Reviewer's report

Title: Inhaled Drugs to Reduce Exacerbations in COPD Patients: a Network Meta-Analysis

Version: 1 Date: 29 August 2008

Reviewer: Luis Nannini

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BMC8 2008

When assessing the work, please consider the following seven points:

1. Is the question posed by the authors new and well defined?
   Not new.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Yes.

3. Are the data sound and well controlled?
   Yes.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Not supported.

6. Do the title and abstract accurately convey what has been found?
   Partially

7. Is the writing acceptable?
   Yes

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. Page 4:.....the predominant question in clinical practice is to choose between treatments rather than deciding whether to treat or not to treat[7, 8]. I think that subjects with FEV1 < 50% predicted, are treated by most of physicians with triple-drugs (ICS+LABA+LAAC) such as in the INSPIRE study (Thorax 2008).

2. The authors could estimate the fail-safe numbers (N) by the Rosenberg’s method to assess for the influence of publication bias on the meta-analysis. ( 

3. Could the authors calculate the number needed to treat (NNT) with every treatment arm in order to prevent a severe exacerbation when comparing with placebo?

4. The cut off point < 40% pred FEV1 was important; because GOLD recommended ICS under 50% plus exacerbations in symptomatic subjects. It was interesting that there was no effect modification when stratified for FEV1# or # 50%. This evidence could induce a modification in the next updating of GOLD.

5. Page 15. I am not sure if physicians are more familiar with odds ratios or relative risks than with mean differences in exacerbation rates or worthy percentage of reduction with any treatment.

6. The authors wrote that their review could help physicians in indicating treatment. However, I wonder which combined therapy and which ICS dose? There were lesser publications with formoterol/budesonide than with salmeterol/fluticasone and different doses of fluticasone and budesonide alone. We (physicians) need more consistent help for the day to day practice.

7. Ongoing trials with LABA and tiotropium from a single device probably confirm the hypothesis that it was largely better not to use single therapy in COPD despite severity.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Appendix 2 numbers between parentheses did not correspond to the reference number.

2. Fig 2 and 3 did not show significance (p) neither their legends.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. Sources: EMBASE, regulatory authority websites in the US and UK, and manufacturers trial registries were not mentioned in data sources and selection.

2. Why the authors did not include mortality as well as exacerbation rate in the analysis? There were enough studies (18?) with at least 6 months to dismiss mortality rate as the major outcome. Furthermore, there are at least 2 reviews with opposite findings regarding mortality and these reviews included studies with # 4 weeks duration.
3. Ref 53. The mean age of 44.8 yr in the placebo arm, the great proportion of
never smokers and the mean FEV1 of 83.3 and 86 % for fluticasone and placebo
respectively, confirmed the old tendency of Dutch authors to include both
asthmatic and COPD subjects. Then, this study should not be included because
FEV1 post bronchodilator must be less than 80% pred. (COPD definition
according to GOLD). DIMCA means Detection, Intervention and Monitoring of
COPD and Asthma program.

4. Page 16. Since mortality was not taken into account in this review; it would be
too speculative to recommend treatments.

5. Could the authors find any difference if only considering hospitalization or
systemic corticosteroids as criteria of COPD exacerbation?

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an
article of importance in its field

**What next?:** Unable to decide on acceptance or rejection until the authors have
responded to the major compulsory revisions

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the
statistics.

**Declaration of competing interests:**

I have received some fees from AstraZeneca as speaker and as investigator in
clinical trial.