Author's response to reviews

Title: Tachykinin receptors antagonism for asthma: a systematic review

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Author's response to reviews: see over
4th July 2011

Dear Professor Simon Harold:

Please find enclosed our revised manuscript (MS 8281822704403875) entitled "Tachykinin receptors antagonism for asthma: a systematic review" to be considered for publication as an article in the BMC Pulmonary Medicine.

We carefully reviewed the issues raised by reviewers and we would like to thank the valuable comments that helped us to improve our manuscript.

All authors will take the public responsibility for the content of the manuscript and provide any relevant data upon request. No portion of the work has been or is currently under consideration for publication elsewhere and no portion of the work has been published or posted on the internet. All authors have read and approved the final manuscript.

We hope you will consider the manuscript suitable for publication in the BMC Pulmonary Medicine. We are also prepared to further improve the manuscript according to your suggestions.

Yours sincerely,

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REPLY TO REVIEWER’S COMMENTS.

Manuscript MS 8281822704403875 entitled "Tachykinin receptors antagonism for asthma: a systematic review".

Dear Professor Simon Harold:

Please find below our responses to the reviewers comments.

We would like to thank the reviewers for their thorough review and critique of the manuscript.

Reviewer #1

Comments to the Author

...A key part of the author’s interpretation of the results and their assertion that neurokinin receptor antagonists deserve further evaluation in asthma is their conclusion that the published literature shows that this class of drugs reduces airways hyperresponsiveness. This is clearly overstated. In fact, the literature shows that the NK2 receptor antagonists SR48968, DNK333, AVE5883, CS-003 and MEN11420 produce statistically significant or trends toward significant shifts in the concentration response curves to NKA, an NK2 receptor agonist. It is inappropriate to interpret these results as evidence for an effect on airways hyperresponsiveness, which is typically assessed by methacholine challenge, and to some extent histamine, AMP and hypertonic saline challenges. Surely the authors would agree that histamine receptor antagonists provide little or no benefit in asthma and have no effect on responsiveness to methacholine, but would still likely produce a shift in a histamine concentration response curve in patients. Rather, what these studies show is two-fold: First, that these drugs are indeed NK2 receptor antagonists, and secondly, given the very modest shifts in the NKA concentration response curves, nearly all of these drugs were underdosed in these studies. The doses of ipratropium and tiotropium used in COPD or of montelukast in asthma would produce 100-fold shifts in the methacholine and leukotriene concentration response curves, respectively.

Reply to reviewer: We agree with the reviewer. We inserted a new sentence in the results section: “These studies show, first, these drugs are indeed tachykinin receptors antagonists, and secondly, given the very modest shifts in the concentration response curves, nearly all of these drugs were underdosed”. We also rephrased outcomes in table 1 to “airway responsiveness to tachykinin receptors antagonists”. 
... Based on what data did the authors conclude that the drugs studied had an effect on lung function? This assertion should be tempered or removed entirely.

Reply to reviewer: We tempered the assertion. In the first paragraph of the discussion we inserted the sentence: “...and may improve lung function.” In fact, only the data from Boot et al., 2007 showed a reversion of the NKA-induced bronchoconstriction with the NK-1/NK-2 antagonist tested.

... Additional limitations that the authors should mention is that each of the 7 studies used a different drug, most of these studies failed to document adequate dosing (given that they couldn't even shift an NKA concentration response curve), and nearly every study targeted a different combination of the NK1, NK2 and NK3 receptors. These receptors have very different effects on airway and vascular smooth muscle, inflammatory cells, CNS reflexes and epithelial cells.

Reply to reviewer: This has been added. In the second paragraph of the discussion we inserted the sentence: “Additional limitations were: each of seven studies used a different drug, most of these studies failed to document adequate dosing, and nearly every study targeted a different combination of the NK1, NK2 and NK3”.

... A diagram or table describing the known actions of NK1, NK2 and NK3 receptors on human airway cells would be helpful.

Reply to reviewer: This has been added. Table 3 describes the effects of tachykinins receptors NK1, NK2 and NK3 on human airway cells.

We add to the acknowledgments: “We thank the reviewers for their comments that helped us to improve the manuscript.”

Reviewer #2
Comments to the Author

... Page 2, lines 42-43: Abstract – “Symptoms, airway inflammation, lung function and airway inflammation were considered as outcomes” should be presented in the paragraph "Method" rather than in the "Results".

Reply to reviewer: This has been done.

...Page 2-3, lines 47-52: Conclusion – The conclusion based on the results of this systematic review should be "The limited available evidence suggests that tachykinin receptors antagonist
may decrease airway responsiveness and improve lung function in patients with asthma. Further large randomized trials are still required.”

Reply to reviewer: This has been changed.

...Page 6, lines 112-118: Studies, participants, interventions and outcomes – Adverse events of the treatment should be considered as one of the outcomes.

Reply to reviewer: This has been added.

...Page 7, lines 130-142: Data collection and analysis – The number of screened titles and abstracts and the number of studies finally included in the review should be presented in the “Results” rather than in this method paragraph. A flowgram showing selection process is strongly recommended.

Reply to reviewer: This has been changed and a flowchart of selection process has been added. In the Results section we included the sentence: “Based on title, nineteen studies were identified as potentially relevant. However, based on abstract, only seven studies appeared to meet the inclusion criteria and their full text was obtained (Figure 1)”

......Page 7, lines 130-142: Data collection and analysis – The authors stated that the methodological quality of the included trials was assessed with particular emphasis on allocation concealment and randomization. However, the authors used a grade system which evaluates the quality of a body of evidence rather than the quality of individual study. The reference for this grade system should be cited. The assessment of risk of bias for individual study according to Cochrane Collaboration should be reported.

Reply to reviewer: The reference has been added (Data collection and analysis section, Line 139). The assessment of risk of bias for individual study has been summarized in Figure 2 and in the Results section Lines 156 -159 we included the sentence: “Reviewer author’s judgments about risk of bias for each included study was summarized in Figure 2.” We also included in Results section the sentences: “As shown in Figure 3, methodological quality of the included trials was graded as very low (Figure 2). Data extraction from included studies was summarized in Table 2.”

...Page 7, lines 130-142: Data collection and analysis – In this paragraph, the authors should state that meta-analysis was not conducted due to small number of included trials and heterogeneity across studies.
Reply to reviewer: This has been added. In the last paragraph of this section we included the sentence: “Meta-analysis was not conducted due to small number of included trials and heterogeneity across studies.”

...How many trials reported adverse events of treatment with tachykinin receptors antagonist? The results of this outcome should be reported in the "Results".
Reply to reviewer: This has been added. In the section Results, lines 180 – 192 we included an entire paragraph describing the report of adverse events as an outcome.

....... Page 14: Table 2 – p values for comparison of two groups in individual trial should be presented in the table.
Reply to reviewer: This has been added.

...Quality of written English: Needs some language corrections before being published.
Reply to reviewer: Manuscript has been reviewed.

We add to the acknowledgments: “We thank the reviewers for their comments that helped us to improve the manuscript.”