

Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials

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Aims: To determine the effectiveness of over the counter (OTC) cough medicines for acute cough in children.

Methods: Systematic review of randomised controlled trials (RCTs). An all language search of the Cochrane Acute Respiratory Infections Group specialised register, Cochrane Controlled Trials Register, Medline, Embase, and the UK Department of Health National Research Register was performed. RCTs comparing oral OTC cough preparations with placebo in children suffering from acute cough as a result of upper respiratory tract infection (URTI) in ambulatory settings, using cough symptoms as an outcome, were included.

Results: Six trials involving 438 children met all inclusion criteria. Antitussives, antihistamine-decongestant combinations, other fixed drug combinations, and antihistamines were no more effective than placebo in relieving symptoms of acute cough. Based on a single study, the mucolytic preparation letosteine was superior to placebo, with differences in cough scores ranging from 0.1 to 0.3 points from day 4 to day 10. Most drugs appeared to be well tolerated with a low incidence of mostly minor adverse effects.

Conclusion: OTC cough medicines do not appear more effective than placebo in relieving symptoms of acute cough. Even if statistically significant, effect sizes were small and of doubtful clinical relevance. The number of trials in each category was small, and the results of this systematic review have to be interpreted with caution. Based on the available evidence from a small number of studies, we cannot recommend OTC cough medicines as a first line treatment for children with acute cough.

Acute cough caused by upper respiratory tract infection (URTI) can be a very troublesome symptom for children, and parents often seek medical advice about its treatment. Over the counter (OTC) cough medicines are widely available and on sale to the public without prescription, but paediatricians, general practitioners (GPs), and other health professionals cannot be sure whether they should recommend these preparations to parents as a first line treatment for acute cough in their children. According to their perceived mode of action, conventional OTC cough medicines can be divided into different groups (table 1).

Total consultation rates in general practice for acute respiratory infections in children under the age of 4 were over 13 000 per 10 000 patient years in 1991/92 in the UK,¹ and a survey in the USA reported that almost 40% of preschool chil-

dren had been given one or more OTC cold medications during the preceding month.² OTC cough medicines are widely self prescribed, with retail sales having risen by 6.8% to £337.4 million between 1998 and 1999 in the UK.³ The *NHS direct healthcare guide* recommends simple cough medicines for dry cough.⁴ By 2002, all National Health Service (NHS) direct sites nationally will be able to refer callers to their local pharmacy, where appropriate, for advice on OTC medications.⁵

There is little evidence for the effectiveness of OTC cough medicines in children with acute URTI. We know of two previous reviews on this topic which did not show OTC products to be better than placebo in relieving symptoms of acute cough in children.^{6,7} One of these reviews was limited to trials published in English between 1966 and 1991 retrieved from the Medline database,⁷ and the other did not provide any details about the process of searching for studies.⁶ We therefore carried out a systematic review to answer the question whether conventional (non-homoeopathic) OTC cough medicines for acute cough associated with URTI in children are effective. This review is based on a Cochrane systematic review of adults and children.⁸

METHODS

Searching

We identified original randomised controlled trials (RCTs) by searching the Cochrane Acute Respiratory Infections Group specialised register, the Cochrane Controlled Trials Register

Table 1 Modes of action in groups of OTC cough medicines

Antitussives	Centrally acting opioid derivatives or peripherally acting agents ¹⁶
Mucolytics	Aiming to decrease the viscosity of bronchial secretions, making them easier to clear through coughing ¹⁷
Antihistamine-decongestant combinations	Combine histamine H ₁ receptor antagonists and α adrenoceptor agonists which cause vasoconstriction of mucosal blood vessels ¹⁸
Other drug combinations	Fixed drug combinations using different ingredients
Antihistamines	Histamine H ₁ receptor antagonists

Abbreviations: NHS, National Health Service; OTC, over the counter; RCT, randomised controlled trial; URTI, upper respiratory tract infection

Search strategy*

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

(The Cochrane Library issue 2, 2000), Medline (up to December 1999), Embase (up to December 1999), the UK Department of Health National Research Register (December 2000), our personal collections of references, and reference lists of all retrieved articles (search strategy shown in box). We wrote to authors of original studies, pharmaceutical companies, and the Proprietary Association of Great Britain for information on unpublished studies and made no constraints based on language or publication status.

Study selection and validity assessment

We selected studies for review if: (1) the population of interest was composed of children and adolescents (less than 16 years of age) with acute cough (less than three weeks' duration) as a result of URTI in an ambulatory setting; (2) the interventions were OTC cough preparations; (3) a reported outcome was cough (for example, frequency, duration); and (4) studies were RCTs with a contemporaneous control group receiving a placebo.

We excluded studies if: (1) they tested OTC cough medicines in chronic cough (more than three weeks' duration or caused by a chronic underlying disease such as asthma or tuberculosis); (2) cough was induced artificially in healthy volunteers; (3) they used non-conventional (for example, herbal or homoeopathic) or non-oral preparations.

We (KS and TF) screened potentially relevant citations independently and applied the selection criteria using an in/out/pending sheet in duplicate. We resolved any differences at any stage of the review through discussion. To be included a study had to meet all our inclusion criteria. We extracted data and assessed the quality of studies independently. We contacted investigators for additional information if necessary and obtained translations of abstracts or papers written in languages other than English or German. We were not masked with regard to trial authors or journals and instead of applying a trial quality score, we listed data on potential sources of bias such as randomisation, blinding, and follow up in a separate table (table 2).

Table 2 Quality assessment of included trials and potential sources of bias

Study	Blinding to treatment allocation				Drop outs/losses to follow up			Other			
	RP	Pt	Pr	OA	Total (n)	IG (n)	CG (n)	Reasons given?	PC?	HS?	Comments
Antitussives Taylor <i>et al</i> ⁶	NR	Yes	Yes	NR	8/57 (14%)	NR	NR	Yes	Yes	Yes	Post hoc power calculation shows 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.
Mucolytics Nespoli <i>et al</i> ¹⁰	NR	Yes	Yes	Yes	NR	NR	NR	Yes	No	No	High likelihood of bias.
Antihistamine-decongestant combinations Clemens <i>et al</i> ¹¹	NR	NR	Yes	Yes	NR	NR	NR	No	Yes	Yes	Patients stated to be "randomly assigned in a double blind fashion".
Hutton <i>et al</i> ¹²	NR	Yes	Yes	Yes	12/96 (12.5%)	6/36 (16.6%)	3/27 (11.1%)	Yes	Yes	Yes	Some children in open treatment group (n=9) and drug group (n=3) took other medication.
Other combinations Reece <i>et al</i> ¹³	NR	Yes	NR	NR	NR	NR	NR	No	No	No	High likelihood of bias, medication sponsored by medical director of a laboratory who also performed the analyses.
Antihistamines Sakchaimont <i>et al</i> ¹⁴	NR	Yes	Yes	Yes	7/150 (4.6%)	NR	NR	Yes	No	Yes	Bonferroni correction for multiple comparisons used.

RP, randomisation process used; Pt, patient; Pr, provider; OA, outcome assessor; IG, intervention group; CG, control group; PC, power calculation reported; HS, hypothesis stated a priori; NR, not reported or unclear.

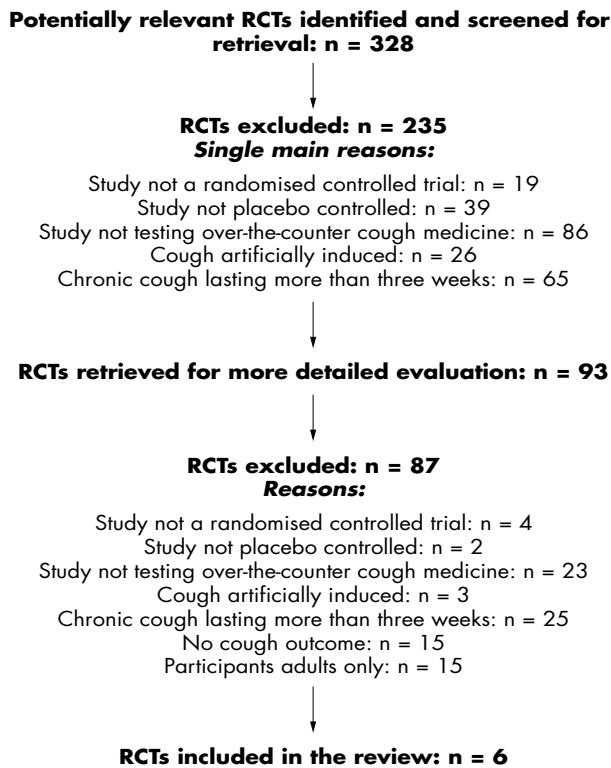


Figure 1 Progress through the stages of the systematic review.

RESULTS

Trial flow

We evaluated 328 citations and abstracts from all sources, of which six trials involving 438 children met all our inclusion criteria (fig 1).⁹⁻¹⁴

Study characteristics

Table 3 summarises the characteristics of included RCTs which we grouped into five drug classes (see table 1). The number of trials in each group ranged from one to a maximum of two. Cough outcomes included frequency and severity and were reported by the parents using cough scores. Four studies reported data on adverse effects.

The methodological quality of included studies was generally low (table 2). None of the six RCT reports stated the randomisation process. In four studies the outcome assessors were blind to treatment allocation, and three studies did not report whether participants and/or treatment providers were blinded. Loss to follow up was documented in three studies, with differential loss to follow up in the treatment arms reported in only one study. None of the studies fulfilled all the quality criteria. Three trials reported a power calculation.

Quantitative data synthesis

We felt that pooling of the results was inappropriate because of the small numbers of trials in each category, the limited quantitative data available, and the notable differences between trials in terms of participants, interventions, and outcome measurements.

Effects on cough

Table 3 summarises the impact of OTC cough preparations on cough outcome.

Antitussives

One study involving 57 children with night cough compared a single dose for three nights of dextromethorphan and codeine with placebo.⁹ 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 3. Adverse effects included drowsiness, diarrhoea, and hyperactivity with no statistically significant differences between the three groups.

Mucolytics

One study involving 40 children compared the mucolytic leto-steine with placebo.¹⁰ The symptom score on a four point scale favoured active treatment from day 4 until day 10, with an average difference of about 0.2 points ($p < 0.01$). No adverse effects were reported in both groups.

Antihistamine–decongestant combinations

Two studies involving 155 children compared antihistamine–decongestant combinations with placebo.^{11 12} Brompheniramine/phenylpropanolamine was no more effective than placebo in reducing the number of children coughing two hours after each dose (49.0% v 43.1%, $p = 0.66$). A higher proportion of children were 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.¹¹

In the second study ($n = 96$), brompheniramine/phenylephrine/phenylpropanolamine was no more effective than placebo or no treatment in improving cough symptoms (67% v 58% and 70%, $p = 0.5$ and $p = 0.8$ respectively).¹²

Other drug combinations

One trial involving 43 children tested two paediatric cough syrups (Triaminicol syrup and Dorcol pediatric cough syrup).¹³ 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 ($p = 0.5$). Adverse effects were not reported.

Antihistamines

One trial involving 143 children compared the antihistamines clemastine and chlorpheniramine with placebo.¹⁴ 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 ($p = 0.2$). Drowsiness and sleepiness were reported in 20% of children, with no statistically significant difference between the groups.

DISCUSSION

Summary of key findings

In this systematic review we found that there is no good evidence for or against the effectiveness of OTC cough medicines in acute cough. This concurs with the findings of previous reviews.^{6 7} In the only study showing a statistically significant result, the effect size was small and of doubtful clinical relevance. OTC cough preparations were generally well tolerated and did not lead to major adverse effects. Many of the reported adverse effects could in fact have been a result of the underlying URTI.

Study limitations and potential sources of bias

The results of this systematic review have to be interpreted with caution, as the number of trials in each category was small. Studies were very different with regard to settings, populations, interventions (drugs, doses, and frequency) and outcome measures, making them difficult to compare. Individual RCTs were of variable methodological quality with respect to randomisation, blinding of outcome assessment, and losses to follow up. Many studies described differences in cough scores between the treatment groups, which are difficult to interpret for the purpose of making informed treatment decisions.

Table 3 Characteristics of RCTs of OTC cough preparations versus placebo for the treatment of acute cough

Study	Participants		Intervention				Outcome	Results	
	Participant characteristics (no., age, sex, smoking status), setting, country	Definition of illness	Drug	Dosage	Frequency	Treatment duration	Method of measuring main cough outcome	Efficacy	Adverse effects
Antitussives Taylor <i>et al</i> ⁸	57 children, mean age 4.7 years (range 18 months to 12 years), 53% boys, 82% white, private paediatric practices, USA	Night cough due to URTI	1. Dextromethorphan/guaiphenesin 2. Codeine/guaiphenesin	15mg/5ml (dextromethorphan), 100mg/5ml (guaiphenesin) 10mg/5ml (codeine) 100mg/5ml (age 18 months to 5 years: 2.5ml; 6 to 11 years: 5ml)	Single dose at bedtime	3 nights	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	Mainly drowsiness, diarrhoea and hyperactivity: placebo: 7/13 (54%), dextromethorphan: 6/19 (32%), p=0.2, codeine: 5/17 (29%), p=0.8
Mucolytics Nespoli <i>et al</i> ⁹	40 children, age range 2 to 12 years (median 7.5 years), paediatric clinic, Italy	Acute febrile bronchitis	Letosteine	25mg	Three times daily	10 days	Cough score from 0 to 3, unclear how 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 four to 10, p<0.01)	No side effects in both groups reported
Antihistamine-decongestant combinations Clemens <i>et al</i> ¹¹	59 preschool children (6 months to 5 years, mean age 2 years), 4 paediatric offices, USA	URTI of less than 7 days duration	Brompheniramine Phenylpropanolamine	2mg/5ml 12.5mg/5ml (6 mths to 1 year: ½ teaspoon, 2 to 5 years: 1 teaspoon)	4-hourly 'as needed'	48 hours	Parent questionnaire, 7-point likert scale, also counted 'responses' after each dose	Mean cough scores 4.67 (active treatment) and 4.57 (placebo), p=0.53.	Not reported. Higher proportion asleep in the active treatment group (41/88 responses = 47%) compared to placebo (28/65 responses = 26.5%)
Hutton <i>et al</i> ¹²	96 inner-city black children, 6 months to 5 years, mean age about 2 years, primary care clinic, USA	Symptoms of URTI	Brompheniramine Phenylephrine Propranolamine	4mg/5ml 5mg/5ml 5mg/5ml (doses calculated to achieve brompheniramine dosage of 0.5 to 0.75 mg/kg/day)	Three times daily	2 days	9-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 treatment (p=0.5 and 0.8 respectively)	Loose stools (n=1) in the placebo group and hyperactivity in the active treatment group (n=1)
Other combinations Reece <i>et al</i> ¹³	43 children, mean age 3.6 years (range 2 months to 12 years), 58% boys, ambulatory private practice, USA	Cough due to URTI	1. Triaminicol syrup: Phenylpropanolamine Pheniramine, Pyrilamine Dextromethorphan Ammonium chloride 2. Dorcol paediatric cough syrup: Dextromethorphan Phenylpropanolamine Glyceril guaiacolate Alcohol	12.5mg, 6.25mg, 6.25mg, 15mg, 90mg 7.5mg 8.75mg 37.5mg 5%	Unclear	Unclear	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*	Not reported

Table 3 Continued

Hypothesis stated a priori?	Participants		Intervention			Outcome		Results	
	Participant characteristics (no., age, sex, smoking status), setting, country	Definition of illness	Drug	Dosage	Frequency	Treatment duration	Method of measuring main cough outcome	Efficacy	Adverse effects mg/kg/day
Antihistamines Sakchainanont <i>et al</i> ¹⁴	143 children under 5 years, mean age 23 months (range 1.5 to 60 months), 50% girls, paediatric outpatients, Thailand	Common cold	Group I: clemastine Group II: chlorpheniramine	0.05mg/kg/day 0.35mg/kg/day	Twice daily Three times daily	3 days	Parent assessment using 4-level symptom score	Cough 'improved' in 19/48 (39.6%) in the demastine group and in 19/48 (39.6%) in the chlorpheniramine group compared with 13/47 (27.6%) taking placebo (p=0.2)	Increased drowsiness and sleepiness reported in 20% of children with no differences between treatment groups

* p values calculated from percentages.
URTI, upper respiratory tract infection.

Although we attempted to obtain information on unpublished studies, we received little response from pharmaceutical companies and study authors. If studies with negative results were less likely to be submitted for publication, this could have led to publication bias.

Implications

Cough caused by URTI can be a very troublesome symptom for a child, and for a health professional, not to offer any treatment may seem unacceptable to many parents and lay people. However, as this systematic review shows, there is very little evidence to suggest that OTC cough medicines are effective. For this reason, we cannot recommend these as first line treatment for acute cough. It is, however, vital that paediatricians, GPs, and other health care workers take the symptoms of acute cough seriously, taking a careful history and performing a thorough physical examination to search for possible underlying diagnoses. If a viral URTI seems the most likely diagnosis, the treatment options and the lack of evidence for the effectiveness of OTC cough medicines should be discussed carefully with parents. Whether a child is being treated or not, parents should always be offered a further appointment in case the cough persists, which may suggest the possibility of another underlying condition.

At present, the NHS encourages self medication for acute self limiting illnesses and the use of cough preparations as a home remedy.⁴ Though OTC cough preparations appear to be relatively free from adverse effects, their safety in children has been questioned.¹⁵ In addition, purchase of OTC cough medicines may lead to an unnecessary financial burden for health care consumers.

If health professionals want to recommend OTC cough medicines to parents of children who suffer from cough caused by acute URTI, advice should be restricted to less expensive preparations until more evidence about their effectiveness becomes available.

Suggestions for future research

Health professionals need more evidence from carefully designed RCTs before recommending OTC cough medicines to their patients. Identification of effective self care treatments may help reduce suffering in children with cough as well as the number of consultations in primary care. Future studies should therefore use outcome measures that can be easily used in a primary care setting and that produce clinically meaningful results.

Conclusions

We conclude from the limited evidence available that OTC cough medicines do not appear to be more effective than placebo in acute cough caused by URTI and should not be recommended as a first line treatment for the resolution of acute cough. Although these medicines are generally well tolerated, their use may lead to unnecessary expenses for health care consumers.

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Schoolchildren born of heroin dependent mothers

A report from Jerusalem (Asher Ornoy and colleagues. *Developmental Medicine and Child Neurology* 2001;**43**:668–75) has shown the effects of maternal heroin dependency on school age children. The study included 65 children born to heroin dependent mothers, 34 of whom had been adopted. They were compared with 33 children of heroin dependent fathers, 32 children with environmental deprivation but no parental addiction, and 30 control children. All children in the study were aged 5–12 years and attending mainstream schools. The children of heroin dependent mothers raised at home were of low gestational age (mean 35 weeks) and birthweight (mean 2410 g). On tests of verbal and performance skills, reading, and arithmetic the environmentally deprived, drug dependent father, and home-raised drug dependent mother groups all did significantly worse than the control group. The adopted children born of drug dependent mothers, however, performed normally apart from poor performance skills. Attention deficit hyperactivity disorder (ADHD) was common among all children of heroin dependent parents and among environmentally deprived children, but commonest among home raised children of heroin dependent mothers. These mothers also had a high rate of childhood ADHD.

The children of drug dependent parents performed poorly at school when raised at home. Those adopted at an early age performed almost normally. ADHD was common in the children and their mothers.