Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage

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Supplementary File 1

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The tables in this document describe:

- Characteristics of the included trials
- Calculation of the daily elemental Zn dose from the lozenges (marked by bold)
- The effect of zinc on the common cold duration (marked by yellow)

Eby (1984) [1]	https://doi.org/10.1128/AAC.25.1.20 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC185426
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	Reported as a randomized trial, but the method of randomization was not described.
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	Reported as double-blind, which implies that participants and personnel were blinded.
Blinding of outcome assessment	Blinded "subjects recorded the presence and severity of 10 common cold symptoms on a report form" (p. 20)
Losses to follow-up and late exclusions	Originally there were 93 participants who had been ill for ≤3 days before starting the treatment. "11 zinc-treated subjects and 5 placebo-treated subjects prematurely stopped recording symptoms and had to be treated as dropouts. Of those receiving zinc, 7 dropped out on day 1, most of them due to objection to treatment. Of those receiving placebo, 2 dropped out on day 1 and the others dropped out later" (p. 21-22). Additional participants "failed to return reports at the end of the experiment (estimated 12 subjects with colds of 3 days or less, equally divided among zinc and placebo groups) " (p. 23). Thereby, the analysis was restricted to 65 participants who had complete reports. In addition to participants who had been ill for ≤3 days before starting the treatment, some of Eby's randomized participants had colds for >3 days before starting the treatment. Participants with such long delay in the initiation of treatment may be clinically nonrelevant. For example Mossad (1996), Prasad (2000), and Prasad (2008) included only participants who had been ill for ≤24 hr before starting the treatment. Therefore the post-randomization exclusion of participants who had colds for >3 days before starting the treatment seems justified.
Participants	Included in the analysis: 37 Zn and 28 placebo participants (see Losses to follow-up and late exclusions) 35 M 30 F, mean age 37 yr (range 11 to 63 yr) **Participants:** Local media were used to invite persons with colds to volunteer for the trial. All were accepted who were diagnosed by a physician to have the common cold.
Common cold definition	Presence of any of 10 common cold symptoms: headache, fever, muscle pain, sneezing, nasal drainage, nasal obstruction, sore throat, scratchy throat, cough, hoarseness (p. 20).
Delay between cold onset and treatment initiation	Inclusion of participants to the analysis required that the cold had lasted for **≤3 days** (p. 20-21). The mean duration of the common cold was 1.6 days at study entry. See Losses to follow-up and late exclusions.
Outcome definition	Explicit operational definition is not given in Methods, however, "asymptomatic" and "... subjects reported no symptoms" (Results, p. 21) indicates that recovery was defined as there being no remaining symptoms.
Intervention	Zn gluconate: one lozenge contained **23 mg Zn** (p. 20). Placebo lozenges contained Ca lactate Initial dose for all participants was 2 lozenges, one followed by the other, dissolved in the mouth for 10 to 20 min each. Thereafter, adults and youths dissolved 1 tablet every 2 hr awake, not exceeding 12 and **9 lozenges daily,** respectively. Children under 27 kg received ½ tablet every 2 hr awake, not exceeding 6 lozenges daily (p. 20).
Daily Zn dose from the lozenges	**207 mg/d** = 9/d × 23 mg 9/day is based on the instruction to use "1 tablet every 2 wakeful hr" This is based on assuming that participants were awake for 16 hours (p. 20).

Lozenges	“unflavored zinc gluconate tablets commonly available over-the-counter as nutritional supplements, with matching placebos. Tablets contained 23 mg of zinc or 50 mg of calcium lactate. Both tablets were manufactured by Truett Laboratories of Dallas, Tex., and were otherwise identical, including excipients of dicalcium phosphate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and FD&C yellow no. 5 and blue no. 1” (p. 20). “dissolved in the mouth as lozenges (about 10 to 20 min each) ” (p. 20).
Mean and SD of the common cold duration	Eby (1984) modeled the duration of common cold episodes by an exponential model and calculated the estimates for average duration of colds [1]: Zn group: average common cold duration: 3.9 d Placebo group: average common cold duration: 10.8 d The SD values were not reported. The mean and SD for the duration of colds in this meta-analysis is based on previous imputation and calculation [2]: Zn group: **mean** cold duration **3.92 d (SD 2.61)** Placebo group: **mean** cold duration **7.54 d (SD 3.18)**

Godfrey (1992) [20]	https://doi.org/10.1177/030006059202000305 http://imr.sagepub.com/content/20/3/234 https://www.ncbi.nlm.nih.gov/pubmed/1397668
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"Randomization by a third party was used to assign the 87 participants to treatment groups. A pharmacist, using a randomization table provided by the study statistician, packaged containers for individual subjects with lozenges according to the production run number and subject identification number" (p. 236).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"Patients, investigators and the pharmacist were, therefore, all blinded as to which treatment individual patients had received" (p. 236).
Blinding of outcome assessment	Blinded subjects "kept diaries recording the severity of their symptoms" (p. 236).
Losses to follow-up	8 Zn and 6 placebo participants withdrew from the trial: other diseases (5), failure to appear at follow-up (4), efficacy doubted by the participant (2), nausea (1 Zn, 1 placebo), sports injury (1).
Participants	Included in the analysis: 35 Zn and 38 placebo participants 44 M 29 F, median age 21 yr (range 18 to 40 yr) **Participants** were recruited from among Darthmouth College students and staff who spontaneously presented to the cold clinic at the College Health Service. **Exclusions:** a positive bacteriological throat culture, pregnancy, symptoms consistent with influenza or any other illness
Common cold definition	"All patients were examined and diagnosed by a physician or nurse clinician as having shown, for no more than 2 days, between two and nine symptoms consistent with a common cold. These symptoms included any of the following: cough, fever, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, and/or sneezing" (p. 235).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for ≤**2 days** (p. 235). The mean duration of the common cold was 1.34 days at entry (p. 236).
Outcome definition	"the strict criterion of complete disappearance of all symptoms was used as the definition of the cold being over" (p. 237)
Intervention	Zn gluconate glycine: one lozenge contained **23.7 mg Zn** Placebo lozenges contained tannic acid, glycine and Ca saccharinate Participants "were instructed (both verbally and in vriting) to suck, not chew, the lozenges at not less than 2-hr intervals taking up to a maximum of 8 lozenges per day" **The reported mean number of lozenges used per day in the Zn group was 8.1** (p. 242).
Daily Zn dose from the lozenges	**192 mg/d** = 8.1/d × 23.7 mg
Lozenges	Lozenges "contained US Pharmacopoeia tannic acid, glycine and calcium saccharinate in an orange-flavoured, boiled candy base, weighed 4.5 g and was identical to the ZGG lozenges in all characteristics. The ZGG lozenges, which were prepared in the same boiled candy base as the placebo contained glycine and zinc gluconate trihydrate, and the zinc content was 5.26±0.20 mg/g, or 23.7 mg zinc in each 4.5 g lozenge."

Mean and SD of the common cold duration	Godfrey (1992) reported (p. 237 [20]): Zn group: mean cold duration: **4.86 d** Placebo group: mean cold duration: **6.13 d** The SD values were not reported For the difference between the two groups, the authors reported t(71 df) = 2.01. Given the difference in the mean duration between the groups (1.27 days), the t(71 df) = 2.01 corresponds to **SD = 2.70 for both groups.**
Maintenance of blinding	"At their final visits, the patients were asked by the nurse which treatment they thought they had received. A total of 19 patients in each group guessed correctly; 12 of those who had received ZGG and 15 of those who received the placebo guessed incorrectly. In each treatment group there were four who did not know, and these eight patients were divided evenly among the four cells for the test of independence. The resulting chi^2-value of 0.8975 was not significant; thus, the patients did not know which treatment they had received" (p. 242).

Mossad (1996) [21]	http://dx.doi.org/10.7326/0003-4819-125-2-199607150-00001 http://www.annals.org/content/125/2/81 https://www.ncbi.nlm.nih.gov/pubmed/8678384
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"A statistical consultant prepared a computer-generated randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. The study medication was distributed by the study nurse, who was masked to treatment assignments" (p. 82).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"Double-blind" (p. 81). "The study medication was distributed by the study nurse, who was masked to treatment assignments" (p. 82).
Blinding of outcome assessment	"[Blinded] patients were asked to complete a daily log documenting the severity of symptoms " (p. 83).
Losses to follow-up	"One patient in the zinc group withdrew from the study on the first day because she could not tolerate the lozenges" (p. 83).
Participants	Included in the analysis: 49 Zn and 50 placebo participants 19 M 80 F, mean age 37 yr (range 21 to 69 yr) **Participants** were recruited from among the Cleveland Clinic staff through announcements in internal clinic publications and by word of mouth **Exclusions:** pregnancy, a known immune deficiency
Common cold definition	"Patients must have had ≥2 of the 10 following symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, or an oral temperature >37.7°C" (p. 82).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for **≤24 hr** (p. 82).
Outcome definition	"Cold resolution was defined as resolution of all symptoms (a total symptom score of 0) or resolution of all but one mild symptom (a total symptom score of 1)" (p. 83).
Intervention	Zn gluconate: one lozenge contained **13.3 mg Zn** Placebo lozenges contained Ca lactate Participants were instructed to dissolve 1 lozenge in their mouth every 2 hr while awake **The reported mean number of lozenges used per day in the Zn group was 6** (p. 84).
Daily Zn dose from the lozenges	**80 mg/d** = 6/d × 13.3 mg
Lozenges	"The zinc gluconate-glycine and placebo lozenges were supplied by the Quigley Corporation of Doylestown, Pennsylvania. The zinc lozenges consisted of a boiled hard-candy base prepared with approximately equal proportions of sucrose and corn syrup, zinc gluconate trihydrate, a molar proportion of glycine (aminoacetic acid), and lemon and lime flavoring oils. The mixture was formed into lozenges that weighed 4.4 g and contained 13.3 mg of zinc. Placebo lozenges, also weighing 4.4 g, were prepared from the same flavored hard-candy base and contained 5.0% calcium lactate pentahydrate. Placebo and active lozenges were identical in weight, appearance, flavoring content, and texture. The zinc lozenges, however, were more astringent than the placebo lozenges." (p 82).

Mean and SD of the common cold duration	Mossad (1996) reported (p. 84 [21]): Zn group: **median** time to resolution of cold symptoms: 4.4 d Placebo group: **median** time to resolution of cold symptoms: 7.6 d The mean and SD for the duration of colds in this meta-analysis is based on previous measurements of Mossad's fig 1 [2], and a recalculation for this meta-analysis which led to a minor difference in the placebo group duration, see Supplementary file 2 (p. 7). Zn group: **mean** cold duration **5.20 d (SD 2.83)** Placebo group: **mean** cold duration **9.20 d (SD 5.32)**
Maintenance of blinding	“All patients were called on the second day of medication use to make sure that they were not developing a more serious illness and to assess the adequacy of the masking through responses to a questionnaire” (p. 82). “Questions to evaluate the efficacy of masking to group assignment were asked after the first day of treatment and at the end of the study. Patients were asked to guess their assignment from among seven choices: certainly placebo, probably placebo, possibly placebo, do not know, certainly active, probably active, or possibly active. By assigning all guesses that mentioned "placebo" as placebo and all guesses that mentioned "active" as zinc, the following results were obtained. On the initial questionnaire, 50% of the placebo recipients (25 of 50) and 55.2% of the zinc recipients (27 of 49) correctly guessed their study assignment. At the end of the study, 54% of the placebo recipients (27 of 50) and 53.1% of the zinc recipients (20 of 49) correctly guessed their treatment assignment. Sixty-five of the 99 patients (65.7%) maintained their original guess at the end of the study. Because no clear pattern of movement of guesses was seen between the groups, masking appears to have been maintained during the study” (p. 85).
Adverse effects	“We ascertained side effects in two ways. During the study, we asked patients to list all of the side effects of their medication. This open-ended question was the only one asked during the study period. Seventeen of 49 zinc recipients reported that no side effects developed with their medication before the conclusion of the study. In these patients, the mean (4.7) and median (4.0) numbers of days until only one mild symptom remained was the same as the number in the 32 patients with identified side effects. The zinc recipients with and without identified side effects also had a similar mean (5.1 days and 5.5 days, respectively) and median (4.5 days and 6.0 days, respectively) time until symptoms completely resolved ($P > 0.2$). ” “The second method used to determine side effects entailed listing all of the common side effects of zinc and asking patients at the end of the study whether these or other side effects developed while they were taking the study medication (Table 3). As expected, patients described more side effects in response to this question than in response to the open-ended question alone. Patients in the zinc group reported more side effects per person (25 zinc recipients and 5 placebo recipients had two or more side effects; $P< 0.001$), significantly more nausea (10 patients compared with 2 patients; $P = 0.02$), and more bad-taste reactions (39 patients compared with 15 patients; $P < 0.001$). The other symptoms described (vomiting, abdominal pain, diarrhea, constipation, mouth irritation, and dry mouth) did not differ significantly between the two groups ” (p. 85-86).

Petrus (1998) [22]	https://doi.org/10.1016/S0011-393X(98)85058-3 http://www.currenttherapeuticres.com/article/S0011-393X%2898%2985058-3/abstract http://www.sciencedirect.com/science/article/pii/S0011393X98850583
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"The bottles of the zinc lozenges and placebo were sent by the manufacturer and each bottle was identical except a sequential number. At registration, after qualifying for the study each patient was given a bottle of 180 lozenges. At the conclusion of the study, when the diaries were assembled, the code for the bottles was sent by the manufacturer, and the patients were placed in the zinc or placebo category. Then the results were tabulated and the statistical analysis was undertaken" (Edward Petrus 24 March 2016).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	Participants and personnel were blinded.
Blinding of outcome assessment	Blinded "subjects were also informed that they were required to rate and record their symptoms in a diary " (p. 598). "Subjects recorded their symptoms every day until their symptoms ceased (p. 598).
Losses to follow-up	1 patient was lost to follow-up.
Participants	Included in the analysis: 52 Zn and 49 placebo participants 47 M 54 F, mean age 26 yr (range 18 to 54 yr) **Participants** were recruited from the campus of the University of Texas through posted announcements (p. 597). **Exclusions:** serious illnesses, organ transplants, disability (p. 597). "This study was conducted during July and August 1997, when pollen was at its lowest level" (p. 598).
Common cold definition	"subjects had to have ≥2 common cold symptoms (nasal drainage, nasal congestion, cough, fever, myalgia, headache, sore throat, scratchy throat, hoarseness, sneezing, or malaise) " (p. 598).
Delay between cold onset and treatment initiation	"97 of the 101 subjects started using zinc lozenges on the first day of enrollment in the study (4 started on day 2 of enrollment), but the dataset doesn't contain any information on the length of time between onset of symptoms and start of zinc therapy." (Kenneth Lawson, email 11 Dec 2014) "Many patients had a delay over 24 hours before the zinc lozenge treatment was started, but there are no data about the distribution of the delay" (Edward Petrus, email 21 Feb 2017).
Outcome definition	**Two outcomes** were reported: **1)** mean duration of all observed cold symptoms of the individual **2)** duration of the longest-lasting common cold symptom
Intervention	Zn acetate: one lozenge contained **9 mg Zn** (p. 597). Placebo lozenges contained sucrose octaacetate Participants were instructed to use 1 lozenge every 1½ hr while awake during day 0, then 1 lozenge every 2 hr while awake on following days **"averaged 9.9 lozenges per subject per day as long as symptoms persisted"** (p. 599).
Daily Zn dose from the lozenges	**89 mg/d** = 9.9/d × 9 mg

Lozenges	"The lozenges with zinc contained 9 mg of zinc in a 2.7 g dextrose base" (p. 597). "To achieve masking, sucrose octaacetate (0.169 mg) was used in the placebo, and both the placebo and zinc lozenges were peppermint flavored. A review of subjects' diary entries revealed that 4 subjects noted a chalky taste, 4 experienced a metallic aftertaste, and 3 complained of an upset stomach; none of the subjects noted a bitter taste. Most subjects liked the peppermint flavor. " (p. 599). "The lozenges ... dissolved in the mouth in about 15 minutes" (p. 602). "Lozenges dissolved in about 15 min " (p. 31 on [7]). "The Petrus and Prasad compressed lozenges were designed by the present author and were identical in composition. In addition to ZA, they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-sterate (2.5% tablet weight) as tablet lubricant, stevia for added sweetness and peppermint oil for flavor, with the composition compressed to near maximal hardness for slowest dissolution. Those ingredients were chosen specifically because they do not react with iZn. " (p. 31 on [7]). "Lozenges were small zinc acetate lozenges consisting of a dextrose tablet base, 2.5% glycerol monostearate lubricant, stevia and peppermint oil on silica gel compressed with a force sufficient to allow them to dissolve in 15 min in the human mouth" (p. 485 in [8]).
Mean and SD of the common cold duration	Petrus (1998) reported (table II [22]): **Outcome 1):** Zn group: mean cold duration: 3.8 d (SE 0.2) Placebo group: mean cold duration: 5.1 d (SE 0.4) **Outcome 2):** Zn group: duration of longest-lasting cold symptom: 5.3 d (SE 0.4) Placebo group: duration of longest-lasting cold symptom: 7.1 d (SE 0.6) To an inquiry for more accurate trial results, Kenneth Lawson (statistician of the study) replied (email 4 March, 2009): Zn group: mean duration of longest-lasting symptom: **5.288 d (SD 2.569)** Placebo group: mean duration of longest-lasting symptom: **7.061 d (SD 3.907)** These latter figures were used in the current meta-analysis. In a previous meta-analysis [2], the outcome 1) was used, but there is no material difference between the effect of zinc on the two outcomes. The definition of Outcome 2 is closer to the outcome definitions of the other trials.
Adverse effects	"Only 1 subject was lost to follow-up, and none of the remaining 101 subjects discontinued because of side effects from the lozenges. .. A review of subjects' diary entries revealed that 4 subjects noted a chalky taste, 4 experienced a metallic aftertaste, and 3 complained of an upset stomach; none of the subjects noted a bitter taste. Most subjects liked the peppermint flavor" (p. 599).

Prasad (2000) [23]	https://doi.org/10.7326/0003-4819-133-4-200008150-00006 https://www.ncbi.nlm.nih.gov/pubmed/10929163
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"A research consultant prepared the randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. A research assistant who was blinded to treatment assignments distributed the study medication" (p. 246).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"A research assistant who was blinded to treatment assignments distributed the study medication" (p. 246).
Blinding of outcome assessment	Blinded "participants were asked to complete a daily log documenting the severity of symptoms " (p. 246).
Losses to follow-up	"Two persons in the placebo group dropped out on day 2 and were lost to follow-up. One of the two persons had a sore mouth, and the other developed an ear infection for which care was transferred to a physician outside of Detroit Medical Center" (Legend to Table 1, p. 247).
Participants	Included in the analysis: 25 Zn and 23 placebo participants 18 M 30 F, mean age 37 yr (SD 11 yr) **Participants** were students, staff, and employees at Wayne State University, Michigan, who were ≥18 yr (p.246). **Exclusions:** pregnancy, a known immunodeficiency disorder, chronic illnesses, previous use of zinc lozenges (p.246).
Common cold definition	Presence of ≥2 of "the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever" (p. 246).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for **≤24 hr** (p.246).
Outcome definition	"Resolution of cold symptoms was defined as resolution of all symptoms (a total symptom score of 0) or resolution of all but one mild symptom (a total symptom score of 1)" (p. 246).
Intervention	Zn acetate: one lozenge contained **12.8 mg Zn** (p. 245). Placebo lozenges contained sucrose octaacetate Participants were asked to dissolve 1 lozenge in their mouth every 2 to 3 hr while awake **The reported mean number of lozenges used per day in the Zn group was 6.2** (p. 249).
Daily Zn dose from the lozenges	**80 mg/d** = 6.2/d × 12.8 mg

Lozenges	“Each zinc lozenge consisted of 42.96 mg of zinc acetate dihydrate, 6.0 mg of peppermint oil, 16.0 mg of silica gel, 4.0 mg of stevia extract powder , 3.8 g of directly compressible dextrose, and 100 mg of glycerol monostearate. Each lozenge contained 12.8 mg of zinc. Each placebo lozenge contained 0.25 mg of sucrose octa acetate, 6.0 mg of peppermint oil, 16.0 mg of silica gel, 3.9 g of dextrose DC, and 100 mg of glycerol monostearate. The placebo and zinc lozenges were identical in weight (4 g), appearance, flavor, and texture” (p. 246). “The Petrus and Prasad compressed lozenges were designed by the present author and were identical in composition. In addition to ZA, they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-sterate (2.5% tablet weight) as tablet lubricant, stevia for added sweetness and peppermint oil for flavor, with the composition compressed to near maximal hardness for slowest dissolution. Those ingredients were chosen specifically because they do not react with iZn [ionic zinc] . The slower dissolution of the 4-g size lozenges was an advantage over the smaller lozenges in terms of efficacy. ” (p. 31 on [7]). “compressed with a force sufficient to allow them to dissolve in 30 min in the mouth” (p. 485 in [8]).
Mean and SD of the common cold duration	Prasad (2000) reported (table 2: overall symptoms [23]): Zn group: mean cold duration: 4.5 d (SD 1.6) Placebo group: mean cold duration: 8.1 d (SD 1.8) The mean and SD for the duration of colds in this meta-analysis is based on the previous calculation [2]: Zn group: mean cold duration: **4.44 d (SD 1.56)** Placebo group: mean cold duration: **8.09 d (SD 1.81)**
Maintenance of blinding	“Comparability in taste between zinc and placebo was tested in healthy volunteers. Ten participants were given a zinc lozenge and 10 received a placebo lozenge. One week later, the participants who received zinc were given placebo and those who received placebo were given zinc. At each visit, the participants filled out a questionnaire in which they were asked to guess whether they received a zinc or placebo lozenge... [we] categorized participants as “correct,” “incorrect,” or “do not know.” We assessed the adequacy of blinding among study participants by administering the questionnaire used to assess comparability of taste in healthy volunteers. Participants filled out the questionnaire at the beginning and at the end of the trial” (p. 247). “Of 20 participants who received zinc, 5% correctly guessed that they were receiving active therapy. Of 20 participants who received placebo, 10% correctly guessed that they were receiving placebo. Therefore, participants did not correctly guess which type of lozenge they were receiving much better than by chance. In addition, at the beginning of the trial, 48% of zinc recipients and 26% of placebo recipients correctly identified the lozenges ($P > 0.2$). At the end of the study, 56% of zinc recipients and 26% of placebo recipients correctly identified the lozenges ($P = 0.09$). None of these percentages exceeded 50%, indicating that blinding was adequate at the outset and was maintained throughout the study” (p. 248-249).
Adverse effects	“Except for mouth dryness and constipation, no statistically significant side effects occurred in zinc recipients compared with placebo recipients” (p. 250).

Prasad (2008) [24]	https://doi.org/10.1086/528803 https://www.ncbi.nlm.nih.gov/pubmed/18279051
Maintenance of blindingMethods	Randomized, placebo-controlled, double-blind trial
Randomization	"A research consultant prepared the randomization code and the packages of medication. The packages were identical in appearance except for the randomization numbers. A research assistant who was blinded to treatment assignments distributed the study medication " (p. 796).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"A research assistant who was blinded to treatment assignments distributed the study medication " (p. 796). "The clinical assistant who collected all of the clinical information and remained in touch with the subjects who were recruited for the study remained completely blinded regarding the contents of the zinc and placebo pills" (Ananda Prasad 15 Dec 2014).
Blinding of outcome assessment	Blinded "participants were asked to complete a daily log documenting the severity of symptoms" (p. 796).
Losses to follow-up	No drop outs.
Participants	Included in the analysis: 25 Zn and 25 placebo participants 16 M 34 F, mean age 35 yr (SD 14 yr) **Participants** were students, staff, and employees at Wayne State University, Michigan, who were ≥18 yr (p. 796). "In general, subjects were recruited during fall and winter months" (p. 796). **Exclusions:** pregnancy, any known immune deficiency disorder or chronic illness, previous use of zinc lozenges (p. 796).
Common cold definition	Presence of ≥2 of "the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever" (p. 796).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for **≤24 hr** (p. 796).
Outcome definition	"Resolution of cold symptoms was defined as resolution of all symptoms (a total symptom score of 0) or resolution of all but 1 mild symptom (a total symptom score of 1)" (p. 797).
Intervention	Zn acetate: one lozenge contained **13.3 mg Zn** (p. 796). Placebo lozenges contained sucrose octaacetate Participants were asked to dissolve 1 lozenge in their mouth every 2 to 3 hr while awake. **The reported mean number of lozenges used per day in the Zn group was 6.9** (p. 799).
Calculation of the daily Zn dose from lozenges	**92 mg/d** = 6.9/d × 13.3 mg

Lozenges	“The lozenges were cherry oil–flavored Fast Dry zinc acetate lozenges, manufactured by F & F Foods (Chicago, IL). The active lozenges contained 13.3 mg of zinc as zinc acetate in a hard candy that contained 3.8 g of sucrose and corn syrup and that was prepared using the open-pot batch method, with the active ingredient added last. One hundred percent of the zinc was available at physiologic pH 7.4 in positively charged, ionic form. The placebo lozenges were of identical composition, except that they contained 0.25 mg of sucrose octa acetate rather than the active ingredient, zinc. There were no fats, metal chelators, or other zinc ion– binding agents in either the active or placebo lozenges. The placebo and zinc lozenges were identical in weight, appearance, flavor, and texture and were supplied by George Eby” (p. 796).
Mean and SD of the common cold duration	Prasad (2008) reported (table 2: overall symptoms, all subjects [24]): Zn group: mean cold duration: **4.00 d (SD 1.04)** Placebo group: mean cold duration: **7.12 d (SD 1.26)**
Maintenance of blinding	“Comparability in taste between zinc and placebo was tested in the participants at the beginning and the end of the trial. The participants filled out a questionnaire in which they were asked to guess whether they had received zinc or placebo lozenges... [we] categorized participants as correct, incorrect, or do not know” (p. 797). “In the zinc group at the beginning of the study, only 1 subject identified the lozenges as certainly zinc, and 2 subjects identified them as probably zinc. Thus, 3 (12%) of 25 subjects in this group were correct. At the end of the study, 2 (8%) were correct; 1 subject identified the lozenges as certainly zinc, and another subject identified them as probably zinc. In the placebo group at the beginning of the study, 1 subject said that the lozenges were certainly placebo, and another subject identified them as probably placebo. Thus, 2 subjects (8%) in this group were correct. At the end of the study, none of the subjects identified the placebo lozenge correctly” (p. 799).
Adverse effects	“Adverse effects of the zinc and placebo lozenges are compared in table 3. The zinc and placebo groups did not differ significantly in the incidences of any of the adverse effects, including diarrhea, constipation, sweet taste, sour taste, bitter taste, aftertaste, dry mouth, mouth irritation, or bad taste. None of the subjects complained of either abdominal pain or vomiting” (p. 799).

Smith (1989) [19]	https://doi.org/10.1128/AAC.33.5.646 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC172506
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"Upon enrollment, subjects were randomly assigned to receive either zinc gluconate or placebo" (p. 646).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"Both subjects and investigators were blinded to treatment" (p. 646).
Blinding of outcome assessment	Blinded "subjects rated the severity of 11 symptoms" (p. 646).
Losses to follow-up	64 were excluded because of insufficient dose (<10 lozenges on any day) or insufficient duration of therapy. 2 were lost to follow-up
Participants	Included in the analysis: 57 Zn and 53 placebo participants M/F ratio not described. All were students ≥18 yr **Participants** were recruited from among the students of three colleges and from one family practice. **Exclusions:** serious acute or chronic medical conditions, seasonal allergies, productive cough, indication for antibiotic therapy, had taken treatment for symptoms within 8 hr of the baseline evaluation
Common cold definition	"Upon enrollment and at the end of each study day, subjects rated the severity of 11 symptoms and the overall severity of their URI on a scale of 0 to 3 (absent to severe). The individual symptoms assessed were sneezing, runny nose, stopped-up nose, sore or scratchy throat, hoarseness, postnasal drip, cough, watery eyes, headache, chilliness, muscle aches" (p. 646).
Delay between cold onset and treatment initiation	Not described
Outcome definition	Explicit operational definition is not given in Methods, however, "... who continued to have symptoms on each day of treatment" (Results, p. 647) suggests that recovery was defined as there being no remaining symptoms.
Intervention	Zn gluconate: one lozenge contained **11.5 mg Zn (two lozenges 23 mg Zn)**, see below Placebo lozenges contained sucrose octaacetate An initial dose of 4 lozenges was used, followed by **2 lozenges** dissolved in the mouth every 2 hr while awake, corresponding to **9 times 2 lozenges per day** (p. 646).
Daily Zn dose from the lozenges	**207 mg/d** = 9/d × 2 × 11.5 mg 9/day × 2 is based on the instruction to dissolve 2 lozenges in the mouth "every 2 hr while awake" (p. 646).

Lozenges	"Identical-appearing lozenges containing either 11.5 mg of elemental zinc or sucrose octaacetate were used" (p. 646). The zinc lozenge of Smith (1989) had "14 molar equivalents of mannitol (relative to zinc), and 16 molar equivalents of sorbitol", which bind zinc ions, see [8, pp. 128 and 129]. Smith was a co-author in the Godfrey et al. [20] study which stated in its introduction (p. 235) that: "it has been demonstrated that … mannitol/sorbitol inactivate zinc by chelation in saliva" and "mannitol/sorbitol [zinc lozenge] formulations release no zinc ions when dissolved in the mouth" referring explicitly to the Smith (1989) trial [19].
Mean and SD of the common cold duration	Smith (1989) reported the proportion of participants who were symptomatic as a function of time (fig. 1 [19]). Median duration cannot be measured, because half of the placebo participants did not become asymptomatic by the end of the follow-up The mean and SD for the duration of colds were, see [2]: Zn group: mean cold duration: **7.23 d (SD 2.29)** Placebo group: mean cold duration: **7.57 d (SD 3.01)**
Notes	**Because Smith considered afterwards that the lozenges of the 1989 trials were not functional, this trial is not included in the current analysis, see above "Lozenges".**

Turner (2000) [25]	https://doi.org/10.1086/317437 http://cid.oxfordjournals.org/content/31/5/1202 https://www.ncbi.nlm.nih.gov/pubmed/11073753
Methods	Randomized, placebo-controlled, double-blind trial
Randomization	"Subjects who met the criteria for randomization to treatment were randomly assigned to 1 of the 4 treatments in accordance with the drug-randomization code" (p. 1202).
Allocation concealment	Participants and personnel did not know to which group the participants were allocated.
Blinding of participants and personnel	"the investigator and the subject were blinded to the identification of the test medications " (p. 1202).
Blinding of outcome assessment	"After randomization, the symptom scores were recorded by the [blinded] subject " (p. 1203).
Losses to follow-up	None described.
Participants	Included in the analysis: 68 Zn gluconate and 71 placebo participants M/F ratio not described; age range 18 to 65 yr, but no mean or median reported **Participants** were recruited at 4 different study sites: IMTCI (Lenexa, KS), GFI Pharmaceutical Services (Evansville, IN), TKL Research (Paramus, NJ), and Research Across America (RAA; Dallas). Characteristics of the participants were poorly described. **Exclusions:** no descriptions
Common cold definition	Presence of ≥2 of the following symptoms: sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, hoarseness (p. 1203).
Delay between cold onset and treatment initiation	Inclusion required that the cold had lasted for ≤1 calendar days ("effectively **<36 hr**")(p. 1203).
Outcome definition	"The duration of the cold was defined as the time from the start of study-medication administration to the first of the 2 consecutive symptom scores ≤1" (p. 1203).
Intervention	Zn gluconate: one lozenge contained **13.3 mg Zn** Placebo lozenges contained tannic acid, sucrose octaacetate, quinine The study medications were dissolved in the mouth and taken every 2 to 3 hr while awake ("total of **6 lozenges per day"**) (p. 1202).
Daily Zn dose from the lozenges	**80 mg/d** = 6/d × 13.3 mg
Lozenges	"zinc gluconate lozenges (13.3 mg; Cold-Eeze, Quigley Corp., Doylestown, PA), and placebo lozenges contained tannic acid, sucrose octaacetate, sugar, glucose syrup, quinine hydrochloride, artificial flavoring, and artificial coloring" (p. 1202).
Mean and SD of the common cold duration	Turner (2000) reported (p. 1204 [25]): Zn group: **median** cold duration: 6.0 d Placebo group: **median** cold duration: 5.5 d Turner did not report the mean and SD The mean and SD for the duration of colds in this meta-analysis is based on a previous imputation and calculation [2]: Zn group: **mean** cold duration: **7.41 d (SD 3.88)** Placebo group: **mean** cold duration: **7.55 d (SD 3.96)**