Over-the-counter medications for acute cough in children and adults in ambulatory settings.

AUTHOR(S)

Susan Smith, Knut Schroeder, Tom Fahey

Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings (Review)

Smith SM, Schroeder K, Fahey T

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 1

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 2
OBJECTIVES 3
METHODS 3
RESULTS 5
DISCUSSION 9
AUTHORS' CONCLUSIONS 10
ACKNOWLEDGEMENTS 10
REFERENCES 11
CHARACTERISTICS OF STUDIES 13
DATA AND ANALYSES 31
APPENDICES 31
WHAT'S NEW 31
HISTORY 31
CONTRIBUTIONS OF AUTHORS 32
DECLARATIONS OF INTEREST 32
SOURCES OF SUPPORT 32
NOTES 32
INDEX TERMS 33

[Intervention Review]

Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings

Susan M Smith[1], Knut Schroeder[2], Tom Fahey[3]

[1]Department of Public Health and Primary Care, Trinity College Centre for Health Sciences, Dublin, Ireland. [2]Academic Unit of Primary Health Care, Department of Community Based Medicine, Cotham Hill, UK. [3]Department of Family Medicine and General Practice, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland

Contact address: Susan M Smith, Department of Public Health and Primary Care, Trinity College Centre for Health Sciences, AMNCH, Tallaght, Dublin, 24, Ireland. susmith@tcd.ie.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2010.
Review content assessed as up-to-date: 7 April 2010.

Citation: Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD001831. DOI: 10.1002/14651858.CD001831.pub3.

ABSTRACT

Background

Acute cough due to upper respiratory tract infection (URTI) is a common symptom. Non-prescription over-the-counter (OTC) medicines are frequently recommended as a first-line treatment, but there is little evidence as to whether these drugs are effective.

Objectives

To assess the effects of oral OTC cough preparations for acute cough.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), MEDLINE (January 1966 to March, week 2, 2010), EMBASE (January 1974 to March 2010) and the UK Department of Health National Research Register (March 2010).

Selection criteria

Randomised controlled trials (RCTs) comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in ambulatory settings. We considered all cough outcomes and secondary outcomes of interest were adverse effects.

Data collection and analysis

Two review authors independently screened potentially relevant citations, extracted data and assessed study quality. We performed quantitative analysis where appropriate.

Main results

Twenty-six trials (18 in adults, eight in children) involving 4037 people (3421 adults and 616 children) were included.

In the adult studies six trials compared antitussives with placebo and had variable results. Two trials compared the expectorant guaifenesin with placebo; one indicated significant benefit whereas the other did not. One trial found that a mucolytic reduced cough frequency and

symptom scores. Two studies examined antihistamine-decongestant combinations and found conflicting results. Four studies compared other combinations of drugs with placebo and indicated some benefit in reducing cough symptoms. Three trials found antihistamines were no more effective than placebo in relieving cough symptoms.

In the children studies antitussives (two studies), antihistamines (two studies), antihistamine decongestants (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. No studies using expectorants met our inclusion criteria. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group.

Authors' conclusions

There is no good evidence for or against the effectiveness of OTC medicines in acute cough. The results of this review have to be interpreted with caution due to differences in study characteristics and quality. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self-care treatments for acute cough.

PLAIN LANGUAGE SUMMARY

Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings

Acute cough is a common and troublesome symptom in people who suffer from acute upper respiratory tract infection (URTI). Many people self-prescribe over-the-counter (OTC) cough preparations and health practitioners often recommend their use for the initial treatment of cough. The results of this review suggest that there is no good evidence for or against the effectiveness of OTC medications in acute cough. The results of this review have to be interpreted with caution because the number of studies in each category of cough preparations was small. Many studies were of low quality and very different from each other, making evaluation of overall efficacy difficult.

BACKGROUND

Description of the condition

Acute cough due to upper respiratory tract infection (URTI) is one of the most common symptoms worldwide. A large number of people self-prescribe non-prescription over-the-counter (OTC) cough medicines for themselves or their children, and many health professionals in primary care settings recommend them to their patients as a first-line treatment (PAGB 2000). OTC medicines are available to the public from pharmacies, chemists and shops without medical or dental prescription in most countries, as opposed to prescription only medicines (POM). A national telephone survey of medication use in the US indicated that in a given week, 10% of children are given an OTC cough preparation by their carers (Vernacchio 2008). Numerous OTC cough preparations are available but evidence regarding their efficacy is inconclusive. Some studies of cough preparations have been shown to reduce cough symptoms, whereas others found no effect compared with placebo (Banderali 1995; Freestone 1997; Kurth 1978; Smith 1993).

Description of the intervention

Many studies have involved patients from different populations that have included participants with chronic cough due to underlying disease such as asthma or chronic obstructive pulmonary disease or were carried out on healthy volunteers in whom cough had been induced by chemical irritants (Gastpar 1984; Irwin 1993; Smith 1993). Other randomised controlled trials (RCTs) compared active agents and did not include a placebo. Cough preparations may contain different drugs with a variety of modes of action which can make them difficult to compare (Morice 1998).

How the intervention might work

Non-prescription oral OTC medicines for cough have different modes of action based on their active ingredients as follows.

1. Antitussives, for example centrally acting opioid derivatives (Irwin 1993) or other peripherally active agents, act by reducing the cough reflex.
2. Expectorants, i.e. drugs leading to increased bronchial mucous production, make secretions easier to remove by cough

or ciliary transport (Ziment 1976).

3. Mucolytics, i.e. drugs aiming to decrease the viscosity of bronchial secretions, act to make secretions easier to clear through coughing (Reynolds 1993).

4. Antihistamine-decongestant combinations, i.e. drugs that are combined antihistamine H1-receptor antagonists and alpha-adrenoceptor agonists, act by causing vasoconstriction of mucosal blood vessels thus reducing congestion (Morice 1998).

5. Other drug combinations, i.e. fixed drug combinations using different ingredients, have mechanisms of action based on individual ingredients.

6. Antihistamines, i.e. antihistamine H1-receptor agonists, act by reducing histamine release and thus reducing local congestion and production of secretions.

Why it is important to do this review

Recent systematic reviews of OTC cough and cold preparations revealed that there is insufficient evidence for or against an effect of OTC cough preparations compared to placebo (Anonymous 1999; Smith 1993). However, these reviews did either not use a systematic search for RCTs (Anonymous 1999) or performed searches that were limited to the MEDLINE database (Smith 1993). By using a more extensive search strategy, this systematic review aims to answer the question of whether OTC medications used for the treatment of acute cough associated with URTI are effective.

OBJECTIVES

The main objective of this review was to assess the effects of oral OTC preparations for acute cough (less than three weeks' duration) in children and adults in ambulatory settings. Because many different groups of OTC medicines are available, we aimed to make comparisons only within groups of preparations with a similar mode of action or other similar features.

METHODS

Criteria for considering studies for this review

Types of studies

All placebo-controlled RCTs of oral OTC cough preparations for acute cough.

Types of participants

1. Ambulatory settings in primary care and hospital outpatients.

2. Children and adults with acute onset of cough (less than three weeks' duration).

Studies testing OTC medicines for chronic cough (more than three weeks' duration), cough due to underlying respiratory disease (such as asthma, chronic obstructive pulmonary disease, pneumonia, tuberculosis, lung malignancy) were excluded. We also excluded studies where cough was induced artificially (through inhalation of chemicals) in healthy volunteers.

Types of interventions

Non-prescription oral OTC medicines for cough are classified according to their mode of action as outlined above and we have grouped them as follows.

1. Antitussives, for example, centrally acting opioid derivatives.

2. Expectorants, i.e. drugs leading to increased bronchial mucous production (Ziment 1976).

3. Mucolytics, i.e. drugs aiming to decrease the viscosity of bronchial secretions (Reynolds 1993).

4. Antihistamine-decongestant combinations, i.e. drugs that are combined antihistamine H1-receptor antagonists and alpha-adrenoceptor agonists which cause vasoconstriction of mucosal blood vessels (Morice 1998).

5. Other drug combinations, i.e. fixed drug combinations using different ingredients.

6. Antihistamines, i.e. antihistamine H1-receptor agonists.

We excluded studies that used non-oral preparations (for example, nasal sprays, inhalers, nebulised solutions) or that tested ingredients other than those accepted in Western (allopathic) medicine (for example, herbal or homeopathic medicines) because we felt that this review would have become too broad.

Types of outcome measures

Primary outcomes

All cough outcomes (such as frequency, severity, amount of sputum, improvement in cough symptoms using continuous and categorical data and different ways of measurement including cough sound pressure levels, cough counts, patient questionnaires, physician assessment, etc). We did not consider global patient or physician ratings of wellness or recovery as outcomes, unless these were directly related to cough symptoms.

Secondary outcomes

Significant adverse effects.

Search methods for identification of studies

Electronic searches

This review was first published in 2001. We searched the Cochrane Controlled Trials Register (*The Cochrane Library*, 2000, issue 2), MEDLINE (January 1998 to December 1999), EMBASE (January 1998 to December 1999) and the UK Department of Health National Research Register (December 2000).

For the 2004 review update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2004, issue 2), MEDLINE (January 1966 to June Week 3, 2004), EMBASE (January 1990 to March 2004) and the UK Department of Health National Research Register (December 2003).

For the 2007 review update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, issue 4), MEDLINE (January 1966 to January Week 1, 2007), EMBASE (January 1990 to January 2007) and the UK Department of Health National Research Register (June 2007, http://www.update-software.com/National/nrr-frame.html).

For this 2010 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), MEDLINE (January 1966 to March, week 2, 2010), EMBASE (January 1974 to March 2010) and the UK Department of Health National Research Register (March 2010).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision maximising version (2008 revision) Ovid format (Lefebrve 2008). The search string was modified slightly to search EMBASE (see Appendix 1).

MEDLINE (OVID)

1 exp COUGH/
2 cough$.mp.
3 or/1-2
4 exp Antitussive Agents/
5 exp expectorants/
6 exp Cholinergic antagonists/
7 exp Histamine H1 Antagonists/
8 exp Drug Combinations/
9 exp Drugs, Non-Prescription/
10 exp Self medication/
11 (antituss$ or expectorant$ or anticholinerg$ or antihistamin$ or (cough adj suppress$) or mucolytic$ or (drug adj combination$) or over-the-counter or OTC or non prescription).mp.
12 or/4-11
13 3 AND 12

Searching other resources

We searched personal collections of references and reference lists of articles and wrote to authors of original studies, pharmaceutical companies and the Proprietary Association of Great Britain about information on unpublished studies. There were no constraints based on language or publication status.

Data collection and analysis

Selection of studies

Two review authors (SS, TF) independently screened potentially relevant citations and applied the selection criteria using an in/out/pending sheet. Any differences at any stage of the review were resolved by discussion.

Data extraction and management

Two review authors (SS, TF) independently extracted data and assessed the quality of studies. We contacted investigators for additional information if necessary and obtained translations of abstracts or papers if they were written in languages other than English or German.

Assessment of risk of bias in included studies

For the 2010 update of this review we adapted our original quality assessment using the new 'Risk of bias' tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the methodological quality of included studies. These assessments were carried out independently by two review authors (SS, TF). The elements considered are now described within the Characteristics of included studies table. They included the following

1. Adequate sequence generation?
2. Allocation concealment?
3. Blinding?
4. Incomplete outcome data addressed?
5. Free of selective reporting?
6. Free of other bias?

Measures of treatment effect

Because of the small numbers of trials in each category, the limited quantitative data available and the marked differences between trials in terms of participants, interventions and outcome measurement we felt that pooling of the results was inappropriate and no meta-analysis was undertaken. The effect of individual treatments is summarised as outlined in the original studies using mean differences in scores for continuous data or simple comparison of proportions for dichotomous data.

Unit of analysis issues

All included studies were RCTs with randomisation occurring at the level of individual participants so there was no indication to consider unit of analysis errors in this review.

Dealing with missing data

Due to the limited quantitative data available for this review, simple descriptions of individual study outcomes were presented within the pre-specified grouping of different treatment groups. Issues relating to missing data and follow up are presented in the Risk of bias sections in the Characteristics of included studies table.

Assessment of heterogeneity

The studies included in this review were clinically heterogeneous and provided limited data so no meta-analysis was undertaken.

Assessment of reporting biases

There is no reason to suspect that publication bias affected the outcomes of this review. We conducted a comprehensive search of the literature with no language or publication restrictions. For the original review information was also sought from experts in the area including pharmaceutical companies and the Proprietary Association of Great Britain and Ireland. As no meta-analysis was performed we did not generate funnel plots.

Data synthesis

No meta-analysis was undertaken for this review.

Subgroup analysis and investigation of heterogeneity

Effects of treatment are presented within relevant treatment groups for both children and adults to allow comparison of related medications.

Sensitivity analysis

No meta-analysis was undertaken and limitations of the review are addressed within the Discussion section.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our initial search in 2001 identified 328 potentially relevant RCTs which we screened for retrieval of paper copies. At that stage we excluded 235 abstracts for the following main single reasons: study not an RCT (n = 19 trials); study not placebo controlled (n = 39); study not testing an OTC cough medicine (n = 86); cough artificially induced (n = 26); or participants with chronic cough lasting more than three weeks (n = 65). Paper copies of 93 RCTs were retrieved for more detailed evaluation. We excluded a further 72 trials because studies were not RCTs (n = 4); were not placebo controlled (n = 2); were not testing OTC cough medicines (n = 23); induced cough artificially (n = 3); included participants with chronic cough (n = 25); or did not report any cough outcomes (n = 15).

The search conducted for the update in 2004 identified three additional RCTs, with two of these being different arms of a three-arm RCT (Korppi 1991a; Korppi 1991b; Pavesi 2001).

The search conducted for the update in 2007 identified one additional RCT (Paul 2004) and the search conducted for this 2010 update identified one additional RCT (Mizoguchi 2007).

Included studies

In this 2010 update we included 26 RCTs involving 4037 participants. Eighteen of these trials were in adults (n = 3421) and eight in children (n = 616). The Characteristics of included studies table contains data on the number of participants randomised to the interventions, age, sex, smoking status, study setting, definition of illness, drug dosage, frequency and duration of treatment, and outcome information. Most adult trials were on young adults with mean ages ranging from 23 to 48 years. Ages in studies on children ranged from six months to 18 years. Six trials were more than 20 years old. Half the studies (12 out of 26) were carried out in the USA, with the remaining trials located in the UK (five), Finland (three), Germany (two), Italy (one), India (one), South Africa (one) and Thailand (one). The ages of participants ranged from six months to over 70 years. Most studies were different in their definition of illness, the content of the drug preparation, drug dosage, the frequency of doses and the treatment duration (ranging from a single dose to 18 days), making comparison of trials and quantitative analysis difficult.

Excluded studies

The commonest reasons for excluding studies were that cough was artificially induced or lasted longer than three weeks or cough outcomes were not clearly reported. See Characteristics of excluded studies table.

Risk of bias in included studies

Allocation

Most studies did not report sufficient details on randomisation and allocation schedules to make meaningful conclusions about the potential for selection bias. Only four of the 26 trial reports stated the randomisation process which was adequate in three trials.
Loss to follow up was well documented in 17 studies with differential loss to follow up in the treatment arms reported in five studies, with the potential for attrition bias difficult to assess for the remaining studies. Only one of the studies fulfilled all the quality criteria. Only six trials reported a power calculation.

Blinding

In seven studies the outcome assessors were blinded to treatment allocation and six studies did not report whether participants and/or treatment providers were blinded with a potential for detection and performance bias.

Incomplete outcome data

Because a number of studies dated back many years, it was often impossible to obtain additional trial data. Because the reporting of potential causes of bias was poor in many trials, we did not formally examine the trial efficacy versus the trial quality and therefore only summarised the available data in the 'Risk of bias' section of the Characteristics of included studies. These contain summary data on randomisation processes used, blinding to treatment allocation, drop-outs/losses to follow up and any additional comments.

Other potential sources of bias

Eleven of the 26 included studies (Adams 1993; Berkowitz 1991; Gaffey 1988; Mizoguchi 2007; Parvez 1996; Pavesi 2001; Reece 1966; Robinson 1977; Sakchainanont 1990; Thackray 1978; Tukiainen 1986) were fully or partly supported by pharmaceutical companies which provided grants, supplied the drugs in question or gave assistance with the study. Eight out of the 11 studies supported by the pharmaceutical industry showed positive results compared to three out of 15 trials where no support was reported.

Effects of interventions

We grouped the trials according to drug class into antitussives, expectorants, mucolytics, antihistamine-decongestant combinations, other combinations and antihistamines. The number of studies in each group ranged from one to a maximum of six. Cough outcomes included frequency, severity and night-time symptoms and were measured in many different ways, for example, participant self-report by symptom scores (interviews, questionnaires, diaries), physician assessment, observation by parents, cough sound pressure levels obtained by recordings via a microphone and tape recordings. Seventeen studies out of 26 reported data on adverse effects and five studies reported data on compliance with medication. Eleven out of the 26 trials reported quantitative data for the cough that could potentially have been used for meta-analysis. Because of the small numbers of trials in each category, the limited quantitative data available and the marked differences between trials in terms of participants, interventions and outcome measurement we felt that pooling of the results was inappropriate.

1. Antitussives

1.1 Studies in adults

We included six trials involving 1526 participants that compared antitussives with placebo.
Codeine was tested in two trials and appeared no more effective than placebo in reducing cough symptoms (Eccles 1992; Freestone 1997). One of these studies (n = 81) tested codeine in a two-phase study (laboratory and home) at a dose of 30 mg four times daily for four days (Eccles 1992) and codeine was no more effective than placebo either as a single dose or in a total daily dose of 120 mg, reported on a five-point cough severity score ($P > 0.2$). The second study (n = 82) of codeine only tested the effect of a single 50 mg dose (Freestone 1997) and cough was assessed via microphone using cough sound pressure levels 90 minutes after drug administration, cough frequency counts and subjective scores. The mean subjective score on a five-point rating scale was reduced from 2.0 to 1.0 90 minutes after treatment ($P = 0.8$) in both treatment groups. Both studies did not provide any data on side effects.
Dextromethorphan was tested in three of the included studies (Lee 2000; Parvez 1996; Pavesi 2001). One report on a series of three successive studies on a total of 451 adults (Parvez 1996) favoured dextromethorphan 30 mg given in a single dose to placebo in terms of cough counts (measured through cough acoustic signals using a microphone on the nose) and subjective visual analogue scales. Differences in mean changes of cough counts between active treatment and placebo varied from 19% to 36% ($P < 0.05$) in the three studies (up to a net difference of eight to 10 coughing bouts every 30 minutes). This study did not report on side effects.
A recent study of dextromethorphan tested a single 30 mg dose versus placebo (Lee 2000). Both treatment groups showed a decline in cough frequency (from 50 to 19 per 10-minute period in the active treatment arm compared with 42 to 20.5 in the placebo arm, $P = 0.38$ at 180 minutes follow up). Mean subjective cough scores showed a decline from 2.0 to 1.0 in the active treatment group compared to a decline from 2.0 to 1.5 in the placebo group ($P = 0.08$).
Pavesi and colleagues also tested a single 30 mg dose of dextromethorphan versus placebo (Pavesi 2001). Outcomes were measured through a three-hour continuous cough recording, measuring cough bouts, cough components, cough effort, cough intensity and cough latency. Average treatment difference was 12%

to 17% in favour of dextromethorphan for cough bouts (P = 0.004), cough components (P = 0.003) and cough effort (P = 0.001) with an increase in cough latency (P = 0.002).

One trial on 108 adults (Adams 1993) comparing moguisteine at a total daily dose of 600 mg for three and a half days with placebo showed no difference apart from cough reduction in individuals with more severe night cough (mean score difference of about 0.5 on a scale from 0 to 9, P < 0.05 using Bonferroni correction for multiple comparisons). There were more side effects in the treatment group (22%) compared to placebo (8%) which mainly included nausea, vomiting and abdominal pain. There were four withdrawals in the treatment group due to adverse effects.

1.2 Studies in children

One study involving 57 children with night cough compared a single dose for three nights of dextromethorphan and codeine with placebo (Taylor 1993). Mean cough and composite scores decreased in each of the three treatment groups on each day of the study. Neither dextromethorphan (cough score reduction of 2.1, P = 0.41) nor codeine (cough score reduction of 2.2, P = 0.70) was more effective than placebo (cough score reduction of 2.2) on day three.

Another study involving 50 children compared dextromethorphan 1.5 mg per ml 5 ml three times a day for children under seven years and 10 ml three times daily for older children (Korppi 1991a) with placebo. There were no differences between the groups in terms of parent-recorded symptom scores or adverse effects, which were generally mild.

A third study involving 100 children compared a single nocturnal dose of dextromethorphan (dose based on child's age: age two to five, 7.5 mg; age six to 11, 15 mg; age 12 to 18, 30 mg with either a single dose of an antihistamine or with placebo) (Paul 2004). Dextromethorphan was no more effective than diphenhydramine or placebo in reducing cough frequency or impact on child or parental sleep.

2. Expectorants

2.1 Studies in adults

Two trials with a total of 304 participants compared guaifenesin with placebo (Kuhn 1982; Robinson 1977). In the larger study (n = 239), 75% of participants taking guaifenesin stated that the medicine was helpful in terms of reducing cough frequency and intensity compared to 31% in the control group (P < 0.01) at 72 hours (Robinson 1977). Four participants (two in each group) reported side effects including nausea and hives in the active treatment group and headaches, drowsiness and excessive perspiration in the placebo group.

The second study (n = 65) evaluated an antitussive rather than expectorant effect of guaifenesin, which is usually classified as an expectorant (Kuhn 1982). Individuals in both groups reported improvement with respect to cough frequency (100% in the active group versus 94% for placebo, P = 0.5) and cough severity (100% in the active treatment group versus 91% in the placebo group, P = 0.2) at 36 hours. Guaifenesin reduced sputum thickness significantly in 96% of participants compared to 54% in the placebo group (P = 0.001). This study allowed aspirin and paracetamol for participants after inclusion in the study, and the vehicle contained 95% alcohol. Adverse effects were not reported on.

2.2 Studies in children

We did not include any studies that tested expectorants in children, partly because none of the outcomes under study were reported on.

3. Mucolytics

3.1. Studies in adults

One trial involving 99 participants compared bromhexine 5 mg three times daily for an average of four days with placebo (Nesswetha 1967). Frequent cough (every two to five minutes) was more prevalent in the placebo group (15.2%) compared to active treatment (8.6%, P < 0.02) leading to a risk ratio reduction of about 50% for frequent cough. This study did not report on any adverse effects.

3.2 Studies in children

One trial involving 40 children compared the mucolytic letosteine (preparation not available in the UK and other parts of the world) at a dose of 25 mg three times daily for 10 days with placebo (Nespoli 1989). The symptom score on a four-point scale favoured active treatment from day four until day 10 with an average difference of about 0.2 points (P < 0.01). No adverse effects were reported in either group.

4. Antihistamine-decongestant combinations

4.1 Studies in adults

Two trials on adults with a total of 356 participants compared antihistamine-decongestant combinations with placebo (Berkowitz 1989; Curley 1988). One trial comparing loratadine/pseudoephedrine (5 mg/120 mg twice daily for four days) with placebo (n = 283) did not show statistically significant differences in cough scores reported in patient diaries between both groups (Berkowitz 1989). Thirty percent of participants in the active treatment group reported adverse effects including dry mouth, headache and insomnia compared to 21% in the control group.

The second trial (n = 73) compared dexbrompheniramine/pseudoephedrine (6 mg/120 mg twice daily for one week) with placebo. The mean severity rank of cough on a scale from zero to four obtained through a patient diary was less in the active treatment group (1.4) than in the placebo group (2.0) on days three to five (P < 0.05) (Curley 1988). There was an increased severity of dizziness and dry mouth in the active drug group on days 5 to 7, and 2 to 10, respectively (exact figures not reported, P = or < 0.01).

4.2 Studies in children

Two studies involving 155 children compared antihistamine-decongestant combinations with placebo (Clemens 1997; Hutton 1991). Brompheniramine/phenylpropanolamine (2 mg/12.5 mg, half the dose for children from six months to one year, on a four-hourly 'as needed' basis for 48 hours) was no more effective than placebo in reducing the number of children coughing two hours after each dose (49.0% versus 43.1%, P = 0.66). A higher proportion of children was reported asleep in the active treatment group (46.6%) than in the placebo group (26.5%, P = 0.53), and no other adverse effects were reported (Clemens 1997).

In the second study (n = 96), a combination of brompheniramine/phenylephrine/propanolamine (see Characteristics of included studies table for full dosage details) led to a not statistically significant improvement in cough in 67% of children (reported by their parents) compared to 58% in the placebo group and 70% in the group receiving no treatment (Hutton 1991). Side effects were rare and included one child with loose stools in the placebo group and one child reported hyperactive in the active drug group. A second child in the drug group was reported sleepier than usual.

5. Other drug combinations

For the constituent ingredients of the drug combination formulations included in the review please refer to the Characteristics of included studies table.

5.1 Studies in adults

Four studies involving 836 people compared other combinations with placebo (Kurth 1978; Thackray 1978; Tukiainen 1986). These studies were very heterogeneous and used very different drug preparations and dose frequency, limiting their comparability.

In one trial (n = 113) EM-VIER (Minetten) given six times daily was more effective in reducing coughing fits (25% versus 11%, P < 0.01) and the urge to cough (27% versus 14%, P < 0.01) compared to placebo in the first seven days (Kurth 1978). There were no adverse effects in either group.

In a trial of Vicks Medinite syrup (n = 70) at a single dose at bedtime for two days, 57.6% of participants in the active treatment group rated the formulation as "good" or better in relieving cough compared to 32.2% in the placebo group (P < 0.01) (Thackray 1978). Seven subjects in the active treatment group reported giddiness/drowsiness compared to four subjects in the placebo group.

Another study (n = 108) compared a dextromethorphan/salbutamol combination and dextromethorphan alone with placebo (Tukiainen 1986). There was spontaneous improvement of cough in all groups, and there were no statistically significant differences in cough scores between active treatments and placebo for both cough frequency and severity during the day. Dextromethorphan/salbutamol was superior to placebo or dextromethorphan alone in relieving cough at night (mean symptom score 0.19 versus 0.67 and 0.44, respectively on day four, P < 0.01). The dextromethorphan/salbutamol combination led to more tremor than placebo (no figures given, P < 0.05), and no serious adverse effects were reported.

A further study (n = 545), identified for the 2009 update of this review, compared a single nocturnal dose of a compound containing four agents each with potential to deal with the different symptoms of the common cold, i.e. paracetamol plus dextromethorphan plus doxylamine plus ephedrine (Mizoguchi 2007). We only report the cough-related outcomes. The outcomes in this study were measured over the following two days and included proportions who reported improvements in cough three hours after taking the treatment and mean cough scores on day 1 and day 2. There was a significant improvement in mean cough score the morning after treatment and the following day (mean cough score 2.5 versus 2.08 on day 2, P < 0.0001). There were also improvements in the proportion reporting improvement in cough three hours after taking the medication (intervention 57% and control 43%). There were 19 adverse events in the study in 14 patients with no difference between treatment and control. However, there was one serious adverse event described as a severe episode of somnolence in the active treatment group.

5.2 Studies in children

One trial involving 43 children tested two paediatric cough syrups (Triaminicol syrup and Dorcol paediatric cough syrup) (Reece 1966). Compared to placebo, 69% of children in both active treatment groups showed a satisfactory response reported by their parents compared to 57% of children in the placebo group which did not reach statistical significance (P = 0.5). Adverse effects were not reported.

One RCT in 51 children compared a combination of dextromethorphan 1.5 mg per ml and salbutamol 0.2 mg per ml 5 ml three times daily for children under the age of seven or 10 ml three times a day for older children (Korppi 1991b) with placebo. There were no differences between the groups in terms of parent-recorded symptom scores or adverse effects, which were generally mild.

6. Antihistamines

6.1 Studies in adults

Three trials involving 1900 adult participants compared antihistamines with placebo (Berkowitz 1991; Gaffey 1988; MRC 1950). Antihistamines were no more effective than placebo in relieving cough symptoms. Terfenadine was tested in two studies. In one of these studies (n = 100), terfenadine at a dose of 120 mg twice daily for four to five days led to a mean cough score (measured by physicians' evaluation on a scale from zero to three with higher scores meaning more coughing) of 0.8 in the active treatment group compared to 0.65 in the placebo group, a difference which was not statistically significant (P = 0.35) (Berkowitz 1991). Possible adverse effects were rare in both groups, with headache being the most common complaint (6.1% of participants in the active treatment group compared to 4% in the placebo group).

The second study (n = 250) tested terfenadine at a dose of 60 mg twice daily for three and a half days (Gaffey 1988). There were no statistically significant differences in self-reported symptoms scores for cough (exact figures not reported) between groups. Side effects were uncommon in both treatment groups, with the most common complaint being excess fatigue in 12% of subjects receiving terfenadine compared to 10% in the placebo group.

Thonzylamine at a dose of 50 mg three times a day for three days led to an improvement or cure of cough in 61.8% of subjects in the active treatment group compared to 59.8% in the placebo group which was not statistically significant (P = 0.5) (MRC 1950). Adverse effects were reported by 20.9% of individuals in the active treatment group compared to 19.2% in the placebo group, with the most common complaints being drowsiness, giddiness and headache.

6.2 Studies in children

Two trials involving 243 children compared antihistamines with placebo. One compared the antihistamines clemastine (0.05 mg/kg/day) and chlorpheniramine (0.35 mg/kg/day) for three days with placebo (Sakchainanont 1990). There was spontaneous improvement in all groups. In both active treatment groups, cough scores observed by physicians and participants improved in 39.6% of individuals compared with 27.6% in the placebo group which did not reach statistical significance (P = 0.2). Drowsiness and sleepiness were reported in 20% of children with no difference between the groups. The second trial included an arm in which children received diphenhydramine in a single nocturnal dose and were compared with children receiving placebo (Paul 2004). Diphenhydramine was no more effective than dextromethorphan or placebo in reducing cough frequency or impact on child or parental sleep.

DISCUSSION

Most studies failed to provide quantitative data on cough as our main outcome of interest, which made it very difficult to assess whether positive study results were clinically relevant. Quantitative data that could be combined showed wide confidence intervals, although there was no evidence of statistical heterogeneity. Many included studies failed to report adverse effects adequately and patient compliance with the treatment was not discussed in the vast majority of study reports. Three studies carried out multiple comparisons, thereby increasing the probability of a type I error (Berkowitz 1989; Parvez 1996; Pavesi 2001). A number of studies were supported by pharmaceutical companies, whereas the others failed to report their sources of funding or any conflict of interest.

Summary of main results

We found no good evidence for or against the effectiveness of OTC medications in acute cough which confirms the findings of two previous reviews (Anonymous 1999; Smith 1993). The number of trials in each group of drugs was small, there was poor overall quality of the studies, and studies showed conflicting evidence. In total, 11 of the 26 included trials showed a positive result, whereas 15 did not show active treatment to be superior to placebo. Eight out of the 11 studies that were supported by the pharmaceutical industry showed positive results compared to three positive studies out of the 15 trials that did not report any conflict of interest. The results of trials did not appear to be related to their sample size or length of follow up. We did not formally examine the trial efficacy versus trial quality because of the lack of reported data.

Overall completeness and applicability of evidence

The results of this systematic review have to be interpreted with caution as the number of trials in each group was small. There were marked differences between the studies even within groups of drugs with similar mode of action, making it difficult to compare trials directly. In addition, there is variation between countries in relation to medications available over the counter, making international comparisons more difficult. Inclusion and exclusion criteria for participants varied, and active drugs were administered in different total daily doses. The duration of drug therapy varied from a single-dose treatment to an 18-day course. For example, six studies testing antitussives either alone or in combination with other agents, used short-term cough relief after a single dose as an outcome (Freestone 1997; Lee 2000; Mizoguchi 2007; Parvez 1996; Paul 2004; Pavesi 2001), whereas more relevant outcomes for patients would be the effect after one day, three days or a week. Outcomes were assessed and measured in many different ways which included questionnaires, cough severity scores, acoustic signals, tape recordings, daily diaries and assessment by a physician.

Most studies failed to provide quantitative data on cough as our main outcome of interest, which made it very difficult to assess whether positive study results were clinically relevant. Quantitative data that could be combined showed wide confidence intervals, although there was no evidence of statistical heterogeneity. Many included studies failed to report adverse effects adequately, and patient compliance with the treatment was not discussed in the vast majority of study reports. Three studies carried out multiple comparisons, thereby increasing the probability of a type I error (Berkowitz 1989; Parvez 1996; Pavesi 2001). A number of studies were supported by pharmaceutical companies, whereas the others failed to report their sources of funding or any conflict of interest.

Quality of the evidence

The overall quality of trials is dubious and there are conflicting results between trials in each medication group. The method of outcome measurement and the resulting magnitude of effect were unclear or not very well reported in some studies.

Potential biases in the review process

Eleven of the 26 included studies were funded by the pharmaceutical industry as outlined in the 'Risk of bias' section in the Results. Studies funded in this way were more likely to report positive results. However, despite this potential bias the review does not provide evidence of the effectiveness of OTC cough medicines for acute cough.

Agreements and disagreements with other studies or reviews

The findings of this review and other related published evidence were considered by an expert panel of the US Food and Drug in October 2007 and there was consensus that there is limited evidence to support the recommendation to use OTC cough medicines for acute cough in children (FDA 2007). The review findings are also supported by a recent non-Cochrane systematic review which found few studies that examined the effectiveness of diphenhydramine for acute cough despite its widespread use and these studies indicated limited clinical effectiveness (Bjornsdottir 2001).

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence for or against the effectiveness of OTC cough medicines and from the studies included in this review it remains unclear whether these medications are helpful for the treatment of acute cough. Although a number of RCTs have compared OTC cough preparations with placebo, the number of trials in each group was small. This review suggests that most preparations appear to be safe, based on those studies reporting side effects which only described a low incidence of mainly minor adverse effects. However, more serious concerns about the safety of OTC cough medicines have arisen since this review was last updated, particularly in young children and, in general, larger numbers of patients are required to pick up serious though less common adverse effects (Smith 2008a). This systematic review confirms the lack of evidence for or against an effect of OTC cough preparations despite using an extensive search strategy. This lack of evidence of effectiveness also has implications for the regulatory bodies and brings into question how these products can continue to be promoted using language that implies that their effectiveness is not in doubt.

The results of this review have to be interpreted with caution because study designs, populations, interventions and outcomes varied markedly between studies, limiting the generalisability of the results. All results were based on a small number of studies. It is also questionable as to whether all of the positive results obtained with unclear outcome measures are clinically relevant.

Implications for research

Further high quality RCTs of OTC cough preparations are needed as the results of this review are based on a small number of often underpowered studies. More evidence about the effectiveness of OTC cough preparations would be helpful, as identification of effective self-care treatments may help reduce the burden of days lost at work due to acute cough as well as the number of consultations in primary care. Research should also include individuals who self-medicate with OTC cough preparations, as there is likely to be a variation between countries in the proportion of individuals using these medications, with or without professional advice, particularly given the international variation in what products are available OTC or on a prescription basis. There is also a need to identify ineffective preparations in order to lower costs for consumers and health care providers. Studies will need to be rigorously designed and should use clinically relevant outcome measures, including cough frequency, severity and duration. It is important that future RCTs use OTC drugs in doses recommended by the manufacturers for an appropriate length of time, as drugs tested in a single and possibly too low a dose are likely to be ineffective. Trials should also report details on effect sizes and provide data on adherence and adverse effects. This review also highlights a need for an outcome measure for acute cough that is clinically relevant, valid, reliable and easy to use in RCTs.

ACKNOWLEDGEMENTS

We thank the editorial team of the Cochrane Acute Respiratory Infections (ARI) Group for their excellent support and help with the literature searches. Steve McDonald and Ron D'Souza from the ARI Group helped design the initial search strategy and performed additional searches. Liz Dooley, Ruth Foxlee and Sarah Thorning provided further help and support with additional searches for the 2004, 2007 and the 2010 updates.

We thank Professor Debbie Sharp (Division of Primary Health Care, University of Bristol) and Professor Massimo Pignatelli (Department of Histopathology, Bristol Royal Infirmary) for their help with the French and Italian translations.

Many thanks also to Bruce Arroll, Keith Dear, Warren McIsaac and Amy Zelmer for their very helpful comments on an earlier draft of this review. Thanks to Basem Saab, Martin Schultz, Mark Jones and Chris Del Mar for commenting on the 2007 revised draft. Finally, thanks also to Ntambwe Gustav Malangu, Nina Griese, Max Bulsara, Chris Del Mar and again to Martin Shultz for commenting on the 2010 revised draft.

REFERENCES

References to studies included in this review

Adams 1993 *{published data only}*
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. *Advances in Therapy* 1993;**10**(6): 263–71.

Berkowitz 1989 *{published data only}*
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. *Annals of Allergy* 1989;**63**(4):336–9.

Berkowitz 1991 *{published data only}*
Berkowitz RB, Tinkelman DG. Evaluation of oral terfenadine for treatment of the common cold. *Annals of Allergy* 1991;**67**:593–7.

Clemens 1997 *{published data only}*
Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children?. *The Journal of Pediatrics* 1997; **130**(3):463–6.

Curley 1988 *{published data only}*
Curley FJ, Irwin RS, Pratter MR, Stivers DH, Doern GV, Vernaglia PA, et al.Cough and the common cold. *American Review of Respiratory Diseases* 1988;**138**(2):305–11.

Eccles 1992 *{published data only}*
Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *Journal of Clinical Pharmacy and Therapeutics* 1992;**17**(3):175–80.

Freestone 1997 *{published data only}*
Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *Journal of Pharmacy and Pharmacology* 1997;**49**:1045–9.

Gaffey 1988 *{published data only}*
Gaffey MJ, Kaiser DL, Hayden FG. Ineffectiveness of oral terfenadine in natural colds: evidence against histamine as a mediator of common cold symptoms. *Pediatric Infectious Diseases Journal* 1988;**7**(3):215–42.

Hutton 1991 *{published data only}*
Hutton N, Wilson MH, Mellits ED, Baumgartner R, Wissow LS, Bonuccelli C, et al.Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. *Journal of Pediatrics* 1991;**118**(1):125–30.

Korppi 1991a *{published data only}*
Korppi M, Laurikainen K, Pietikaenen M, Silvasti M. Antitussives in the treatment of acute transient cough in children. *Acta Paediatrica Scandinavia* 1991;**80**:969–71.

Korppi 1991b *{published data only}*
Korppi M, Laurikainen K, Pietikaenen M, Silvasti M. Antitussives in the treatment of acute transient cough in children. *Acta Paediatrica Scandinavia* 1991;**80**:969–71.

Kuhn 1982 *{published data only}*
Kuhn JJ, Hendley JO, Adams KF, Clark JW, Gwaltney JMJr. Antitussive effect of guaifenesin in young adults with natural colds. *Chest* 1982;**82**(6):713–8.

Kurth 1978 *{published data only}*
Kurth W. Secure therapeutic effectiveness of the traditional antitussive agent minetten in a double-blind study [Gesicherte therapeutische Wirksamkeit des traditionellen Antitussivums Minetten im Doppelblindversuch]. *Medizinische Welt* 1978;**29**(48):1906–9.

Lee 2000 *{published data only}*
Lee PCL, Jawad MSM, Eccles R. Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory infection. *Journal of Pharmacy and Pharmacology* 2000;**52**:1137–42.

Mizoguchi 2007 *{published data only}*
MIzoguchi H, Wilson A, Jerdack GR, Hull JD, Goodale M, Grender JM, et al.Efficacy of a single evening dose of a syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulphate in subjects with multiple common cold symptoms. *International Journal of Clinical Pharmacology and Therapeutics* 2007;**45**: 230–6.

Nespoli 1989 *{published data only}*
Nespoli L, Monafo V, Bonetti F, Terracciano L, Savio G. Clinical evaluation of letostein activity in the treatment of acute febrile bronchitis in paediatric age. Controlled double blind vs placebo investigation [Valutazione clinica dell'attivita della letosteina nel trattamento della bronchite acuta febbrile in eta pediatrica. Indagine controllata in doppio cieco vs placebo]. *Minerva Pediatrica* 1989;**41**(10): 515–20.

Nesswetha 1967 *{published data only}*
Nesswetha W. Criteria of drug testing in industrial practice, demonstrated by a cough remedy [Kriterien der Arzneimittelpruefung in der werksaerztlichen Praxis, dargestellt am Beispiel eines Hustenloesers]. *Arzneimittelforschung* 1967;**17**(10):1324–6.

Parvez 1996 *{published data only}*
Parvez L, Vaidya M, Sakhardande A, Subburaj S, Rajagopalan TG. Evaluation of antitussive agents in man. *Pulmonary Pharmacology* 1996;**9**(5-6):299–308.

Paul 2004 *{published data only}*
Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al.Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004;**114**(1):E85–E90.

Pavesi 2001 *{published data only}*
Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. *Chest* 2001;**120**:1121–8.

Reece 1966 *{published data only}*
Reece CA, Cherry ACJr, Reece AT, Hatcher TB, Diehl AM. Tape recorder for evaluation of coughs in children. *American Journal of Diseases of Children* 1966;**112**(2):124–8.

Robinson 1977 *{published data only}*
Robinson RE, Cummings WB, Deffenbaugh ER. Effectiveness of guaifenesin as an expectorant: a cooperative double-blind study. *Current Therapeutic Research* 1977;**22** (2):284–96.

Sakchainanont 1990 *{published data only}*
Sakchainanont B, Ruangkanchanasetr S, Chantarojanasiri T, Tapasart C, Suwanjutha S. Effectiveness of antihistamines in common cold. *Journal of the Medical Association Thailand* 1990;**73**(2):96–101.

Taylor 1993 *{published data only}*
Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. *Journal of Paediatrics* 1993; **122**:799–802.

Thackray 1978 *{published data only}*
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. *Journal of International Medical Research* 1978;**6** (2):161–5.

Tukiainen 1986 *{published data only}*
Tukiainen H, Karttunen P, Silvasti M, Flygare U, Korhonen R, Korhonen T, et al.The treatment of acute transient cough: a placebo-controlled comparison of dextromethorphan and dextromethorphan-beta 2-sympathomimetic combination. *European Journal of Respiratory Diseases* 1986;**69**(2):95–9.

References to studies excluded from this review

Kim 2009 *{published data only}*
Kim YW, Lee SM, Lee CT, Chung HS, Chang J, Ahn CM. Clinical efficacy of theobromine for the treatment of cough in adults. *Respirology* 2009;**14**:A132.

MRC 1950 *{published data only}*
Medical Research Council. Clinical trials of antihistaminic drugs in the prevention and treatment of the common cold. *British Medical Journal* 1950;**2**:425–9.

Paul 2007 *{published data only}*
Beiler PIM, McMonagle J, Shaffer A, Duda ML, Berlin LCM Jr. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Archives of Pediatrics and Adolescent Medicine* 2007;**161**(12):1140–6.

Additional references

Anonymous 1999
Anonymous. Cough medications in children. *Drugs and Therapeutics Bulletin* 1999;**37**(3):19–21.

Banderali 1995
Banderali G, Riva E, Fiocchi A, Cordaro CI, Giovannini M. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. *Journal of International Medical Research* 1995;**23**:175–83.

Bjornsdottir 2001
Björnsdóttir I, Einarson TR, Gudmundsson LS, Einarsdóttir RA. Efficacy of diphenhydramine against cough in humans: a review. *Pharmacy World and Science* 2007;**29**:577–83.

FDA 2007
Food, Drug Administration. Nonprescription Drug Advisory Committee Meeting. Cold, cough, allergy, bronchodilator, antiasthmatic drug products for over-the-counter human use. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4323b1-02-FDA.pdf (accessed 6 October 2008) 2007.

Gastpar 1984
Gastpar H, Cricuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. *Current Medical Research and Opinion* 1984;**9**:21–7.

Irwin 1993
Irwin RS, Curley FJ, Bennett FM. Appropriate use of antitussives and protussives. A practical review. *Drugs* 1993; **46**(1):80–91.

Lefebrve 2008
Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for*

Systematic Reviews of Interventions. Chichester, UK: Wiley-Blackwell, 2008.

Morice 1998
Morice A, Abdul-Manap R. Drug treatments for coughs and colds. *Prescriber* 1998;**9**(17):74–9.

PAGB 2000
The Proprietory Association of Great Britain. Annual Review and Report. PAGB London: 2000.

Reynolds 1993
Reynolds JEF. Cough suppressants, expectorants and mucolytics. In: Martindale editor(s). *The Extra Pharmacopeia*. 30th Edition. The Pharmaceutical Press, 1993:741–53.

Smith 1993
Smith MBH, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *JAMA* 1993;**269**(17):2258–63.

Smith 2008a
Smith SM, Henman M, Schroeder K, Fahey T. Over the counter (OTC) cough medicines in children: neither safe or efficacious?. *British Journal of General Practice* 2008;**58** (556):757–8.

Vernacchio 2008
Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Cough and cold medication use by US children, 1999-2006: Results from the Slone survey. *Pediatrics* 2008;**122**(2): e323–e9.

Ziment 1976
Ziment I. What to expect from expectorants. *JAMA* 1976; **236**:193–4.

References to other published versions of this review

Schroeder 2001
Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD001831.pub3]

Schroeder 2004
Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD001831.pub3]

Smith 2008b
Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD001831.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adams 1993

Methods	RCT
Participants	108 adults, mean age 48 years, 70% women, 60% smokers, UK primary care, acute dry or slightly productive cough
Interventions	Antitussive: moguisteine 200 mg 3 times daily for 3.5 days
Outcomes	Patient recorded cough scale from 0 to 9. Mean score difference of 0.5 between groups, P less than 0.05
Notes	More side effects in treatment group (22%) compared to placebo (8%) mainly including nausea, vomiting and abdominal pain. Four withdrawals in the treatment group due to adverse effects

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patient and provider blinded but not outcome assessor
Incomplete outcome data addressed? All outcomes	Yes	10% loss to follow up and reasons reported
Free of other bias?	No	Trial supported by pharmaceutical industry

Berkowitz 1989

Methods	RCT
Participants	283 adults, mean age 30 years, mainly Caucasian, 52% women, 3 'centres', USA, common cold
Interventions	Antihistamine-decongestant combination: loratadine 5 mg and pseudoephedrine 120 mg combination twice daily for 5 days
Outcomes	Patient diaries, cough score from 0 to 3. No significant difference in cough score reduction (0.8 in active treatment group versus 0.6 in the placebo group, P greater than 0.05)
Notes	Adverse effects (dry mouth, headache and insomnia) more common in active treatment group (30%) compared to placebo group (21%)

Risk of bias

Berkowitz 1989 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Overall 92% follow up and similar in both groups
Free of other bias?	Unclear	Many multiple comparisons made

Berkowitz 1991

Methods	RCT
Participants	100 adults, mean age 32, 56% women, non-smokers, single centre (setting not reported) , USA, common cold
Interventions	Antihistamine: terfenadine 120 mg twice daily for 4 to 5 days
Outcomes	Patient diary and symptom score from 0 to 3. No statistically significant difference between cough scores in active treatment group (0.81, standard error 0.13) and placebo (0.61, standard error 0.12), P = 0.35
Notes	Possible adverse effects rare in both groups. Headache most common (6.1% in active treatment group versus 4% in placebo group)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as "randomly assigned"
Blinding? All outcomes	Unclear	Blinding assumed but not clearly stated
Incomplete outcome data addressed? All outcomes	Yes	Overall 96% follow up and similar in both groups
Free of other bias?	No	Trial supported by pharmaceutical industry

Clemens 1997

Methods	RCT
Participants	59 pre-school children, mean age 2 years (6 months to 5 years), 4 paediatric offices, USA, URTI of less than 7 days' duration
Interventions	Antihistamine-decongestant combination: brompheniramine maleate 2 mg/5 ml and phenyl-propanolamine-hydrochloride 12.5 mg/5 ml (6 months to 1 year: 1.5 teaspoon and 2 to 5 years: 1 teaspoon) every 4 hours "as needed" for 48 hours
Outcomes	Parent questionnaire, 7-point Likert scale, also counted 'responses' after each dose. Mean cough scores 4.67 (active treatment) versus 4.57 (placebo), P = 0.53
Notes	Higher proportion of children asleep in the active treatment group (46.6%) versus placebo (26. 5%)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as patients "randomly assigned in a double blind fashion"
Blinding? All outcomes	Yes	Patients, providers and outcome assessor blinded, patient blinding unclear

Curley 1988

Methods	RCT
Participants	73 adults, mean age 31 years, 60% women, 19% active smokers, outpatient department, USA, common cold of less than 72 hours duration
Interventions	Antihistamine-decongestant combination: dexbrompheniramine maleate 6 mg and pseudoephedrine sulphate 120 mg combination twice daily for 1 week
Outcomes	Patient diary and cough score from 0 to 4. Mean severity cough score 1.4 (active) versus 2.0 (placebo), P less than 0.05 on days 3 to 5
Notes	Increased severity of dizziness and dry mouth in the active drug group compared to placebo (P equal or less than 0.01, exact figures not reported)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported

Curley 1988 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	85% follow up, difference between groups not reported. Overall drop-outs due to inconvenience of study and not due to side effects

Eccles 1992

Methods	RCT
Participants	81 adults, mean age 23 years (range 18 to 71), 52% men, hospital research clinic, UK, cough associated with URTI
Interventions	Antitussive: codeine linctus 30 mg/10 ml 4 times daily for 4 days
Outcomes	Cough severity score (5-point scale) from diaries expressed as area under the curve for 8 measures over 5 days. Mean cough scores 18.8 (placebo) versus 17.2 (codeine), P = 0.23
Notes	No data on adverse effects provided

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	90% follow up; no reporting of differences between groups

Freestone 1997

Methods	RCT
Participants	82 university students and staff, mean age 24 years (range 18 to 46), 62% men, 'common cold centre', university department, UK, cough associated with URTI
Interventions	Antitussive: codeine phosphate 50 mg as a single dose
Outcomes	Five-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). Also no significant differences for cough sound pressure levels and cough frequency
Notes	No data on adverse effects reported

Risk of bias

Freestone 1997 (*Continued*)

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Unclear	Follow up not reported
Free of other bias?	Unclear	No power calculation reported

Gaffey 1988

Methods	RCT
Participants	250 adults, mean age 23 years, 65% women, internal medicine clinic, USA, common cold
Interventions	Antihistamine: terfenadine 60 mg twice daily for 3.5 days
Outcomes	Patient diary and symptom score from zero to three. Symptom scores for cough "virtually the same in the terfenadine and placebo recipients", but no exact scores reported
Notes	Side effects uncommon in both groups, with the most common complaint being excess fatigue (12% in active versus 10% in placebo group)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as "subjects received sequential admission numbers and were randomly assigned"
Blinding? All outcomes	Unclear	Blinding presumed but not clearly reported
Incomplete outcome data addressed? All outcomes	Yes	94% follow up; difference between groups not reported. Non-compliers were considered to be drop-outs
Free of other bias?	No	Participants were "compensated for participation" Trial supported by pharmaceutical industry

Hutton 1991

Methods	RCT
Participants	96 inner-city African-American children, 6 months to 5 years, mean age about 2 years, primary care clinic, USA, symptoms of URTI
Interventions	Antihistamine-decongestant combination: brompheniramine maleate 4 mg/5 ml, phenylephrine 5 mg/5 ml, propanolamine 5 mg/5 ml (doses calculated to achieve brompheniramine dosage of 0.5 to 0.75 mg/kg/d) 3 times daily for 2 days
Outcomes	Nine-point symptom score by parents or physician, follow-up telephone interviews. "Improvement" reported in 20/30 (67%) in the active treatment group compared to 14/24 (58%) in the placebo group and 21/30 (70%) in the group receiving no treatment (P = 0.5 and 0.8, respectively)
Notes	Side effects were rare including one child with loose stools in the placebo group and one child reported as hyperactive in the active treatment group. A second child in the drug group was reported sleepier than usual

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Follow up 86% in active treatment group and 89% in placebo group

Korppi 1991a

Methods	RCT
Participants	Arm of 3-arm RCT, 50 children with respiratory infection, private paediatric practices, mean age 3.8 years, 53% boys, Finland
Interventions	Antitussive: dextromethorphan 1.5 mg per ml 5 ml 3 times daily for children under 7 years and 10 ml 3 times daily for older children
Outcomes	Daily symptom score recorded by parents including cough frequency and severity on a scale from 0 to 3. Scores dropped in both groups with no difference between groups
Notes	Small study with no power calculation reported. Low incidence of adverse effects with no differences between groups

Risk of bias

Korppi 1991a (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as "randomly divided" into treatment groups
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Reported as double-blind; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	Follow up 96%

Korppi 1991b

Methods	RCT
Participants	Arm of 3-arm RCT, 51 children with respiratory infection, private paediatric practices, mean age 3.8 years, 53% boys, Finland
Interventions	Other combination: dextromethorphan 1.5 mg per ml and salbutamol 0.2 mg per ml 5 ml 3 times daily for children under 7 years and 10 ml 3 times daily for older children
Outcomes	Daily symptom score recorded by parents including cough frequency and severity on a scale from 0 to 3. Scores dropped in both groups with no difference between groups
Notes	Small study with no power calculation reported. Low incidence of adverse effects with no differences between groups

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Kuhn 1982

Methods	RCT
Participants	65 adults (mostly university students), age range 18 to 30 years, university research centre, USA, URTI with cough for less than 48 hours
Interventions	Mucolytic: expectorant: guaifenesin 480 mg/30 ml every 6 hours for 30 hours
Outcomes	Tape recordings of cough frequency, questionnaire on 6 symptoms. Cough frequency: 33/33 (100%) improved in the active treatment group versus 30/32 (94%) in the placebo group, P = 0.5. Cough severity: improved in 33/33 (100%) in the active treatment group versus 29/32 (91%) in the placebo group, P = 0.2

Kuhn 1982 (*Continued*)

Notes	Study did not report on adverse effects	
Risk of bias		
Item	**Authors' judgement**	**Description**
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up
Free of other bias?	Unclear	No power calculation reported

Kurth 1978

Methods	RCT	
Participants	113 adults, 57% men, age range from under 30 to over 70 years (no details given), primary care, Germany, cough due to URTI	
Interventions	Other combination: EM-Vier Minetten: Extr thymi aquos.sicc 5 mg, succus liquiritiae depurat. inspiss. 20 mg, menthol 3.5 mg, ephedrine hydrochloric 2 mg, ol. eucalypti 2 mg, ol. menthae piperitae 0.7 mg 6 times daily for 14 to 18 days	
Outcomes	Outcome measurement unclear. 26/58 (44.8%) in the active treatment group improved within the first 3 days compared to 15/55 (27.3%) in the placebo group, P = 0.05	
Notes	No adverse effects in either group	
Risk of bias		
Item	**Authors' judgement**	**Description**
Blinding? All outcomes	Yes	Patients blinded; blinding of providers and outcome assessors not reported
Incomplete outcome data addressed? All outcomes	Unclear	95% follow up. No difference between groups
Free of other bias?	Unclear	No power calculation reported

Lee 2000

Methods	RCT
Participants	44 adults from 18 to 60 years (mean age 23 years), 70% women, university staff and students and general city population, UK
Interventions	Antitussive: dextromethorphan 30 mg as a single dose
Outcomes	Cough frequency recordings, cough sound pressure levels, questionnaire on cough severity (scale from 0 to 3). Decline in cough frequency of 31.0 (active) versus 21.5 (placebo) , P = 0.38. Mean decline in cough score 1.0 (active) versus 0.5 (placebo), P = 0.08
Notes	Side effects not reported

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Unclear	98% follow up; remaining 2% reported as being due to lack of motivation to participate in the study
Free of other bias?	Unclear	Only retrospective power calculation reported

Mizoguchi 2007

Methods	RCT
Participants	485 adult volunteers with URTI with cough, for greater than 1 day and less than 5 days, aged 18 to 65 attending 10 study centres in the USA
Interventions	Single 30 ml dose of a test syrup containing 15 mg dextromethorphan; 7.5 mg doxycycline; 8 mg ephedrine and 600 mg paracetamol
Outcomes	Mean cough score on day 1 and day 2 following active treatment: active treatment 2.5 versus placebo 2.08 on day 2 % with improved cough 3 hours following active treatment: 57% improved in active treatment group compared with 43% in placebo group Adverse events: 5/224 in treatment group (1 serious event described as a severe episode of somnolence) and 9/208 in control group
Notes	Other outcomes relating to URTI were also presented but we included only cough-related outcomes

Risk of bias

Item	Authors' judgement	Description

Mizoguchi 2007 (*Continued*)

Adequate sequence generation?	Yes	Subjects stratified by sex and overall symptom severity score and block randomised
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	Overall 89% completed full follow up, 79% had per protocol analysis, minimal imbalance between groups
Free of other bias?	No	Interim power calculation carried out during study by independent external statistician Trial supported by pharmaceutical industry

Nespoli 1989

Methods	RCT
Participants	40 children, age range 2 to 12 years (median 7.5 years), paediatric clinic, Italy, acute febrile bronchitis
Interventions	Mucolytic: letosteine 25 mg 3 times daily for 10 days
Outcomes	Cough score from 0 to 3, unclear how this was measured. Lower cough scores in the active treatment group compared to placebo (difference between groups ranging from 0.1 to 0.3 points from day 4 to 10, P less than 0.01)
Notes	No adverse effects reported in both groups

Risk of bias

Item	**Authors' judgement**	**Description**
Blinding? All outcomes	Yes	
Free of other bias?	Unclear	Interim power calculation carried out during study by independent external statistician

Nesswetha 1967

Methods	RCT
Participants	99 factory workers in the chemical industry, age range 15 to 44 years, Germany, URTI
Interventions	Mucolytic: bisolvon linctus (N-cyclohexyl-N-methyl-(2-amino-3,5-dibrombenzyl) ammonium chloride 4 mg in 5 ml 3 times daily for an average of 4 days

Nesswetha 1967 (*Continued*)

Outcomes	Outcome measurement not clearly described, used 4-point scale. Frequent cough (defined as cough every 2 to 4 minutes) present in 4/46 (8.6%) in the active treatment group versus 7/46 (15.2%) in the placebo group (P less than 0.02)
Notes	Study did not report on adverse effects

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	93% follow up; difference between groups not reported
Free of other bias?	Unclear	No power calculation reported

Parvez 1996

Methods	RCT
Participants	451 adults in 3 different studies, mean age 30 years, 65% men, mainly non-smokers, corporate health centre, India, URTI
Interventions	Antitussive: dextromethorphan 30 mg as a single dose
Outcomes	Cough acoustic signals captured via microphone over 180 minutes. Differences in mean changes between cough counts varied from 19 to 36 per cent (P less than 0.05) in the 3 studies (up to a net difference of 8 to 10 coughing bouts every 30 minutes)
Notes	This study did not report on adverse effects

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Minimisation using a computer program
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Unclear	Not reported but drop outs unlikely due to short period of follow up

Parvez 1996 (*Continued*)

Free of other bias?	No	Many multiple comparisons with no corrections and high probability of type I error Trial supported by pharmaceutical industry

Paul 2004

Methods	RCT
Participants	100 children (age range 2 to 18 years), cough due to URTI, university affiliated paediatric practices in USA
Interventions	Antitussive: dextromethorphan as single dose based on age Antihistamine: diphenhydramine as single dose 1.25 mg/kg
Outcomes	Cough frequency score on 7-point scale Sleep disturbance in children and their parents
Notes	Adverse effects: 13/33 in dextromethorphan arm 9/33 in diphenhydramine arm 9/33 in placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up

Pavesi 2001

Methods	Meta-analysis of 5 RCTs
Participants	710 adults in 5 different studies, mean age 30 years, 50% women, 90% non-smokers, settings 'clinics' and 'in-home' studies, South Africa and India, uncomplicated upper respiratory infection
Interventions	Antitussive: dextromethorphan 30 mg as a single dose
Outcomes	Three-hour continuous cough recording, measuring cough bouts, cough components, cough effort, cough intensity and cough latency. Average treatment difference 12% to 17% in favour of dextromethorphan in cough bouts (P = 0.004), cough components (P = 0.003) and cough effort (P = 0.001) with an increase in cough latency (P = 0.002)

Pavesi 2001 (*Continued*)

Notes	Study funded and conducted by pharmaceutical company. Results poorly reported

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	
Free of other bias?	No	No power calculation reported. Medication sponsored by medical director of a laboratory who also performed the analysis

Reece 1966

Methods	RCT
Participants	43 children, mean age 3.6 years (range 2 months to 12 years), 58 % boys, ambulatory private practice, USA, cough due to URTI
Interventions	Other combination: dextromethorphan, guaifenesin and pseudoephedrine (Triaminicol syrup) and dextromethorphan, guaifenesin and pseudoephedrine (Dorcol paediatric cough syrup), treatment frequency and duration unclear
Outcomes	Parent assessment. 'Satisfactory' response in 11/16 (69%) and 9/13 (69%) in the intervention groups compared to 8/14 (57%) in the placebo group, P = 0.5 for both comparisons (responses and P values were calculated from the percentages)
Notes	Adverse effects were not reported

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patients blinded; blinding of providers and outcome assessors not reported
Incomplete outcome data addressed? All outcomes	Unclear	Follow up not reported
Free of other bias?	No	No power calculation reported. Medication sponsored by medical director of a laboratory who also performed the analysis

Robinson 1977

Methods	RCT
Participants	239 adults, mean age about 38 years, smokers and non-smokers evenly distributed, office or clinic outpatients, USA, acute URTI
Interventions	Expectorant: guaifenesin 200 mg/10 ml 4 times daily for 3 days
Outcomes	Patient questionnaires, cough scores from 0 to 3. 79/105 (75%) in the active treatment group found the MEDLINE helpful compared with 33/106 (31%) in the placebo group, P less than 0.01
Notes	Two participants in each group reported side effects including nausea and hives in the active treatment group and headaches, drowsiness and excessive perspiration in the placebo group

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	89% follow up; no difference between groups
Free of other bias?	No	No power calculation reported Trial supported by pharmaceutical industry

Sakchainanont 1990

Methods	RCT
Participants	143 children under 5 years, mean age 23 months (range 1.5 to 60 months), 50% girls, paediatric out-patient department, Thailand, common cold
Interventions	Antihistamine: 2 groups: clemastine fumarate (0.05 mg/kg/d twice daily) and chlorpheniramine maleate syrup (0.35 mg/kg/d 3 times daily) for 3 days
Outcomes	Parent assessment using 4-level symptom score. Cough "improved" in 19/48 (39.6%) in the chlorpheniramine group compared with 13/47 (27.6%) taking placebo, P = 0.2
Notes	Drowsiness and sleepiness reported in 20% of children with no difference between the treatment groups

Risk of bias

Item	Authors' judgement	Description

Sakchainanont 1990 (*Continued*)

Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	95% follow up; no difference between groups
Free of other bias?	No	No power calculation reported. Bonferroni correction for multiple comparisons used Trial supported by pharmaceutical industry

Taylor 1993

Methods	RCT
Participants	57 children, mean age 4.7 years (range 18 months to 12 years), 53% boys, 82% white, private practices, USA, night cough due to URTI
Interventions	Antitussive: dextromethorphan 15 mg/5 ml and codeine 10 mg/ 5 mg as a single dose at bed time for 3 nights
Outcomes	Parent questionnaire, cough score from 0 to 4. Mean reductions in cough scores 2.2 (codeine) and 2.1 (dextromethorphan) versus 2.2 in the placebo group, P = 0.52 and 0.97 respectively
Notes	Both active treatments also contained guaifenesin 100 mg/5 ml. Adverse effects mainly drowsiness, diarrhoea and hyperactivity: placebo 7/13 (54%), dextromethorphan 6/19 (32%, P = 0.2) and codeine 5/17 (29%, P = 0.8)

Risk of bias

Item	**Authors' judgement**	**Description**
Blinding? All outcomes	Yes	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	86% follow up; difference between groups not reported
Free of other bias?	Unclear	Post hoc power calculation demonstrates that study was powered to detect a difference of 0.9 in cough score which is equivalent to natural resolution of cough at day 3. Authors argue that smaller reductions in cough scores are unlikely to be clinically important

Thackray 1978

Methods	RCT
Participants	70 adults, mean age 34 years (range 18 to 60), 61% women, 21 general practices, UK, common cold
Interventions	Other combination: Vicks Medinite syrup (dextromethorphan 15 mg, ephedrine 600 mg, doxylamine 7.5 mg, paracetamol 600 mg per dose) single dose at bedtime for 2 days
Outcomes	Questionnaire, 6-point rating scale. Cross-over design: 34/59 (57.6%) of subjects rated active treatment good or better compared to 19/59 (32.2%) in the control group, P less than 0.01
Notes	Seven subjects in the active treatment group reported giddiness/drowsiness compared to 4 subjects in the placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Patients allotted by a random number code"
Blinding? All outcomes	Unclear	Patients and providers blinded; outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up
Free of other bias?	No	Main investigator was medical director of the company supplying the drug for the study. Cross-over after 1 day, no washout period

Tukiainen 1986

Methods	RCT
Participants	108 outpatients, mean age about 38 years, 55% women, 48% smokers, Finland, cough associated with URTI
Interventions	Other combination: dextromethorphan (30 mg) alone and in combination with salbutamol (2 mg) 3 times daily for 4 days
Outcomes	Patient diary and symptom score from 0 to 3. No statistically significant differences between mean treatment scores for daytime cough on day 4 1.26 (dextromethorphan plus salbutamol), 1.28 (dextromethorphan) and 1.15 (placebo), no exact P value given. Dextromethorphan/salbutamol was more effective in suppressing cough at night compared to plain dextromethorphan (0.45 +/- 0.10 versus 0.92 +/- 0.14, P less than 0.01) on day 3

Tukiainen 1986 (*Continued*)

Notes	Dextromethorphan/salbutamol combination led to more tremor than placebo (no figures given, P less than 0.05), no serious adverse effects reported

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	Patients and providers blinded, outcome assessor blinding not reported
Incomplete outcome data addressed? All outcomes	Unclear	Follow up not reported
Free of other bias?	No	No power calculation reported Trial supported by pharmaceutical industry

RCT: randomised controlled trial
URTI: upper respiratory tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kim 2009	Abstract only published and inclusion criteria unclear. Main publication awaited
MRC 1950	Cough outcome not clearly reported
Paul 2007	No placebo control group

URTI: upper respiratory tract infection

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Embase.com search strategy

12. #8 AND #11
11. #9 OR #10
10. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR ((doubl* OR singl*) NEAR/2 (blind* OR mask)):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti
9. 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'randomized controlled trial'/exp
8. #3 AND #7
7. #4 OR #5 OR #6
6. 'cough suppressant':ab,ti OR 'cough suppressants':ab,ti OR 'drug combination':ab,ti OR 'drug combinations':ab,ti OR 'over the counter':ab,ti OR 'over-the-counter':ab,ti OR otc:ab,ti OR 'behind the counter':ab,ti OR 'behind-the-counter':ab,ti OR 'non prescription':ab,ti OR 'non-prescription':ab,ti OR nonprescription:ab,ti
5. antituss*:ab,ti OR expectorant*:ab,ti OR anticholinerg*:ab,ti OR antihistamin*:ab,ti OR mucolytic*:ab,ti
4. 'antitussive agent'/exp OR 'expectorant agent'/exp OR 'cholinergic receptor blocking agent'/exp OR 'histamine h1 receptor antagonist'/exp OR 'drug combination'/exp OR 'behind the counter drug'/exp OR 'non prescription drug'/exp OR 'self medication'/exp
3. #1 OR #2
2. cough*:ab,ti
1. 'coughing'/de OR 'irritative coughing'/de

WHAT'S NEW

Last assessed as up-to-date: 7 April 2010.

Date	Event	Description
19 March 2010	New search has been performed	One study added (Mizoguchi 2007) to this update but did not lead to any major changes in the conclusions of this review

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 3, 2001

Date	Event	Description
6 August 2009	Amended	Contact details updated.
8 May 2009	Amended	Contact details updated.
2 June 2008	Amended	Converted to new review format.
4 July 2007	New search has been performed	Searches conducted.
25 July 2004	New search has been performed	Searches conducted.
12 December 1999	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Knut Schroeder (KS) and Tom Fahey (TF) conceived and designed the original review, undertook the searches, performed data collection, screened the search results, screened retrieved papers against the inclusion criteria, appraised the quality of the papers, extracted data from papers, interpreted the data, organised the retrieval of papers, wrote to authors of papers for additional information, managed the data, entered data into Review Manager and wrote the review.

Susan Smith (SS) updated the review in 2007 and in 2010, including screening updated search results, data extraction, quality appraisal and rewriting the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Division of Primary Health Care, University of Bristol, UK.

External sources

- South & West Research and Development Directorate, UK.
- NHS Primary Care Career Scientist Fund, UK.

NOTES

A single randomised controlled trial (RCT) was added to this review in the 2007 update (Paul 2004).

Paul et al tested a single nocturnal dose of dextromethorphan, or a single nocturnal dose of diphenhydramine versus placebo. The outcomes in this study were measured the following morning and included a cough severity index and a measure of sleep difficulty both for the affected children and their parents. This study showed no significant treatment differences between the two intervention groups and the control group.

Average treatment differences between 12% and 17% in favour of dextromethorphan for cough bouts (P = 0.004), cough components (P = 0.003) and cough effort (P = 0.001) with an increase in cough latency (P = 0.002).

A further single RCT was added for the 2010 update (Mizoguchi 2007).

Mizoguchi et al compared a single nocturnal dose of a combination test syrup containing dextromethorphan, doxycycline, ephedrine and paracetamol with placebo. The outcomes in this study were measured the over the following two days and included proportions reporting improvements in cough three hours after taking the treatment and mean cough scores on day 1 and day 2. This study showed significant treatment differences between the two intervention groups and the control group in terms of reduction in mean cough scores on day 2.

The addition of these study did not lead to any major changes in the conclusions of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Ambulatory Care; Antitussive Agents [*administration & dosage]; Cough [*drug therapy]; Drug Therapy, Combination; Expectorants [administration & dosage]; Histamine H1 Antagonists [administration & dosage]; Nonprescription Drugs [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans