

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

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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. In 1991-2, there were over 4000 consultations per 10 000 patient years in general practice for acute respiratory infections.³ Cough medicines are widely available to the public without medical prescription in most countries, and retail sales rose by 3.0% to £94m between 1998 and 1999 in the United Kingdom.⁴ However, many studies of cough preparations have involved patients from different populations and included participants with chronic cough due to underlying dis-

ease or were carried out on healthy volunteers in whom cough had been induced artificially through chemical irritants.⁵⁻⁸ Previous systematic reviews have either focused on children or were limited to trials retrieved from Medline.⁹⁻¹¹ We conducted this systematic review to determine whether over the counter cough 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.¹²

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 (box). We wrote to study authors, the Proprietary Association of Great Britain, and pharmaceutical companies for information on unpublished studies. We considered studies in all languages regardless of publication status.

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 arti-

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Search strategy

cough
 cough*:ME
 (#1 or #2)
 antitussive-agents*:ME
 expectorants*:ME
 cholinergic-antagonists*:ME
 drug-combinations*:ME
 prescriptions-non-drug*:ME
 #4 or #5 or #6 or #7 or #8 or #9
 #3 and #10
 cough
 (common next cold)
 colds
 #12 or #13 or #14
 antitussiv*
 expectorant*
 antihistamin*
 anticholinergic*
 suppressant*
 mucolytic*
 (drug next combinations)
 over-the-counter
 non-prescription*
 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
 #15 and #24
 #11 or #25
 *for searching the Cochrane Controlled Trials Register.
 Slightly amended versions were used for searching Medline
 and Embase

ficially induced in healthy volunteers; or they used non-conventional (herbal or homoeopathic) or non-oral preparations.

Both authors assessed relevant citations independently and applied the selection criteria with the help of an in/out/pending sheet, which was filled out in duplicate. We resolved differences in opinion at any stage of the review by discussion. A study had to meet all our inclusion criteria to be included. We also extracted data and assessed the quality of studies independently. If necessary, we contacted study authors for additional information and data. For studies written in languages other than English or German we obtained translations of abstracts or papers. We did not mask studies with regard to trial authors or journals. We listed data on potential sources of bias such as randomisation, blinding, and follow up in a table (table 1) instead of applying a quality score. Drugs were divided into six categories according to their mode of action (table 2).

Results

After evaluating 328 citations and abstracts from all sources, we included 15 trials involving 2166 participants (figure).¹⁶⁻³⁰

Table 3 shows the main characteristics of the included randomised controlled trials. The number of studies for each type of drug 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 (table

1). Four of the 15 studies reported the randomisation process, which 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

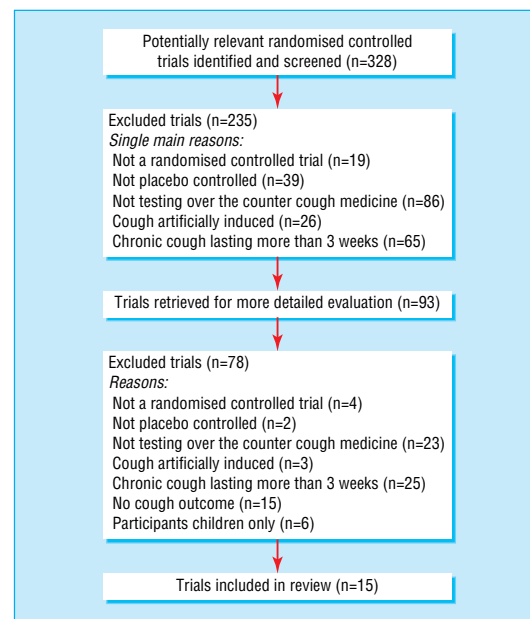
We could not pool the results because there was clear clinical heterogeneity between trials in terms of participants, interventions, and outcome measurements. Furthermore, the number of trials in each category was small and the amount of quantitative data available limited.

Antitussives

Five trials tested antitussives versus placebo (table 3). 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. Mogueistine (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.¹⁷⁻²⁰ Nausea, vomiting, and abdominal pain were more common in participants treated with mogueistine than placebo (22% v 8%),¹⁷ and in one trial participants did not report any adverse effects from dextromethorphan.²⁰

Expectorants

Participants in one study found guaifenesin more helpful than placebo (75% v 31%, $P < 0.01$).²¹ However, a second trial found no significant differences between the groups (table 3).²² Guaifenesin led to a low



Evaluation of trials for inclusion in review

Table 1 Quality assessment of included trials and potential sources of bias

Study	Randomisation process used	Blinding to treatment allocation			No (%) of dropouts/losses to follow up				Power calculation reported	Hypothesis stated before data collection	Comments
		Patient	Provider	Outcome assessor	Total	Intervention group	Control group	Reasons given			
Antitussives											
Eccles 1992	NR	Yes	Yes	NR	10/91 (11)	NR	NR	No	No	No	Two separate phases of study (laboratory and home)
Adams 1993	NR	Yes	Yes	NR	11/108 (10)	NR	NR	Yes	No	No	Newly developed peripherally acting antitussive, trial supported by pharmaceutical company
Parvez 1996	Minimisation using computer program	Yes	Yes	NR	NR	NR	NR	NR	No	No	Many multiple comparisons with no corrections and high probability of type I error. Dropouts unlikely because of short length of follow up
Freestone 1997	NR	Yes	Yes	NR	NR	NR	NR	NR	No	No	Potential sources of bias poorly reported
Lee 2000	NR	Yes	Yes	NR	1/44 (2)	NR	NR	Yes	No	Yes	
Expectorants											
Robinson 1977	NR	Yes	Yes	Yes	27/239 (11)	14/121 (12)	13/118 (11)	No	No	Yes	
Kuhn 1982	NR	Yes	Yes	NR	None	None	None	NR	No	Yes	Aspirin and paracetamol were allowed after inclusion in the study. Vehicle contained 95% alcohol
Mucolytics											
Nesswetha 1967	No	Yes	Yes	NR	7/99 (7)	NR	NR	No	No	Yes	Potential sources of bias poorly reported
Antihistamine-decongestant combinations											
Curley 1988	Computer generated	Yes	Yes	NR	13/86 (15)	6/44 (14)	7/42 (17)	Yes	No	No	Patients "randomised in a double-blind fashion"; dropouts due to inconvenience of study and none due to side effects
Berkowitz 1989	Computer generated	Yes	Yes	Yes	22/283 (8)	9/142 (6)	13/141 (9)	Yes	No	No	Many multiple comparisons made
Other combinations											
Kurth 1978	NR	Yes	NR	NR	6/113 (5)	NR	NR	NR	No	Yes	High likelihood of bias
Thackray 1978	"Random number code"	Yes	Yes	NR	0	NR	NR	NR	No	Yes	Investigator was medical director of the company supplying the drug for study. Crossover after 1 day, no washout period
Tukiainen 1986	NR	Yes	Yes	NR	0	NR	NR	NR	No	Yes	Losses to follow up not reported
Antihistamines											
Gaffey 1988	NR	NR	NR	NR	16/250 (6)	7/126 (6)	9/124 (7)	NR	No	No	Subjects were "compensated" for participation, blinding presumed but not clearly stated, subjects received "sequential admission numbers and were randomly assigned" active treatment or placebo. Non-compliers were considered dropouts. Other drugs taken: aspirin/non-steroidal anti-inflammatory in 7 patients, paracetamol 7 patients
Berkowitz 1991	NR	NR	NR	NR	4/100 (4)	NR	NR	Yes	Yes	Yes	Patients "randomly assigned," blinding presumed but not clearly stated

NR=not reported or unclear.

incidence of nausea and urticaria in the active treatment group in one trial²¹; the other did not report on adverse effects.²²

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%, $P < 0.02$).²³ 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, $P < 0.05$).²⁴ The other trial found no significant differences between the two treatments (table 3).²⁵ 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 (table 3).²⁶⁻²⁸ 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, $P = 0.05$).²⁶ 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.²⁷ Dextromethorphan plus salbutamol was better than placebo or dextromethorphan alone in relieving cough at night but there were no significant differences for cough

Table 2 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 ¹³	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 ¹⁴	Bromhexine hydrochloride	Bisolvon linctus
Antihistamine-decongestant combinations	Combine histamine H ₁ receptor antagonists and α adrenoceptor agonists, which cause vasoconstriction of mucosal blood vessels ¹⁵	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 thyme extract, eucalyptus oil, and menthol)	Vicks Medinite Minetten
Antihistamines	Histamine H ₁ receptor antagonists	Loratadine	Claritin allergy syrup

symptoms during the day.²⁸ 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 (table 3).^{29, 30} 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 than placebo. The positive results in the other six stud-

ies 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 clini-

Table 3 Characteristics of randomised controlled trials of over the counter cough preparations versus placebo for acute cough

Study	Participants, setting, country	Definition of illness	Intervention				Method of measuring main cough outcomes	Results	
			Drug	Dose (mg)	Frequency	Treatment duration		Efficacy	Adverse effects
Antitussives									
Eccles 1992	81 adults, mean age 23 years (18 to 71), 52% men; hospital research clinic, UK	Cough associated with URTI	Codeine	30	Four times daily	4 days	Cough severity score (5 point scale) from diaries expressed as area under curve for 8 measures over 5 days	Mean cough scores 18.8 (placebo) v 17.2 (codeine), P=0.23	No data provided
Adams 1993	108 adults, mean age 48 years, 70% women, 60% smokers; UK primary care (6 centres)	Acute dry or slightly productive cough	Moguisteine	20	Three times daily	3.5 days	Patient reported cough scale from 0 to 9	Mean score difference of about 0.5 between groups on days 2 and 3 in patients with severe cough, P<0.05, but no difference at final follow up	Mainly nausea, vomiting and abdominal pain; 22% (active) and 8% (placebo)
Parvez 1996	451 adults in 3 different studies, mean age 30 years, 65% men, mainly non-smokers; corporate healthcare centre, India (combined report of 3 studies)	URTI	Dextromethorphan	30	Single dose	—	Cough acoustic signals captured via microphone, visual analogue scales over 180 min	Differences in mean changes between cough counts varied from 19% to 36% (P<0.05) in 3 studies (up to a net difference of 8-10 coughing bouts every 30 min)	No data provided
Freestone 1997	82 university students and staff, mean age 24 years (18 to 46), 62% men; common cold centre at university department, UK	Cough associated with URTI	Codeine	50	Single dose	—	5 point subjective rating scale, cough sound pressure levels, cough frequency	Mean score reductions from 2.0 to 1.0 in both treatment groups (P=0.8); no significant differences for cough sound pressure levels and cough frequency	No data provided
Lee 2000	44 adults aged 18 to 60 years (mean age 23 years), 70% women; university staff and students and general city population, UK	URTI	Dextromethorphan	30	Single dose	3 hours	Cough frequency recordings, cough sound pressure levels, questionnaire on cough severity (scale 0-3)	Decline in cough frequency of 31 (active) v 21.5 (placebo), P=0.38; mean decline in cough score 1 (active) v 0.5 (placebo), P=0.08	None reported from participants

(Continued on next page)

Table 3 (Continued from previous page)

Study	Participants, setting, country	Definition of illness	Intervention				Method of measuring main cough outcomes	Results	
			Drug	Dose (mg)	Frequency	Treatment duration		Efficacy	Adverse effects
Expectorants									
Robinson 1977	239 adults, mean age 38 years, smokers and non-smokers evenly distributed; office or clinic outpatients, US	URTI	Guaifenesin	20	Four times daily	3 days	Patient questionnaires, cough scores from 0 to 3	79/105 (75%) found medicine helpful compared with 33/106 (31%) in the placebo group, P<0.01	Nausea, hives (2 in active group); headache and drowsiness (2 in placebo group)
Kuhn 1982	65 adults (mostly university students), age range 18 to 30 years; university research centre, US	Acute respiratory illness with cough for <48 h	Guaifenesin	480	Every 6 hours	30 hours	Tape recordings of cough frequency, questionnaire on 6 symptoms	Cough frequency: 33/33 (100%) improved in active group v 30/32 (94%) in placebo group, P=0.5. Cough severity: 33/33 (100%) improved in active treatment group v 29/32 (91%) in placebo group, P=0.2	No data provided
Mucolytics									
Nesswetha 1967	99 factory workers in chemical industry, age range 15 to 44 years; Germany	URTI	Bisolvon linctus (bromhexine hydrochloride)	4	Three times daily	Average of 4 days	Not clearly described; used 4 point scale	Frequent cough (every 2-5 min) in 4/46 (9%) in active group v 7/46 (15%) in placebo group (P<0.02)	No data provided
Antihistamine-decongestant combinations									
Curley 1988	73 adults, mean age 31 years, 60% women, 19% active smokers; presumably outpatients, US	Common cold for <72 h	Dexbrompheniramine Pseudoephedrine	6 120	Twice daily	1 week	Patient diary, cough score from 0 to 4	Mean severity cough score 1.4 (active) v 2.0 (placebo) on days 3-5 (P<0.05)	Severity of dizziness and dry mouth significantly increased in active group (P<0.01), but no figures reported
Berkowitz 1989	283 adults, mean age 30 years, mainly white, 52% women; 3 centres in US	Common cold	Loratadine Pseudoephedrine	5 120	Twice daily	5 days	Patient diaries, cough score from 0 to 3	No significant difference in cough score reduction (0.8 in active group v 0.6 in placebo group, P>0.05)	Dry mouth, headache, and insomnia more common in active group (42/142, 30%) than placebo group (29/141, 21%)
Other combinations									
Kurth 1978	113 adults, 57% men, age range <30 to >70 years; primary care, Germany	Cough due to URTI	EM-Vier (Minetten): Extract of thyme Succus Liquiritiae depurat Menthol Ephedrine Eucalyptus oil Menthae piperitae oil	5 2 3.5 2 2 0.7	Six times daily	14 days	Unclear	26/58 (45%) in active treatment group improved within first 3 days v 15/55 (27%) in placebo group (P=0.05)	No adverse effects in both groups
Thackray 1978	70 adults, mean age 34 years (range 18 to 60), 61% women; 21 general practices, UK	Common cold	Vicks Medinite syrup: Dextromethorphan Ephedrine Doxylamine Paracetamol	15 8 7.5 600	Single dose at bedtime	2 days	Questionnaire, 6 point rating scale	Crossover design: 34/59 (58%) subjects rated active treatment as good or better compared with 19/59 (32%) for placebo treatment (P<0.01)	Giddiness or drowsiness reported in 7 (active) and 4 (placebo) participants
Tukiainen 1986	108 outpatients, mean age about 38 years, 55% women, 48% smokers, Finland	Cough associated with URTI	Dextromethorphan (D) Dextromethorphan + salbutamol (D+S)	30 30 + 2	Three times daily	4 days	Patient diary and symptom score from 0 to 3	No significant differences between mean treatment scores for daytime cough on day 4 1.26 (D+S), 1.28 (D), and 1.15 (placebo); no exact P value given. Dextromethorphan/salbutamol more effective in suppressing cough at night than dextromethorphan alone (0.45 v 0.92, P<0.01)	Dextromethorphan/salbutamol led to more tremor than placebo (P<0.05), but no figures were given. No serious adverse effects reported
Antihistamines									
Gaffey 1988	250 adults, mean age 23 years, 65% women; internal medicine clinic, US	Common cold	Terfenadine	60	Twice daily	3.5 days	Patient diary and symptom score from 0 to 3	Syptom scores for cough "virtually the same in the terfenadine and placebo recipient," but no exact scores reported	Low incidence of adverse effects; most common were sedation or excess fatigue (12% of active group and 10% of placebo group)
Berkowitz 1991	100 adults, mean age 32, 56% women, non-smokers; single centre (setting not stated), US	Common cold	Terfenadine	120	Twice daily	4 to 5 days	Patient diary and symptom score from 0 to 3	No significant difference in cough scores between active treatment (0.81, SE 0.13) and placebo (0.65, SE 0.12), Pp=0.35	Low incidence of headache (6% in active group and 4% in placebo group)

URTI=upper respiratory tract infection.
SE=standard error.

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

cally 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 NHS encourages self treatment for acute self limiting illnesses, and the use of over the counter cough preparations as a home remedy.² Although these medicines are generally well tolerated, their purchase could lead to unnecessary expense for the healthcare consumer. The advice 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.

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