OVER-THE-COUNTER (OTC) MEDICATIONS FOR ACUTE COUGH IN CHILDREN AND ADULTS IN AMBULATORY SETTINGS

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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.

Objective
To assess the effects of oral OTC cough preparations for acute cough in children and adults.

REVIEW_ABS_OTHER

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012 Issue 3 which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to March week 1 2012), EMBASE (January 1974 to March 2012), CINAHL (January 2010 to March 2012), LILACS (January 2010 to March 2012), Web of Science (January 2010 to March 2012) 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.

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

Acute cough is a common and troublesome symptom in people who suffer from acute upper respiratory tract infection. Many people self prescribe over-the-counter (OTC) cough preparations and health practitioners often recommend their use for the initial treatment of cough. Twenty-six trials involving 4037 people were included. The results of this review suggest that there is no good evidence for or against the effectiveness of OTC medications in acute cough. A few studies reported adverse effects and described infrequent, mainly minor side effects such as nausea, vomiting, headache and drowsiness. 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.

WHAT’S NEW

What’s new
Last assessed as up-to-date: 22 March 2012.

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**BACKGROUND**

**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 OF THE REVIEW**

**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**

Ambulatory settings in primary care and hospital outpatients.

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 intervention**

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.

- Antitussives, for example, centrally acting opioid derivatives.
- Expectorants, i.e. drugs leading to increased bronchial mucus production (Ziment 1976).
- Mucolytics, i.e. drugs aiming to decrease the viscosity of bronchial secretions (Reynolds 1993).
- Antihistamine-decongestant combinations, i.e. drugs that are combined antihistamine H1-receptor antagonists and alpha-adrenoceptor agonists which cause vasoconstriction of mucosal blood vessels (Moric 1998).
- Other drug combinations, i.e. fixed drug combinations using different ingredients.
- 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**

For this 2012 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 3, part of The

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 (Lefebvre 2011). We adapted the search string to search EMBASE (see Appendix 2), CINAHL (see Appendix 3), LILACS (see Appendix 4) and Web of Science (see Appendix 5).

MEDLINE (OVID)

1 Cough/
2 cough*.mp.
3 1 or 2
4 exp Antitussive Agents/
5 exp Expectorants/
6 exp Cholinergic Antagonists/
7 exp Histamine H1 Antagonists/
8 exp Drug Combinations/
9 exp Nonprescription Drugs/
10 Self Medication/
11 (cough* adj5 (suppress* or mixtur* or medicin* or remed* or relief* or formula* or syrup* or medicat*)).tw.
12 (antituss* or expectorant* or anticholinerg* or antihistamin* or anti-histamin* or mucolytic*).tw.
13 (over-the-counter or otc or nonprescrip* or nonprescrib* or non-prescrip* or non-prescrib*).tw.
14 (drug adj2 combination*).tw.
15 or/4-14
16 3 and 15

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

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. We resolved any differences at any stage of the review 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 and 2012 updates 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. Two review authors (SS, TF) independently carried out these assessments. The elements considered are now described within the Characteristics of included studies table. They included the following

Adequate sequence generation?
Allocation concealment?
Blinding?
Incomplete outcome data addressed?
Free of selective reporting?
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 we undertook no meta-analysis.

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
We undertook no meta-analysis 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
We undertook no meta-analysis and limitations of the review are addressed within the Discussion section.

M E T H O D O L O G I C A L  Q U A L I T Y

RESULTS

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 the 2010 update identified one additional RCT (Mizoguchi 2007).

The search conducted for the update in 2012 identified no additional eligible studies. We identified one new study that was excluded as it had no placebo control group (Shadkam 2010).

Included studies
In this 2012 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 lack of a placebo control, 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, and 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; Sakchaianont 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. Neither study provided 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 counts, 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 of 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
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 severity 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 (Neswetha 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 per cent 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 non 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 participants in the active treatment group reported giddiness/drowsiness compared to four participants 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 participants 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 participants 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

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. This review confirms the lack of evidence for or against an effect of OTC cough preparations despite using an evidence-based approach.

Summary of main results

We found no good evidence for or against the effectiveness of over-the-counter (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. This review does not provide evidence of the effectiveness of OTC cough medicines for acute cough.

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 (Bjomsdottir 2001).

Implications for practice

There is no good evidence for or against the effectiveness of over-the-counter (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 randomised controlled trials (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. 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. 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

A U T H O R S ’ C O N C L U S I O N S
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.

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NOTES

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Hutton 1991 {published data only}


Korppi 1991a {published data only}


Korppi 1991b {published data only}


Kuhn 1982 {published data only}


Kurth 1978 {published data only}


Lee 2000 {published data only}


Mizoguchi 2007 {published data only}


Nespoli 1989 {published data only}


Nesswetha 1967 {published data only}


Parvez 1996 {published data only}


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COVER SHEET

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

Reviewer(s) Smith Susan M, Schroeder Knut, Fahey Tom

Contribution of Reviewer(s)

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Issue review first published 2001 issue 3

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Most recent changes

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HISTORY

History
Protocol first published: Issue 4, 1999

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