Author's response to reviews

Title: A multicentre, randomised, double-blind, single-dose study comparing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge with a non-medicated lozenge in the relief of acute sore throat

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Version: 2 Date: 8 October 2010

Author's response to reviews: see over
Dear Adrian Aldcroft,

Re: MS: 8333518083976723

Thank you for allowing us to revise our manuscript, now entitled ‘A multicentre, randomised, double-blind, single-dose study comparing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge with a non-medicated lozenge in the relief of acute sore throat’.

In the revised manuscript enclosed, we have endeavoured to address the reviewers’, editor’s and editorial comments as best as possible with all amendments highlighted as requested – please see below our response about the changes made to each of the comments received (in bold).

We hope that you will find this manuscript now acceptable for publication.

Yours sincerely,

Alan G. Wade

Editor/Editorial Requests
We would also like to stress the referees' comments asking that you revise your manuscript to project a more scientific tone, and we consider this essential for further consideration in the journal.

- As this study investigated the effect of current and future over-the-counter treatment options in the symptomatic relief of acute sore throat, the efficacy parameters examined not only included the analgesic measures but also functional and sensorial measures; the latter two of which may not sound as scientific in the traditional manner, but are nonetheless important endpoints for acute sore throat.
- Where possible throughout the manuscript, we have revised wording to project a more scientific tone, and without losing the true meaning of what was investigated in this study.

1. Please ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.
   - The manuscript has now been formatted using the guidelines in the above link provided.

2. Please provide some contextual information in the Background section of your abstract.
   - This has now been added.

3. Please state in your "Competing Interests" section what authors are employed by the funders of the study as well as mentioning that the study was funded by the manufacturers of Strepsils.
   - This has now been added.

Reviewer 1’s report
It is not possible from the design of the study to determine if it is the flavouring or the medication that provides symptom relief.

- The efficacy effects of the medication (i.e. the active ingredients AMC and DCBA) of AMC/DCBA throat lozenges have previously been investigated in
patients with acute sore throat (by McNally et al, 2010). Thus the aim of this study was not only to confirm the efficacy of 2 new variants of this lozenge with differing formulations (i.e. the only difference being that one contains warming and the other containing cooling excipients), but also to investigate the sensorial benefits of these new formulations, which contribute to the overall experience of the patients. Moreover, this study examined the effects of two new lozenge variants as a whole, in the treatment of acute sore throat, compared with a non-medicated placebo lozenge matched for demulcency and appearance.

- We have now made this clearer in the Background section.

The authors regularly refer to comparisons between the medicated and the non-medicated lozenges but in fact the patient is also comparing powerfully flavoured lozenges with cooling and warming actions to an insipid sugar control lozenge.

- This study examined the effects of two new lozenge variants as a whole, and not just the 'medicated' i.e. active ingredients, or just the flavourings, in the treatment of acute sore throat. Please see our response above regarding the difference in the comparisons made in this study compared with an earlier study by McNally et al (2010).
- The non-medicated lozenge was matched for demulcency and appearance.

The study is not truly blinded as blindfolding the patients will not mask any cooling or warming sensation. Presumably the patients were informed about the aims of the study in the patient information leaflet and they would immediately know which lozenge they were given because of the cooling and warming sensations.

In general I am impressed by the results and believe they are a very interesting and useful addition to the literature on the treatment of sore throat by cooling and warming agents.

- Treatment lozenges were provided in opaque blister packs and so it was not possible for the investigational staff or the patients to determine which treatment lozenge it was – this information has now been added in the Methods section for clarity.
- Regarding the second point, the patients were merely informed that they MAY experience a cooling or warming sensation. It was not suggested that the efficacy of the lozenge was associated with any sensation which they may or may not experience.

Major Compulsory Revisions
1. It should be made clear that the design of the study does not allow any conclusion that the medications in the lozenges were responsible for the effects found in the study. If the authors wish to claim that the medications were effective then the correct comparison would be between unflavoured medicated lozenges versus identical unflavoured lozenges without any medications.

- Earlier this year, McNally et al published a study comparing the effects of AMC/DCBA throat lozenges with non-medicated placebo lozenges. They found that compared with non-medicated placebo lozenges, AMC/DCBA throat lozenges provided a significantly more rapid analgesic effect that lasted for 2 hours. They also reported that the analgesic effects and improvements in functional impairment scores translated into pain relief benefits that were clinically meaningful and were over and above the demulcent effects of the placebo lozenge. Therefore, in this study, we have investigated not only the analgesic and functional effects of the two formulation variants, but also the sensorial benefits, i.e. the effects of these lozenges as a whole, in the patients with sore throat.
• We have added a sentence in the ‘Background’ section about the study by McNally et al., to make it clear to the reader that evidence already exists demonstrating not only analgesic but also functional benefits associated with AMC/DCBA throat lozenges in the treatment of acute sore throat, which can be attributable to the active ingredients, AMC and DCBA.
• Furthermore, in a study by Buchholz et al (2009), AMC and DCBA were shown to act in a local anaesthetic-like manner, which is supported by the numbing effects found in this study.

2. The paper should discuss the sensory impact of the lozenges and the likely impact of this in enhancing a placebo effect on sore throat symptoms.
   • This paper does report the sensorial effects associated with each of the lozenge variants. We have now added a short paragraph in the Discussions section to explain that this study does not investigate the likely impact of sensory effects on enhancing the placebo effect, and have advocated further investigation to explore this.

3. I am not sure about the policy of the journal as regards promoting proprietary names but it is not really necessary to use the proprietary name of the product- Strepsils – in the title and throughout the paper. The proprietary name could be mentioned in the methods but the clinical importance of the paper is in comparing different formulations of lozenges.
   • This has now been done.

4. The blinding of the study should be discussed – were any attempts made to determine if the patients knew which type of lozenge they were administered. My own view is that the study is unblended. Some information should be given about what the patient information contained as regards the cooling and warming aspects of the lozenges- was this mentioned in the PIL?
   • Each patient was blindfolded and provided with a single lozenge in the clinic by an independent member of the investigational staff who was not involved in the study assessments. Before lozenge administration, the patients were informed that they MAY experience a cooling or warming sensation. However, it was not suggested that the efficacy of the lozenge was associated with any sensation which they may or may not experience.
   • Treatment lozenges were provided in opaque blister packs and so it was not possible for the investigational staff or the patients to determine which treatment lozenge it was – this information has now been added in the Methods section for clarity.

Minor Essential Revisions
It would be useful to know the exact composition of the cooling and warming flavourings. Many cooling and warming agents have pharmacological effects. Menthol is a cooling agent with local anaesthetic actions and capiscum which is sometimes used as a warming agent interacts with nociceptors and could influence the sensation of pain etc.
• We don’t believe that adding the exact composition of the cooling and warming flavourings would be useful information for the readers in the context of the study objectives. Therefore we have not included this information in the manuscript.
• However, for your information the AMC/DCBA Cool lozenge contained the excipients, xylitol, cool mint sensation flavour, levomenthol, spearmint flavour, eucalyptus oil. The flavours for the AMC/DCBA Warm lozenge were a blend of soothing cream, warm sensation, warm ginger spice and fruity plum flavours.
• If this is unacceptable, please let us know.
Reviewer 2’s report

This report reads too much like a drug ad.

- As this study investigated the effect of current and future over-the-counter treatment options in the symptomatic relief of acute sore throat, the efficacy parameters examined not only included the analgesic measures but also functional and sensorial measures; the latter two of which may not sound as scientific in the traditional manner, but are nonetheless important endpoints for acute sore throat.
- As requested by the Editor, we have endeavoured to revise the manuscript where possible to project a more scientific tone without losing the true meaning of what was investigated in this study.

References
