Echinacea for the Prevention of Upper Respiratory Tract Infections

Melchart D, Walther E, Linde K, Brandmaier R, Lersch C. Echinacea root extracts for the prevention of upper respiratory tract infections. Arch Fam Med 1998; 7:541-5

Clinical question **Do extracts of *Echinacea pupurea* or *Echinacea augustifolia* prevent the development of upper respiratory tract infections (URIs)?**

Background Echinacea, the top selling herbal product in the United States for the past 4 years, is widely used in the United States and Europe for the treatment of URIs. Few adverse effects of echinacea preparations have been reported. Despite the widespread use of echinacea products for the prevention and treatment of URIs, their efficacy is controversial. Clinical studies to support their use in the treatment of URIs are primarily published in German, use many different doses and formulations, and frequently involve multiple herbal products in combination with echinacea.[1] The authors of this trial attempted to determine if the immunomodulatory effects of echinacea would provide benefit in the prevention of URIs.

Population studied Volunteers aged 18 to 65 years (n = 289) who were "free of acute illness" were recruited from 4 military sites and one industrial plant in Munich, Germany, over 2 winter seasons. Volunteers were excluded if they had experienced acute URI or other infections in the 7 previous days; had a serious progressive disease; required steroid, antibiotic, or immunosuppressive therapy; had a history of allergy to the *Compositae* family; or were pregnant. Nearly half of each group had previously taken an echinacea product.

Study design and validity This was a randomized double-blind placebo-controlled trial of 50 drops of ethanolic root extracts (plant extract ratio 1:11 in 30% alcohol) of *E pupurea*, *E augustifolia*, or placebo (colored ethanolic solution) given twice daily for 5 days each week for 12 weeks. Patients were evaluated at baseline, 4, 8, and 12 weeks, with instructions to contact a study physician in the event of any symptoms of a URI. Study physicians evaluated patients on the basis of a standardized form and subjectively classified the severity of infection. Patients were given a symptom diary when they reported to a study physician for evaluation of URI. No other symptom or adverse event diaries were kept. Data were analyzed on an intention-to-treat basis. A major concern is that subjects did not report concurrent use of echinacea in other forms, or any use of other pharmacologic agents (allopathic and complementary) that may potentially impact URI incidence or severity. A further concern noted by the authors is the near impossibility of blinding for the echinacea extracts because of their characteristic taste.

Outcomes measured The primary outcome measure was time to first URI. Secondary outcome measures included adverse effects, "global assessment" (by the participants), and the number of volunteers with at least one URI.

Results Forty-five patients dropped out of the study (15 patients in each group) because of adverse effects, lack of efficacy, and "other reasons." There were no significant differences between the 3 groups in mean days to first URI, the percentage of patients with one or more infections, and number of participants reporting adverse effects. The relative risk of development of at least one URI was .87 (95% CI, .59-1.30) in the *E augustifolia* group and .80 (95% CI, .53-1.31) in the *E pupurea* group compared with placebo. The only significant result was that more patients in the 2 echinacea groups believed they had received benefit from their treatment ($P = .04$), possibly because of the lack of blinding of the echinacea extracts.

Recommendations for clinical practice **The specific ethanolic extracts of echinacea used in this trial, while without significant toxicity, do not appear to have a clinically or statistically significant effect on the prevention of URIs. While this study does not support the effectiveness of echinacea in the prevention of URIs, it also does not address the efficacy of echinacea in the treatment of URI symptoms. Further evaluations of echinacea should be conducted, using standardized, readily available formulations, and with sufficient numbers of patients to detect clinically and statistically significant effects of echinacea in the prevention and treatment of URIs.**

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Low-Dose Omeprazole for Erosive Esophagitis

Bardhan KD, Cherian P, Vaishnavi A, et al. Erosive esophagitis: outcome of repeated long term maintenance treatment with low dose omeprazole 10 mg or placebo. Gut 1998; 43: 458-64.

Clinical question **In patients with endoscopically diagnosed erosive esophagitis, is low-dose omepra-**

zole safe and effective in preventing recurrence of disease?

Background A meta-analysis of long-term omeprazole trials found both 10 and 20 mg per day omeprazole regimens to be superior to either standard dose ranitidine or placebo in preventing relapse of esophagitis. The 20-mg dose omeprazole daily was significantly more effective than the 10-mg per day dose.[1]

Population studied Adults who were referred to an open-access gastroenterology clinic by their general practitioners for symptoms of gastroesophageal reflux disease (GERD) were considered for enrollment. The authors argue that this open-access scheme led to a study population that was more reflective of a primary care physician's practice, which is probably true. Exclusion criteria included esophageal stricture, duodenal or gastric ulcer, pregnancy, lactation, esophagitis unresponsive to 3 months of treatment with H2 antagonists, and suspicion of upper gastrointestinal malignancy.

Study design and validity This was a randomized double-blind placebo-controlled study of omeprazole 10 mg per day for the maintenance therapy of erosive esophagitis. All patients initially underwent endoscopy to determine disease presence and severity; only those with grade 2 disease or higher (moderate to severe esophagitis) were entered. All patients were treated with omeprazole 20 mg 4 times daily for 12 weeks; those unhealed by repeat endoscopy were treated with omeprazole 40 mg 4 times daily for 12 additional weeks. The patients were then randomized to omeprazole 10 mg 4 times daily or placebo, and monitored for return of symptoms and recurrence of disease by endoscopy. Any recurrence (by symptoms or endoscopy) was re-treated with omeprazole 20 mg 4 times daily for 12 weeks, then the maintenance therapy was restarted. Any further relapse was similarly re-treated, but maintenance was begun with open-label omeprazole at 20 mg 4 times per day for all. Intention-to-treat analysis was appropriately carried out.

Outcomes measured The primary outcome measured was relapse (symptomatic or silent) during the initial maintenance phase and during the second maintenance phase, when applicable.

Results Of the 300 people who entered the study, 263 were randomized after the initial treatment phase. Relapse rates were significantly different in the 2 groups: 40% in the omeprazole group and 85% in the placebo group (number needed to treat over 18 months to prevent 1 relapse was 2.2; 95% confidence interval [CI], 2 - 3). There were no statistically significant differences observed between the rates of silent and symptomatic relapse. The relapse rates for the second maintenance phase (n=116, 28 in omeprazole group and 88 in placebo group) were 79% for omeprazole and 91% for placebo (absolute risk ratio=12%, 95% CI, -4% to 28%, therefore not significant). Success rates of treatment with omeprazole 20 mg were consistently greater than 90% regardless of retreatment status or previous maintenance therapy. For those patients who required maintenance therapy with open-label omeprazole 20 mg 4 times daily (n=118), it remained effective (9% relapse rate by 24 months). There were no adverse events attributable to omeprazole therapy or GERD.

Recommendations for clinical practice **This study confirms that low-dose omeprazole is safe and moderately effective compared with placebo in preventing relapse of erosive esophagitis in those patients endoscopically diagnosed with moderate to severe disease. In primary care practice, however, GERD symptoms are often treated empirically, and the grade (or even the presence) of esophagitis is often not known. From this study, symptom relief alone was achieved with similar numbers needed to treat as remission of esophagitis. The authors suggest that a reasonable approach to therapy would be to start with a 10-mg maintenance dose for mild to moderate esophagitis and progress to 20-mg daily maintenance if retreatment is required. This is especially appropriate when cost is an issue, since only 40% of patients requiring maintenance therapy would benefit from the higher dosage.**

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Treating Average Cholesterol Levels in Patients with Coronary Heart Disease

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349-57.

Clinical question **Does reduction of average cholesterol levels with pravastatin in patients with coronary heart disease (CHD) reduce mortality and cardiovascular events?**