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Common Cold Treatment Using Zinc

To the Editor The JAMA Clinical Evidence Synopsis on zinc for the common cold by Drs Das and Singh¹ was a summary of their Cochrane review.² I noticed inconsistencies in the synopsis and so attempted to replicate their data.

In the Evidence Profile section of the synopsis, the authors stated that the number of randomized clinical trials included was “14 therapeutic (lozenges: low-dose = 5, high-dose = 7, syrup = 2) ... and 2 prophylactic ...,” which implies that the reported findings are purely based on randomized comparisons. However, their estimate of 3.43-day shorter colds for high-dose vs low-dose zinc lozenge users appears not to be based on a comparison of randomized groups but rather on an arbitrary selection of 5 high-dose zinc groups from 7 trials compared with 5 low-dose zinc groups from different trials.

There have not been 5 published randomized clinical trials that directly compared high-dose and low-dose zinc lozenges.^{2,3} The pairing of the selected high-dose and low-dose zinc groups also appeared arbitrary.

Furthermore, 3 of the 5 low-dose zinc trials had problems in the formulation of their zinc lozenges so that zinc was not released freely,³ and therefore, the low dosage of zinc was not the only problem in the low-dose studies.

Das and Singh¹ stated: “Zinc lozenges were associated with a higher incidence of adverse events compared with placebo (46.5% for lozenges vs 36.4% for placebo; number needed to harm [NNH], 10).” This calculation was based on Analysis 2.12 of their Cochrane review.²

However, that analysis table counted the placebo group from the study by Turner and Cetnarowski⁴ 3 times. A meta-analysis should not count the same randomized participants more than once. The lower rate of adverse events in the placebo group may have been a statistical artifact caused by the triple-counting of a single placebo group.

The negative findings for the low-dose zinc lozenge trials may be caused by the low doses or problems in the lozenge formulations. Therefore, the estimation of zinc lozenge effects should focus on high-dose zinc lozenge studies. Three high-dose zinc acetate lozenge trials found that colds were 42% (95% CI, 35%-48%) shorter in the zinc groups.³

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Das RR, Singh M. Oral zinc for the common cold. *JAMA*. 2014;311(14):1440-1441.

2. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev*. 2013; 6:CD001364.

3. Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. *Open Respir Med J*. 2011;5:51-58.

4. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis*. 2000;31(5):1202-1208.

In Reply The findings reported in the JAMA Clinical Evidence Synopsis were based on randomized clinical trials, as was our Cochrane review.¹ The comparison of the 2 doses (≥ 75 mg/d vs < 75 mg/d) of zinc was performed as a part of a network meta-analysis, which is a valid technique to assess the comparative effectiveness of interventions among similar study populations that have not been compared directly in randomized clinical trials.²

The prerequisite of a network meta-analysis is that the trials should have used the same intervention in the same population and setting, for the same health problem, and measured the same outcome. We therefore selected trials using zinc lozenges that were conducted in the same country (United States), in the same setting (outpatient setting), in the same population (mostly adults), for the same health problem (naturally acquired cold), and for the same outcome (duration of cold). This analysis was not included in the Cochrane review.

We agree with Dr Hemilä's point that 3 of the 5 low-dose zinc trials had problems in the formulation of their zinc lozenges (were nonacetate lozenges) so that zinc was not released freely. However, similar kinds of formulations that released more and less ionic zinc were included in both low-dose and high-dose groups.

There are many possible analytic approaches in a meta-analysis, and we originally chose to triple count adverse event data for 1 study.³ A more commonly used method is to combine all relevant intervention groups into a single group, and to combine all relevant control groups into a single control group.⁴

We reanalyzed the data in this way and found a minimal but insignificant difference from the previous calculation (60.2% for lozenges vs 48.4% for placebo; number needed to harm [NNH], 9). The conclusion remains the same: “zinc lozenges were associated with a higher incidence of adverse events compared with placebo.” This is consistent with findings from published clinical trials on zinc lozenges for the common cold.⁵

Moreover, regarding the study in question,³ the authors reported adverse events to be more common in the lozenges group (13%-19%; mean, 16%) than in the placebo group (10%).

We agree with Hemilä that the negative findings for the low-dose (< 75 mg/d) zinc lozenge trials may be related to the low dose or problems in formulations, and the estimation of zinc lozenge effects should focus on trials using high doses (≥ 75 mg/d) of zinc.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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2. Chambers JD, Naci H, Wouters OJ, et al. An assessment of the methodological quality of published network meta-analyses: a systematic review. *PLoS One*. 2015;10(4):e0121715.
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CORRECTION

Incorrect Dose in Figure: In the Original Contribution entitled "Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial" published in the July 14, 2015, issue of *JAMA*,¹ an incorrect study drug dose appeared in a figure. In Figure 2, the starting patiromer dose reported as 16.2 in the x-axis for both stratum 1 and stratum 2 in both the left and the right plots should have appeared as 16.8. This article was corrected online.

1. Bakris GL, Pitt B, Weir MR, et al; AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161.

Wording Errors in the Text: In the Viewpoint entitled "Innovations of the Americans With Disabilities Act: Confronting Disability Discrimination in Employment" published in the June 9, 2015, issue of *JAMA*,¹ the article should have stated more clearly that the pre-Americans with Disabilities Act Amendments Act (ADAAA) requirements for establishing coverage under the "regarded as" part of the defini-

tion are no longer required under the ADAAA. Under the ADAAA, an individual is regarded as having a disability if he or she has been subject to discrimination "because of an actual or perceived physical or mental impairment whether or not the impairment limits or is perceived to limit a major life activity." This article was corrected online.

1. Rothstein MA. Innovations of the Americans with Disabilities Act: confronting disability discrimination in employment. *JAMA*. 2015;313(22):2221-2222.

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