Zinc lozenges and vitamin C for the common cold are not examples of placebo effect in action

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Looking at the acceptance and (online) publication dates of our respective articles [2,3], it seems that we were working on the idea of using finite mixture models for diagnostic meta-analyses simultaneously. Furthermore, we both identified two clusters for the computed tomography data in the meta-analysis by Schuetz et al. [4].

We appreciate the idea of Eusebi et al. [2] to describe the within-study variability with a binomial distribution. This approach is known to be superior [5] to the logit-transformation data applied in our approach.

However, the construction of summary receiver operator curves based on their approach is not an easy task. For that reason, we used the logit transformation of sensitivity and specificity.

Using the approach presented by Eusebi et al., one needs to fix the number of clusters in advance and has to apply a forward or backward selection strategy to determine the number of clusters. In contrast, using the VEM-algorithm [6] of the R package CAMAN [7], it is possible to leave the number of clusters unspecified at the beginning of the analysis.

Finally, we agree with Eusebi et al. that the further development of latent variable methods may give valuable input when analyzing heterogeneity within diagnostic meta-analyses.

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In the introduction to their article on the reporting of blinding in trial publications, Bello et al. [1] write that compromised blinding has raised concerns and, as examples, refer to studies on zinc lozenges and vitamin C for the common cold [2–4].

In 1975, Karlowski et al. [2] concluded from their vitamin C and common cold trial that “the effects [of ascorbic acid] demonstrated might be explained equally well by a break in the double blind.” The placebo consisted of lactose, which is easily distinguishable from ascorbic acid by taste. Statisticians and clinical trialists have frequently cited the Karlowski study in textbooks, the CONSORT statement [5], and other publications as an example of the placebo effect in action. In 1996, however, I showed in this journal that the Karlowski report contained erroneous analysis [6]. For example, 42% of the common cold episodes were missing from the comparison of the “blinded” vs. “unblinded” participants although Karlowski presented those two groups as if they were complementary. Karlowski’s placebo effect explanation also contains several other problems [6,7]. Over two dozen trials with valid placebos, such as citric acid, have clearly shown that the effects of vitamin C on the common cold are not placebo effects [8]. Because the benefits of vitamin C demonstrated in the Karlowski trial are consistent with those observed in other studies, the Karlowski trial should not be claimed as an example of placebo effect in action.

References


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In 1984, Eby et al. [3] reported that therapeutically administered zinc gluconate lozenges significantly shortened the duration of colds. In this journal, Farr and Gwaltney [4] proposed that the apparent benefit of zinc lozenges in the Eby trial may have resulted from the placebo effect because the lozenges may have tasted bad. However, Farr and Gwaltney provided no evidence that bad taste shortens the duration of colds. A dozen trials have examined the effect of zinc lozenges on the duration of the common cold [9]. Five studies with the lowest doses of zinc uniformly found no benefit, whereas three trials with high doses of zinc in the form of acetate found a 42% [95% confidence interval (CI): 35%, 48%] reduction in the duration of colds and five studies with high doses of zinc in the form of other salts found a 20% (95% CI: 12%, 28%) reduction. Depending on their composition, zinc gluconate lozenges can taste bad with time, whereas zinc acetate lozenges do not [10]. The most recent zinc acetate trial found no differences between zinc and placebo groups in bitter or bad taste or other adverse effects [11]. In their 1984 study, Eby [10, p.29] used a high dose of zinc gluconate, but the lozenges “were not bitter, rather they were chalky and bland in taste.” Concluding from other studies with high doses of zinc as zinc lozenges [9], Eby’s findings are attributable to high doses of zinc rather than the bad taste proposed by Farr and Gwaltney [4].

In an extensive Cochrane review that compared placebo arms with no-treatment arms, the authors concluded that they “did not find that placebo interventions have important clinical effects in general” [12]. Although the methodology of controlled trials is important, one should avoid exaggerating the role of binding.

Presenting zinc lozenges and vitamin C for the common cold as examples of the placebo effect in action has two unfortunate consequences. First, readers may understand falsely that there is more evidence for the clinical effects of placebo than there actually is. Second, readers may understand wrongly that the effects of zinc lozenges and vitamin C on the common cold are placebo effects.