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

K Schroeder, T Fahey

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.

Table 1: Modes of action in groups of OTC cough medicines

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Modes of action in groups of OTC cough medicines</th>
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</thead>
<tbody>
<tr>
<td>Antitussives</td>
<td>Centrally acting opioid derivatives or peripherally acting agents</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>Aiming to decrease the viscosity of bronchial secretions, making them easier to clear through coughing</td>
</tr>
<tr>
<td>Antihistamine–decongestant combinations</td>
<td>Combine histamine H1 receptor antagonists and α adrenergic agonists which cause vasoconstriction of mucosal blood vessels</td>
</tr>
<tr>
<td>Other drug combinations</td>
<td>Fixed drug combinations using different ingredients</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Histamine H1 receptor antagonists</td>
</tr>
</tbody>
</table>

Abbreviations: NHS, National Health Service; OTC, over the counter; RCT, randomised controlled trial; URTI, upper respiratory tract infection
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.
One study involving 57 children with night cough compared a single dose for three nights of dextromethorphan and codeine with placebo.7 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 dextromethorphan against 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 (26.3%, p = 0.53), and no other adverse effects were reported.8 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 demecolamine 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.8,9 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>
<thead>
<tr>
<th>Study</th>
<th>Participant characteristics</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Antitussives</td>
<td>57 children, mean age 4.7 years (range 18 months to 12 years), 53% boys, 82% white, private paediatric practices, USA</td>
<td>Dextromethorphan/guaiphenesin, Codeine/guaiphenesin</td>
<td>Parent questionnaire, cough score from 0 to 4</td>
<td>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</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>40 children, age range 2 to 12 years (median 7.5 years), paediatric clinic, Italy</td>
<td>Letosteine</td>
<td>Cough score from 0 to 3, unclear how measured</td>
<td>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&lt;0.01)</td>
</tr>
<tr>
<td>Antihistamine–decongestant combinations</td>
<td>59 preschool children (6 months to 5 years, mean age 2 years), 4 paediatric offices, USA</td>
<td>Brompheniramine, Phenylephrine, Propanolamine</td>
<td>Parent questionnaire, 7-point Likert scale, also counted ‘responses’ after each dose</td>
<td>Mean cough scores 4.67 (active treatment) and 4.57 (placebo), p=0.53.</td>
</tr>
<tr>
<td>Hutton et al</td>
<td>96 inner-city black children, 6 months to 5 years, mean age about 2 years, primary care clinic, USA</td>
<td>Brompheniramine, Phenylephrine, Propanolamine</td>
<td>‘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)</td>
<td>Not reported. Higher proportion asleep in the active treatment group (41/88 responses = 47%) compared to placebo (28/65 responses = 26.5%) in the placebo group and hyperactivity in the active treatment group (n=1) in the placebo group.</td>
</tr>
<tr>
<td>Other combinations</td>
<td>43 children, mean age 3.6 years (range 2 months to 12 years), 58% boys, ambulatory private practice, USA</td>
<td>Triaminicol syrup: Phenylpropanolamine, Pheniramine, Pyrilamine, Dextromethorphan, Ammonium chloride, Dextrocin, Dextrophan</td>
<td>Parent assessment</td>
<td>‘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</td>
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</table>
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. Though OTC cough preparations appear to be relatively free from adverse effects, their safety in children has been questioned. 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.

ACKNOWLEDGEMENTS
We thank Steve McDonald and Ron D’Souza for their support in designing the search strategy and performing additional searches. Many thanks also to Debbie Sharp and Massimo Pignatelli for their help with the French and Italian translations. Both authors were involved in all stages of the review. This review is registered for inclusion in the Cochrane database of systematic reviews. The Division of Primary Health Care, University of Bristol and the South & West Research and Development Directorate funded this study. KS is funded through an MRC Training Fellowship in Health Services Research. TF is funded through the NHS R&D National Primary Care Career Scheme.

Table 3
Continued

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

*p values calculated from percentages.

URTI, upper respiratory tract infection.

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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.