

Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults

Knut Schroeder, Tom Fahey



The full version of this article appears on bmj.com

Abstract

Objectives To determine whether over the counter cough medicines are effective for acute cough in adults.

Design Systematic review of randomised controlled trials.

Data sources Search of the Cochrane Acute Respiratory Infections Group specialised register, Cochrane Controlled Trials Register, Medline, Embase, and the UK Department of Health National Research Register in all languages.

Included studies All randomised controlled trials that compared oral over the counter cough preparations with placebo in adults with acute cough due to upper respiratory tract infection in ambulatory settings and that had cough symptoms as an outcome.

Results 15 trials involving 2166 participants met all the inclusion criteria. Antihistamines seemed to be no better than placebo. There was conflicting evidence on the effectiveness of antitussives, expectorants, antihistamine-decongestant combinations, and other drug combinations compared with placebo.

Conclusion Over the counter cough medicines for acute cough cannot be recommended because there is no good evidence for their effectiveness. Even when trials had significant results, the effect sizes were small and of doubtful clinical relevance. Because of the small number of trials in each category, the results have to be interpreted cautiously.

Introduction

General practitioners and other health professionals are encouraged to recommend over the counter cough medicines as a first line treatment for acute cough,¹ but evidence regarding their effectiveness is inconclusive. The NHS direct healthcare guide also recommends simple cough medicines for dry cough.²

Acute cough is a common symptom and cough medicines are used by many patients. In the United Kingdom retail sales of over the counter cough medicines rose by 3.0% to £94m between 1998 and 1999.^{3,4} We conducted this systematic review to determine whether these medicines are effective for acute cough due to upper respiratory tract infections in adults. This review is based on a Cochrane systematic review of over the counter treatments in adults and children.⁵

Methods

Searching

We searched the Cochrane Acute Respiratory Infections Group specialised register (database of studies of acute respiratory infections based on regular database searches, personal contributions from Cochrane review group members, and hand searching of journals), the Cochrane Controlled Trials Register (issue 2, 2000, which includes randomised controlled trials published in Medline and Embase up to 1998), Medline (January 1998 to December 1999), Embase (January 1998 to December 1999), the UK Department of Health National Research Register (December 2000), personal collections of references, and reference lists of all retrieved articles for original randomised controlled trials. We wrote to study authors, the Proprietary Association of Great Britain, and pharmaceutical companies for information on unpublished studies. Details of the search strategy are available on bmj.com.

Study selection and validity assessment

We selected studies for review if (a) the participants were adults (aged 16 years or older) with acute cough (less than three weeks' duration) due to upper respiratory tract infection (presumed to be viral in origin with no auscultatory chest signs or signs on chest radiography) in an ambulatory setting; (b) the interventions were over the counter cough preparations; (c) a reported outcome was cough (frequency or duration assessed with any assessment tool); and (d) studies were randomised controlled trials with a contemporaneous control group receiving placebo or no intervention. We excluded studies if participants had chronic cough (more than three weeks' duration or due to a chronic underlying disease such as asthma, tuberculosis, or bronchial malignancy); cough was artificially induced in healthy volunteers; or they used non-conventional (herbal or homoeopathic) or non-oral preparations. A study had to meet all our inclusion criteria to be included. Drugs were divided into six categories according to their mode of action (table).

Results

After evaluating 328 citations and abstracts from all sources, we included 15 trials involving 2166 participants.⁹⁻²³ The main characteristics of the included randomised controlled trials are available on bmj.com. The number of studies for each type of drug

Division of Primary Health Care, University of Bristol, Bristol BS6 6JL

Knut Schroeder
MRC training fellow in health services research

Tom Fahey
senior lecturer in general practice

Correspondence to: K Schroeder
k.schroeder@bristol.ac.uk

BMJ 2002;324:329-31

Method of action and examples of different types of over the counter cough medicines

Group	Mechanism of action	Examples of proposed active ingredients	Examples of relevant preparations
Antitussives	Centrally acting opioid derivatives or peripherally acting agents ⁵	Codeine, moguisteine Dextromethorphan	Famel original cough syrup Benylin dry coughs, Robitussin dry cough
Expectorants	Increased bronchial mucus production, making secretions easier to remove through cough or ciliary transport ⁶	Guaifenesin, ipecacuana	Adult Meltus expectorant, Beechams VENO's expectorant, Benylin chesty coughs (non-drowsy), Benylin children's chesty coughs, Hill's balsam chesty cough liquid, Vicks vaposyrup for chesty coughs
Mucolytics	Decrease the viscosity of bronchial secretions, making them easier to clear through coughing ⁷	Bromhexine hydrochloride	Bisolvon linctus
Antihistamine-decongestant combinations	Combine histamine H ₁ receptor antagonists and α adrenoceptor agonists, which cause vasoconstriction of mucosal blood vessels ⁸	Pseudoephedrine plus guaifenesin	Sudafed expectorant, Robitussin chesty cough with congestion
Other drug combinations	Fixed drug combinations using different ingredients	Dextromethorphan, ephedrine, doxylamine, paracetamol EM-Vier (containing extract of thyme, eucalyptus oil, and menthol)	Vicks Medinite Minetten
Antihistamines	Histamine H ₁ receptor antagonists	Loratadine	Claritin allergy syrup

was small, ranging from one to five. Outcomes included frequency and severity of cough and were measured in many different ways—for example, self report, physician assessment, cough sound pressure levels, and tape recordings. Ten studies reported data on adverse effects.

The methodological quality of included studies in terms of randomisation, blinding, and reports of losses to follow up was variable and generally not high. The randomisation process was adequate in three trials. Only two studies reported blinding of outcome assessors. It was unclear for three trials whether participants or treatment providers were blinded. Loss to follow up was well documented in 12 studies, with differential loss to follow up in both treatment arms reported in four studies. One trial reported a power calculation, and only one study fulfilled all the quality criteria. Many trials were too small to detect clinically important differences.

Quantitative data synthesis

We could not pool the results because there was clear clinical heterogeneity between trials in terms of participants, interventions, and outcome measurements. Furthermore, the number of trials in each category was small and the amount of quantitative data available limited.

Antitussives

Five trials tested antitussives versus placebo. Two studies tested codeine and found it no more effective than placebo. One of two studies of dextromethorphan favoured active treatment over placebo (differences in mean changes of cough counts 19% to 36% in three substudies, $P < 0.05$), whereas the other found no significant effect. Moguisteine (one trial) led to mean differences in cough scores of about 0.5 in groups with severe cough on days 2 and 3 ($P < 0.05$), but there were no differences between groups at final follow up. Only two trials reported adverse effects.^{10–13} Nausea, vomiting, and abdominal pain were more common in participants treated with moguisteine than placebo (22% *v* 8%),¹⁰ and in one trial participants did not report any adverse effects from dextromethorphan.¹³

Expectorants

Participants in one study found guaifenesin more helpful than placebo (75% *v* 31%, $P < 0.01$).¹⁴ However, a second trial found no significant differences between the groups.¹⁵ Guaifenesin led to a low incidence of

nausea and urticaria in the active treatment group in one trial¹⁴; the other did not report on adverse effects.¹⁵

Mucolytics

In the only study of mucolytics, frequent cough was less prevalent in the Bisolvon linctus group than the placebo group (8.6% *v* 15.2%, $P < 0.02$).¹⁶ This study did not report on adverse effects.

Antihistamine-decongestant combinations

One of the two trials of antihistamine-decongestant combinations showed a lower mean severity cough score in the active treatment group on days 3–5 (1.4 in active group *v* 2.0 in placebo group, $P < 0.05$).¹⁷ The other trial found no significant differences between the two treatments.¹⁸ Antihistamine-decongestant combinations seemed to have a slightly higher incidence of adverse effects than placebo. These included dry mouth, dizziness, headache, and insomnia.

Other drug combinations

We included three studies of medicines containing fixed drug combinations.^{19–21} These studies were very heterogeneous and used different drug preparations, limiting their comparability. In a study of EM-Vier, more participants in the treatment group improved within the first three days than in the placebo group (26/58 *v* 15/55, $P = 0.05$).¹⁹ In a crossover trial of Vicks Medinite syrup, 58% of participants rated active treatment good or better in relieving cough symptoms compared with 32% for placebo.²⁰ Dextromethorphan plus salbutamol was better than placebo or dextromethorphan alone in relieving cough at night but there were no significant differences for cough symptoms during the day.²¹ Adverse effects for all preparations were rare and usually mild.

Antihistamines

Based on two trials, terfenadine was no more effective than placebo in relieving cough symptoms.^{22–23} The incidence of adverse effects, which included excess fatigue and headache, was low with no significant differences between the groups.

Discussion

We found only a small number of randomised controlled trials investigating each category of cough medicine, so evidence on effectiveness is limited. In nine out of 15 trials, active treatment was no better

What is already known on this topic

The NHS encourages self treatment of acute self limiting illnesses

Over the counter cough medicines are commonly used as first line treatment for acute cough

What this study adds

There is little evidence for or against the effectiveness of over the counter cough medicines

Although cough medicines are generally well tolerated, they may be an unnecessary expense

Recommendation of over the counter cough medicines to patients is not justified by current evidence

than placebo. The positive results in the other six studies were of questionable clinical relevance. Most over the counter cough preparations were generally well tolerated and did not lead to serious adverse effects.

Study limitations and potential sources of bias

The included studies varied with respect to settings, populations, interventions (drugs, doses, and frequency), and outcome measures, which makes comparison difficult. Our results should therefore be interpreted with caution. Potential sources of bias such as randomisation procedure, blinding of outcome assessment, and losses to follow up were inadequately reported in several studies, suggesting poor methodological quality. The effect sizes of active treatment over placebo were often reported as differences between cough scores, which are difficult to interpret in a clinically meaningful way. Several studies were supported by the pharmaceutical industry, and others did not report their sources of funding or conflicts of interest.

We tried to obtain information on unpublished studies from study authors and pharmaceutical companies but obtained a limited response. If studies with negative results were less likely to be submitted for publication, this could have led to publication bias.

Implications

It remains unclear whether over the counter cough preparations are helpful in acute cough. We therefore cannot yet recommend these medicines as first line treatment for cough associated with upper respiratory tract infection. The advice given by NHS direct to use over the counter cough medicines should therefore be restricted until more evidence becomes available on their effectiveness. Future studies should use outcome measures that can be easily assessed in a primary care setting and that produce clinically meaningful results, such as patient satisfaction, disturbance at night, side effects, or time to return to normal daily activities.

We thank Steve McDonald and Ron D'Souza for their support in designing the search strategy and performing additional searches. We also thank Debbie Sharp and Massimo Pignatelli for help with the French and Italian translations and Bruce

Arroll, Keith Dear, Warren McIsaac, and Amy Zelmer for their earlier comments on the review.

Contributors: See bmj.com

Funding: Division of Primary Health Care, University of Bristol and the South and West Research and Development Directorate. KS is funded through an MRC training fellowship in health services research. TF is funded through the NHS primary care career scientist fund.

Competing interests: None declared.

- Moss C. Putting self-care into your consultation. In: *OTC Directory 2001/2002*. London: Proprietary Association of Great Britain, 2001.
- Banks I. *The NHS Direct healthcare guide*. London: Stationery Office, 2001.
- Royal College of General Practitioners, Office of Population Censuses and Surveys, and Department of Health. *Morbidity statistics from general practice. Fourth national study 1991-1992*. London: HMSO, 1992.
- Proprietary Association of Great Britain. *Annual review and report*. London: PAGB, 2000.
- Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2001;(3):CD001831.
- Ziment I. What to expect from expectorants. *JAMA* 1976;236:193-4.
- Reynolds JEF. Cough suppressants, expectorants and mucolytics. In: *Martindale's: the extra pharmacopoeia*. London: Pharmaceutical Press, 1993: 741-53.
- Morice A, Abdul-Manap R. Drug treatments for coughs and colds. *Prescriber* 1998;9:74-9.
- Eccles R, Morris S, Jawad MS. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *J Clin Pharm Ther* 1992;17:175-80.
- Adams R, Hosie J, James I, Khong T, Kohn H, Smith I, et al. Antitussive activity and tolerability of moguisteine in patients with acute cough: a randomized, double-blind, placebo-controlled study. *Adv Ther* 1993;10:263-71.
- Parvez L, Vaidya M, Sakhardande A, Subburaj S, Rajagopalan TG. Evaluation of antitussive agents in man. *Pulm Pharmacol* 1996;9:299-308.
- Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *J Pharm Pharmacol* 1997;49: 1045-9.
- Lee PC, Jawad MS, Eccles R. Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory tract infection. *J Pharmacol Pharmacol* 2000;52:1137-42.
- Robinson RE, Cummings WB, Deffenbaugh ER. Effectiveness of guaifenesin as an expectorant: a cooperative double-blind study. *Curr Ther Res Clin Exp* 1977;22:284-96.
- Kuhn JJ, Hendley JO, Adams KF, Clark JW, Gwaltney JM Jr. Antitussive effect of guaifenesin in young adults with natural colds. *Chest* 1982;82:713-8.
- Nesswetha W. Kriterien der Arzneimittelprüfung in der werksaerztlichen Praxis, dargestellt am Beispiel eines Hustenloesers. *Arzneimittelforschung* 1967;17:1324-6.
- Curley EJ, Irwin RS, Pratter MR, Stivers DH, Doern GV, Vernaglia PA, et al. Cough and the common cold. *Am Rev Respir Dis* 1988;138:305-11.
- Berkowitz RB, Connell JT, Dietz AJ, Greenstein SM, Tinkelman DG. The effectiveness of the non-sedating antihistamine loratadine plus pseudoephedrine in the symptomatic management of the common cold. *Ann Allergy* 1989;63:336-9.
- Kurth W. Gesicherte therapeutische Wirksamkeit des traditionellen Antitussivums Minetten im Doppelblindversuch. *Med Welt* 1978;29:1906-9.
- Thackray P. A double-blind, crossover controlled evaluation of a syrup for the night-time relief of the symptoms of the common cold, containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulphate. *J Int Med Res* 1978;6:161-5.
- 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-beta 2-sympathomimetic combination. *Eur J Resp Dis* 1986;69:95-9.
- Gaffey MJ, Kaiser DL, Hayden FG. Ineffectiveness of oral terfenadine in natural colds: evidence against histamine as a mediator of common cold symptoms. *Pediatr Infect Dis J* 1988;7:223-8.
- Berkowitz RB, Tinkelman DG. Evaluation of oral terfenadine for treatment of the common cold. *Ann Allergy* 1991;67:593-7.

(Accepted 5 November 2001)

Endpiece

A hideous demon

Three shapes a doctor wears. At first we hail
The angel; then the god, if he prevail.
Last, when, the cure complete, he asks his fee,
A hideous demon he appears to be.

Doctor and Patient (translated by
W F H King in *Classical Foreign Quotations*)

Submitted by Fred Charatan,
retired geriatric physician, Florida