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**ARTICLE DETAILS**

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: A systematic review and network meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Tricco, Andrea; Strifler, Lisa; Veroniki, Areti Angeliki; Yazdi, Fatemeh; Khan, Paul; Scott, Alistair; Ng, Carmen; Antony, Jesmin; Mrklas, Kelly; D'Souza, Jennifer; Cardoso, Roberta; Straus, Sharon</td>
</tr>
</tbody>
</table>

**VERSION 1 - REVIEW**

| REVIEWER            | Kayleigh M Kew  
|                     | St George's, University of London  
|                     | United Kingdom |
| REVIEW RETURNED     | 15-Jul-2015 |

**GENERAL COMMENTS**

This is an incredibly thorough and well conducted piece of work. My comments are below, which I believe can be incorporated with revisions or additions to the manuscript.

My major concerns, described in more detail below, are:
1) Including trials of all durations
2) Incomplete transitivity assessment prior to conducting the networks
3) The large number of nodes in the networks
4) Out of date search

The abstract would benefit from more information on the methods and less detail of the results, especially the secondary outcomes. In particular, I would like to see the basic trial inclusion criteria stated (RCTs, list of combinations, all durations), and whether the networks were constructed to compare separate drugs, different doses, or classes of drugs. The objective would be better stated as it is later in the background as "what is the comparative safety and effectiveness of long-acting inhaled agents (ICS, LABA, LAMA), alone or in combination, for patients with COPD?"

The abstract conclusions could do with fleshing out a little to say something a bit more specific - what are the implications?

Given the nature of some of the outcomes, it might have been more reliable to look only at trials of at least 8 weeks (or similar) rather than any duration. I appreciate that a meta-regression was done to explore study duration, but I would like to see a more comprehensive assessment for transitivity between comparisons with regard to the patient severity characteristics and length of study in particular to justify combining the studies in a network. We found
that the sponsoring drug companies differed significantly in the average duration of their trials and this may have affected the validity of the networks. Perhaps a table presenting key patient and study data for each comparison would rectify this, to go alongside the tables for each study you have in Appendix 7 and 8.

I would like to see more detail in the methods about how study arms were grouped for analysis. It appears that all treatments/treatment combinations were dealt with as individual nodes, but this is not clear until the results. As a result of wide eligibility criteria and including all treatments and combinations separately, there are a lot nodes and sometimes hundreds of comparisons which has lead to results and outputs that are very difficult to interpret clinically, and vague conclusions.

The discussion does a good job placing this work in the wider research context. I think the comparisons with other reviews might benefit from a discussion regarding differences in their eligibility criteria and the effect this might have had on a) the differences in results and b) the reliability and applicability of the findings.

I did not spot the search date until the discussion and I would suggest stating this in the methods. It's a shame that it is already 19 months out of date and presumably more by publication, and unfortunately this does limit the results, especially in light of preparations that have emerged in that time (as you correctly recognise).

Nb. Apologies if my comments relate to information that was presented in the figures - the PDF I received could not display them.

REVIEWER
Rita Pavasini, MD
University Hospital of Ferrara (Italy)

REVIEW RETURNED
17-Jul-2015

GENERAL COMMENTS
The Authors wrote a complete and well-organized NMA on comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease.

Minor revision:

1- A definition of cardiovascular related mortality is necessary, or better a table that resume the definition in every study of cardiovascular mortality (also available as supplementary material).
2- Authors valued the association between the treatment with long-acting inhaled agents and arrhythmias, but which kind of arrhythmias did the author consider? Brady or tachyarrhythmia? And which one of those? Please a definition is necessary.
3- Are data used for the analysis all-present in full papers or did you need to ask authors for some of these? If yes, please specify in methods.
4- There is no mention of any of the factors used at multivariate analysis in studies, please specify.
5- A better description of the role of inhaled corticosteroids alone and cardiovascular mortality is necessary, both in the main text of the article and also in the table 3, if possible.

Discretionary revision:
1- I think that some of the forest plot could be used in the main article and not in supplementary material.

REVIEWER  Andrea Berghold  
Institute for Medical Informatics, Statistics and Documentation,  
Medical University of Graz, Austria

REVIEW RETURNED  05-Aug-2015

GENERAL COMMENTS  The authors did a tremendous amount of work comparing safety and effectiveness of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD in a systematic review and network meta-analysis. They included parallel-group RCTs regardless of duration of follow-up, date of dissemination or publication status. It is a very well written and organized manuscript. 

Just a few minor comments and a question: 
In the abstract I would like to read a more informative conclusion as is stated so far (cf see conclusion of discussion part). In Appendix 7 the characteristics of the trials are listed: correct Sugiura – 2 instead of 1 treatment; published 2003 instead of 2002 (reference list number 40). Did you do any explorative subgroup analysis by severity of COPD, gender and age as stated in the protocol? Perhaps just a short statement could be given.

VERSIO 1 – AUTHOR RESPONSE

Reviewer #1

1. This is an incredibly thorough and well conducted piece of work. My comments are below, which I believe can be incorporated with revisions or additions to the manuscript. My major concerns, described in more detail below, are:
   1) Including trials of all durations
   2) Incomplete transitivity assessment prior to conducting the networks
   3) The large number of nodes in the networks
   4) Out of date search

Response: Thank you very much for taking the time to review our paper. We will respond to each of your major concerns below.

2. The abstract would benefit from more information on the methods and less detail of the results, especially the secondary outcomes. In particular, I would like to see the basic trial inclusion criteria stated (RCTs, list of combinations, all durations), and whether the networks were constructed to compare separate drugs, different doses, or classes of drugs. The objective would be better stated as it is later in the background as "what is the comparative safety and effectiveness of long-acting inhaled agents (ICS, LABA, LAMA), alone or in combination, for patients with COPD?"

Response: We have now included additional information on the methods, specifically the basic trial inclusion criteria (RCTs, all drug combinations). We added the phrase “alone or in combination” on line 35 to clarify the inclusion criteria and therefore did not revise our objective to include this phrase: “LABA, LAMA, and/or ICS, alone or in combination, versus each other or placebo.”

3. The abstract conclusions could do with fleshing out a little to say something a bit more specific what are the implications?
Response: We have revised our discussion in the abstract on lines 62 to 64, as follows “Many inhaled agents are available for COPD, some are more effective than others and some may increase the risk of harm (e.g., pneumonia). Our results can be used by patients and physicians to tailor administration of these agents.” However, we are only allowed 300 words for the abstract, so it is difficult for us to make further comments on the implications here. The abstract has been shortened and is now 294 words.

4. Given the nature of some of the outcomes, it might have been more reliable to look only at trials of at least 8 weeks (or similar) rather than any duration. I appreciate that a meta-regression was done to explore study duration, but I would like to see a more comprehensive assessment for transitivity between comparisons with regard to the patient severity characteristics and length of study in particular to justify combining the studies in a network. We found that the sponsoring drug companies differed significantly in the average duration of their trials and this may have affected the validity of the networks. Perhaps a table presenting key patient and study data for each comparison would rectify this, to go alongside the tables for each study you have in Appendix 7 and 8.

Response: Thank you for your comment. As noted in our paper on lines 163 to 168, we examined several factors to assess the transitivity assumption: “Before conducting the analyses, we assessed the transitivity assumption by exploring whether any systematic differences were prevalent in the distribution of potential treatment effect modifiers across treatment comparisons in the network. For each outcome, we examined the percentage of female participants (gender) in the RCTs and the risk of bias results. For the moderate-to-severe exacerbations outcome, we also examined RCTs with eligibility criteria focusing on patients who experienced an exacerbation in the past year and severity of COPD.” As well, we conducted meta-regression on the study duration, as noted by the reviewer. It would have been much easier for us to exclude studies that were less than 8 weeks in duration, but our study is more comprehensive than this approach. We would gladly insert these tables, but there would be many of them (we have 5 outcomes) and all of the information is already included in our Appendix, which is over 100 pages.

5. I would like to see more detail in the methods about how study arms were grouped for analysis. It appears that all treatments/treatment combinations were dealt with as individual nodes, but this is not clear until the results. As a result of wide eligibility criteria and including all treatments and combinations separately, there are a lot nodes and sometimes hundreds of comparisons which has lead to results and outputs that are very difficult to interpret clinically, and vague conclusions.

Response: We have clarified on lines 156 to 162 in the methods that all single treatments and treatment combinations were dealt with as individual nodes: “The treatment nodes of the network were selected based on input from clinicians, methodologists, and statisticians on the team. Due to the complexity of the analysis, we did not account for differences in doses and durations assuming that all impact the treatment effect equally. Specifically, when a study compared different doses of an intervention against another intervention, we included only the recommended dose in the analysis. As well, we conducted a specific drug analysis versus a drug class analysis, as this was what the policy-makers associated with the ODPRN requested.” We acknowledge and agree that our eligibility criteria and approach of including all treatments/treatment combinations as individual nodes has led to results and outputs that are difficult to interpret. However, we felt that it did not make sense clinically to combine treatments/treatment combinations within the same node, as this is a specific drug analysis and not a drug class analysis, which our policy-makers and clinicians felt was more relevant.

6. The discussion does a good job placing this work in the wider research context. I think the comparisons with other reviews might benefit from a discussion regarding differences in their eligibility criteria and the effect this might have had on a) the differences in results and b) the reliability and applicability of the findings.
Response: Thank you for the suggestion. We have now added information on the eligibility criteria (in particular study duration criteria) for the other systematic reviews mentioned in our discussion, and have noted that differences in eligibility criteria may lead to different results, reliability, and applicability of findings on lines 345 to 350 "Inclusion criteria included patients with moderate to severe COPD and trials of at least 24 weeks’ duration. A second network meta-analysis of inhaled drugs for COPD in trials of at least 4 weeks’ duration concluded that ICS/LABA combination therapy reduced exacerbations only in patients with low forced expiratory volume.[8] Differences in study eligibility will lead to slightly different network meta-analysis results, reliability, and applicability, due to variations in the network of trials.”.

7. I did not spot the search date until the discussion and I would suggest stating this in the methods. It’s a shame that it is already 19 months out of date and presumably more by publication, and unfortunately this does limit the results, especially in light of preparations that have emerged in that time (as you correctly recognise).

Response: The search date is stated on line 127 in the methods section, under the heading Information sources and literature search. We have re-run our full search strategy since our last search date, in December 2013, and included a summary of the published trials meeting our inclusion criteria in our Supplementary File: Appendix 15. We have provided a summary of these trials in the discussion on lines 393 to 407: “First, we are aware of 21 new trials that have been published in 16 papers since our original literature search in December of 2013 (Appendix 15). This is particularly apparent for the LABA/LAMA combinations. The number of new trials that would be included by outcome are: 4 trials with 157 patients for moderate-to-severe exacerbations (comparisons include LAMA vs. LAMA, ICS/LABA vs. LABA, and LABA/LAMA vs. LAMA vs. LABA vs. placebo); 16 trials with 104 patients for mortality (comparisons include LABA vs. LABA vs. placebo, ICS/LABA vs. LABA, ICS/LABA vs. LAMA, ICS/LABA vs. ICS/LABA, and LABA/LAMA vs. LAMA vs. LABA vs. placebo); 16 trials with 148 patients for pneumonia (comparisons include LABA vs. LABA vs. placebo, ICS/LABA vs. LABA, ICS/LABA vs. LAMA, ICS/LABA vs. ICS/LABA, and LABA/LAMA vs. LAMA vs. LABA vs. placebo); 13 trials with 125 patients for serious arrhythmia (comparisons include LAMA vs. LAMA, ICS/LABA vs. LABA, ICS/LABA vs. ICS/LABA, and LABA/LAMA vs. LAMA vs. LABA vs. placebo); and 7 trials with 11 patients for cardiovascular-related mortality (comparisons include ICS/LABA vs. ICS/LABA, and LABA/LAMA vs. LAMA vs. LABA vs. placebo)."

8. Nb. Apologies if my comments relate to information that was presented in the figures the PDF I received could not display them.

Response: All of your comments were greatly appreciated and informative.

Reviewer #2

1. The Authors wrote a complete and well-organized NMA on comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease.

Response: Thank you very much for taking the time to review our paper.

2. Minor revision 1: A definition of cardiovascular related mortality is necessary, or better a table that resume the definition in every study of cardiovascular mortality (also available as supplementary material).

Response: We have a list of the different definitions of cardiovascular mortality used in the studies included in our analysis and can share this upon request. Definitions of cardiovascular mortality
included cardiac arrest, aortic aneurysm, and myocardial infarction. We have added these on lines 281 to 282.

3. Minor revision 2: Authors valued the association between the treatment with long-acting inhaled agents and arrhythmias, but which kind of arrhythmias did the author consider? Brady or tachyarrhythmia? And which one of those? Please a definition is necessary.

Response: We considered all types of arrhythmias as part of our inclusion criteria. For our NMA, we looked at serious arrhythmia (including atrial fibrillation, tachycardia) as we felt it did not make sense clinically to combine all types of arrhythmias. We have a list of the different definitions of serious arrhythmia used in the studies included in our analysis and can share this upon request. We have clarified this on lines 324 to 325 and have specified that we were specifically looking at serious arrhythmias throughout the paper.

4. Minor revision 3: Are data used for the analysis all present in full papers or did you need to ask authors for some of these? If yes, please specify in methods.

Response: Our analysis is based on data as reported by the study authors, we did not ask for additional data. We did contact authors of study protocols, conference abstracts and non-English articles to ask for full text publications in English. We have clarified this in our methods section on lines 122 to 124: “Authors were contacted for unpublished data obtained through study protocols and conference abstracts, as well as English translations of non-English articles.”

5. Minor revision 4: There is no mention of any of the factors used at multivariate analysis in studies, please specify.

Response: Since we included the raw data of the randomized trials, we did not specifically examine factors used in multivariate analysis in the included studies. For the multi-variate analysis that we conducted, the only covariate was the study duration, which is noted in our methods section on lines 174 to 176: “We explored the effect of study duration in a random-effects meta-regression analysis for mortality and exacerbation outcomes, assuming a common fixed coefficient across treatment comparisons”.

6. Minor revision 5: A better description of the role of inhaled corticosteroids alone and cardiovascular mortality is necessary, both in the main text of the article and also in the table 3, if possible.

Response: We report the results for ICS and cardiovascular mortality on line 289: “In addition, fluticasone was superior to tiotropium (Soft Mist Inhaler)” and on lines 293 to 296: “According to the SUCRA curves (Supplementary File: Appendix 12), the following were the most harmful: triamcinolone acetonide (81% probability of being the most harmful because of a greater risk of cardiovascular-related mortality)...”. Table 3 reports only the statistically significant comparisons for this, and all other, outcomes. Given the large number of comparisons we were unable to report them all in the table. One of the postulated concerns about use of LABA is potential for increased risk of cardiovascular mortality but we did not find a significantly increased risk. Similarly, we did not see an increased risk of arrhythmia with these agents.

7. Discretionary revision 1: I think that some of the forest plot could be used in the main article and not in supplementary material.

Response: Unfortunately, we are limited in the number of figures we can present in our paper. The BMJ Open asks to include only 5 figures, so we have now included forest plots for Moderate-to-severe exacerbations and Mortality in the main text as Figures 4 and 5, respectively.
Reviewer #3

1. The authors did a tremendous amount of work comparing safety and effectiveness of long-acting inhaled agents (ICS, LABA, LAMA) for patients with COPD in a systematic review and network meta-analysis. They included parallel-group RCTs regardless of duration of follow-up, date of dissemination or publication status. It is a very well written and organized manuscript. Just a few minor comments and a question:

Response: Thank you very much for providing comments on our paper.

2. In the abstract I would like to read a more informative conclusion as is stated so far (cf see conclusion of discussion part).

Response: We have revised our discussion in the abstract on lines 62 to 64, as follows “Many inhaled agents are available for COPD, some are more effective than others and some may increase the risk of harm (e.g., pneumonia). Our results can be used by patients and physicians to tailor administration of these agents.” However, we are only allowed 300 words for the abstract, so it is difficult for us to make further comments on the implications here.

3. In Appendix 7 the characteristics of the trials are listed: correct Sugiura – 2 instead of 1 treatment; published 2003 instead of 2002 (reference list number 40).

Response: Thank you for identifying these errors in Appendix 7. For the study by Sugiura et al., we have corrected the number of treatment groups from 1 to 2, and the publication date from 2002 to 2003 in Appendix 7.

4. Did you do any explorative subgroup analysis by severity of COPD, gender and age as stated in the protocol? Perhaps just a short statement could be given.

Response: As noted in our methods section on lines 163 to 168, we looked as these factors as potential effect modifiers: “Before conducting the analyses, we assessed the transitivity assumption by exploring whether any systematic differences were prevalent in the distribution of potential treatment effect modifiers across treatment comparisons in the network. For each outcome, we examined the percentage of female participants (gender) in the RCTs and the risk of bias results. For the moderate-to-severe exacerbations outcome, we also examined RCTs with eligibility criteria focusing on patients who experienced an exacerbation in the past year and severity of COPD.” Since the transitivity assumption was met, we did not do any further analysis on these. In addition, we did a meta-regression analysis on study duration, as noted in our methods section on lines 174 to 176: “We explored the effect of study duration in a random-effects meta-regression analysis for mortality and exacerbation outcomes, assuming a common fixed coefficient across treatment comparisons.” We also did sensitivity analysis on the risk of bias results. We also examined gender and this has been added.
Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis

Andrea C Tricco, Lisa Strifler, Areti-Angeliki Veroniki, Fatemeh Yazdi, Paul A Khan, Alistair Scott, Carmen Ng, Jesmin Antony, Kelly Mrklas, Jennifer D'Souza, Roberta Cardoso and Sharon E Straus

*BMJ Open* 2015 5:
doi: 10.1136/bmjopen-2015-009183

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