

Echinacea in the Prevention of Induced Rhinovirus Colds: A Meta-Analysis

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ABSTRACT

Background: The therapeutic effectiveness of *Echinacea* in the treatment and the prevention of colds has been debated. Studies of naturally occurring colds are hampered by variability in time from onset of symptoms to treatment and by heterogeneity in trial design. Experimental infection studies allow for the standardization of time to initiation of treatment, virus type and dose, and immune competence of volunteers.

Objective: To determine whether the negative results obtained in previous studies of *Echinacea* were a consequence of efficacy or of inadequate sample size, we performed a meta-analysis of experimental rhinovirus infection studies on the efficacy of *Echinacea* extracts to prevent symptomatic development of an experimentally induced cold.

Methods: We carried out a systematic search of English- and German-language literature using the MEDLINE, EMBASE, CAsplus, BIOSIS, CABA, AGRICOLA, TOXCENTER, SCISEARCH, NAHL, and NAPRALERT, databases and the search terms *Echinacea*, *black Sampson*, *coneflower*, and *Roter Sonnenhut*. Matching documents were then searched for ≥ 1 of the following terms: *rhinovirus*, *RV*, *inoculation*, *Inokulation*, *induced*, *induziert*, *artificial*, and *artifiziell*. Suitable studies were identified and pooled for analysis. The primary end point was the development of symptomatic clinical colds, as defined by the authors of the original studies. Results were reported as differences in the proportion of subjects with symptomatic episodes of a common cold, expressed as odds ratios (ORs) and 95% CIs. The secondary outcome was the difference in total symptom severity scores between treatment groups (assessed daily by integrating the severity scores of 8 individual cold-related symptoms that were rated on a scale from 0 [absent] to 4 [very severe]).

Results: A total of 234 articles were identified through the literature search; 231 were excluded from the analysis because they related to studies of spontaneous common colds. Three suitable studies were selected for pooling of data. Based on the analysis, the likelihood of experiencing a clinical cold was 55% higher with placebo than with *Echinacea* (OR, 1.55 [95% CI, 1.02–2.36]; $P < 0.043$). The absolute difference in total symptom scores between groups was -1.96 (95% CI, -4.83 to 0.90 ; $P = \text{NS}$).

Conclusions: This meta-analysis suggests that standardized extracts of *Echinacea* were effective in the prevention of symptoms of the common cold after clinical inoculation, compared with placebo. Further prospective, appropriately powered clinical studies are required to confirm this finding. (*Clin Ther.* 2006; 28:174–183) Copyright © 2006 Excerpta Medica, Inc.

Key words: *Echinacea*, rhinovirus, inoculation, meta-analysis, prophylaxis.

INTRODUCTION

Native American tribes discovered the potential of *Echinacea* in the treatment of cough, sore throat, snake bites, and analgesia.^{1,2} Current interest focuses on the role of *Echinacea* in the prevention and treatment of common colds.³ Preparations mainly include the leaves and roots of dried or fresh *Echinacea purpurea*, *Echi-*

Accepted for publication December 29, 2005.

Express Track online publication February 8, 2006.

doi:10.1016/j.clinthera.2006.02.001

0149-2918/06/\$19.00

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nacea angustifolia, and *Echinacea pallida*, and are manufactured using a range of extraction methods.^{4,5}

Although some clinical studies of *Echinacea* in spontaneously occurring colds have reported positive results, others have reported negative findings, so that the efficacy of *Echinacea* remains uncertain.^{3,6-8} Moreover, the quality of many clinical trials, and of some investigated products, has been challenged.⁹ Variation among the extracts used, medication regimens, and study designs might be partly responsible for the conflicting outcomes.¹⁰

A recent Cochrane review¹¹ found 5 randomized trials of adequate methodologic quality that investigated the prophylactic efficacy of *Echinacea* in spontaneously acquired colds. In 2 studies, a statistically significant reduction in the incidence of upper respiratory tract infections was observed.^{12,13} One trial found a significantly shorter duration of cold episodes in the *Echinacea*-treated group.¹² The authors concluded that there was still insufficient evidence to promote *Echinacea* for the prevention of common colds and commented that the observed effect size (ie, the difference in mean values between groups) of 5% to 15% was of questionable clinical relevance.

However, several studies of the efficacy of *Echinacea* for the treatment of the common cold have produced positive results. For example, in a study investigating an alcoholic fresh-plant tincture from *E purpurea*, treatment was associated with 120% better resolution of symptoms during a cold episode than was placebo ($P = 0.02$).¹⁴ This double-blind, placebo-controlled, randomized clinical trial investigated the relative reduction of 12 cold-related symptoms, rated on a scale ranging from 0 (absent) to 3 (severe) in 246 patients. Detailed and comprehensive reviews on the efficacy of *Echinacea* in the prevention and treatment of the spontaneous common cold were recently published by Barrett³ and Barnes et al.⁶

A crucial factor in the investigation of a cold remedy is the timely initiation of treatment. It was recently argued that medication must be started immediately after occurrence of the first symptoms for beneficial effects to be observed.¹⁵ If the optimal time point has already passed, then the effect of a potentially active remedy might not be demonstrated. In various trials with *Echinacea*, the start of medication varied from the time of occurrence of first symptoms to several hours afterward; therefore, it is not surprising that the outcome of these studies differed substantially.

Unfortunately, such variables within a normal field study of the common cold are difficult to circumvent; thus, this system can result in a critical divergence of results.^{16,17}

Much work has been done to standardize both the investigational products used in medical studies and the settings in which these products have been tested. The experimental induction of common colds was developed for this reason. Rhinoviruses are by far the most frequent causative agent in cold episodes and most studies have used rhinoviruses for this reason.^{18,19} The experimental system allows previously uncontrollable variables, such as time to initiation of treatment, virus type and dose, and immune competence of volunteers, to be standardized. Therefore, experimental systems represent useful and accurate settings in which to investigate the efficacy of remedies in the prevention and the treatment of the common cold.¹⁷

Three rhinovirus inoculation studies investigated the prophylactic effects of well-standardized *Echinacea* extracts.²⁰⁻²² In these studies, the rate of infection (defined by detection of rhinoviruses in nasal secretions and/or rise of antibody titers in the serum) was investigated as a primary outcome variable. All trials reported a negative outcome in the prevention of infection. In all 3 studies, *Echinacea* appeared to inhibit development and severity of symptomatic colds, although no significant difference from placebo was found. Measures of variance in the data were generally high. With an expected effect size of 10% to 40%, it is possible that these studies were underpowered to detect any benefit for the parameters likely to be influenced by *Echinacea*.^{3,6} The statistical power was calculated to be 29% for the study published by Sperber et al.²¹ and ~15% for those from Turner et al.^{20,22}

To determine whether the negative results obtained in these studies were a consequence of efficacy or of inadequate sample size, we performed a meta-analysis of experimental rhinovirus infection studies on the efficacy of *Echinacea* extracts to prevent symptomatic development of an experimentally induced cold.

METHODS

Study Selection

A systematic search of English- and German-language literature was performed using the MEDLINE, EMBASE, CAPLUS, BIOSIS, CABA, AGRICOLA, TOXCENTER, SCISEARCH, NAHL, and NAPRALERT

databases and the search terms *Echinacea*, *black Sampson*, *coneflower*, and *Roter Sonnenhut*. Matching documents were then searched for ≥ 1 of the following terms: *rhinovirus*, *RV*, *inoculation*, *Inokulation*, *induced*, *induziert*, *artificial*, and *artifiziell*.

The articles identified through the literature search were assessed for suitability for analysis using Quality of Reporting of Meta-analyses criteria,²³ and those that were found to be relevant were further evaluated for quality of design, as assessed by Jadad score²⁴; the process of randomization and the efficacy of blinding were rated together with the follow-up of dropouts and withdrawals. In the case of inappropriate randomization or blinding, 1 point was deducted.

The primary outcome of the present meta-analysis was the development of symptomatic clinical cold, as defined by Gwaltney et al¹⁷ and Jackson et al.¹⁸ A clinical cold was considered to be present if a 5-day symptom score of ≥ 5 ²¹ or ≥ 6 ^{20,22} was reached and if, on 3 successive days, rhinorrhea occurred and/or the patient felt that he or she had developed a cold.^{17,18}

A secondary analysis investigated the severity of symptoms after viral challenge.

Statistical Methods

A formal meta-analysis was performed in which the results of the eligible studies were pooled. Differences in the proportion of subjects with symptomatic episodes of a common cold were expressed as odds ratios (ORs) and 95% CIs. ORs > 1.0 indicated a beneficial effect of *Echinacea*, corresponding to a higher likelihood of avoiding a symptomatic clinical cold when a potential infection source was present. To combine the results of the single studies, we calculated weighted means of the log-ORs, as proposed by Whitehead.²⁵ In our analysis, we focused on the effects of *Echinacea* in the prevention of symptomatic cold episodes among all virally challenged participants, comparing active agent with placebo.

In a secondary analysis, the efficacy of *Echinacea* on the basis of symptom severity during cold episodes was investigated. Mean total symptom scores (TSS) were obtained by integrating the scores for individual cold-related symptoms, each of which was rated on a numeric scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe,²¹ 4 = very severe^{20,22}). Results for the effect on TSS were expressed as absolute mean differences; negative differences indicated lower severity of symptoms in subjects who received *Echinacea* rather than placebo.

The variance of the effect size was calculated as residual restricted maximum likelihood estimate.²⁶ The results of all studies were combined by weighted means of the mean TSS of single studies, as proposed by Whitehead.²⁵ All presented effect sizes and ratios between *Echinacea* and placebo were calculated from percentages of all inoculated subjects.

We examined heterogeneity in the treatment difference parameters between trials with the classical test proposed by Hedges and Olkin.²⁷ Overall estimators and tests for difference between groups were calculated using both a general fixed-effects parametric approach and a general random-effects parametric approach. In the analyses, heterogeneity was not significant; therefore, fixed-effects estimates are presented in this article.

The validated program MetaSub, version 1.1.05 (IDV, Gauting/Munich, Germany), was used in this analysis.

RESULTS

A total of 234 matches were found in the literature search. Of these, 231 were excluded from this analysis because they related to studies of spontaneous common colds. The remaining 3 inoculation studies were of high quality, being double blind, placebo controlled, and adequately randomized (Table I).²⁰⁻²² With Jadad total scores of 4 and 5, the studies were all of high quality. Furthermore, they used similar inoculation protocols, with the same parameters investigated and with standardized investigational products,²⁰⁻²² making them eligible for data pooling. Prophylactic treatment started 7 days^{21,22} or 14 days²⁰ before virus challenge and continued until day 5^{20,22} or day 7.²¹ In both studies by Turner et al,^{20,22} 300 mg was applied 3 times daily; the first study used extract of *E purpurea*,²⁰ and the second used extract of *E angustifolia*.²² Sperber et al²¹ treated subjects 3 times daily with an *E purpurea* preparation corresponding to 176 mg of crude extract (according to the manufacturer).¹⁹ Controlled testing was achieved by calculating 95% CIs and *P* values.

Turner et al²⁰ and Sperber et al²¹ tested preparations made from *E purpurea*. In the more recent study by Turner et al,²² a 20%, a 60% alcoholic, and a CO₂ extract from *E angustifolia* were investigated. Each of them was compared with the same placebo group. Because meta-analyses should compare independent studies, the data for the eligible *Echinacea* extracts were pooled and compared with placebo. For the

Table 1. Quality of included studies according to Jadad score.^{24*}

Study	Randomization			Double Blinding		Dropouts/ Withdrawals		Jadad Score
	Yes/No	Described	Inappropriate	Yes/No	Described	Inappropriate	Described	
Turner et al ²⁰	1	0	0	1	1	0	1	4
Sperber et al ²¹	1	0	0	1	1	0	1	4
Turner et al ²²	1	1	0	1	1	0	1	5

*1 Point was awarded for each *yes* answer. An additional point could be awarded if the methods for generating the randomization sequence were both fully described and appropriate, and/or if the double-blinding methods were both fully described and appropriate. A point could be deducted if the methods for generating the randomization sequence were fully described but inappropriate, or if the double-blinding methods were fully described but inappropriate. A point was awarded if the report included the number (and reasons for withdrawal) of participants who did not complete the observation period or who were not included in the analysis, even if only to state that no one withdrew.

analysis of occurrence of symptomatic colds, the appropriate numbers in the *Echinacea* groups were combined and the OR between *Echinacea* and placebo was calculated. For the mean TSS, the weighted mean (weights were corresponding group sizes) of the individual study groups was calculated and its variance determined as the weighted mean of within-group variances.

Table II shows the number of patients in each study who were challenged with rhinovirus (inoculated) and in whom infection was detected or symptomatic colds developed. The second study by Turner et al²² was the largest, with a total of 149 and 103 challenged volunteers in the *Echinacea* (pooled verum groups) and placebo groups, respectively. As shown in Table II, Turner et al²² observed a detectable infection rate of 87% (218 infections in 252 challenged subjects) in both the *Echinacea* and placebo groups; symptomatic colds developed in only 49% of subjects treated prophylactically with *Echinacea* and in 56% of subjects without prophylaxis. Incidences of symptomatic clinical colds among *Echinacea*-treated subjects ranged

from 22% to 58%, compared with 33% to 82% among those who received placebo.²⁰⁻²²

Table III shows the ORs and CIs for the differences between the proportions of patients from each group who developed a symptomatic cold in each of the 3 studies,²⁰⁻²² along with an overall estimate of the treatment difference from the pooled results. (Heterogeneity of treatment effects between studies was not found, so the study results can be combined.) The OR was 1.55 (95% CI, 1.02-2.36; $P < 0.043$). Thus, the odds of escaping a clinical cold were 55% higher when ingesting *Echinacea* rather than placebo in the studies included in this analysis. Figure 1 illustrates the effect sizes of all of the *Echinacea* preparations assessed in these 3 studies,²⁰⁻²² along with the overall pooled estimate. The pooled result was between the accepted benchmark values of 1.437 (small effect size) and 2.475 (medium effect size).²⁸ The CI for the pooled OR did not cross 1.0, indicating statistical significance. Using random-effects models, comparable point estimates were achieved (data not shown).

Table II. Effects of *Echinacea* treatment on the occurrence of infection and development of symptomatic cold episodes. Values are given as number (%) of subjects.

Study	<i>Echinacea</i>			Placebo		
	Inoculated	Infections	Symptomatic Colds	Inoculated	Infections	Symptomatic Colds
Turner et al ²⁰	50	22 (44)	11 (22)	42	24 (57)	14 (33)
Sperber et al ²¹	24	22 (92)	14 (58)	22	21 (95)	18 (82)
Turner et al ²²	149	130 (87)	73* (49)	103	88 (85)	58 (56)

*Consisting of 24, 24, and 25 patients allocated to treatment with a 20%, a 60% alcoholic, and a CO₂ *Echinacea* extract, respectively.

Table III. Efficacy of *Echinacea* for the incidence of symptomatic cold episodes in comparison with placebo.

Study	OR (95% CI)	P
Turner et al ²⁰	1.77 (0.70-4.48)	0.25
Sperber et al ²¹	3.21 (0.83-12.45)	0.11
Turner et al ²²	1.34 (0.81-2.22)	0.31
Pooled	1.55 (1.02-2.36)	Heterogeneity: <0.471 Fixed effect: <0.043

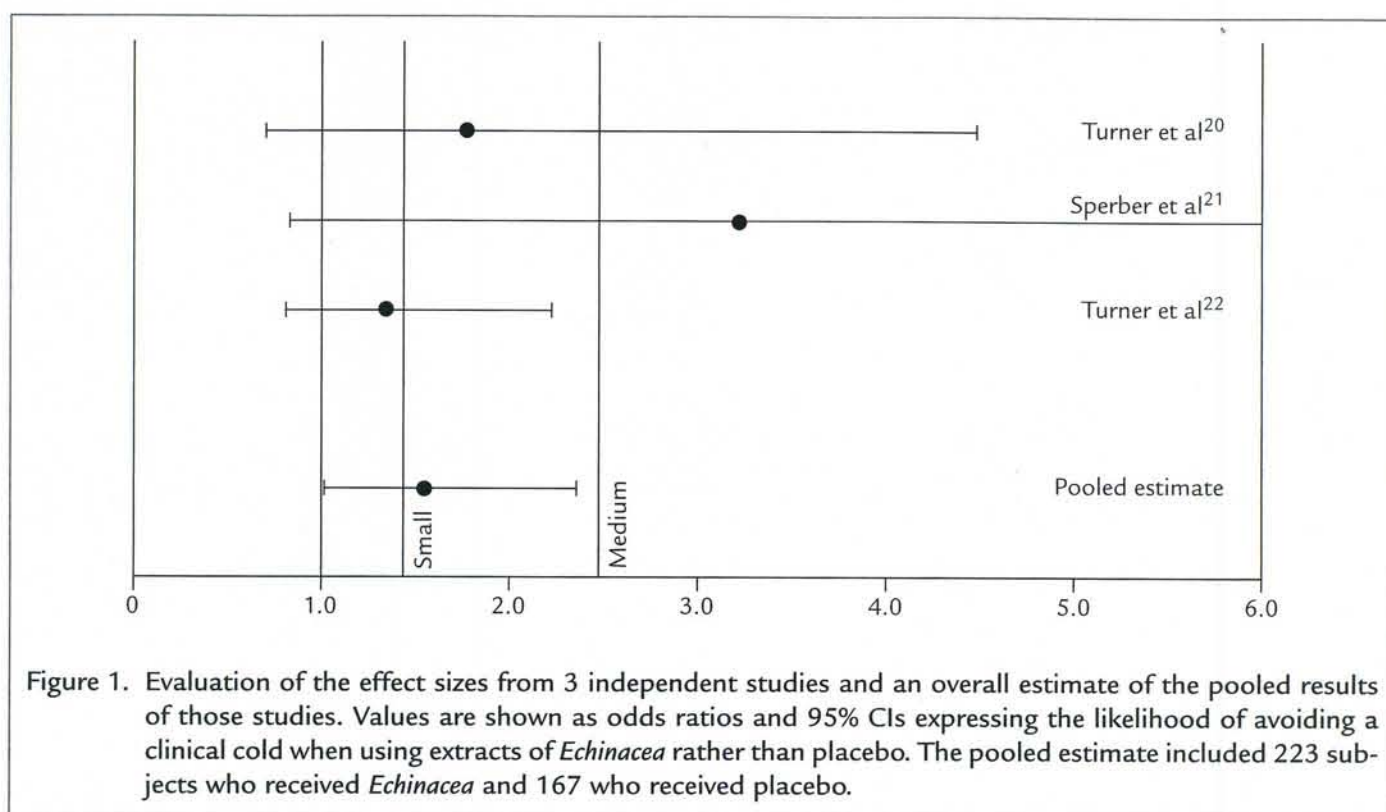


Figure 1. Evaluation of the effect sizes from 3 independent studies and an overall estimate of the pooled results of those studies. Values are shown as odds ratios and 95% CIs expressing the likelihood of avoiding a clinical cold when using extracts of *Echinacea* rather than placebo. The pooled estimate included 223 subjects who received *Echinacea* and 167 who received placebo.

A secondary analysis investigated the severity of cold-related symptoms. In all 3 studies, symptomatic colds were assessed daily by rating sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, and chilliness using the scoring system described previously in this article. Single symptom scores were not given in all of the studies; therefore, Table IV presents the TSS for these parameters. Effect sizes (and 95% CIs) for TSS for the 3 studies individually and an overall estimate for all studies pooled are given. Again,

the study results could be pooled because there was no evidence of heterogeneity of treatment effects. Mean differences of TSS between groups in the individual studies ranged from -1.56 to -2.83 , and the overall estimate of difference for the pooled studies was -1.96 (95% CI, -4.83 to 0.90 ; $P = \text{NS}$) (Table IV; Figure 2).

DISCUSSION

The common cold is one of the most common diseases in western countries, resulting in direct medical costs

Table IV. Efficacy of *Echinacea* for severity of cold symptoms, as measured by total symptom scores, compared with placebo.*

Study	Mean Difference (95% CI)	P
Turner et al ²⁰	-2.20 (-12.11 to 7.71)	0.66
Sperber et al ²¹	-2.83 (-8.32 to 2.66)	0.32
Turner et al ²²	-1.56 (-5.13 to 2.00)	0.39
Pooled	-1.96 (-4.83 to 0.90)	Heterogeneity: <0.930 Fixed effect: <0.180

*Total symptom score was based on total of ratings for 8 individual symptoms (0 = absent, 1 = mild, 2 = moderate, 3 = severe,²¹ 4 = very severe^{20,22}).

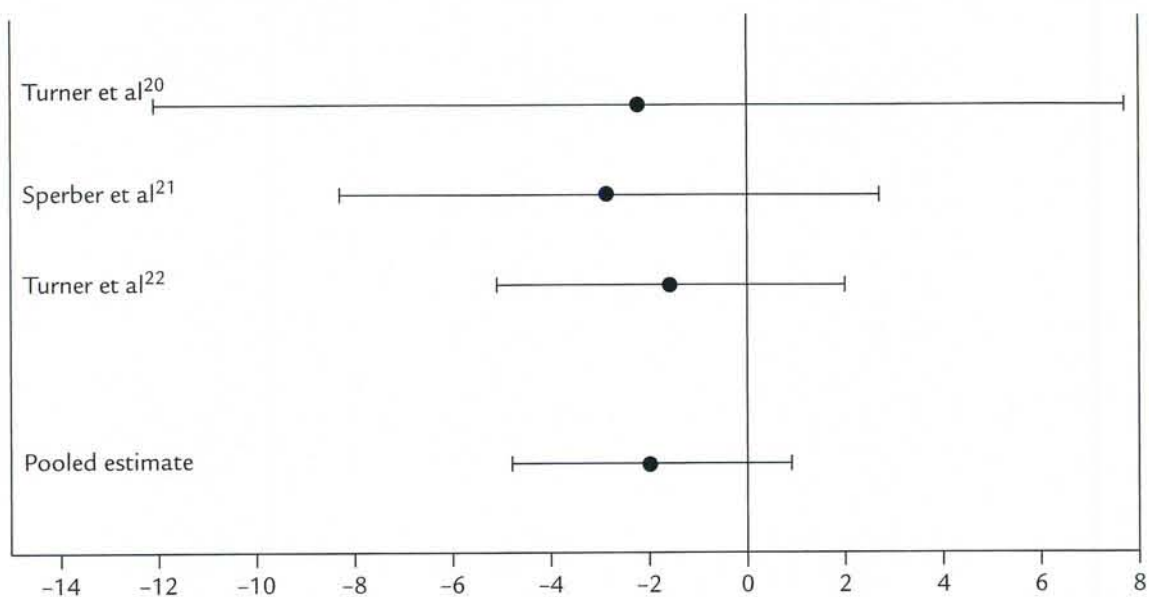


Figure 2. Mean differences between groups in total symptom scores (with 95% CIs) for each of 3 studies and an overall estimate of the treatment difference based on the pooled results of those studies. The pooled estimate included 223 subjects who received *Echinacea* and 167 who received placebo.

of more than US \$16.8 billion annually.²⁹ There is great interest in the development of medication to prevent and treat this disease. Many remedies are commercially available, but conclusive proof of their efficacy is often lacking.³⁰ Much confusion and conflicting outcomes result from studies with inappropriate designs or population sizes. Clear clinical benefits and clinical recommendations have not been determined for zinc, vitamin C, local antihistamines, anti-tussives, expectorants, and other locally active remedies. Some medications are effective, but because of adverse events, rebound effects, or cost/benefit ratios, they have not proved to be adequate for the treatment of self-limited forms of the common cold.^{31–35} Vaccination for rhinoviruses, which are the major cause of colds, remains elusive due to the variability of this group of >100 serotypes.³⁶

Perhaps due to the lack of specific therapies, associated risks with certain treatment, and the relatively mild nature of the symptoms, phytomedicines are a popular approach to managing the common cold. In recent years, a growing interest in remedies containing refined *Echinacea* has paralleled the increasing demand for alternative treatment options.³⁷ With annual sales of more than US \$300 million, *Echinacea* is one of the best-selling herbal products in the United States.^{5,38,39}

As with most cold remedies, the clinical data on *Echinacea* that have been gathered so far have not been definitive. Randomized, placebo-controlled, double-blind clinical trials have reported its efficacy for the treatment of spontaneous common colds, but the results of other high-quality studies have called into question the clinical benefit of *Echinacea*.^{7–9,12,14,40–42} A detailed and comprehensive review on *Echinacea* concluded that the available literature suggests some efficacy in the treatment of the common cold, although it must be noted that this conclusion was not based on statistical analysis.³

However, some of the latest trials using experimentally induced common colds failed to show any significant superiority over placebo. Experimental-infection studies provide homogeneous study design and were found, in the preliminary stages of the present study, to be suitable for inclusion in a meta-analysis: A total of 3 studies were identified that investigated rates of infection and development of symptomatic clinical colds in induced rhinovirus infections.^{20–22} However, the clinical burden of the common cold in direct and indirect costs, including absence from work, is not caused by detection of virus in secretions or of serum antibodies, but rather by perceived symptoms. Thus, prevention of symptomatic colds is the most rele-

vant outcome and the primary one chosen for our meta-analysis.

In our analysis, we intended to show the relative benefit of *Echinacea*, in comparison with placebo, for reducing the risk of developing symptoms of the common cold. The studies included in this analysis reported considerable variance in the data; however, it should be noted that these studies enrolled few subjects.²⁰⁻²² The sample sizes were half or one fourth of the size that would have been necessary to detect even medium treatment effects (~90 patients per group).

To obtain an adequate sample size, we decided to perform a formal meta-analysis, pooling the results of all suitable studies. To our knowledge, this is the first meta-analysis to find prophylactic efficacy of *Echinacea*. The likelihood of developing a clinical cold was 55% higher in the placebo group than in the *Echinacea* group (OR, 1.55 [95% CI, 1.02-2.36]; $P < 0.043$). The statistical power to detect this difference on the basis of a sample size, as available from the meta-analysis, was calculated to be 51%. To detect an effect size of 1.55 (the OR noted in the present meta-analysis) with a power of 80% and a significance level of 5%, a clinical study would have to include ~340 patients per group.

Our findings support the results of placebo-controlled, double-blind, randomized clinical trials reporting the efficacy of *Echinacea* for the prevention of spontaneous colds. During 2 months of administration of *Echinacea* or placebo to 108 volunteers, Schoeneberger⁴³ observed significantly shorter duration of illness and fewer participants suffering from a cold after being exposed to the virus. A 50% reduction in the number of colds ($P < 0.001$) in children who received a combination of *Echinacea*, vitamin C, and propolis instead of placebo was observed after 12 weeks of administration.⁴⁴ Furthermore, Taylor et al⁸ found significantly more recurrent infections after treatment of first episodes in 64% of children treated with placebo, compared with 52% in the *Echinacea* group ($P = 0.015$). Although not designed as a classical prevention trial, and although the primary end point of the trial produced negative results, the study by Taylor et al⁸ supports the findings of the present meta-analysis.

Based on the available evidence, it is likely that *Echinacea* has a beneficial effect in diseases with a predominantly inflammatory component. The anti-inflammatory and immune-modulatory effects of

Echinacea observed in vitro could thus have direct ameliorating effect on virus-induced inflammation. It has been reported that symptoms accompanying a common cold are clearly associated with levels of inflammatory cytokines such as interleukin-1 β (IL-1 β), IL-6, IL-8 or interferon- γ .^{45,46} Also, it is indicative that asymptomatic courses of colds are not associated with elevated levels of cytokines, showing a strong correlation between cytokines and perceived symptoms.⁴⁷ Decreased secretion of anti-inflammatory cytokines might be a reasonable therapeutic strategy to relieve inflammation-related symptoms during a cold episode.^{48,49} The effects of *Echinacea* on levels of proinflammatory cytokines in nasal secretions during cold episodes remain to be determined in vivo.

Rhinoviruses are the most common agent causing upper respiratory tract diseases that can also be associated with asthma exacerbations, otitis media, acute sinusitis, and even subsequent development of pneumonia.^{36,50,51} Experimentally transmitted rhinovirus colds are, therefore, a suitable means for testing the preventive efficacy of remedies. Although the efficacy of *Echinacea* to prevent symptomatic cold as summarized in the present article cannot easily be applied to other causative agents, our findings suggest that the reduced risk of developing clinical colds observed with the use of *Echinacea* could result in a substantial economic and socioeconomic benefit. An adult person suffers from 2 to 4 colds per year and preschool-aged children experience up to 12 colds annually, together accounting for ~23 million days of work absence and ~26 million days of school absence in the United States annually; therefore, reducing cold risk by using *Echinacea* could similarly reduce the immense direct and indirect medical costs, loss of wages, and personal discomfort associated with colds.^{29,34,35} A possible limitation of the present analysis might be the relatively low number of eligible studies. Large clinical trials are warranted to quantify the effect of prophylactic treatment with *Echinacea*.

CONCLUSIONS

This meta-analysis suggests that standardized extracts of *Echinacea* were effective in the prevention of symptoms of the common cold after clinical inoculation, compared with placebo. Further prospective, appropriately powered clinical studies are desired to confirm this finding.

ACKNOWLEDGMENT

A. Vogel Bioforce AG manufactures *Echinacea* products.

REFERENCES

- Smith HH. Ethnobotany of the Meskwaki Indians. *Bull Pub Museum Milwaukee*. 1928;4:175-326.
- Bauer R. Geschichte. In: Bauer R, Wagner H, eds. *Echinacea: Handbuch für Ärzte, Apotheker und andere Naturwissenschaftler*. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft; 1990:9-21.
- Barrett B. Medicinal properties of Echinacea: A critical review. *Phytomedicine*. 2003;10:66-86.
- Wichtl M. Herbal drugs and phytopharmaceuticals. In: Wichtl M, ed. *A Handbook for Practice on a Scientific Basis*. Stuttgart, Germany: Medpharm Scientific Publishers; 2004.
- Breevort P. The booming US botanical market. *HerbalGram*. 1998;44:33-48.
- Barnes J, Anderson LA, Gibbons S, Phillipson JC. Echinacea species (*Echinacea angustifolia* (DC.) Hell., *Echinacea pallida* (Nutt.) Nutt., *Echinacea purpurea* (L.) Moench): A review of their chemistry, pharmacology and clinical properties. *J Pharm Pharmacol*. 2005;57:929-954.
- Barrett BP, Brown RL, Locken K, et al. Treatment of the common cold with unrefined echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2002;137:939-946.
- Taylor JA, Weber W, Standish L, et al. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: A randomized controlled trial. *JAMA*. 2003;290:2824-2830.
- Caruso TJ, Gwaltney JM Jr. Treatment of the common cold with Echinacea: A structured review. *Clin Infect Dis*. 2005;40:807-810.
- Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines. A Guide for Healthcare Professionals*. 2nd ed. London, UK: Pharmaceutical Press; 2004.
- Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev*. 2004;3:CD000530.
- Hoheisel O, Sandberg M, Bertram S, et al. Echinagard treatment shortens the course of a common cold: A double blind, placebo controlled clinical trial. *Eur J Clin Res*. 1997;9:261-268.
- Forth H, Beuscher N. Effect on the frequency of banal cold infections by esberitox [in German]. *ZFA (Stuttgart)*. 1981;57:2272-2275.
- Brinkeborn RM, Shah DV, Degenring FH. Echinaforce and other Echinacea fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine*. 1999;6:1-6.
- Gwaltney JM. Clinical significance and pathogenesis of viral respiratory infections. *Am J Med*. 2002;112(Suppl 6A):13S-18S.
- Melchart D, Linde K, Worku F, et al. Immunomodulation with Echinacea: A systematic review of controlled clinical trials. *Phytomedicine*. 1994;1:245-254.
- Gwaltney JM Jr, Hendley JO, Patrie JT. Symptom severity patterns in experimental common colds and their usefulness in timing onset of illness in natural colds. *Clin Infect Dis*. 2003;36:714-723.
- Jackson GG, Dowling HF, Spiesman IG, Boand AV. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. *AMA Arch Intern Med*. 1958;101:267-278.
- Bardin PG, Sanderson G, Robinson BS, et al. Experimental rhinovirus infection in volunteers. *Eur Respir J*. 1996;9:2250-2255.
- Turner RB, Riker DK, Gangemi JD. Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob Agents Chemother*. 2000;44:1708-1709.
- Sperber SJ, Shah LP, Gilbert RD, et al. Echinacea purpurea for prevention of experimental rhinovirus colds. *Clin Infect Dis*. 2004;38:1367-1371.
- Turner RB, Bauer R, Woelkart K, et al. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med*. 2005;353:341-348.
- Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement (Quality of Reporting of Meta-analyses). *Lancet*. 1999;354:1896-1900.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
- Whitehead A. *Meta-analysis of controlled clinical trials*. Chichester, UK: Wiley; 2002.
- Searle SR, Casella G, McCulloch CE. *Variance Components*. New York, NY: Wiley; 1992.
- Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. London, UK: Academic Press; 1985.
- Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. *Psychol Bull*. 1995;117:167-178.
- Fendrick AM, Monto AS, Sarnes M, et al. The economic burden of viral respiratory infection in the United States. ISPOR Fourth Annual European Congress Contributed Presentation Abstracts. *Value Health*. 2001;4:412.
- Lasek R, Müller-Oerlinghausen B. Akute Atemwegsinfektionen. In: *Arzneiverordnung in der Praxis*. 2. Auflage. Köln, Germany: Arzneimittelkommission der deutschen Ärzteschaft; 2002:1-23.
- Schroeder K, Fahey T. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. *BMJ*. 2002;324:329-331.

32. Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *J Clin Pharm Ther.* 1992;17:175-180.
33. Lurie A, Mestiri M, Strauch G, Marsac J. Drugs acting on mucociliary transport and surface tension. In: Munson PL, Mueller RA, Breese GR, eds. *Principles of Pharmacology.* New York, NY: Chapman & Hall; 1995:621-627.
34. Turner RB. The common cold. *Pediatr Ann.* 1998;27:790-795.
35. Turner RB. Epidemiology, pathogenesis, and treatment of the common cold. *Ann Allergy Asthma Immunol.* 1997;78:531-540.
36. Treanor J, Falsey A. Respiratory viral infections in the elderly. *Antiviral Res.* 1999;44:79-102.
37. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. *JAMA.* 1998;280:1569-1575.
38. Canedy D. Real medicine or medicine show? Growth of herbal sales raises issues about value. *New York Times.* July 23, 1998:C1.
39. Herbal Rx: The promises and pitfalls. *Consum Rep.* 1999;64:44-48.
40. Schulten B, Bulitta M, Ballering-Bruhl B, et al. Efficacy of *Echinacea purpurea* in patients with a common cold. A placebo-controlled, randomised, double-blind clinical trial. *Arzneimittelforschung.* 2001;51:563-568.
41. Goel V, Lovlin R, Barton R, et al. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: A randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther.* 2004;29:75-83.
42. Goel V, Lovlin R, Chang C, et al. A proprietary extract from the echinacea plant (*Echinacea purpurea*) enhances systemic immune response during a common cold. *Phytother Res.* 2005;19:689-694.
43. Schoeneberger D. The influence of the immunostimulating effects of pressed juice from *Echinacea purpurea* on the course and severity of cold infections [in German]. *Forum Immunologie.* 1992;8:18-22.
44. Cohen HA, Varsano I, Kahan E, et al. Effectiveness of an herbal preparation containing echinacea, propolis, and vitamin C in preventing respiratory tract infections in children: A randomized, double-blind, placebo-controlled, multicenter study. *Arch Pediatr Adolesc Med.* 2004;158:217-221.
45. Röseler S, Holtappels G, Wagenmann M, Bachert C. Elevated levels of interleukines IL-1beta, IL-6, IL-8 in naturally acquired viral rhinitis. *Eur Arch Otorhinolaryngol.* 1995;252 (Suppl):61-66.
46. van Kempen M, Bachert C, Van Cauwenberge P. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology.* 1999;37:97-103.
47. Gentile DA, Villalobos E, Angelini B, Skoner D. Cytokine levels during symptomatic viral upper respiratory tract infection. *Ann Allergy Asthma Immunol.* 2003;91:362-367.
48. Gertsch J, Schoop R, Kuenzle U, Suter A. Echinacea alkylamides modulate TNF-alpha gene expression via cannabinoid receptor CB2 and multiple signal transduction pathways. *FEBS Lett.* 2004;577:563-569.
49. Barak V, Birkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J.* 2002;4 (Suppl 11):919-922.
50. Busse WW, Lemanske RF Jr, Dick EC. The relationship of viral respiratory infections and asthma. *Chest.* 1992;101(Suppl):385S-388S.
51. Brooks GF, Butel JS, Ornston LN, eds. *Jawetz, Melnick & Adelberg's Medical Microbiology.* 19th ed. Norwalk, Conn: Appleton & Lange; 1991.

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