ization process would have corrected any results due to this difference. In our study, both the echinacea group and the placebo group would have started their treatment at the onset of the same number of symptoms, and there is no difference in case definition between the 2 groups. Finally, Caruso and Gwaltney [2] failed to address the most fundamental deficiency in the 2 "perfect" studies (Barrett et al. [3] and Taylor et al. [4]), as well as the other articles they chose to include in their meta-analysis. None of these studies used a *standardized* echinacea extract. In contrast, the echinacea preparation used in our study was standardized and had already been shown to be effective in animal studies [5, 6]. We are disappointed in Caruso and Gwaltney's superficial review of our paper and the misrepresentation that resulted.

We sincerely hope that these errors will be rectified in your journal at the earliest opportunity.

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Echinacea, Vitamin C, the Common Cold, and Blinding

Sir—Caruso and Gwaltney [1] reviewed the effect of echinacea treatment on the common cold, identifying 9 placebo-controlled trials. A quality score was calculated for each trial, and the main focus was put on 2 trials that received maximum scores and reported negative results. However, the use of quality scores in literature reviews has been strongly discouraged. For example, Greenland [2] commented that quality scoring "introduces an unnecessary and somewhat arbitrary subjective element into the analysis via the scoring scheme. Quality scoring can and should be replaced by direct categorical and regression analyses of the impact of each quality item. Such item-specific analyses let the data, rather than the investigator, indicate the importance of each item in determining the estimated effect" (p. 672). Also, the Cochrane Handbook [3] states that "reviewers should avoid the use of quality scores and undue reliance on detailed quality assessments. It is not supported by empirical evidence, it can be time-consuming, and it is potentially misleading" (p. 66).

Six echinacea trials found positive results, but none of them provided proof that blinding was confirmed, which led Caruso and Gwaltney [1] to propose that the benefit in these 6 trials might be explained by the placebo effect. To support this suggestion, they referred to an old review on vitamin C and the common cold [4] by commenting that the author, Chalmers, "described a study that initially showed a positive therapeutic effect of capsules containing vitamin C on the common cold. However, blinding was not maintained, because many subjects bit through the capsules to taste the contents, which they correctly identified. When data from the unblinded subjects were discarded, 'there were no differences in the durations of colds' [p. 534]" [1, p. 810].

The Chalmers review [4] was shown to be erroneous a decade ago; it has data inconsistent with the original study publications, errors in calculations, and other problems [5, 6]. The particular trial referred to by Chalmers [4] was undertaken by Karlowski et al. [7]. It was initiated as a double-blind, placebo-controlled trial, but, after the trial, several participants correctly guessed their treatment, and this led Karlowski to carry out a subgroup analysis according to "correct" and "incorrect" guessing. In this analysis, the benefit of vitamin C was restricted to participants with "correct" guesses. Thus Karlowski concluded that "the effects demonstrated might be explained equally well by a break in the double blind" [7, p. 1038]. Because of such spectacular findings in this subgroup analysis, the Karlowski trial has often been cited as an example of the placebo effect in action. However, the subgroup analysis excluded 105 episodes of common cold (42% of all episodes of cold), even though the 2 subgroups were presented as if they were complementary [8]. There are numerous additional problems with Karlowski's placebo effect explanation, and, consequently, it is not a valid interpretation to the study results [8]. Furthermore, a recent meta-analysis of trials comparing placebo and no-treatment groups with respect to diverse medical topics found no or minimal evidence for the placebo effect, which indicates that it is not as large as commonly assumed [9].

A recent Cochrane Review [10] of placebo-controlled trials found that regular vitamin C supplementation reduced the duration of common cold infection in adults by 8% (95% CI, 3%–13%), and in children by 13.5% (95% CI, 5%–21%). Furthermore, although vitamin C showed no effect on the incidence of common cold in the general population (relative risk, 0.98; 95% CI, 0.95–1.00), it reduced

the incidence of colds in 6 trials with participants who were under heavy acute physical and/or cold stress (relative risk, 0.50; 95% CI, 0.38–0.66). Even though more studies are needed to evaluate the practical importance of vitamin C supplementation on colds, the Chalmers review [4] and the Karlowski trial [7] should not be cited as evidence that the effects of vitamin C are explained by the placebo effect. Also, the Karlowski trial should not be used as a basis to propose the placebo-effect explanation for other potential treatments for the common cold [1]. Echinacea may or may not be practically useful, but the conclusions of its usefulness should not be based on a methodologically unsatisfactory analysis, and mere speculations about placebo effect in placebo-controlled trials.

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Reply to Barton and to Hemilä

After meticulous review of the echinacea study by Goel et al. [1], of which Barton [2] was one of the authors, we [3] found that it failed to meet 4 criteria. Barton [2] contends that these 4 criteria are indeed met, and that it was our "superficial" review of their study that led to this "misinterpretation." Below are the explanations for the points made by Barton [2]. It should be noted that all of these rationales were presented in our review [3].

With respect to randomization, Barton [2] accurately notes that the method of randomization was stated in Goel et al. [1]. However, this is not the reason credit was not given. In table 2 of our review, one column reads "method of randomization specified and similarity of groups." It is imperative to prove similarity of the control and treatment groups. In figure 2 of their study [1], symptom scores begin on day 2. Oddly, there is no data from day 1, but they state that "symptoms were assessed daily" [1, p. 77]. With no baseline symptom scores, it cannot be assumed that the groups started the trial with similar scores. The slope of the trend line in figure 2 in [1] would suggest that the groups did not.

With respect to intention-to-treat analyses, Barton [2] fails to note that the definition of intention-to-treat analyses requires not only inclusion of all subjects enrolled, but also all data collected for each subject. Their study collected data on 13 cold symptoms, assessed daily, but reports results for only 7 of these symptoms, as shown in figure 3 in [1]. Scores for day 1 were also not reported (noted in table 2 of our review [3]).

Proof of blinding should ideally be completed before the study commences. When done afterward, it is only acceptable in studies with negative results. In the study by Goel et al. [1], post-study proof of blinding is unacceptable because the study reported positive results. There is no way to determine whether judgments were made on the basis of a therapeutic effect.

With respect to the validated case definition, Barton [2] incorrectly believed that the failure of Goel et al. [1] to provide a validated case definition was based on the symptom scale used. The study used a case definition that included fever. Fever is not associated with a common cold [4, 5]; thus, this is an invalid case definition.

Our article [3] was published as a structured review, not as a meta-analysis, as Barton [2] states. We acknowledge the lack of use of standardized extracts in echinacea treatment studies. This fact alone precludes a complete a meta-analysis. Although some progress has been made on the determination of the immunostimulatory agents in echinacea, research with human subjects has yet to yield a consensus on all the active ingredients in each echinacea species. For this reason, we chose not to consider standardized treatment a necessary component of these echinacea trials.

Hemilä [6] references Greenland [7] and the Cochrane Handbook [8] with regard to methodology used in meta-analyses. Our study [3] was published as a review of treatment studies of echinacea, not as a meta-analysis. We made no attempt to assign quality scores to the trials. We stated whether 11 features of valid design were present or not. As the Cochrane Handbook states, with reference to reviews, "failure to meet one or more validity criteria may indicate such a high risk of bias in some reviews that it constitutes