

Clinical Trial Examining Effectiveness Of Three Cough Syrups

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Abstract: Background: Cough is one of the most common symptoms of respiratory infections for which patients seek relief. This study was done to assess the effectiveness of three commonly prescribed cough syrups.

Methods: In this multipractice, office-based, randomized clinical trial, guaifenesin was compared with guaifenesin plus codeine or guaifenesin plus dextromethorphan in patients with uncomplicated respiratory tract infections. Family physicians enrolled 97 patients between February 1988 and April 1990. Patients were randomly assigned to treatment and were interviewed by telephone at 2, 4, and 10 days to assess cough relief, treatment adherence, and side effects. There were no statistically significant differences among treatment groups at base line.

Results: At day 2 there were no statistically significant differences among treatment groups for any of the outcome measures. At day 4 five of the outcome measures of cough quality, frequency, sleep disturbances, and absenteeism were not statistically significantly different among groups. The only statistically significant difference was the ability to keep up with usual activities, which improved least in patients assigned to dextromethorphan than in patients in other groups. There were no statistically significant differences among the three groups at day 10 for any of the outcomes.

Conclusion: It appears that codeine, dextromethorphan, and guaifenesin are equally effective in relieving cough symptoms. (J Am Board Fam Pract 1993; 6:109-115.)

Each adult in the United States experiences two to four respiratory tract infections annually,¹ accounting for more than 10 percent of ambulatory patient encounters with primary care physicians.² Cough is one of the most common symptoms of respiratory tract infections for which patients seek relief. Although usually self-limited, cough can keep the patient awake or cause absence from work or school. In addition, cough transmits disease.

Patients often turn to physicians when home remedies fail.³ In one study,⁴ 23 percent of persons with a respiratory tract infection visited a physician for evaluation and advice on relief of symp-

toms. Having established that an infection is uncomplicated, the physician's role in management is to provide reassurance and to prescribe advice and medications to relieve symptoms; however, the medical literature provides little information to guide the physician in symptomatic treatment.

Codeine is the most widely accepted antitussive agent.⁵ Most studies of the effectiveness of codeine-containing cough remedies have reported that codeine-containing cough syrups are more effective than placebo in relieving chronic cough.^{6,7} Although codeine is an effective cough suppressant, its side effects include nausea, constipation, and sedation. Codeine is also a common cause of death by accidental overdose in young children⁸ and potentiates the toxic effects of many other drugs. For these reasons, alternatives have been sought. Among them is dextromethorphan, a nonnarcotic antitussive reported to be as effective as codeine in animal experiments and chronic cough studies in humans.⁷ In contrast to codeine, neither dextromethorphan nor guaifenesin, a commonly used over-the-counter cough preparation, has been reported to have any serious side effects.

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Our study was done to compare the effectiveness of a codeine-containing cough syrup, a dextromethorphan-containing cough syrup, and a guaifenesin-containing cough syrup in patients with uncomplicated respiratory tract infections who were seen in the offices of family physicians and for whom a decision had already been made to prescribe a cough remedy.

Methods

Seven family physicians participated in this multi-practice randomized clinical trial. Patients with uncomplicated respiratory tract infection were recruited to the trial between 1 February 1988 and 1 April 1990, with enrollment limited to the peak viral season (October through March). Preliminary sample size calculations indicated that a total of 204 patients were needed to detect a 30 percent reduction in cough symptoms between the treatment groups. Patients were considered eligible for the study if they were older than 18 years, spoke English, and did not have any contraindications to codeine. They were then assigned at random to one of three cough treatments, either guaifenesin, guaifenesin plus dextromethorphan, or guaifenesin plus codeine. Treatments were assigned at random in blocks of 30 treatments per physician, with 10 patients receiving each treatment, using the Moses and Oakford algorithm.⁹

To study those cough preparations commonly available to physicians and commonly used in practice, the cough syrups were chosen and developed in consultation with pharmacists, pharmacologists, and family physicians. The most commonly prescribed cold preparations at the University of California, San Francisco, outpatient pharmacy in January 1987 were dextromethorphan and codeine-containing preparations with a guaifenesin-base syrup (personal communication: G. McCart, PharmD, Drug Usage Report for January 1987, University of California, San Francisco, 13 July 1987). Because each preparation contained a guaifenesin base and physicians would not randomize patients to a placebo syrup or to no treatment, the control treatment consisted of a cough syrup containing 100 mg of guaifenesin per 5-mL dose.

The experimental treatments consisted of codeine and dextromethorphan. A standard dose of codeine cough syrup was used, containing 15 mg of codeine and 100 mg of guaifenesin per 5-mL

dose. The dextromethorphan-guaifenesin preparation contained 30 mg of dextromethorphan and 100 mg of guaifenesin per 5-mL dose. The strength of the dextromethorphan preparation was doubled in comparison to the over-the-counter dosage to enable testing of two prescription-level drugs. Each patient was asked to take 2 teaspoons (10 mL) of the syrup, four times a day and was advised not to exceed 12 teaspoons in any 24-hour period. In addition, each patient was given an advice sheet that provided general recommendations on cold relief, a restatement of directions for taking the cough syrup, and cautionary statements to avoid alcohol or other drugs while taking the cough syrup. This regimen was to be followed for 5 days or until the cough resolved. Neither the patient nor the physician knew which preparation was assigned. To assess the adequacy of blinding, we asked patients to guess which syrup they were taking at the end of the day 10 interview: 53 percent of the patients receiving codeine, 16 percent receiving dextromethorphan, and 28 percent receiving guaifenesin correctly guessed the medication they were taking.

Subjects completed a base-line questionnaire in which they provided information about their age, race, smoking habits, history of chronic illness, the frequency and severity of symptoms of cough, measures taken to relieve cough, and the degree to which the cough kept them from sleeping. At 2, 4, and 10 days after treatment assignment, telephone interviews were used to assess the frequency and severity of cough, the degree to which cough interfered with sleep, the subjective benefit of the cough remedy, side effects, adherence to the treatment regimen, the number of days lost from work or school, and the duration of cough symptoms. For day 2 data, patients had to be reached between the morning of day 2 and the middle of day 3. Day 4 data consisted of information gathered from the middle of day 3 to the middle of day 5, and day 10 data consisted of information gathered from the middle of day 9 until the middle of day 11.

To assess the adequacy of randomization, base-line characteristics of patients were compared for the three treatment groups. In addition, base-line characteristics were compared for those who completed follow-up interviews and those who were lost to follow-up at days 2, 4, or 10.

Statistical significance of categorical variables was assessed using the chi-square statistic for measures of association, whereas continuous variables were assessed using t-tests and one-way analysis of variance. Each of the seven categorical outcome measures was then dichotomized to indicate improvement or nonimprovement, and the percentage of improved patients, with respective 95 percent confidence interval estimates, was calculated.¹⁰ Multiple logistic and linear regression analyses were used to control for potential confounding variables while assess-

ing treatment effects for each of the outcome measures.

Results

Physicians enrolled 97 patients into the trial. Nearly equivalent percentages of patients were randomized to codeine (33 percent), dextromethorphan (31 percent), and guaifenesin (36 percent). There were no statistically significant differences among treatment groups with regard to demographic characteristics, smoking status, or severity of illness as measured by the number of

Table 1. Base-line Characteristics (Percentages) of 97 Participants in a Clinical Trial of Cough Syrups by Treatment Group.

Patient Characteristics	Codeine (n = 32)	Dextromethorphan (n = 30)	Guaifenesin (n = 35)	P Value
Women	69	70	60	0.65
Education				0.27
High school or less	43	40	34	
Some college	19	27	23	
College graduate	15	7	23	
Unknown	22	27	20	
Ethnicity				0.86
White, non-Hispanic	44	50	57	
White, Hispanic	9	7	6	
African-American	6	10	6	
Asian	9	7	11	
Other	9	3	0	
Unknown	22	23	20	
Ever smoked cigarettes	47	70	46	0.10
Now smoke cigarettes				0.33
Regular smoker	40	19	25	
Occasional smoker	13	38	19	
Quit during illness	13	10	0	
Quit previously	33	33	56	
Number of days troubled by coughing				0.70
1-4	34	40	43	
5-10	47	40	32	
> 10	16	20	26	
Unknown	3	0	0	
Bouts of coughing				0.58
None or few	25	20	14	
1-2 per hour	19	10	17	
> 1-2 hour	41	40	51	
Constantly	16	30	17	
Trouble getting to sleep	88	93	71	0.05
Awakened from sleep	84	83	80	0.89
Maintain usual activities	37	47	46	0.66
Absenteeism (days)				0.67
None	44	53	40	
1-2	31	20	31	
3-4	9	13	20	
5-7	6	7	3	
> 7	3	7	0	
Unknown	6	0	6	

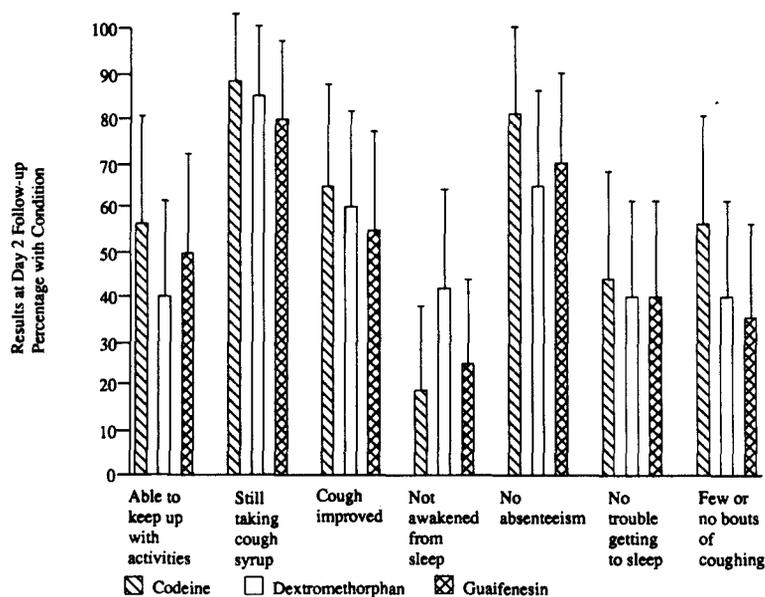


Figure 1. Percentage of patients in each treatment group showing improvement as indicated by outcome measures at day 2 (n = 57). (Bars indicate upper 95 percent confidence interval.)

days troubled by coughing, frequency of bouts of coughing, frequency of being awakened from sleep, ability to maintain usual activities, or absenteeism from work or school (Table 1). A marginally ($P = 0.05$) significant difference was found among treatment groups in the frequency of patients who reported having trouble getting to sleep at base line.

usual activities ($P = 0.62$ and 0.50 for days 2 and 10, respectively), awakened from sleep ($P = 0.97$, 0.69 , and 0.93 for days 2, 4 and 10), had trouble getting to sleep ($P = 0.56$, 0.88 , and 0.87), was absent from work or school ($P = 0.29$, 0.94 , and 0.69), had frequent bouts of coughing ($P = 0.42$, 0.25 , and 0.62), or thought their cough had improved ($P = 0.84$, 0.29 , and 0.20). More than 84 percent of patients in each treatment group were continuing to take their cough syrup at day 2 compared with 54 percent at day 4 and 19 percent at day 10. The average number of total doses reported taken at each interview is displayed in Table 2.

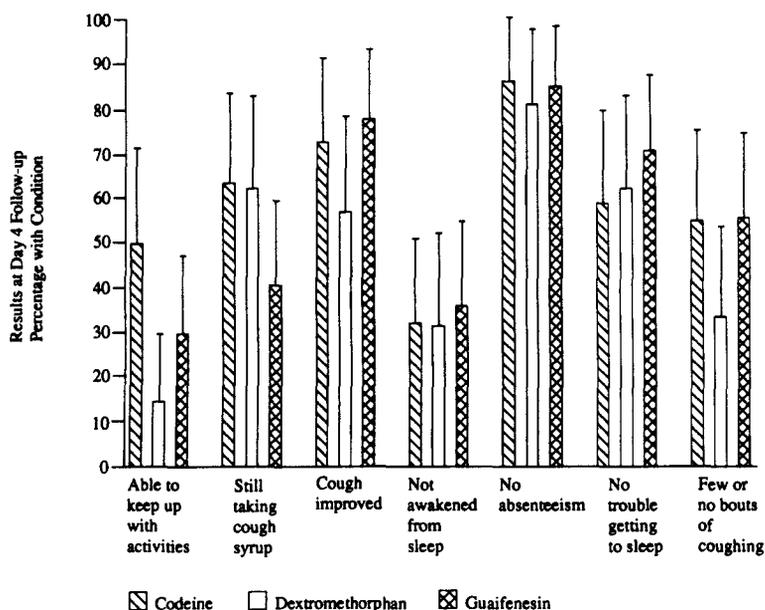


Figure 2. Percentage of patients in each treatment group showing improvement as indicated by outcome measures at day 4 (n = 70). (Bars indicate upper 95 percent confidence interval.)

At day 2 follow-up, only 57 (59 percent) patients could be contacted within the required 30-hour period compared with 70 (72 percent) patients at day 4 and 67 (69 percent) patients at day 10. Figures 1, 2, and 3 show the percentage of patients in each treatment group reporting improvement as indicated by dichotomized outcome measures at days 2, 4, and 10, respectively.

The overlapping confidence interval estimates for the dichotomized outcome measures in all three figures, as well as chi-square analyses of multicategorical versions of the same measures, indicated that there were no statistically significant differences between treatment groups according to whether the patient was able to keep up with usual activities ($P = 0.62$ and 0.50 for days 2 and 10, respectively), awakened from sleep ($P = 0.97$, 0.69 , and 0.93 for days 2, 4 and 10), had trouble getting to sleep ($P = 0.56$, 0.88 , and 0.87), was absent from work or school ($P = 0.29$, 0.94 , and 0.69), had frequent bouts of coughing ($P = 0.42$, 0.25 , and 0.62), or thought their cough had improved ($P = 0.84$, 0.29 , and 0.20). More than 84 percent of patients in each treatment group were continuing to take their cough syrup at day 2 compared with 54 percent at day 4 and 19 percent at day 10. The average number of total doses reported taken at each interview is displayed in Table 2.

The only statistically significant difference among treatment groups was the patient's ability to keep up with usual activities at day 4; 50 percent of patients in the codeine group were able to keep up with usual activities compared with 14 percent of patients in the dextromethorphan group and 30 percent of patients in the guaifenesin group ($P = 0.04$). Because potential differences in smoking and antibiotic use between treatment groups could have confounded the results, logistic regression was used to compare treat-

ments for this outcome, controlling for antibiotic use, other medication use, amount of syrup taken, and whether the person ever smoked. The adjusted odds ratio for not being able to keep up with usual activities for patients taking codeine compared with patients taking dextromethorphan was 12.1 at day 4 (95 percent confidence interval 1.8, 80.5) and 9.8 at day 10 (95 percent confidence interval 1.0, 99.7).

Analyses comparing those who were lost to follow-up at 2, 4, or 10 days with patients for whom information was available for the same day indicated that there were no statistically significant differences between the two groups with regard to treatment, physician, patient sex, whether the patient ever smoked cigarettes or currently smoked cigarettes, the number of days troubled by coughing, cough frequency, whether the patient had trouble getting to sleep, was awakened from sleep, was able to maintain usual activities, or missed work or school. The only statistically significant differences were that patients unavailable for the day 2 follow-up were less likely to have indicated their educational attainment ($P = 0.02$) or ethnicity ($P = 0.01$), and patients unavailable for the day 4 follow-up were younger ($P = 0.02$).

The frequency of side effects was examined for each group. More than 40 percent of patients in all three treatment groups experienced more drowsiness after receiving the cough syrup than before. At day 4, a larger percentage of patients (41 percent) taking the codeine cough syrup experienced nausea compared with those taking dextromethorphan (33 percent) or guaifenesin (15 percent) ($P = 0.12$). As a large percentage of patients in all three groups were also taking antibiotics at day 4 (62 percent, 50 percent, and 63 percent for codeine, dextromethorphan, and guaifenesin, respectively), and antibiotic use is known to be associated with nausea and diarrhea, antibiotic use was controlled for in the analysis of side effects by treatment group. After stratifying by antibiotic use, 37 per-

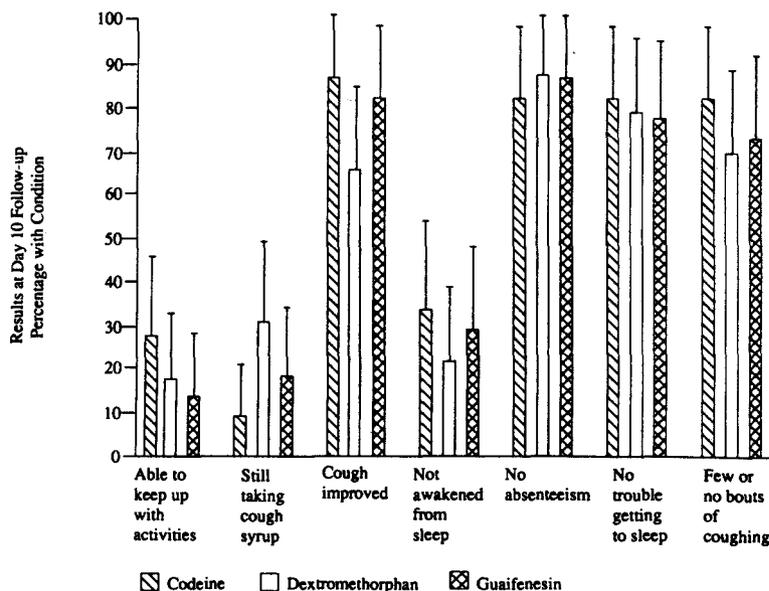


Figure 3. Percentage of patients in each treatment group showing improvement as indicated by outcome measures at day 10 (n = 67). (Bars indicate upper 95 percent confidence interval.)

cent of nonantibiotic users taking the codeine cough syrup continued to experience nausea at day 4 compared with 50 percent of dextromethorphan users and 20 percent of guaifenesin users ($P = 0.39$). Thus, there was no statistically significant difference in side effects for the three treatments, although the number of patients who contributed to this comparison was small.

Discussion

In this study codeine, dextromethorphan, and guaifenesin were equally effective in relieving cough symptoms and had similar side-effect profiles. No other studies comparing the efficacy or effectiveness of codeine and dextromethorphan in patients with acute cough could be found from an extensive review of the medical literature. It is only possible, therefore, to compare the results of this study with those of similar studies conducted on patients with chronic or induced

Table 2. Average Number (and Standard Deviation) of Doses Taken by Treatment Group at Days 2, 4 and 10.

Day	Codeine	Dextromethorphan	Guaifenesin	P Value
2	7.4 (±3.9)	6.6 (±2.7)	8.5 (±4.0)	0.25
4	10.4 (±5.4)	11.8 (±6.0)	12.0 (±6.5)	0.62
10	16.3 (±7.7)	15.2 (±8.9)	15.7 (±9.7)	0.92

cough. One such study¹¹ compared the effectiveness of codeine with dextromethorphan for relief of cough symptoms among 16 patients with chronic, stable cough. Dextromethorphan and codeine were equally effective in decreasing cough frequency, and compared with a placebo, both showed significant improvement. By subjective measures, the majority of patients considered dextromethorphan the better antitussive. In a study by Empey, et al.,⁶ codeine and dextromethorphan were equally effective antitussives when studied in persons with experimentally induced cough.

Although limited to uncomplicated upper respiratory tract infections, a large percentage (59 percent) of patients in this study were taking antibiotics, the most common being erythromycin. This finding is in accordance with a study recently conducted by Slawson, et al.¹² in which 50 percent of patients with clinical signs and symptoms of pharyngitis were prescribed antibiotics regardless of the patient's culture status.

Although the time for enrollment was extended, and diligent efforts were made to encourage patient enrollment, participating physicians were unable to enroll the 204 study subjects we had initially hoped to enroll. A single provider who was particularly devoted to the project and who had a large pool of eligible patients recruited 73 percent of the study population. While this study is somewhat limited by the relatively low number of subjects, power calculations based on the final sample size indicated that the study had a 73 percent chance to detect a 30 percent improvement in cough symptoms. In addition, it is of equal size^{13,14} or larger¹⁵ than studies conducted on the effectiveness of other cough preparations in chronic, acute, or induced cough.

If additional studies with larger study populations confirm the equivalent effectiveness of these three treatments for cough and uncomplicated upper respiratory tract infection, the need for prescribing codeine could be diminished. The number and risks of adverse effects or overdose from codeine cough preparations could be substantially reduced if codeine were less frequently prescribed.

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References

1. Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults. Incidence, etiology, and impact. *Am J Med* 1985; 78(Suppl 6B): 32-7.
2. Dixon RE. Economic costs of respiratory tract infections in the United States. *Am J Med* 1985; 78(Suppl 6B):45-51.
3. Simon HB. Management of the common cold. In: Goroll AH, May LA, Mulley AG Jr, editors. *Primary care medicine*. Philadelphia: JB Lippincott, 1981: 232-3.
4. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974; 227:164-9.
5. Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief. Geneva: World Health Organization, 1970.
6. Empey DW, Laitinen LA, Young GA, Bye CE, Hughes DT. Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscapine 30 mg using citric acid-induced cough in normal subjects. *Eur J Clin Pharmacol* 1979; 16:393-7.
7. Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief, 4. Potential alternates for cough relief. *Bull World Health Organ* 1969; 40:639-719.
8. von Muhlendahl KH, Scherf-Rahne B, Krienke EG, Baukloh G. Codeine intoxication in childhood. *Lancet* 1976; 2:303-5.
9. Meinert CL. *Clinical trials. Design, conduct and analysis*. New York: Oxford University Press, 1986: 97-100.
10. Swinscow TD. *Statistics at square one*. 4th edition. London: British Medical Association, 1978:28.
11. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; 11:92-100.
12. Slawson DC, Baer LJ, Richardson MD. Antibiotic use in the treatment of nonstreptococcal pharyngitis. *Fam Med* 1991; 23:198-201.
13. Tukiainen H, Karttunen P, Silvasti M, Flygare U, Korhonen R, Korhonen T. The treatment of acute transient cough: a placebo-controlled comparison of dextromethorphan and dextromethorphan-beta2-sympathomimetic combination. *Eur J Respir Dis* 1986; 69:95-9.

14. Chakrabarti A, Pandhi P, Jindal SK, Malik SK, Sharma PL. A comparative randomized double-blind clinical trial of hexapneumine and clistine as antitussive agents. *Int J Clin Pharmacol Ther Toxicol* 1987; 25:310-2.

15. Karttunen P, Tukiainen H, Silvasti M, Kolonen S. Antitussive effect of dextromethorphan and dextromethorphan-salbutamol combination in healthy volunteers with artificially induced cough. *Respiration* 1987; 52:49-53.

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