Zinc acetate lozenges may improve the recovery rate of common cold patients: an IPD meta-analysis

Supplementary File 1

This is supplementary material to a paper by Hemilä et al. (2017).
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http://www.mv.helsinki.fi/home/hemila/
http://www.mv.helsinki.fi/home/hemila/Zinc.htm (papers on zinc and the common cold)

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The tables in this document describes

the selection of patients,

the definition of outcomes,

dosage of zinc,

details of methods, and

other essential characteristics of the three included trials.

Petrus (1998) [11]	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	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients and personnel	Reported as double-blind, which implies that patients 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 (p. 597).
Patients	Included in the analysis: 52 Zn and 49 placebo patients 47 M 54 F, mean age 26 yr (range 18 to 54 yr) **Patients** 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	Presence of 2 or more of the following 11 symptoms: nasal drainage, nasal congestion, cough, fever, myalgia, headache, sore throat, scratchy throat, hoarseness, sneezing, 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.
Measurement of severity of the baseline cold	"Subjects were also informed that they were required to rate and record their symptoms in a diary at the same time each day. Symptoms [see the 11 symptoms above] were graded as follows: 0 = absent; 1 = mild (symptom is present but not particularly a discomfort); 2 = moderate (symptom is clearly evident and a discomfort); or 3 = severe (symptom is a serious problem and clearly evident and a discomfort)" (p. 598). Thus, the maximum of the scale was 33 points. The recorded level of severity at the baseline varied from 2 to 23 points, with the median at 7 points.
Intervention	Zn acetate: one lozenge contained **9 mg Zn** (p. 597). Placebo lozenges contained sucrose octaacetate (p. 599).

	Patients were instructed to use 1 lozenge every 1½ hour while awake during day 0, then 1 lozenge every 2 hour while awake on following days (p. 598). **“averaged 9.9 lozenges per subject per day”** (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 [10]). “The Petrus and Prasad compressed lozenges were designed by the present author [George Eby] and were identical in composition. In addition to ZA [zinc acetate], they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-stearate (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]” (p. 31 in [10]). “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 [1]).
Mean and SD of the common cold duration	Calculated from the IPD data set (the same as reported in 1998): Zn: Mean duration of the longest-lasting symptom: **5.288 days (SD 2.569)** Placebo: Mean duration of the longest-lasting symptom: **7.061 days (SD 3.907).**
Allergy testing	“Because common colds and nasal allergies cause many of the same symptoms, skin tests were performed on each subject to determine whether allergies were present. All subjects were skin tested with 20 different allergy extracts, …The extracts included ragweed mix, burweed marsh elder, cedar elm, Bermuda grass, Johnson grass, perennial rye grass, mountain cedar (juniper), Virginia live oak, pecan, American elm, Alternaria alternata, Hormodenorum cladospo rioides, Helminthosporium sativum, cockroach mix (American and German), cat dander, dog dander, dust mite mix, Western ragweed, a negative control (diluent), and a positive control (histamine). After a 15- to 30- minute waiting period, the results of the skin test were measured and recorded. Itching, swelling, or redness at the site of allergy extract application indicated a positive reaction to the allergen. Forty-six subjects (46%) tested positive for allergies, and 55 (54%) were negative” (pp. 597-598).
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) [12]	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	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients 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).
Patients	Included in the analysis: 25 Zn and 23 placebo patients 18 M 30 F, mean age 37 yr (SD 11 yr). **Patients** were students, staff, and employees at Wayne State University, Michigan, who were ≥18 yr (p. 246). **Exclusions:** Pregnancy, a known immunodeficiency disorder, chronic illnesses, or previous use of zinc lozenges (p. 246).
Common cold definition	Presence of 2 or more of the following 10 symptoms: cough, headache, hoarseness, muscle ache, nasal discharge, 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 hours or less** (p. 246).
Outcome definition	"Resolution of cold symptoms was defined as the 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).
Measurement of severity of the baseline cold	"Participants were asked to complete a daily log documenting the severity of symptoms [see the 10 symptoms above] and the medications taken throughout the duration of the cold. Every day, the participants graded each symptom as 0 for none, 1 for mild, 2 for moderate, and 3 for severe. Total symptom scores were calculated by summing the scores " (p. 246). Thus, the maximum of the scale was 30 points. The recorded level of severity at the baseline varied from 2 to 26 points, with the median at 11 points.
Intervention	Zn acetate: one lozenge contained **12.8 mg Zn** (p. 246). Placebo lozenges contained sucrose octa acetate (p. 246). patients "were asked to dissolve 1 lozenge in their mouth every 2 to 3 hr while awake" (p. 246). **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 [George Eby] and were identical in composition. In addition to ZA [zinc acetate], they contained directly compressible (agglomerated) dextrose as the tablet base, glycerol mono-stearate (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]" (p. 31 in [10]). "Compressed with a force sufficient to allow them to dissolve in 30 min in the mouth" (p. 485 in [1]).
Mean and SD of the common cold duration	Calculated from the IPD data set (the same as reported in 2000): Zn group: mean cold duration: **4.480 days (SD 1.636)** Placebo group: mean cold duration: **8.086 days (SD 1.807)**
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% [n=1]correctly guessed that they were receiving active therapy. Of 20 participants who received placebo, 10% [n=2] 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) [13]	https://doi.org/10.1086/528803 https://www.ncbi.nlm.nih.gov/pubmed/18279051
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. 796).
Allocation concealment	Patients and personnel did not know to which group the patients were allocated.
Blinding of patients 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.
Patients	Included in the analysis: 25 Zn and 25 placebo patients 16 M 34 F, mean age 35 yr (SD 14 yr) **Patients** 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, or previous use of zinc lozenges (p. 796).
Common cold definition	Presence of 2 or more 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 hours or less** (p. 796).
Outcome definition	"Resolution of cold symptoms was defined as the resolution of all symptoms (a total symptom score of 0) or the resolution of all but 1 mild symptom (a total symptom score of 1)" (p. 797).
Measurement of severity of the baseline cold	"Participants were asked to complete a daily log documenting the severity of symptoms [see the 10 symptoms above] ... the subjects graded each symptom as 0 for none, 1 for mild, 2 for moderate, or 3 for severe. Total symptom scores were calculated by summing the scores of the 10 symptoms for each day" (p. 796-797). Thus, the maximum of the scale was 30 points. The recorded level of severity at the baseline varied from 2 to 20 points, with the median at 8 points.
Intervention	Zn acetate: one lozenge contained **13.3 mg Zn** (p. 796). Placebo lozenges contained sucrose octaacetate. Patients "were asked to dissolve 1 lozenge in their mouth every 2-3 h while awake" (p. 796). **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. 100% 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 octaacetate 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	Calculated from the IPD data set (the same as reported in 2008): Zn group: mean cold duration: **4.00 days (SD 1.04)** Placebo group: mean cold duration: **7.12 days (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).