be efficacious is removed.	No, this outcome was defined a priori. Text revised as follows: "Trials comparing oral antihistamine and oral decongestant assessed "TNSS minus congestion" (defined a priori) because of the known differential efficacy of the drugs for treatment of congestion."
TEP #10	Results, page 100	There is something unsettling about these trials. Knowing that a nasal steroid is overall superior to an oral antihistamine, what is the rationale for these trials?	No response required.

Commentator & Affiliation	Section	Comment	Response
TEP #10	Results, page 100	It is also bizarre that the outcome of this review suggests that the difference of the combination of an oral antihistamine and a nasal steroid against an antihistamine alone appears less impressive than the difference between a nasal steroid and an oral antihistamine (earlier analysis). Is there a suggestion here that adding an oral antihistamine reduces the effectiveness of nasal steroids?	Evidence for efficacy of (1) combination intranasal corticosteroid plus oral selective antihistamine over oral selective antihistamine alone and (2) intranasal corticosteroid over oral selective antihistamine for nasal symptoms was low strength. Although the magnitude of treatment effects for the latter comparison (0.45) were greater than those for the former (0.1 to 0.3), direct comparison of the findings may not be warranted due to differences in timing of outcome assessments (2 weeks vs. 4 weeks) , nasal symptoms assessed, and number of trials reporting (1 vs. 4 to 6).