Annals of Internal Medicine | ORIGINAL RESEARCH

Echinacea for Treating the Common Cold

A Randomized Trial

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Background: Echinacea is widely used to treat the common cold.

Objective: To assess the potential benefits of echinacea as a treatment of common cold.

Design: Randomized, controlled trial. (ClinicalTrials.gov registration number: NCT00065715)

Setting: Dane County, Wisconsin.

Patients: 719 patients, aged 12 to 80 years, with new-onset common cold.

Intervention: Patients were assigned to 1 of 4 parallel groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded, open-label). Echinacea groups received the equivalent of 10.2 g of dried echinacea root during the first 24 hours and 5.1 g during each of the next 4 days. Indistinguishable placebo tablets contained only inert ingredients.

Measurements: The primary outcome was the area under the curve for global severity, with severity assessed twice daily by self-report using the Wisconsin Upper Respiratory Symptom Survey, short version. Secondary outcomes included interleukin-8 levels and neutrophil counts from nasal wash, assessed at intake and 2 days later.

Results: Of the 719 patients enrolled, 713 completed the protocol. Mean age was 33.7 years, 64% were female, and 88% were white. Mean global severity was 236 and 258 for the blinded and unblinded echinacea groups, respectively; 264 for the blinded placebo group; and 286 for the no-pill group. A comparison of the 2 blinded groups showed a 28-point trend (95% CI, −69 to 13 points) toward benefit for echinacea ($P = 0.089$). Mean illness duration in the blinded and unblinded echinacea groups was 6.34 and 6.76 days, respectively, compared with 6.87 days in the blinded placebo group and 7.03 days in the no-pill group. A comparison of the blinded groups showed a nonsignificant 0.53-day (CI, −1.25 to 0.19 days) benefit ($P = 0.075$). Median change in interleukin-8 levels and neutrophil counts were also not statistically significant (30 ng/L and 1 cell/high-power field [hpf] in the no-pill group, 39 ng/L and 1 cell/hpf in the blinded placebo group, 58 ng/L and 2 cells/hpf in the blinded echinacea group, and 70 ng/L and 1 cell/hpf in the open-label echinacea group).

Limitation: Higher-than-expected variability limited power to detect small benefits.

Conclusion: Illness duration and severity were not statistically significant with echinacea compared with placebo. These results do not support the ability of this dose of the echinacea formulation to substantively change the course of the common cold.

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Acute viral respiratory infection (common cold) is the most frequent human illness. Its etiologic agents include rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, adenovirus, enterovirus, and metapneumovirus (1–3). Although influenza-caused illness is the most serious and is often categorized separately, the symptoms are usually indistinguishable from those produced by other viruses (4–7). Excluding influenza, the economic costs of acute respiratory infection are estimated to be about $40 billion, which makes acute respiratory infection 1 of the 10 most expensive illnesses (8). Most of this effect comes from the estimated 20 million physician visits and 40 million school days and workdays lost each year. Available treatments are at best modestly effective at reducing symptoms (9), and none has been proven to shorten illness duration.

The botanical genus *Echinacea* is native to North America, where indigenous peoples used various echinacea preparations for many illnesses (10). However, much of the foundational biomedical research on echinacea was done in Germany, where the plant was introduced in the 1920s and used for various illnesses, including respiratory infection (11, 12). Immunoactivity, including macrophage activation and cytokine expression, has been widely reported (13–22), but the specific pathways, pharmacokinetics, and mechanism of action of the various phytochemical constituents are incompletely understood (23–29). Most commercially available echinacea products derive primarily from 2 species, *Echinacea purpurea* and *E. angustifolia* (30, 31), and can be divided into 2 general categories: stabilized fresh juice of aerial parts of *E. purpurea*, which is rich in such hydrophilic derivatives as polysaccharides and glycoproteins, and an aqueous–ethanolic extract of root material from *E. angustifolia* or *E. purpurea* that is richer in li-

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Context

Echinacea is a popular nonprescription treatment for the common cold. The efficacy of echinacea in this regard continues to be debated after hundreds of studies.

Contribution

In this randomized, controlled trial, a minor, nonstatistically significant decrease in illness duration and severity was found in participants who received either blinded or open-label echinacea compared with those who received blinded placebo or no pills.

Caution

Higher-than-expected variability in the natural history of cold episodes may have limited the power of this study to demonstrate treatment differences.

Implication

This study is unlikely to change the debate on the efficacy of echinacea in treating the common cold.

—The Editors

pophilic constituents, such as alkamides. Other potentially active constituents, such as echinacoside; cynarin; and caffeic, caftaric, cichoric, and chlorogenic acids, are found in various concentrations among the different formulations. When we designed this study in 2002, we decided to use a root-based, alkamide-rich preparation. Research published since that time (32–38) has tended to support our decision.

Several hundred scientific studies on echinacea, including a dozen randomized trials that tested echinacea for preventing or treating the common cold (39), had already been published by the mid-1990s, when echinacea had become popular in the United States. Nearly all of these early trials reported either statistically significant benefit or trends toward benefit (40). However, all were manufacturer-sponsored and of moderate to poor quality. In this context, we found it necessary to conduct our own trial from 1999 to 2000 (41), which yielded negative results. Several new trials have been published since then, some with positive results (42–44) and some with negative results (45–48). Systematic reviews and meta-analyses have varied in their inclusion criteria, review methods, results, and interpretation (49–53). We designed and conducted this trial because the effectiveness of echinacea was still unclear.

METHODS

We asked 3 independent research questions, a somewhat unconventional approach. First, are there placebo effects associated with blinded versus open-label pills? Second, do physician–patient interactions influence cold outcomes? Finally, are there effects attributable specifically to echinacea, as assessed by blinded comparison? This study addresses the third question; studies that address the first 2 questions will be published elsewhere.

Our trial used a 2-way factorial design, in which participants were randomly assigned to receive no, standard, or enhanced clinical interaction in one direction (33.3% chance) and to receive no pills, placebo (blinded), echinacea (blinded), or open-label echinacea (unblinded) in the other direction (25% chance). Details of our rationale and methods have been published elsewhere (54).

Setting and Participants

Our study was conducted at 2 sites in Dane County, Wisconsin. Study promotion included newspaper advertising, posters, community talks, targeted mailings, e-mails, and word of mouth. Prospective participants called an advertised telephone number and were screened for eligibility. Those who were eligible were met in person for informed consent, following procedures approved by the University of Wisconsin (UW) institutional review board. After giving consent, participants rated themselves on several self-report questionnaires. An envelope was then opened to reveal allocation to a no-pill, blinded pill, or open-label echinacea group. Participants received their first dose of pills at the consent visit. Participants self-rated symptoms twice daily until their colds had resolved, up to a maximum of 14 days. Nasal wash, collected at enrollment and 2 days later, was analyzed for interleukin-8 (IL-8) levels and neutrophil counts (55–58). Participants were met for an exit interview after their illness had resolved.

Inclusion and Exclusion Criteria

Prospective participants were required to answer "yes" to either, "Do you think that you have a cold?" or "Do you think you are coming down with a cold?" Symptoms had to start within 36 hours before enrollment. Using Jackson and colleagues' criteria (59), participants had to report at least 1 of nasal discharge, nasal obstruction, sneezing, or sore throat (the other 4 Jackson criteria symptoms are headache, malaise, chilliness, and cough). Participants needed a total Jackson score of 2 or higher, after summing the scores for each symptom on a scale of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). Prospective participants had to be 12 years or older; those aged 12 to 17 years required parental permission. Participants receiving antibiotics, antivirals, nasal steroids, decongestants, antihistamines, combination cold formulas, echinacea, zinc, or vitamin C were excluded, as were those with a history of allergic rhinitis who reported sneezing or itching of the nose or eyes and those with a history of asthma who reported current cough, wheezing, or shortness of breath (to avoid confounding from allergy or asthma symptoms). Participants who self-reported having autoimmune or immune deficiency disease or being pregnant were also excluded.

Random Assignment, Allocation, and Blinding

We used SAS (SAS Institute, Cary, North Carolina) to generate a single block of 804 unique identification num-

bers so that each of 12 cells (3 clinician groups by 4 pill groups) was represented equally. Using these codes, the UW Hospitals Pharmaceutical Research Center Investigational Drug Service prepared consecutively numbered, sealed envelopes to direct allocation. An envelope-within-envelope strategy was used, so that group assignment would be revealed as soon as the participant gave consent and the research assistant opened the larger outer envelope. Allocation concealment for the 2 blinded pill groups was accomplished by using identical coated tablets and plastic pill bottles. For the two thirds of the sample who would see a clinician, a second, smaller envelope that directed allocation to a standard or enhanced visit group was opened by the study clinician before entering the examination room. The randomized allocation key was not shared with investigators until after all data were collected, entered, and cleaned and analysis strategies were determined. Blinding was tested at the exit interview by asking participants which group they thought they had been assigned to.

Echinacea and Placebo

The echinacea and identical placebo tablets were manufactured by MediHerb (Warwick, Queensland, Australia). Echinacea tablets contained the equivalent of 675 mg of *E. purpurea* root and 600 mg of *E. angustifolia* root, each standardized to 2.1 mg of alkamides. Tablet excipients included calcium acid phosphate, cellulose, silica, sodium starch glycolate, hypromellose, and magnesium stearate. Placebo and echinacea tablets contained the same proportions of inert ingredients and were covered with identical digestible coatings.

Participants received 2 tablets at enrollment, followed by 2-tablet doses 3 more times within 24 hours of enrollment. They then received 1 tablet 4 times per day for the next 4 days. Thus, each participant received the equivalent of 10.2 g of dried echinacea root during the first 24 hours and the equivalent of 5.1 g during each of the next 4 days.

Outcomes and Follow-up

We prospectively defined the primary outcome as the area under the curve for global severity, with duration and severity assessed twice daily by self-report. Duration began at enrollment and continued through the last time the participant answered "yes" to, "Do you think you still have a cold?" The date and time when questionnaires were completed was recorded, which allowed duration to be quantified as a continuous measure. To confirm that the illness had ended, the last "yes" answer to, "Do you think you still have a cold?" had to be followed by a "no" answer for 2 days in a row. We chose to limit monitoring to a maximum of 14 days to reduce potential bias from extended illnesses.

Illness severity was assessed twice daily by using the Wisconsin Upper Respiratory Symptom Survey, short version (WURSS-21), a validated illness-specific quality-of-life outcome instrument (60, 61). Items assess symptom severity and functional impairment, with a score of 1 considered to be very mild; 3, mild; 5, moderate; and 7, severe. The first item assesses overall illness severity, and the last item assesses change since the previous day. Summing scores on the intervening 19 items provides a global measure of illness severity. Summing across time points yields an area under the curve for global severity, which we calculated by using trapezoidal approximation.

Secondary outcomes included self-report on psychosocial questionnaires and biomarkers of immune response and inflammation. Self-report measures included general health-related quality of life, perceived stress, interpersonal support, optimism, and mood states. General health was assessed daily by using the Medical Outcomes Study Short Form-8 scale (62), a 24-hour recall version of the highly validated Medical Outcomes Study Short Form-36 scale. The Short Form-8 scale yields separate physical and mental health scores by using an item-weighted algorithm (62). General health was also assessed daily by using the EuroQol's feeling thermometer (63). Perceived stress was assessed at baseline, day 3, and exit by using the 4-item Cohen Perceived Stress Scale (64–66) and daily by using a 100-mm visual analogue scale developed for this study. Interpersonal support and optimism were measured at baseline, day 3, and exit by using the Ryff Personal Relationships scale (67) and the revised Life Orientation Test (68).

Adverse Effects and Safety Monitoring

Although allergic reactions to echinacea have been reported, no major or dose-dependent risks for adverse effects are known (50). We assessed possible adverse effects by asking participants at the exit interview whether they had experienced bad taste, diarrhea, headache, nausea, rash, or stomach upset at any time during their illness. Participants were also asked open-ended questions about possible adverse effects at the day 3 follow-up visit and during telephone contact. A data safety and monitoring committee met once yearly to review enrollment and side effect data.

Data Collection, Entry, and Cleaning

Questionnaire booklets completed by participants were scanned into electronic files by the UW Educational Testing Service. Data collected during telephone monitoring were recorded on paper and hand-entered twice, with discrepancies resolved by comparison with the paper.

Statistical Analysis

Our trial was designed to have 80% power to detect a 20% between-group difference in the area under the curve for global severity. A priori power calculations were based on data collected with a predecessor instrument of the WURSS-21. Assuming an α of 0.05, β of 0.20, 1-sided testing, and proportionally stable standard deviations, the protocol required enrollment of 800 participants to achieve 720 protocol completers. Intervention groups were kept blinded during data cleaning, assessment of missingness and response, and initial descriptive analyses. To calculate

Table 1. **Baseline Characteristics of Participants**

Characteristic	All (n = 719)	No-Pill Group (n = 174)	Unblinded Echinacea Group (n = 182)	Blinded Placebo Group (n = 179)	Blinded Echinacea Group (n = 184)
Mean age (SD), *y*	33.7 (14.4)	32.3 (14.2)	33.9 (14.5)	33.2 (13.5)	35.4 (15.3)
Women, %	64.1	60.9	65.9	63.7	65.8
Nonwhite, %	12.1	13.8	8.2	12.3	14.1
Current smoker, %	12.8	14.4	11.6	11.2	14.1
Annual household income ≤$25 000, %	35.9	40.4	32.6	35.7	35.1
At least some college education, %	84.0	84.0	86.4	85.6	80.0
Mean duration of symptoms before enrollment (SD), *h*	22.8 (8.6)	23.6 (8.0)	22.3 (9.2)	23.3 (8.5)	22.0 (8.5)
Mean WURSS-44 score at enrollment (SD)	85.4 (51.4)	84.3 (50.0)	82.9 (46.6)	89.8 (54.4)	84.7 (54.3)
Mean SF-8 physical health score (SD)	48.5 (6.1)	48.7 (6.2)	48.7 (5.5)	48.2 (6.1)	48.2 (6.6)
Mean SF-8 mental health score (SD)	43.5 (9.7)	42.7 (9.8)	43.7 (10.1)	43.4 (9.1)	44.3 (9.6)

SF-8 = Medical Outcomes Study Short Form-8; WURSS-44 = Wisconsin Upper Respiratory Symptom Survey, long version.

the area under the curve for global severity, we first averaged morning and evening scores for each item of the WURSS-21. If either morning or evening data were missing, existing data were used. Possible patterns of missingness for WURSS-21 items were assessed by using the Little missing completely at random test (69). Where appropriate, the expectancy maximization algorithm was used for a multiple imputation strategy, as outlined by Schafer (70). Box–Cox transformation was considered for data with skewed distribution. Primary efficacy analysis was done by comparing results in the blinded echinacea and blinded placebo groups. Comparisons of group means and medians were done by using the t test and the Mann–Whitney U test, respectively. Potential treatment effects were assessed with a general linear model (71) by using NCSS (NCSS, Kaysville, Utah). Covariates designated as potential confounders and controlled for in this model included duration of symptomatic illness before enrollment, illness severity at enrollment, age, sex, ethnicity, education, income, smoking status, general mental and physical health, and allocation to clinician-related visits. Blinding was tested by using the Fisher exact test of proportional difference. To avoid the hazards associated with multiple testing, statistical testing was limited to primary outcomes in primary comparison groups, and secondary outcomes were compared in terms of CIs rather than P values.

Role of the Funding Source

This trial was sponsored by the National Center for Complementary and Alternative Medicine at the National Institutes of Health. MediHerb provided the echinacea and placebo tablets and conducted the phytochemical content analysis but did not contribute financially.

RESULTS

Enrollment opened in January 2004 and ended in August 2008. Of the 3321 participants screened, 719 were enrolled and randomly assigned (**Appendix Figure**, available at www.annals.org). Retention was high. Two participants were lost to follow-up, and 4 withdrew before primary outcome data could be gathered; reasons given were "too sick or too busy to fill out questionnaires" and "desire to take nonprotocol medications." Approximately 98% of intended data were collected. The largest data gap was with nasal wash, for which 33 participants either declined the second nasal wash or did not return within 24 to 72 hours after the first wash. The Little test showed no discernible patterns of missingness in the 0.27% of missing WURSS-21 items. Imputation of WURSS-21 items and calculation of global severity and duration values were done before unblinding, using the previously outlined methods.

Of the 719 participants, 64% were female, 88% were white, and 84% reported having at least some college education. Age ranged from 12 to 80 years (mean age, 33.7 years [SD, 14.4]). About 12.8% were current smokers. Baseline measures were similar across the 4 groups (**Table 1**). Five hundred twenty-two were enrolled in Madison and 197 in Verona, Wisconsin. No significant between-site differences were found for mean age (33.3 vs. 34.9 years; $P = 0.20$), sex (63.4% vs. 66.0% female; $P = 0.52$), or education level (84.6% vs. 82.3% with some college education; $P = 0.47$).

Primary Outcome

The average area under the curve for global severity and illness duration were lower in the blinded and open-label echinacea groups than in either the blinded placebo or no-pill groups (**Table 2**). Mean global severity was 236 and 258 for the blinded and unblinded echinacea groups, respectively; 264 for the blinded placebo group; and 286 for the no-pill group. A primary efficacy analysis that compared global severity in the blinded echinacea and placebo groups yielded a mean difference of 28 points (95% CI, −69 to 13 points). Statistical testing yielded a T of 1.34 ($P = 0.089$). Because of skewness, the Mann–Whitney U test comparing median severity in the blinded placebo group with that in the blinded echinacea group may be more appropriate (206 vs. 193; $z = 0.97$; $P = 0.170$). Mean illness duration in the blinded and unblinded echinacea groups was 6.34 and 6.76 days, respectively, compared with 6.87 days in the blinded placebo group and

7.03 days in the no-pill group. An efficacy analysis that compared illness duration in the blinded echinacea group with that of the blinded placebo group yielded a mean difference of 0.53 day (CI, −1.25 to 0.19 days) and a T of 1.97 ($P = 0.075$). No statistically significant differences were found when the 2 blinded groups were compared by using a general linear model to control for potential confounders ($P = 0.42$ for area under the curve for severity; $P = 0.74$ for duration.) Box–Cox transformation was used for that model because the distribution of global severity was skewed. Reported P values are based on 1-sided testing and were not adjusted for multiple testing.

Because echinacea is thought to work through immune stimulation, which would make early dosing important, we did a subgroup analysis of the 351 people who were enrolled within 24 hours of their first symptom (**Table 2**). Compared with the no-pill or blinded placebo groups, both echinacea groups had lower illness duration and global severity; however, none of the between-group comparisons in this secondary analysis was statistically significant. Applying the general linear model did not significantly change the results and conclusions.

Secondary Outcomes

Analysis of secondary outcomes did not demonstrate effects clearly attributable to echinacea (**Table 3**). Nasal neutrophil counts and IL-8 levels in nasal wash tended to increase faster in the 2 echinacea groups than in either control group, but these differences were not statistically significant. Self-reported health measures, including those for physical and mental health (Medical Outcomes Study Short Form-8), stress (Cohen Perceived Stress Scale), optimism (revised Life Orientation Test), and social support (Ryff Personal Relationships scale) did not seem to be influenced by random assignment to echinacea.

Adverse Effects

Frequency of potential adverse effects was similar (statistically indistinguishable) in the 4 groups (**Table 4**). The only possible exception was headache, for which 62% of patients in the no-pill group reported having had a headache at some time during their illness, compared with fewer than 50% in the 3 pill groups. Responses to open-ended questions about possible adverse effects during monitoring showed no patterns of adverse effects attributable to echinacea.

Adherence

Adherence to dosing regimen was assessed by asking participants, "Did you take all your pills as directed?" and by counting the pills in returned pill bottles. Of the 545 people who received pills, 518 (95%) reported taking the pills as directed. Of the 524 bottles returned, 486 (93%) were empty, 27 (5%) had 4 or fewer pills, and 11 (2%) had 5 or more pills left in the bottles. Nothing indicated that the patients who received echinacea took their pills differently from the patients who received placebo (**Table 5**).

Test of Blinding

Blinding seemed to be intact. Of the 363 participants who received pills and were blinded, 141 (39%) guessed their assignment correctly, 110 (30%) guessed incorrectly, and 107 (29%) declined to guess (**Table 5**). Of the 179 participants in the blinded placebo group, 72 (40%) correctly guessed their assignment, compared with 69 (38%) in the blinded echinacea group. A Fisher exact test of proportional difference that included only participants who were willing to guess their pill assignment yielded a P value of 0.053 (CI, −0.002 to 0.246). Although this does not allow us to reject the null and conclude blind-breaking, it

Table 2. **Primary Outcomes: Global Severity and Duration of Illness**

Sample	No-Pill Group	Unblinded Echinacea Group	Blinded Placebo Group	Blinded Echinacea Group	Between–Blinded Group Differences
Participants providing main outcome data					
Participants, *n*	173	181	176	183	–
Median global severity (95% CI)	220 (189 to 238)	195 (169 to 213)	206 (177 to 256)	193 (163 to 218)	−13 (−37.8 to 38.4)
Mean global severity (SD)	286 (246)	258 (214)	264 (212)	236 (182)	−28 (−69.0 to 13.0)
Adjusted global severity (95% CI)*	10.3 (9.9 to 10.7)	10.1 (9.7 to 10.5)	10.0 (9.7 to 10.4)	10.1 (9.7 to 10.4)	0.10 (−0.60 to 0.40)
Median duration (95% CI), *d*	6.42 (6.13 to 7.21)	6.16 (5.31 to 6.60)	6.47 (5.82 to 7.12)	6.04 (5.30 to 6.53)	−0.43 (−1.01 to 0.95)
Mean duration (SD), *d*	7.03 (3.49)	6.76 (3.48)	6.87 (3.62)	6.34 (3.31)	−0.53 (−1.25 to 0.19)
Subset enrolled ≤24 h after first symptom					
Participants, *n*	80	97	79	95	–
Median global severity (95% CI)	221 (177 to 277)	177 (140 to 213)	199 (162 to 259)	196 (160 to 250)	−3.0 (−51.5 to 49.2)
Mean global severity (SD)	281 (225)	250 (218)	257 (207)	246 (186)	−11.0 (−69.8 to 47.8)
Adjusted global severity (95% CI)*	10.6 (9.7 to 11.6)	10.1 (9.3 to 10.8)	9.7 (8.6 to 10.7)	10.1 (9.1 to 11.1)	0.41 (−1.83 to 1.03)
Median duration (95% CI), *d*	6.66 (6.13 to 7.30)	6.15 (5.06 to 7.00)	6.38 (4.78 to 7.37)	6.07 (4.98 to 6.68)	−0.31 (−1.13 to 1.10)
Mean duration (SD), *d*	6.83 (3.23)	6.62 (3.47)	6.67 (3.52)	6.47 (3.31)	−0.20 (−1.22 to 0.82)

* Results from a general linear model, controlled for duration of symptoms before enrollment, symptom severity at enrollment, age, sex, ethnicity, education, income, smoking status, physical health, mental health, and factorial allocation to clinician-related visits. Global severity was defined as the area under the time severity curve, with severity assessed by the Wisconsin Upper Respiratory Symptom Survey, short version. Because the distribution of global severity was skewed, Box–Cox transformation was used to better satisfy statistical assumptions.

Table 3. **Secondary Outcomes (Day 3 Assessments)**

Outcome	No-Pill Group	Unblinded Echinacea Group	Blinded Placebo Group	Blinded Echinacea Group	Between–Blinded Group Differences
Biomarker data					
Participants, *n*	164	171	168	170	–
Median change in IL-8 levels (95% CI), *ng/L**	30 (2 to 89)	70 (18 to 134)	39 (12 to 106)	58 (18 to 105)	19.0 (−75.2 to 72.0)
Median change in neutrophil counts (95% CI), *cells/hpf**	1 (−1 to 4)	1 (0 to 4)	1 (−1 to 4)	2 (0 to 5)	1.0 (−4.0 to 3.0)
Self-reported data					
Participants, *n*	174	182	179	184	–
Mean SF-8 physical health score (95% CI)	48.0 (47.1 to 49.0)	47.7 (46.8 to 48.6)	46.9 (45.9 to 48.0)	47.3 (46.2 to 48.4)	0.40 (−1.13 to 1.93)
Mean SF-8 mental health score (95% CI)	43.8 (42.3 to 45.3)	43.7 (42.2 to 45.2)	42.5 (41.0 to 43.9)	44.4 (43.1 to 45.7)	1.90 (−0.06 to 3.86)
Mean feeling thermometer score (95% CI)	60.3 (57.9 to 62.9)	62.5 (59.7 to 65.3)	62.5 (59.5 to 65.5)	63.6 (60.8 to 66.4)	1.10 (−2.88 to 5.08)
Mean PSS-4 stress score (95% CI)	4.3 (3.9 to 4.8)	4.5 (4.1 to 4.9)	4.6 (4.1 to 5.0)	4.5 (4.0 to 5.0)	−0.10 (−0.76 to 0.56)
Mean VAS stress score (95% CI)	38.3 (34.3 to 42.3)	40.0 (36.2 to 43.8)	38.0 (34.5 to 41.5)	36.6 (32.9 to 40.3)	−1.40 (−6.33 to 3.53)
Mean LOT-R optimism score (95% CI)	22.7 (22.1 to 23.4)	22.9 (22.4 to 23.6)	22.1 (21.5 to 22.7)	23.1 (22.5 to 23.7)	1.00 (0.16 to 1.84)
Mean Ryff PR social support score (95% CI)	45.1 (44.1 to 46.3)	45.6 (44.6 to 46.8)	44.5 (43.1 to 45.6)	45.4 (44.2 to 46.4)	0.90 (−0.65 to 2.45)

hpf = high-power field; IL-8 = interleukin-8; LOT-R = revised Life Orientation Test; PSS-4 = 4-item Cohen Perceived Stress Scale; Ryff PR = Ryff Personal Relationships scale; SF-8 = Medical Outcomes Study Short Form-8; VAS = visual analog scale.
* Median change from day 1 intake to day 3.

does leave open the possibility that a few people correctly ascertained the group to which they had been assigned.

Phytochemical Analysis

Laboratories of the manufacturer (MediHerb) and the natural products analysis company Chromadex (Clearwater, Florida) conducted independent phytochemical assays at successive time points from 2004 to 2007. Both companies used high-performance liquid chromatography with reference standards of known purified ingredients. The **Appendix Table** (available at www.annals.org) shows the lowest and highest results from MediHerb's 4 laboratory assays and Chromadex's 3 assays. Phytochemical concentrations seemed stable over time, with no trends toward lower concentration in later years (data not shown).

Discussion

This dose regimen of the echinacea formulation did not have a large effect on the course of the common cold, compared with either blinded placebo or no pills. However, the trends were in the direction of benefit, amounting to an average half-day reduction in the duration of a week-long cold, or an approximate 10% reduction in overall severity. Our previous research (72–74) suggests that few people—no more than 1 in 4—would judge this level of benefit worthwhile, given the cost, inconvenience, and possible adverse effects. Although these results do not allow us to reject the null hypothesis and confidently claim evidence of benefit, data are also insufficient to exclude the possibility of a clinically significant effect. The CIs of between-group differences allow for the possibility of a 24-hour reduction in duration and a 20% reduction in overall severity attributable to echinacea, both of which might be accepted as clinically significant by many persons with the common cold (72–74).

Our study has limitations. Participants were all from Dane County, Wisconsin, and had community-acquired, self-reported colds. The etiologic agents and psychosocial factors that influence colds may be different in other populations or geographic areas. We also made no attempt to base inclusion on viral cause; some of the illnesses represented here may have been caused by influenza or other viruses. Although the age range was wide and both sexes

Table 4. **Potential Adverse Effects***

Adverse Effect	No-Pill Group (*n* = 174)	Unblinded Echinacea Group (*n* = 182)	Blinded Placebo Group (*n* = 179)	Blinded Echinacea Group (*n* = 184)	Between–Blinded Group Differences
Bad taste	–	8.9 (4.7 to 13.1)	9.1 (7.2 to 16.8)	12.4 (7.6 to 17.3)	3.3 (−3.34 to 10.1)
Diarrhea	5.4 (2.0 to 8.9)	9.4 (5.2 to 13.7)	12.0 (7.2 to 16.8)	9.6 (5.3 to 13.9)	−2.4 (−8.70 to 4.90)
Headache	62.1 (54.7 to 69.4)	47.8 (40.5 to 55.1)	49.1 (41.7 to 56.5)	46.3 (39.0 to 53.7)	−2.8 (−12.7 to 8.18)
Nausea	10.2 (5.6 to 14.9)	6.7 (3.0 to 10.3)	12.6 (7.7 to 17.5)	15.8 (10.4 to 21.2)	3.2 (−4.17 to 10.8)
Rash	1.8 (0.0 to 3.8)	1.7 (0.0 to 3.5)	1.1 (0.0 to 2.7)	1.1 (0.0 to 2.7)	0.0 (−3.08 to 3.01)
Stomach upset	16.3 (10.7 to 21.9)	13.3 (8.4 to 18.3)	12.0 (7.2 to 16.8)	14.7 (9.5 to 19.9)	2.7 (−4.04 to 10.7)

* Values are the percentages of participants (95% CI) who indicated at their exit interview that they had this symptom at some time during their illness.

Table 5. **Adherence to Pill Regimen**

Variable	Blinded Placebo Group, *n*	Blinded Echinacea Group, *n*	Unblinded Echinacea Group, *n*
Received pills in bottles	179	184	182
Reported taking all pills as directed	169	173	176
Reported not taking all pills as directed	8	8	4
Lost, withdrawn, or missing data	2	3	2
Empty pill bottles returned	161	162	163
Pill bottles returned with pills left	10	15	13
Bottles not returned or missing data	8	7	6
Responses to testing of blinding*			
Echinacea	56	69	107
Placebo	72	54	3
Don't know or won't guess	49	58	3
Missing data or not answered	2	3	69

* Participants were asked whether they believed that they had received echinacea or placebo. The Fisher exact test of proportional difference tested whether the trend toward guessing the assignment correctly was statistically significant ($P = 0.053$; 95% CI for proportional difference, −0.002 to 0.246).

were well represented, racial and ethnic diversity was limited. In addition, this trial may have been underpowered. Our power estimates used existing data from that time, which showed a 0.70 ratio of standard deviation to mean. Equivalent data from this trial provide a ratio of 0.80. Looking at data gathered from 1999 to 2008, we now conclude that a conventional randomized, controlled trial would need slightly more than 200 people in each of 2 groups to have 80% power to detect a 20% difference in global severity, using the WURSS-21 (61). A trial that used illness duration or prespecified day-to-day change as a primary outcome could be smaller, but the results would be less meaningful. We also note that our results were obtained with only 1 of many possible types of echinacea formulations. Although the dosing and array of phytochemical constituents that we used (**Appendix Table**) are reasonably representative of currently available echinacea preparations, a substantively different formulation could give substantially different results. Finally, because randomized trials provide results in terms of group averages, they may obscure benefits (or harms) for individuals or subgroups.

In conclusion, the pharmacologic activity of echinacea probably has only a small beneficial effect in persons with the common cold. Our interpretation comes not only from the trends observed in this trial but also from a reasonably substantial body of scientific evidence, including positive results from several reported trials and some cautiously optimistic meta-analyses (50–53). Any underlying benefit of echinacea is not large and was not demonstrated by our results. Individual choices about whether to use echinacea to treat the common cold should be guided by personal health values and preferences, as well as by the limited evidence available.

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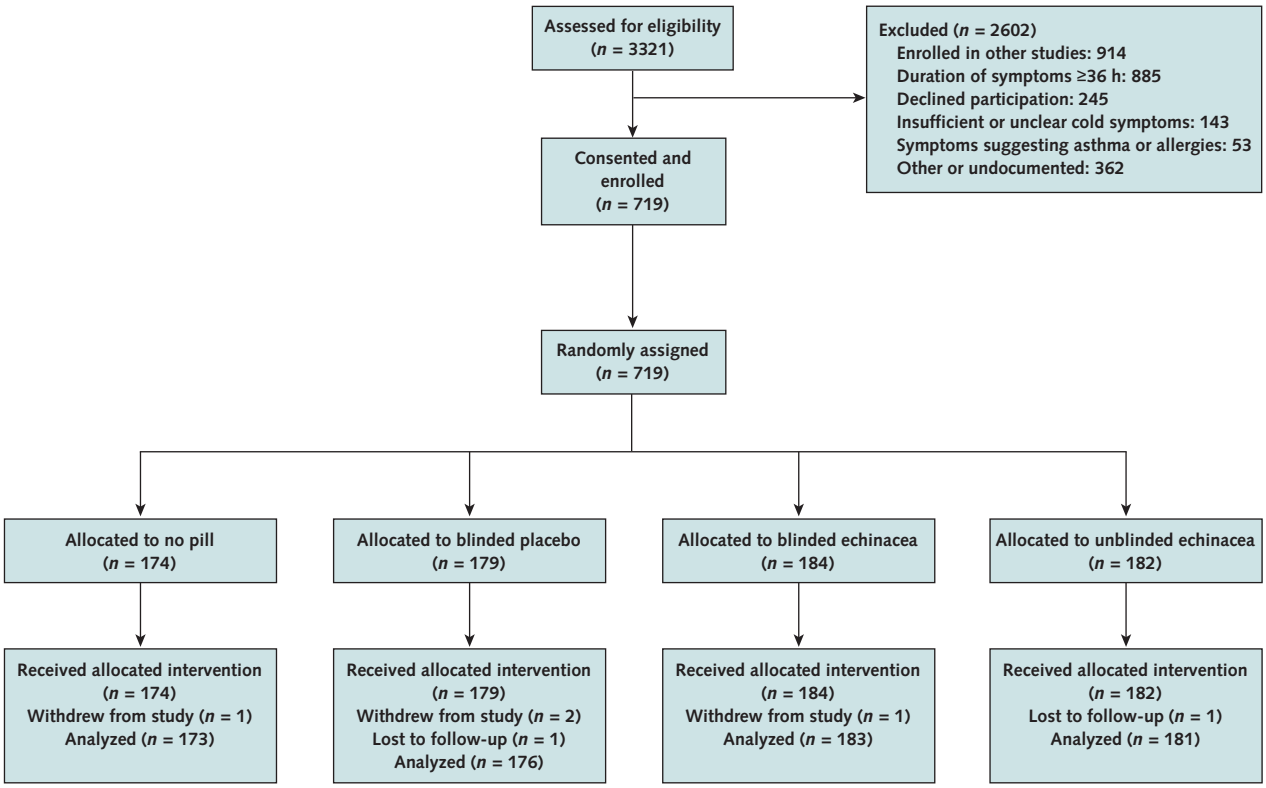
Appendix Figure. **Study flow diagram.**



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Appendix Table. **Phytochemical Composition of Echinacea Tablets***

Component	Range in MediHerb Assays, *mg/tablet*	Range in Chromadex Assays, *mg/tablet*
Caftaric acid	1.85–2.43	1.32–2.14
Chlorogenic acid	NA	0.07–0.38
Cynarin	NA	0.35–0.83
Cichoric acid	7.63–10.04	5.13–6.84
Echinacoside	4.09–5.30	3.80–3.87
Total phenolics†	12.98–16.87	9.80–13.30
DDYIA‡	NA	0.52–2.05
DDIA‡	NA	0.15–0.16
DZTIA‡	NA	1.05–10.2
Total 2-enes	0.54–0.89	NA
Total 2,4 dienes	2.48–3.57	NA
Total alkamides	3.06–4.46	1.73–12.4

DDIA = dodeca-2(E),4(E)-dienoic acid isobutylamide; DDYIA = dodec-2-ene-8,10-diynoic acid isobutylamide; DZTIA = dodeca-2(E),4(E),8(Z),10(Z)-tetraenoic acid isobutylamide; NA = not analyzed.
* Phytochemical content was analyzed independently in 4 assays by MediHerb (Warwick, Queensland, Australia) and 3 assays by Chromadex (Clearwater, Florida) between 2004 and 2007. No time trends were seen.
† Cichoric acid derivatives.
‡ Specific alkamides measured by Chromadex.