Reviewer's report

Title: Efficacy of ambroxol lozenges for pharyngitis: a meta-analysis

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Reviewer: Christian de Mey

Reviewer's report:

The publication "Efficacy of ambroxol lozenges for pharyngitis: a meta-analysis" by Chenot JF et al. describes a meta-analysis of published efficacy data re. the efficacy of ambroxol lozenges in the treatment of acute sore throat. 14 potentially relevant publications were initially identified; five relevant RCTs reported in three publications were retained (1,772 evaluable patients in total). All relevant RCTs and their core data had already been reported in reference 12, albeit that this did not present a pooled analysis of the data. Based on a pooled analysis of the time weighted change of the pain scores from pre-dose baseline (primary criterion), the overall difference vs. placebo was presently estimated to be -0.11 (CI95 [-0.15; -0.07]) for 20 mg and -0.17 (CI95 [-0.24; -0.10]) for 30 mg of ambroxol. Based on the CONSORT criteria for reporting of parallel-group clinical trials, the quality of reporting of the data was considered to be low. Based on their evaluations, the authors conclude that "although ambroxol seems to be more effective in relieving pain in acute pharyngitis than mint flavored lozenges the effect appears to be small". Additionally, the authors conclude that "over the counter analgesic medications might be a better option".

This analysis is affected by several issues – in the following only a few examples are cited (major issues):

- The outcome measures of the fifth trial, although extensively reported in reference 12, were not transferred correctly into the meta-analysis – this has not a large impact, but nevertheless illustrates the lack of methodological robustness of the present publication.

- The primary criterion is reported to have been based on pain scores by means of a visual analogue scale; the source publications leave no doubt that pain was scored by means of a verbal rating scale.

- Table 1 erroneously reports that placebo, ambroxol-20, ambroxol-30, and benzoicaine were investigated in trial no. 5; ref 12 leaves no doubt that ambroxol-30 was not investigated in this trial.

- The publication suggests that more than 50% pain reduction was also achieved with placebo (sucking a mint-flavoured lozenge); such statement is meaningless unless referring to a treatment comparison of the frequency of patients achieving at least 50% pain reduction; no such data were reported in any of the cited publications – see also below. Instead, percentages of patients with overall efficacy scores had been presented in Ref 12 in addition to the primary outcome measure.
Ref 12 is a compact analysis of five trials. This format per se is not meant nor able to comply with the criteria of the CONSORT-initiative (reporting of "parallel group randomised trials"). Characterising ref 12 as deficient, while not complying with the CONSORT-criteria is inappropriate. Additionally, ref 12 contains an explicit statement that more information can be made available to the reader if needed.

In exemplifying the inadequacies of the cited reports, the present paper makes several statements which suggest that the authors might not have read these references carefully: in contrast to what the authors suggest, the tables in ref 12 make it quite easy to identify that all reported analyses relate to the ITT and not to the PP population; in contrast to what the authors suggest, age and gender were well defined for each study (ref 12); in contrast to what the authors suggest ("Although it is stated that all patient were outpatients it remains unclear if patients were recruited in ambulatory care or emergency departments") it is clearly stated (ref 12) that "The studies were conducted in ambulatory fashion by qualified primary care physicians" and "All subjects were investigated in a real-life primary care practice setting.", etc.

Additionally, and foremost, the conclusions drawn by the authors need to be seen with caution: the mean pain reduction (relative to the maximum theoretically achievable effect) with ambroxol ranged from 37 to 42% for ambroxol lozenges 20 mg (and 40 to 49% for ambroxol lozenges 30 mg) vs. 27 to 35% for mint flavoured placebo lozenges. The estimated mean overall difference between ambroxol lozenges 20 mg and placebo was about 11%. It remains unclear why and on which basis the authors comment on this with such reservation ("Although ambroxol seems [sic] to be more effective in relieving pain in acute pharyngitis than mint flavored lozenges the effect appears to be small"). Firstly, on average the effect of ambroxol lozenges 20 mg might (also) be understood as about 33.3% higher as that of sucking a mint-flavored lozenge; secondly, it would have been recommendable if the authors had relied on expert recommendations in this regard: for instance, in-depth research by Farrar et al identified cut-off points of 30% (chronic pain) and 33% (acute pain) in pain intensity difference/pain relief to be clinically relevant/meaningful (Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain. 2000 Dec 1;88(3):287-94; 3. and Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Symptom Manage. 2003 May;25(5):406-11)). In all five trials presently analysed, treatment with ambroxol lozenges met this criterion, whereas treatment with placebo failed this criterion except in one small pilot study (N:21 treated with placebo). Accordingly, there is no reason not to consider treatment with ambroxol to be superior to sucking a mint-flavoured lozenge to a clinically meaningful extent.

Accordingly, the authors' conclusion that "In patients with associated systemic symptoms over the counter analgesic medications might be a better option. Additional benefits of ambroxol lozenges for local pain relieve for those patients is not established" is not substantiated while not investigated and/or evidenced.
by the present publication.

In summary: the present publication presents a pooled analysis of data that already were reported extensively 4 years ago (ref 12); the present publication does not lead to effect estimates that are essentially different from those already reported; however, the present paper is deficient in several important methodological aspects, particularly those pertinent to the evaluation of the clinical relevance of the observed effects and the assessment of the quality of the available study reports.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I confirm to be the author of two publications that have been subject of the publication’s review. I confirm that the work leading to these publications was honoured by a CRO-agreement with the marketing authorisation holder of the medication presently evaluated. This work was ended four years ago.

I made the present assessment on my own responsibility and on my own means.

My evaluation is not influenced by any personal or financial relationship with other people or organizations. I have no financial competing interests; I also have no non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.