

# Treatment of the Common Cold with Unrefined Echinacea

## A Randomized, Double-Blind, Placebo-Controlled Trial

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**Background:** Echinacea preparations are widely used to treat the common cold.

**Objective:** To assess the efficacy of dried, encapsulated, whole-plant echinacea as early treatment for the common cold.

**Design:** Randomized, double-blind, placebo-controlled community-based trial.

**Setting:** University of Wisconsin—Madison, Madison, Wisconsin.

**Participants:** 148 registered students with common colds of recent onset.

**Intervention:** An encapsulated mixture of unrefined *Echinacea purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) taken in 1-g doses six times on the first day of illness and three times on each subsequent day of illness for a maximum of 10 days.

**Measurements:** Severity and duration of self-reported symptoms of upper respiratory tract infection.

**Results:** No statistically significant differences were detected between the echinacea and placebo groups for any of the measured outcomes. Trajectories of severity over time were nearly identical in the two groups. Mean cold duration was 6.01 days in both groups as a whole, 5.75 days in the placebo group, and 6.27 days in the echinacea group (between-group difference,  $-0.52$  day [95% CI,  $-1.09$  to  $0.22$  days]). After controlling for severity and duration of symptoms before study entry, sex, date of enrollment, and use of nonprotocol medications, researchers found no statistically significant treatment effect (adjusted hazard ratio, 1.24 [CI, 0.86 to 1.78]). Multivariable regression models assessing severity scores over time failed to detect statistically significant differences between the echinacea and placebo groups.

**Conclusion:** Compared with placebo, unrefined echinacea provided no detectable benefit or harm in these college students who had the common cold.

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See editorial comment on pp 1001-1002.

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The common cold is one of the world's most prevalent illnesses. Upper respiratory tract infection, characterized by rhinosinusitis, pharyngitis, or tracheobronchitis, is caused by a wide array of agents. While rhinovirus is most common, coronavirus, respiratory syncytial virus, adenovirus, parainfluenza, and influenza virus all play important roles (1–4). Effects on health, well-being, and productivity are significant. Although patients with such complications as asthmatic bronchospasm, bacterial sinusitis, otitis media, streptococcal pharyngitis, or pneumonia might benefit from medical intervention, few if any treatments have proven effective for community-acquired colds (5–10).

Preparations made from plants of the genus *Echinacea* are widely used for the prevention and treatment of colds (11–13). Various whole-plant preparations and extracts made from the flowers, leaves, stems, and roots of *E. purpurea*, *E. angustifolia*, and *E. pallida* are sold worldwide. Hundreds of scientific studies, mostly German, have detailed echinacea's botanical, chemical, and pharmacologic characteristics and its clinical effects (14–19).

There is no clear consensus about whether echinacea can benefit human health. Randomized, controlled trials have focused on the prevention or treatment of colds. Five such trials of prevention (four of which have been published) reported that echinacea had little effect in reducing the incidence of natural colds (20–23; Calabrese C. Personal communication). The findings of the highest-quality study (21) are consistent with a 10% to 15% reduction in relative risk. Results of an induced-cold trial have been reported as negative but are consistent with a benefit of

10% to 15% (24). The 11 published treatment trials are somewhat more positive (25–35), and systematic reviews have been cautiously optimistic (13, 14, 18, 36, 37). Reported benefits have ranged from a 40% to 50% reduction in severity (31) and duration (29) of symptoms in studies with major methodologic limitations to more modest reductions of 10% to 30% in the most recent studies (25, 27, 28). All studies to date have had important limitations, including lack of objective validated outcome measures, lack of description and verification of random allocation and concealment procedures, limitations related to sample size and power, and limited generalizability.

## METHODS

In spring 1999, we conducted a randomized, double-blind, placebo-controlled community-based trial evaluating the efficacy of an encapsulated whole-plant echinacea preparation used as early treatment for the common cold. Participants with early cold symptoms were randomly assigned (with allocation concealed) to echinacea treatment or placebo and were followed with self-reported duration and severity measures for the duration of illness, up to 10 days. All participants provided informed consent before the study, and the University of Wisconsin Medical School human subjects committee approved the protocol.

Shaklee Tecnica (Pleasanton, California) provided the echinacea and placebo preparations. Each active capsule contained a dried mixture of *E. angustifolia* root (50% [123 mg]), *E. purpurea* root (25% [62 mg]), and *E. pur-*

**Context**

Echinacea is an herbal therapy that is widely used to treat the common cold, but there is no consensus about its effectiveness.

**Contribution**

This randomized, controlled trial compared a capsule form of *Echinacea purpurea* herb and root and *E. angustifolia* root with placebo in 148 college students with symptoms of the common cold. Echinacea had no effect on the duration or severity of cold symptoms.

**Implications**

This particular form of echinacea provides no benefit for common cold symptoms in young, healthy adults. It will be necessary to perform similar careful studies of other echinacea preparations, which could differ from the preparation used in this study.

—The Editors

*purea* herb (25% [62 mg]). Echinacea capsules also contained thyme (49 mg) and peppermint (31 mg) to disguise taste and flavor, as well as citric acid (3 mg) as a preservative. The placebo capsules contained 333 mg of alfalfa. Each participant was given a bottle containing 132 capsules and was instructed to take four capsules per treatment dose six times during the first 24 hours of the study, and three times each day thereafter until symptoms resolved, for a maximum of 10 days. Each four-capsule dose totaled 1 g. Thus, the dose schedule was 6 g of echinacea on the first day and 3 g on each subsequent day.

Participants were recruited from 4 February 1999 until 20 May 1999 from the University of Wisconsin—Madison student population. Advertisements throughout the student community (posters, newspaper advertisements, and e-mail messages) asked respondents to call a cellular telephone held by a research assistant at the first sign of cold or flu-like symptoms. Callers were screened by telephone and were invited to meet with a research assistant if eligible, usually within a few hours of the initial call. At the enrollment interview, the research assistant described the study protocol, obtained informed consent, gathered baseline data, and provided instruction on the paper questionnaire and the Web-based survey instrument.

To be included in the study, participants were required to be at least 18 years of age, to answer “Yes” to the question “Do you believe that you are coming down with a cold?”, to report at least 2 of 15 listed cold symptoms (at least 1 of which had to be specific to the respiratory tract), and to be apparently able and willing to adhere to the study protocol. Participants were excluded if they reported having any listed symptom for more than 36 hours; were pregnant; were currently using antibiotics, antihistamines, or decongestants; had specified chronic diseases (autoimmune disease, chronic bronchitis, HIV infection, lupus,

rheumatoid arthritis); or had a history of asthma or allergic rhinitis and corresponding symptoms (itchy eyes, sneezing, wheezing) at the time of enrollment.

Randomization was designed so that each participant would have a 50% chance of assignment to placebo or echinacea. The Investigational Drug Service of the University of Wisconsin Hospitals randomized and sequentially labeled 200 bottles containing echinacea or placebo, using a random-number generator (Microsoft Excel, Microsoft Corp., Redmond, Washington) and a balanced blocks-of-four design. Each sequentially enrolled participant received the next sequentially numbered bottle of capsules. The placebo and echinacea capsules were indistinguishable to study personnel and to the participants. Allocation to echinacea or to placebo was concealed from participants and from the investigational team until all data had been collected, entered, and cleaned.

Primary outcomes were defined prospectively as severity and duration of self-reported symptoms. Duration was defined as the number of days from study enrollment to the last day before the participant answered “No” to the question, “Do you think that you are still sick today?” Symptom severity was measured daily on nine-point Likert scales. The 15 symptoms assessed were dry cough, productive cough, cough interfering with sleep, sore throat, scratchy throat, hoarseness, runny nose, plugged or stuffy nose, sneezing, headache, fever, sweats, muscle aches, feeling “run down,” and loss of appetite. Each reported symptom was rated on a nine-point Likert severity scale with the following label: 1 (very mild), 3 (mild), 5 (moderate), 7 (severe), and 9 (extreme). Global severity of illness (“How sick do you feel today?”) was assessed by using a similar nine-point scale.

For each day of the trial, participants were asked to fill out both a paper and an electronic version of the questionnaire. The electronic version was adapted to a Web page format ([www.fammed.wisc.edu/samplecold](http://www.fammed.wisc.edu/samplecold)). Blinded data were downloaded and inspected periodically throughout the trial. The parallel data collection system enabled us to verify the time and date of response, protecting against errors from retrospective assessments. It also protected against data entry error and missing data and allowed comparison of data reported in electronic and paper formats.

Participants were in contact with the enrolling research assistant by telephone and e-mail throughout the study. They returned for an exit interview upon study completion. Adherence was assessed by pill counts (from bottles returned at the end of the study) and by the daily questionnaire (which asked the participants whether they had taken their pills and how many pills they had taken). Adverse effects were monitored each day and at the exit interview.

Our study was designed to have 150 participants, providing at least 80% power to detect a benefit of 2 days’ duration or an average reduction of two points in severity. These prospective power calculations (38, 39) assumed

variance similar to that observed in cold studies (9, 10) and benefits similar to those reported in previous echinacea trials (27–31). The minimal clinically important benefit for the common cold has not been determined (40, 41). However, research on other illnesses suggests that an average two-point reduction in severity on a nine-point scale or a 2-day reduction in duration would be clinically significant (42–46).

A symptom-dimension measurement model was constructed by using structural equation modeling techniques (47, 48, 51). From the pool of 15 symptoms, 14 items fit neatly into four symptom dimensions. Loss of appetite was an infrequent symptom that contributed insignificantly and was therefore dropped. The four dimensions and their associated reliability coefficients, calculated by using the method of Dillon and Goldstein (48), were cough (0.794), throat (0.668), nasal (0.663), and fever and aches (0.753). Reliability coefficients estimate the proportion of variability that is attributable to participants' symptoms rather than to measurement error (45, 49, 50). Five covariates were investigated as possible confounders: 1) duration of symptoms before study entry, 2) severity of illness at enrollment, 3) date of enrollment (seasonal or etiologic agent effect), 4) use of nonprotocol medications, and 5) sex.

### Statistical Analysis

We considered all available data in our analysis. Methods included simple inspection, frequency analysis, analysis of variance, and multivariable analysis. Confidence intervals were constructed for all outcomes. A simple sum of the 15 symptom scores was selected as an overall severity marker for use in regression models. Changes over time in the summed severity score were explored by using the general linear mixed model for repeated measures (51). Individual symptom scores and dimensional severities were similarly explored by using mixed modeling approaches

**Table. Characteristics of Study Participants**

Characteristic	Echinacea Group	Placebo Group
Participants entering study, <i>n</i>	73	75
Participants completing protocol, <i>n</i>	69	73
Mean age ± SD, <i>y</i>	20.8 ± 2.4	21.0 ± 3.4
Women, <i>n</i> (%)	50 (72)	48 (66)
Current use of tobacco, <i>n</i> (%)	15 (22)	15 (21)
Nonwhite ethnicity, <i>n</i> (%)	4 (5.8)	4 (5.5)
Participants who had taken echinacea before, <i>n</i> (%)	30 (43)	28 (38)

(52). Bootstrap resampling was used to calculate means and confidence intervals for duration (53). A Cox multivariable proportional hazards regression model (54) for cold duration was used to control for potential confounding. The lack of time trends in the Schoenfeld residuals supports the proportional hazards assumption (55). The five potential confounders previously noted were included in all multivariable models. Statistical analyses were done by using SAS software (SAS Institute, Inc., Cary, North Carolina).

### Role of the Funding Sources

The U.S. Department of Health and Human Services and the National Institutes of Health provided funding to Dr. Barrett during the study. Shaklee Tecnica provided monetary support for project costs and provided the study materials, but had no role in the design, conduct, or reporting of the data or in the decision to submit the manuscript for publication.

### RESULTS

Of 148 enrolled participants, 142 (69 in the echinacea group and 73 in the placebo group) completed our protocol successfully (Figure 1). Characteristics of the study sample are shown in the Table. We did not record the number of eligible persons who called the research center but were unwilling to participate in the study; however, it was clear that most eligible callers were enrolled. The mean time from onset of the first recognized symptom to study enrollment was 27 hours.

A total of 853 person-days of illness were reported. Six participants withdrew, 2 in the placebo group (1 because of feeling too sick and 1 for undisclosed reasons) and 4 in the echinacea group (2 because of being too sick to follow the protocol, 1 because the capsules tasted bad and were difficult to swallow, and 1 for undisclosed reasons). In the echinacea group, 27 participants reported taking nonprotocol medications compared with 25 participants in the placebo group. Of the 142 participants who completed the study, 10 (5 in each group) reported having had at least one symptom for more than 36 hours at enrollment. For these 10 persons, the duration from first symptom to enrollment was 36 to 40 hours (*n* = 2), 45 to 48 hours (*n* = 6), 72 hours (*n* = 1), or 168 hours (*n* = 1). Because these protocol violations were discovered after the trial ended, we

**Figure 1. Randomization and patient flow.**

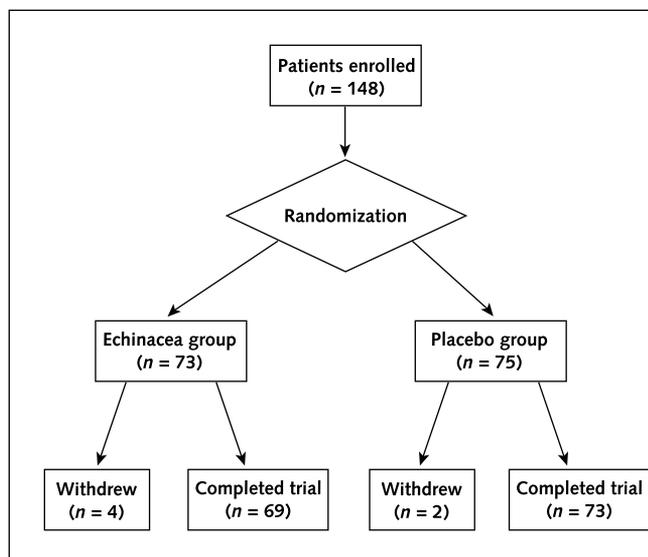
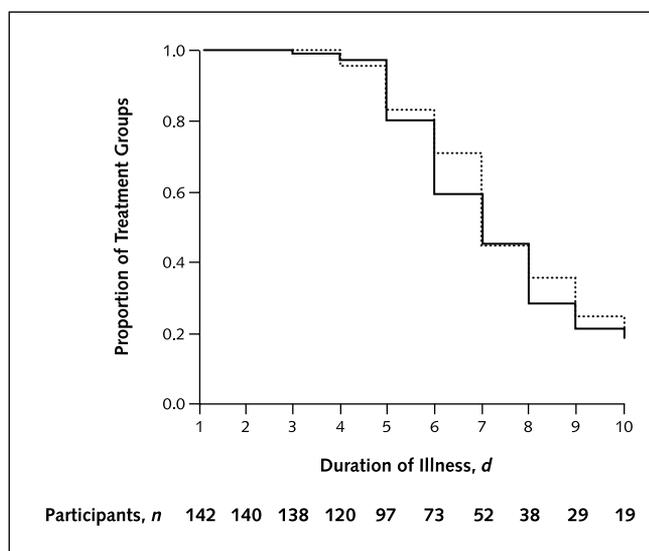


Figure 2. Illness duration.



The dotted line represents the echinacea group; the solid line represents the placebo group.

chose to include data from these 10 persons in our results. For the six persons lost to follow-up, no postenrollment data were available.

After unblinding in July 1999, samples of the echinacea formulation were sent to three independent laboratories for analytic testing. Dr. Rudolph Bauer (Institut fuer Pharmazeutische Biologie, Heinrich-Heine-Universitaet Duesseldorf, Duesseldorf, Germany) analyzed our formulation and found that it contained 0.26% echinoside; 0.77% cichoric acid; and 0.82% alkamides, including 0.42% dodecatetraenoic acid isobutylamide by weight (15, 56, 57). Industrial Labs (Denver, Colorado) analyzed our product using a standardized method developed by their methods validation program and reported that it contained 0.20% echinoside, 0.84% cichoric acid, 0.03% chlorogenic acid, and 0.33% cafeolytartaric acid. Dr. Joseph Rininger at Paracelsian, Inc. (Langmuir Laboratories, Ithaca, New York), used cell culture and simulated digestion methods with bioequivalent doses of our study product to demonstrate macrophage activation and elevated levels of tumor necrosis factor. The equivalent of our first-day dose increased the mean level ( $\pm$ SD) of tumor necrosis factor from  $189 \pm 23$  ng/L to  $3679 \pm 154$  ng/L, while the equivalent of our subsequent daily dose increased the mean level to  $2347 \pm 66$  ng/L. Together, these three analyses demonstrate that our product contained substantial quantities of phytochemicals as active constituents (14, 15).

Pill counts and daily computerized monitoring demonstrated protocol adherence. An overall adherence rate of 92% was calculated by dividing the number of pills missing from the bottles by the number that should have been missing based on the protocol. On the Web-based questionnaires, nearly all of the participants reported taking

their pills nearly every day during their participation in the trial.

Before the study, we conducted several informal tests of blinding. Study personnel, friends, and colleagues could not distinguish between placebo and echinacea capsules. At the exit interview, we asked participants, "Do you think you were taking echinacea or placebo?" Blinding was successful: Thirty-one of 63 persons taking echinacea and 33 of 72 persons taking placebo guessed correctly ( $P > 0.2$ ). Seven participants declined to guess.

Of the 853 person-days of illness, 546 (64%) were captured by both paper and electronic data systems. Two hundred eighty-seven person-days (34%) were captured by paper surveys alone, while 18 (2%) were accounted for solely by the computerized system. Only 2 person-days (0.2%) were not accounted for by either system. Therefore, for 142 participants documenting 853 days of illness, our data capture rate was 99.8%. In constructing the final data set, we used the computerized data whenever available because they were verified by time and date. We used data originally recorded on paper as needed.

Comparing data from the computerized and paper symptom surveys provided some evidence of instrument reliability. Responses to the question about global severity of illness were identical on 512 of the 546 days for which both instruments provided data (94% concordant, 6% discrepant). Of 34 discrepancies, 29 were off by one point on the nine-point Likert scale and 5 were off by two points. Comparing computer and paper responses to the 15 specific-symptom questions also yielded high levels of concordance. Of 8190 answers, 7777 (95%) were concordant and 413 (5%) were classified as data discrepancies. Of these, 293 were off by one point on the nine-point scale, 68 were off by two points, 27 were off by three points, 17 were off by four points, 7 were off by five points, and 1 was off by six points.

We did not detect a difference in cold duration between the echinacea and placebo groups. Among the 142 participants completing our protocol, durations ranged from 2 to 10 days, with a median of 6 days and a mean ( $\pm$ SD) of  $6.01 \pm 2.34$  days (Figure 2). The mean duration was 5.75 days in the placebo group and 6.27 days in the echinacea group (difference,  $-0.52$  day [95% CI,  $-1.09$  to  $0.22$  days]). Therefore, 0.22 day is the largest potential echinacea-related benefit in duration that would be statistically compatible with our results. After adjustment for the five potential confounders, Cox multivariable regression found no statistically significant treatment effects on duration (adjusted hazard ratio, 1.24 [CI, 0.86 to 1.78]), with the trend toward longer duration in the echinacea group.

We did not detect any significant differences in symptom severity between the echinacea and placebo groups. Figures 3 and 4 depict daily mean severities and 95% CIs for the symptoms assessed. The group sizes decrease over time, following recovery from illness. A general linear

mixed model of the unweighted summed severity score (controlling for the five potential confounders) did not reveal any statistically significant differences between the echinacea and placebo groups. Duration of symptoms before study entry, date of enrollment, and sex were not statistically significant. Although use of nonprotocol medications and severity of illness at enrollment had independent effects on subsequent severity, neither potential confounder could account for the lack of observed treatment effects.

Models of individual symptoms and of symptom dimensions (again controlling for the five confounders) similarly failed to demonstrate treatment effects. Although uncontrolled linear models of the cough dimension indicated slightly more rapid recoveries in the placebo group, these differences were not apparent in more complex models that better represented dimension severity over time. More severe illness in the placebo group on the first day of the trial, before treatment was initiated, appeared to explain the trends favoring placebo in the linear models. There were no statistically significant differences between echinacea and placebo in scaled responses to the global severity question, “How sick do you feel today?” Mean scores of responses to this question are shown in Figure 3.

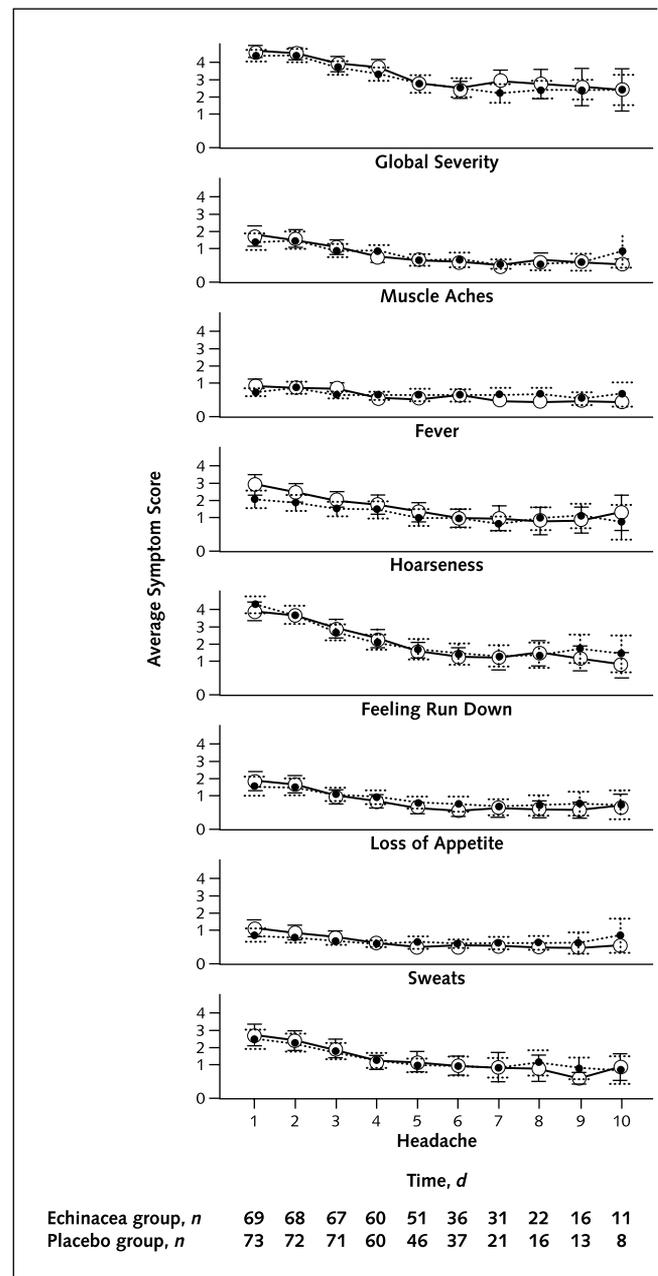
In our analysis, we included all available data from the 142 persons who completed the study protocol. We collected no useful data for the six participants who were enrolled but were lost to follow-up. Regression results described earlier and mean values portrayed in Figures 2, 3, and 4 do not include data for these six participants and therefore do not represent an intention-to-treat analysis. However, to assess whether data from the six persons who withdrew could have affected our results, we performed an analysis that imputed symptom-recovery trajectories for each missing participant based on the average of 1000 randomly selected trajectories. This analysis yielded results very similar to those described earlier (data not shown).

Specific adverse effects were reported on the daily questionnaires 22 times by 15 participants who completed the study (9 times by 7 participants in the placebo group and 13 times by 8 participants in the echinacea group). In the echinacea group, sleeplessness, heartburn, nausea, stomachache, and upset stomach were each reported by one participant and bad taste was noted by three participants. In the placebo group, stomachache was noted by three participants and nausea, belching, thirst, and abdominal pain with diarrhea were each noted by one participant. Reported adverse effects were therefore not statistically different between the echinacea and placebo groups.

## DISCUSSION

We consider the results of this trial to be negative. We did not detect the effect size for which the trial was powered (2 days' duration and two points in average severity on a nine-point scale) or any potentially significant trends.

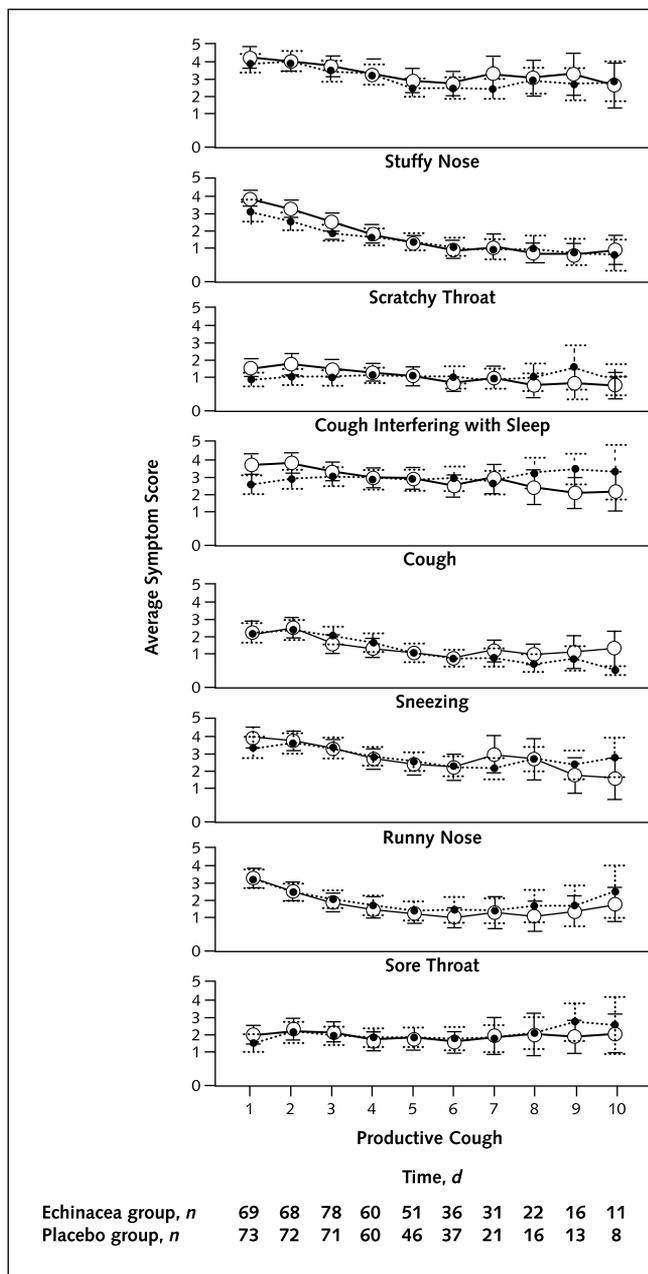
Figure 3. Mean severity of global and general symptoms.



Dotted lines represent the echinacea group; solid lines represent the placebo group. Error bars represent 95% CIs. Although 95% CIs indicate the uncertainty of the severity of symptoms, they should not be used to compare symptom severity on any particular day.

All differences noted between the echinacea and placebo groups could be explained by natural variability in the underlying symptoms measured. Our results do not support a benefit of echinacea in the treatment of common cold symptoms. However, we do not believe that our trial should be the last word on echinacea. Our results contradict the current published evidence, and our trial had limitations. Previous trials have reported statistically significant symptomatic benefit with echinacea taken early in the

Figure 4. Mean severity of specific cold symptoms.



Dotted lines represent the echinacea group; solid lines represent the placebo group. Error bars represent 95% CIs. Although 95% CIs indicate the uncertainty of the severity of symptoms, they should not be used to compare symptom severity on any particular day.

course of an acute upper respiratory tract infection (27–29, 31–35). These trials, especially those by Brinkeborn (28) and Henneicke-von Zepelin (27) and colleagues, are similar to our trial in quality but report positive results. In addition, published systematic reviews have concluded that there may be benefit to early echinacea treatment (13, 18, 36, 37). There are several possible reasons for this discrepancy. The positive results of previous trials could be due to bias or chance, and the widespread belief in echinacea’s benefit could be entirely false.

However, our trial had several limitations that should temper confidence in its negative results. First, the specific echinacea preparation used in our trial, a dried, encapsulated mixture of unrefined *E. angustifolia* root and whole-plant *E. purpurea*, has not been tested previously and may be ineffective because of bioavailability or phytochemical constituents. Previous trials with positive results have used extracts rather than whole-plant products (25, 27–35), and some have combined echinacea with other plant species (27, 32–35). Because phytochemical constituents vary among botanical species, growing conditions, plant part, and extraction method, it is possible that one preparation would provide benefit while another would not.

Second, the type of people included in our study, healthy undergraduate college students, may not gain much benefit from echinacea. Previous trials have tended to include older adults and have sometimes sought to include those with histories of frequent colds. There is a prevailing notion that echinacea provides greatest benefit to persons who are immunocompromised, a state often evidenced by frequent colds or other viral illnesses. We made no effort to seek out such persons.

Third, although our modest-size trial would have detected a large benefit, an effect size of 5% or 10% could easily have been missed among the natural variability of symptoms found in persons with community-acquired colds. From a health measurement perspective, it should be emphasized that our study was limited because we used self-reported symptoms as primary outcomes (44, 45, 58, 59). Subjective self-assessments can introduce several potential biases.

To date, there are no validated instruments for assessing the common cold (10, 40, 41). We have begun refining and validating our instrument (60), but although its face validity is strong, construct validity has not been demonstrated. It should also be noted that we monitored participants for a maximum of 10 days and therefore do not know the frequency of longer illnesses. Finally, five people in each of our study groups received echinacea after having symptoms for 36 hours, which may have masked a benefit of echinacea given earlier in cold presentation. Future research is necessary to provide more definitive evidence about whether echinacea is an effective treatment for the common cold.

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