# Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis

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**Abstract**

**AIMS**

The aim of this study was to determine whether the allergy status and other characteristics of common cold patients modify the effects of zinc acetate lozenges.

**METHODS**

We had available individual patient data for three randomized placebo-controlled trials in which zinc acetate lozenges were administered to common cold patients. We used both one-stage and two-stage meta-analysis to estimate the effects of zinc lozenges.

**RESULTS**

The total number of common cold patients was 199, the majority being females. Eighty percent of them fell into the age range 20-50 years. One third of the patients had allergies. The one-stage meta-analysis gave an overall estimate of 2.73 days (95% CI 1.8 to 3.3 days) shorter colds by zinc acetate lozenge usage. The two-stage meta-analysis gave an estimate of 2.94 days (95% CI 2.1 to 3.8 days) reduction in common cold duration. These estimates are to be compared with the 7 day average duration of colds in the three trials. The effect of zinc lozenges was not modified by allergy status, smoking, baseline severity of the common cold, age, sex, or ethnic group.

**CONCLUSION**

Since the effects of zinc acetate lozenges were consistent between the compared subgroups, the overall estimates for effect seem applicable over a wide range of common cold patients. While the optimal composition of zinc lozenges and the best frequency of their administration should be further investigated, given the current evidence of efficacy, common cold patients may be encouraged to try zinc lozenges for treating their colds.

**What is already known about this subject:**

- Randomized trials have shown that zinc acetate lozenges shorten the duration of common cold episodes.
- One study found that the effect of zinc acetate lozenges was greater for patients with allergies.

**What this study adds:**

- The effect of zinc acetate lozenges is not modified by allergy, smoking, baseline common cold severity, age, sex, or ethnic group.
- The mean effect of 3 day reduction in common cold duration with zinc acetate lozenges is clinically relevant and appears widely applicable.

## Introduction

Interest in zinc lozenges for treating the common cold arose when the cold symptoms of a 3-year-old girl with leukemia disappeared soon after she dissolved a therapeutic zinc tablet in her mouth instead of swallowing it as instructed [1]. The benefit seemed to be obtained from slowly dissolving the tablet in her mouth, which suggested that zinc might have local effects in the pharyngeal region. This observation led the girl's father to conduct the first randomized placebo-controlled trial on the effects of zinc lozenges on common cold patients. In that study, zinc gluconate lozenges shortened the duration of colds significantly [1].

Since then, a series of trials on zinc lozenges have been carried out but the results were variable [2-5]. The daily dosage of elemental zinc in the trials had a 7-fold variation, which explains much of the inconsistency in the study findings [2]. The composition of the lozenges also differed; some of them contained substances that bind zinc tightly, preventing the release of free zinc ions. The composition differences also explain divergent results [3-6].

A previous meta-analysis indicated that 5 low-dose trials of zinc lozenges (<75 mg/d zinc) uniformly produced no effect on the duration of colds. However, 3 high-dose (>75 mg/d) zinc acetate trials produced a 42% reduction in the duration of colds on average, and 5 high-dose zinc gluconate trials found a 20% reduction in cold duration on average [2]. Since acetate binds zinc ions less strongly than gluconate, zinc acetate has been proposed as the best salt for lozenges [4,5]. Although dissolving lozenges in the oro-pharyngeal region leads to the highest zinc levels in that anatomical region, a recent meta-analysis found no evidence that zinc acetate lozenges have less effect on nasal symptoms compared with cold symptoms that originate in lower anatomical regions [7]. Other systematic reviews on zinc and the common cold have been published [8-10], but some

of them had methodological problems [11-13], and a Cochrane review was recently withdrawn [14].

Petrus et al. [15] reported that common cold patients who had positive skin testing for allergies were more responsive to the zinc acetate lozenges than those who were negative for allergies, but that association has not been analyzed in later studies. The effect of zinc lozenges might also be modified by smoking which influences the respiratory system, and by the severity of the common cold which reflects different levels of pathologic changes caused by the respiratory viruses. The goal of the present individual patient data (IPD) meta-analysis was to determine whether the efficacy of high-dose zinc acetate lozenges varies by the allergy status, smoking, baseline common cold severity or by demographic characteristics.

## Methods

### Selection of the trials

This meta-analysis was restricted to placebo-controlled trials on zinc acetate lozenges for patients with naturally acquired common cold infections, in which the elemental zinc dosage was >75 mg/d. We restricted the selection to high-dose trials, since previous analyses demonstrated the lack of effect of low doses of zinc, < 75 mg/day [2,4,5,10]. Previous searches of the literature [2,5,8-10] identified 3 trials that met our selection criteria [15-17]. These three trials are shown in Table 1 and further characteristics are shown in Supplementary file 1. No additional zinc acetate lozenge trials were found by searching PubMed and Scopus using the free search terms “zinc” and “lozenge*” (June 16, 2016). The three datasets for this IPD meta-analysis were made available with the cooperation and collaboration of the authors of the three trials and the lead author. We did not use a protocol for this meta-analysis.

### Outcome

The outcome in this meta-analysis was the duration of colds. Petrus et al. (1998) [15] reported both the mean duration of common cold symptoms and the duration of the longest cold symptom. We used the latter as the outcome for this analysis, since it is consistent with the outcome definition in the two studies by Prasad et al. [16,17].

### Statistical methods

In checking of the IPD for the three studies, we confirmed that the effects of zinc lozenges in the IPD data were consistent with the published effects [15-17].

Pooling of the IPD was done by the one-stage and two-stage approaches. One-stage meta-

analysis indicates that the pooled effect estimates are calculated directly from the IPD. Two-stage meta-analysis indicates that the effect estimates of the individual studies are first calculated from the IPD; thereafter, those study level estimates are pooled by standard meta-analysis methods. In some cases, the one-stage meta-analysis has greater statistical power and sometimes the two approaches lead to different conclusions [18].

We used the lmer procedure of the lme4 statistical package of R [19] for the one-stage meta-analysis. In the mixed models constructed with lmer, we used the study as the random variable for the zinc effect and also as an independent explanatory variable. The interaction between the zinc lozenge effect and each subgroup variable was calculated by first adding the zinc effect and the subgroup variable to the basic model, and thereafter adding their interaction term; the interaction between zinc and the subgroup variable was added as a random variable. The p-value for the interaction was calculated by using the likelihood ratio test.

In the two-stage pooling, we first used the lm procedure [19] to calculate the mean effects and the zinc-subgroup interactions separately in the three trials. Thereafter we pooled those effects by the metagen procedure of the meta package using the inverse-variance and random-effects options [19]. The p-value for the interaction was calculated from the z-value of the pooled interaction effect. We used the $\chi^2$ test and the $I^2$ statistic to assess statistical heterogeneity among the three trials in the two-stage approach. A value of $I^2$ greater than about 70% indicates a high level of heterogeneity [20].

We used the difference in the duration of colds in days as the main measure of the zinc effect. However, since the distributions of viruses differ over time and the operational outcome definitions vary between trials, variation between studies is to be expected. Since relative effect adjusts for

variation in the common cold duration in the placebo groups, we also calculated the overall effect of zinc in the percentage scale so that the duration of each placebo group was normalized to 100%. Thereby the difference between the zinc group and the placebo group directly gives the effect of zinc lozenges in percentages.

Our calculations are described in detail in Supplementary file 2. Two-tailed p-values are used.

**Results**

Table 1 shows the distributions of the baseline variables of the three trials analyzed in this IPD meta-analysis. The trials had 199 common cold patients with the majority being females. Eighty percent of the common cold patients fell into the age range between 20 and 50 years. The majority was white, 23% were African Americans and 10% were of other ethnic origin. In the Petrus et al. study, all common cold patients were skin tested with 20 different allergy extracts including grasses, trees, and cat and dog dander, and 46% of the patients tested positive for allergies [15], see details in Supplementary file 1. In their two trials, Prasad et al. asked about allergies with a questionnaire and 12% [16] and 20% [17] reported having allergies. Petrus et al. did not record information about smoking, whereas in the two studies by Prasad et al., a quarter of participants were smokers. All three studies were randomized, double-blind, placebo-controlled trials, and there were few drop-outs. Further details of the methodology of the three trials are described in Supplementary file 1.

Petrus et al. instructed patients to dissolve in their mouth 1 lozenge every 1½ hour while awake on the first day, and then 1 lozenge every 2 hours on the following days; lozenges dissolved in about 15 minutes [15]. Prasad et al. instructed patients to dissolve 1 lozenge in their mouth every 2 to 3 hours while awake; their lozenges dissolved in about half an hour [5,16,17]. Elemental zinc dose varied between 80 and 92 mg/day in the three studies (Supplementary file 1).

Table 2 shows the estimated effect of zinc acetate lozenges over all participants. The one-stage meta-analysis gives an estimate of a 2.73 day reduction in common cold duration and the two-stage meta-analysis gives an estimate of 2.94 days. These estimates are to be compared with the 7 day average duration of colds in the three trials (Table 2). The small difference between the two pooled estimates is explained by the substantially greater zinc effect and smaller SDs in the two small

studies by Prasad et al. (N = 48 and N = 50), compared with the smaller effect and larger SD in the larger study by Petrus et al. (N = 101), see Table 2. The two-stage method gives a greater effect estimate for zinc lozenges since the total weight of the two studies by Prasad is 75%, although the number of participants is essentially equal with the Petrus et al. study [15], see forest plot in Supplementary file 2.

The effectiveness of zinc acetate lozenges on the duration of colds on the relative scale is also shown in Table 2. One-stage IPD meta-analysis gave an estimate of 36% average reduction in common cold duration and the two-stage pooling gave an estimate of 40% average reduction in the duration of colds.

Table 3 shows the one-stage subgroup analyses of the zinc lozenge effects. The table shows the difference in the zinc lozenge effect between the complementary subgroups. The effect of zinc acetate lozenges was not modified by allergy, smoking, baseline severity of the cold, age, sex, or ethnic group. Age was analyzed as a continuous variable and no interaction with zinc effect was seen for that variable either. The two-stage approach gave similar results, see Supplementary file 2. In the two-stage subgroup analysis, there was no heterogeneity in the interaction between the zinc effect and subgroups between the three trials.

**Discussion**

The effect of zinc acetate lozenges on the common cold was not modified by allergy, smoking, baseline severity of the common cold, age, sex, or ethnic group (Table 3). Our IPD meta-analysis does not support the earlier indication that zinc lozenges might be more effective for participants who have allergies [15].

Since no subgroup differences were found in the effect of zinc acetate lozenges, the overall estimates calculated in Table 2 are the most useful estimates for common cold participants comparable to the patients included in these three trials. Thus, given an average common cold duration of approximately one week (Table 2), zinc acetate lozenges may shorten common cold duration by an average of 3 days over various population groups.

A previous meta-analysis of the same three trials calculated that zinc acetate lozenges shortened the duration of colds on average by 42% [2]. That calculation was based on fixed-effect pooling of the reported study-level estimates. The current one-stage and two-stage IPD meta-analyses give similar overall estimates, though the current study calculated random-effects models.

Our meta-analysis was restricted to three studies with zinc acetate lozenges. Since there is evidence that acetate binds zinc ions less strongly than gluconate, zinc acetate has been proposed as a more suitable salt for lozenges than zinc gluconate [4,5]. Nevertheless, three studies with high doses of zinc as zinc gluconate also reported a statistically significant 21% to 48% reduction in the duration of colds [1,21,22]; see meta-analysis in [2]. The data of those old zinc gluconate studies were no longer available and we restricted our subgroup analysis to the three zinc acetate trials for which we had the IPD available.

Farr and Gwaltney [23] speculated that the apparent benefit of zinc gluconate lozenges reported

by Eby (1984) [1] might have been explained by the bad taste of the lozenges. However, none of the three zinc acetate lozenge trials included in our meta-analysis showed that bad taste was a problem. There was no substantial difference between the zinc and placebo groups in the occurrence of adverse effects and only a few dropouts occurred [15-17]. In the most recent trial [17], a few patients identified the type of lozenge that they were administered, but when the analysis was restricted to those who remained blinded at the end of the trial, the efficacy of zinc lozenges was comparable to the efficacy for all participants.

Zinc doses of 100 to 150 mg/day have been administered to certain patient groups for months with few adverse effects [2,24-27]. Thus, it is unlikely that a zinc dose of some 80 mg/day for one to two weeks, starting soon after the first common cold symptoms, might cause long-term adverse effects. If a patient considers that the taste of the zinc lozenge is bad, he or she can discontinue using the lozenges, whereas other common cold patients may continue its use. Although the evidence is strong that properly formulated zinc lozenges can shorten the duration of colds, it appears that the majority of zinc lozenges on the market have either doses of zinc which are too low or contain substances that bind zinc, such as citric acid [5]. Therefore, the findings of this analysis should not be directly generalized to the wide variety of zinc lozenge formulations on the market.

In conclusion, our IPD meta-analysis found that the effect of zinc acetate lozenges on the duration of the common cold is not modified by allergy, smoking, baseline common cold severity, age, sex, or ethnic group. The calculated 3 day and 36% estimates for the reduction of common cold duration are substantial effects and worth utilizing by common cold patients. The optimal composition of zinc lozenges and the best frequency of their administration should be further investigated. Nevertheless, given the current evidence of efficacy and the low rate of adverse

effects, common cold patients may be encouraged to try zinc acetate lozenges for treating their colds.



Supplementary file 1: Description of the three studies included.

Supplementary file 2: Description of the statistical calculations.

**Conflicts of interests**

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

**Contributions of authors**

AP, JTF, and EJP organized the three trials and collected the data that was analyzed in this study. HH planned and carried out this meta-analysis and wrote a draft manuscript. AP, JTF, and EJP participated in the revision of the manuscript. HH is the guarantor of the paper.

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**Table 1.**
Characteristics of trials

| Characteristic | All participants | Petrus (1998) [15] | Prasad (2000) [16] | Prasad (2008) [17] |
|---|---|---|---|---|
| All participants | 199 | 101 | 48 | 50 |
| Intervention | | | | |
| Zinc | 102 | 52 | 25 | 25 |
| Placebo | 97 | 49 | 23 | 25 |
| Age (y) | | | | |
| median | 27.0 | 22.0 | 37.0 | 34.5 |
| range | 17-61 | 18-54 | 18-61 | 17-60 |
| Sex | | | | |
| Male | 82 | 47 | 18 | 17 |
| Female | 117 | 54 | 30 | 33 |
| Allergy | | | | |
| No | 137 | 55 | 42 | 40 |
| Yes | 62 | 46 | 6 | 10 |
| Ethnic group | | | | |
| White | 132 | 73 | 29 | 30 |
| Black | 47 | 15 | 16 | 16 |
| Other | 20 | 13 | 3 | 4 |
| Smoker * | | | | |
| No | 70 | - | 35 | 35 |
| Yes | 28 | - | 13 | 15 |
| Severity score of the common cold at the baseline | | | | |
| Below median | 102 | 57 | 23 | 22 |
| Above median ** | 97 | 44 | 25 | 28 |

* The Petrus study (1998) [15] did not collect data on smoking.

** The common cold severity above median was ≥8 points in the Petrus study (1998) [15], ≥11 points in the Prasad study (2000) [16], and ≥8 points in the Prasad study (2008) [17], see Supplementary file 1 for details.

**Table 2.** Effect of high-dose zinc acetate lozenges on common cold duration among all participants in the three trials included

| | Duration of colds in the placebo group (days) | | Effect of zinc on cold duration in absolute units (in days) | | Effect of zinc on cold duration in relative terms (in %) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Estimate (in days) | 95% CI | Estimate (in %) | 95% CI |
| Trials: | | | | | | |
| Petrus 1998 [15] | 7.1 | 3.9 | -1.77 | -3.1, -0.47 | -25% | -44%, -6.7% |
| Prasad 2000 [16] | 8.1 | 1.8 | -3.61 | -4.6, -2.6 | -45% | -57%, -32% |
| Prasad 2008 [17] | 7.1 | 1.3 | -3.12 | -3.8, -2.4 | -44% | -53%, -34% |
| The 3 trials pooled: | | | | | | |
| One-stage meta-analysis | 7.3 | | -2.73 | -3.3, -1.8 | -36% | -45%, -24% |
| Two-stage meta-analysis | 7.4 | | -2.94 | -3.8, -2.1 | -40% | -50%, -30% |

**Table 3.** Difference in zinc acetate lozenge efficacy in subgroups: one-stage meta-analysis

| Subgroup | No. patients | Difference in the subgroup effects | | |
|---|---|---|---|---|
| | | Estimate * (days) | 95% CI (days) | Test of interaction (P) |
| Age | 199 | -0.5 | -1.1, +0.06 | 0.2 |
| Allergy | | | | |
| No | 137 | ref. | | |
| Yes | 62 | -0.9 | -2.0, +1.1 | 0.11 |
| Sex | | | | |
| Male | 82 | ref. | | |
| Female | 117 | +0.5 | -0.9, +2.1 | 0.17 |
| Ethnic group ** | | | | |
| White | 132 | ref. | | |
| Black | 47 | -0.1 | -2.0, +1.4 | 0.2 |
| Smoker | | | | |
| No | 70 | ref. | | |
| Yes | 28 | -0.2 | -1.5, +1.0 | 0.3 |
| Severity of the cold at the baseline | | | | |
| Below median | 102 | ref. | | |
| Above median | 97 | +0.4 | -2.0, +2.8 | 0.13 |

* The minus sign in the estimate for the difference indicates that on average zinc lozenges have a greater effect in the second subgroup compared with the zinc lozenge effect in the reference group, or in older participants; however, the P-values indicate that all differences are due to chance variation. The modifying effect of age on the zinc lozenge effect is calculated for a 10 year interval.
** Ethnic groups other than white or African Americans were excluded from this comparison.