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[Intervention Review]

# Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

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## ABSTRACT

### Background

Cough is often distressing for patients with pneumonia. Accordingly they often use over-the-counter (OTC) cough medications (mucolytics or cough suppressants). These might provide relief in reducing cough severity, but suppression of the cough mechanism might impede airway clearance and cause harm.

### Objectives

To evaluate the efficacy of OTC cough medications as an adjunct to antibiotics in children and adults with pneumonia.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to July 2009); OLDMEDLINE (1950 to 1965); and EMBASE (1980 to July 2009).

### Selection criteria

Randomised controlled trials (RCTs) in children and adults comparing any type of OTC cough medication with placebo, or control medication, with cough as an outcome and where the cough is secondary to acute pneumonia.

### Data collection and analysis

We independently selected trials for inclusion. Data were extracted from these studies, assessed for methodological quality without disagreement, and analysed using standard methods.

**Main results**

Four studies were included with a total of 224 participants; one was performed exclusively in children and three in adolescents or adults. One using an antitussive had no extractable pneumonia-specific data. Three different mucolytics (bromhexine, ambroxol, neltenexine) were used in the remaining studies, of which only two had extractable data. They demonstrated no significant difference for the primary outcome of 'not cured or not improved' for mucolytics. A secondary outcome of 'not cured' was reduced (odds ratio (OR) 0.36, 95% confidence interval (CI) 0.16 to 0.77; number needed to treat (NNT) 5, 95% CI 3 to 16 for children and OR 0.32, 95% CI 0.13 to 0.75; NNT 5, 95% CI 3 to 19 for adults). In a post hoc analysis combining data for children and adults, again there was no difference in the primary outcome of 'not cured or not improved' (OR 0.85, 95% CI 0.40 to 1.80) although mucolytics reduced the secondary outcome 'not cured' (OR 0.34, 95% CI 0.19 to 0.60; NNT 4, 95% CI 3 to 8).

**Authors' conclusions**

There is insufficient evidence to decide whether OTC medications for cough associated with acute pneumonia are beneficial. Mucolytics may be beneficial, but there is insufficient evidence to recommend them as an adjunctive treatment for acute pneumonia. This leaves only theoretical recommendations that OTC medications containing codeine and antihistamines should not be used in young children.

## PLAIN LANGUAGE SUMMARY

**Over-the-counter medications to help reduce cough for children and adults on antibiotics for acute pneumonia**

Over-the-counter (OTC) medications, including mucolytics and antitussives, are commonly used by patients and recommended by healthcare staff as adjuncts in the treatment of pneumonia. In this review we found insufficient evidence to draw any conclusions about the efficacy of any OTCs taken as adjuncts for cough associated with acute pneumonia. Mucolytics may be beneficial but the lack of consistent evidence precludes recommending the routine use of mucolytics as an adjunct in the treatment of troublesome cough associated with pneumonia in children or adults.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Mucolytics as an adjunct to antibiotics to reduce cough in acute pneumonia in children and adults**

**Patient or population:** children and adults with acute pneumonia
**Settings:** any
**Intervention:** mucolytics (and antibiotics)[1]
**Comparision:** antibiotics only

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | antibiotics only | mucolytics (and antibiotics) | | | | |
| **Cough score** Scale from: 0 (absent) to 3 (very severe). (follow-up: 3 days) | The mean cough score in the control groups was **1.45** | The mean Cough score in the intervention groups was **0.25 lower** (0.33 to 0.17 lower) | | 120 (1) | ⊕⊕◯◯ **low**[2,3,4] | Data for children only. |
| **Number of people who had not improved or had not been cured** (follow-up: 7 to 10 days) | **16 per 100** | **14 per 100** (7 to 26) | **OR 0.85** (0.4 to 1.8) | 221 (2) | ⊕⊕◯◯ **low**[2,5] | Fewer people represents a benefit |
| **Adverse events** (follow-up: 10 days) | See comment | See comment | Not estimable | 120 (1) | See comment | 1 study in children provided data specific to participants with pneumonia - there were no adverse events |
| **Complications (e.g. medication change)** | See comment | See comment | Not estimable | 0 (0) | See comment | Complications were not measured in the trials. |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidance
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] In addition to antibiotics, people with pneumonia often use over-the-counter (OTC) cough medications when at home or request OTC cough medicaitons when in hospital to suppress an annoying cough. There is a question as to whether suppressing cough may prolong pneumonia. Over-the-counter cough medications can include anti-tussives, expectorants, anti-histamine-decongestants, anti-histamines and mucolytics (such as bromhexine, ambroxol and neltenexine).

[2] Allocation concealment unclear.

[3] Scale not validated.

[4] Sparse data.

[5] Sparse data; confidence interval does not rule out the potential for "more people" not improved or cured with mucolytics.

# BACKGROUND

## Description of the condition

Cough is the most common symptom presenting to general practitioners (Britt 2002; Cherry 2003). It has multiple causes, including pneumonia. Whatever the cause, attempting to reduce the impact of the symptom of cough is reflected in the billions spent on over-the-counter (OTC) cough medications. Cough impairs quality of life (French 2002) and causes significant anxiety to the parents of children (Cornford 1993). Accordingly, patients with pneumonia sometimes self medicate with OTC cough medications in ambulatory settings, or ask for them in hospital.

## Description of the intervention

A Cochrane review showed that antihistamine alone has little clinical benefit in adults or children for the common cold, although in combination they might be of (non-significant) benefit (De Sutter 2003). In the management of acute cough, in the ambulatory setting, combination rather than single OTC drugs showed a benefit (Schroeder 2004). Of the little data available in young children, antihistamines, neither singly nor in combination, were effective for relieving acute cough (De Sutter 2003; Schroeder 2004). Moreover they are associated with potentially significant adverse events including altered consciousness, arrhythmia and death (Gunn 2001; Kelly 2004). Neither of these reviews included patients with pneumonia (De Sutter 2003; Schroeder 2004).

## How the intervention might work

Cough is usually divided into acute or chronic according to its duration and age group. It is defined as chronic if over eight weeks duration in adults; and over three to four weeks in children (Chang 2005). This reflects the different conditions causing chronic cough in different age groups. In contrast, in this review we examined the efficacy of OTC medication for acute cough in acute pneumonia, where the pathophysiological processes (albeit poorly understood) are likely to be the same in children and adults. Methods for determining cough outcomes are similar in adults and children, although these methods remain poorly standardised. Objective measurements of cough include cough frequency and cough sensitivity outcomes, whilst subjective measurements of cough may broadly encompass quality of life and outcomes based on diaries etc. (Birring 2006; Chang 2003).

## Why it is important to do this review

Although OTC cough medications might provide some relief by reducing the severity of the cough, they might also be harmful in prolonging pneumonia (by suppressing the cough reflex, which might cause retention of airway debris). Thus, a systematic review of their benefits or harms is useful to help guide clinical practice.

# OBJECTIVES

To evaluate the efficacy of OTC medications for cough as an adjunct to antibiotics in children and adults with pneumonia.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All randomised controlled trials (RCTs) comparing any type of OTC cough medication with a placebo (or control group) with cough as an outcome and where cough is secondary to acute pneumonia. Quasi-randomised trials were excluded.

### Types of participants

We considered studies of both children and adults with cough of less than four weeks in duration that was related to pneumonia. We specifically excluded studies of cough of more than four weeks in duration and cough related to another underlying cardio-respiratory condition (for example, suppurative lung disease, chronic obstructive airway disease, asthma). However, we considered studies which included cough of mixed aetiologies if data were available for the subgroup of patients with pneumonia.

### Types of interventions

Randomised controlled comparisons of any type of OTC cough medication as an adjunct therapy to antibiotics. Trials comparing only two or more medications without a placebo comparison group were not included. Trials that included the use of other medications or interventions were included if all participants had equal access to such medications (including antibiotics) or interventions.

### Types of outcome measures

We attempted to obtain data on at least one of the following outcome measures.

### Primary outcomes

1. Proportions of participants who were not cured or not substantially improved at follow up (failure to improve was measured according to the hierarchy listed below in Secondary outcomes).

### Secondary outcomes

1. Proportions of participants who were not cured at follow up.
2. Change in quantitative differences in cough (cough frequency, cough scores, other quantitative outcomes based on cough diary).
3. Proportions experiencing adverse effects of the intervention (for example, sleepiness, nausea etc.).
4. Proportions experiencing complications (for example, requirement for medication change etc.).

Individual trial definitions were adopted and recorded.

As it was likely that studies may have differed in their definitions of cure and improvement, we adopted a hierarchical approach that employed the reported outcome measures. For example, if both an objective measure and a subjective measure of cough frequency were reported, we were to adopt the objective measure in assessing the efficacy of treatment. Our hierarchy of outcome measures was as follows.

1. Objective measurements of cough indices (cough frequency, cough receptor sensitivity).
2. Symptomatic (quality of life, Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by the patient (adult or child).
3. Symptomatic (quality of life, Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by the parents or carers.
4. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by clinicians.
5. Fever, respiratory rate, oxygen requirement.
6. Non-clinical outcomes (chest radiology, white cell count, C-reactive protein, erythrocyte sedimentation rate, lung function test (spirometry)).
7. Eradication of micro-organism(s) causing the pneumonia.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to July Week 1, 2009); OLDMEDLINE (1950 to 1965); EMBASE (1980 to July 2009).

The following search strategy was run in MEDLINE and CENTRAL and adapted for EMBASE (see Appendix 1).

**MEDLINE (OVID)**

1 exp Cough/
2 cough.mp.
3 or/1-2
4 exp Pneumonia/
5 pneumonia.mp.
6 or/4-5
7 exp Antitussive Agents/
8 antitussive agent$.mp.
9 exp Expectorants/
10 expectorant$.mp.
11 exp Cholinergic Antagonists/
12 cholinergic antagonist$.mp.
13 exp Histamine H1 Antagonists/
14 histamine H1 antagonist$.mp.
15 mucolytic$.mp.
16 exp Drug Combinations/
17 drug combination$.mp.
18 exp Drugs, Non-Prescription/
19 non prescription drug$.mp.
20 (over-the-counter or over the counter or OTC).mp.
21 or/7-20
22 3 and 6 and 21

There were no language or publication restrictions.

### Searching other resources

We also searched lists of references in relevant publications.

## Data collection and analysis

### Selection of studies

From the title, abstract or descriptors, two review authors (CCC, ABC) independently reviewed the literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text, using specific criteria, the same two review authors independently selected trials for inclusion. There was no disagreement. It was planned that disagreements would have been adjudicated by a third review author (ACC).

### Data extraction and management

Trials that satisfied the inclusion criteria were reviewed and the following information extracted: study setting; year of study; source of funding; patient recruitment details (including number of eligible patients); inclusion and exclusion criteria; other symptoms; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants, care

providers and outcome assessors; dose and type of intervention; duration of therapy; co-interventions; numbers of patients not followed up; reasons for withdrawals from study protocol (clinical, side effects, refusal and other); details on side effects of therapy and whether intention-to-treat analyses were possible. Data were extracted on the outcomes described previously. It was planned that further information would be requested from the trial authors, where required.

### Assessment of risk of bias in included studies

Two review authors (CCC, ABC) independently performed a potential bias assessment on studies included in the review. Four components of potential bias were assessed and are described below under ' Assessment of reporting bias'

### Measures of treatment effect

An initial qualitative comparison of all the individually analysed studies was undertaken to determine if pooling of results (meta-analysis) was reasonable. This took into account differences in study populations, inclusion and exclusion criteria, interventions, outcome assessment and estimated effect size. The results from studies that met the inclusion criteria and reported any of the outcomes of interest were included in the subsequent meta-analyses.

### Unit of analysis issues

Had there been any crossover studies, mean treatment differences would have been calculated from raw data, extracted or imputed and entered as fixed-effect generic inverse variance (GIV) outcomes, to provide summary weighted differences and 95% CIs. Only data from the first arm would have been included in a meta-analysis where data were combined with parallel studies (Elbourne 2002).

### Dealing with missing data

It was planned that authors be contacted for missing data when the studies were less than 15 years old.

### Assessment of heterogeneity

Any heterogeneity between the study results was described and tested to see if it reached statistical significance, using the $I^2$ statistic (Higgins 2003). Heterogeneity is considered significant when the P value of the $Chi^2$ test is < 0.10 (Higgins 2005). The 95% CI estimated using a random-effects model would have been included had there been concerns about statistical heterogeneity.

### Assessment of reporting biases

1. Allocation concealment. Trials were scored as: Grade A, adequate concealment; Grade B, unclear; Grade C, clearly inadequate concealment. (Grade A = high quality)
2. Blinding. Trials were scored as: Grade A, participant, care provider and outcome assessor blinded; Grade B, outcome assessor blinded; Grade C, unclear; Grade D, no blinding of outcome assessor. (Grades A, B = high quality)
3. Reporting of participants by allocated group. Trials were scored as: Grade A, the progress of all randomised children in each group described; Grade B, unclear or no mention of withdrawals or dropouts; Grade C, the progress of all randomised children in each group clearly not described. (Grade A = high quality)
4. Follow up. Trials were scored as: Grade A, outcomes measured in more than 90% (where withdrawals due to complications and side effects are categorised as treatment failures); Grade B, outcomes measured in 80% to 90%; Grade C, unclear; Grade D, outcomes measured in less than 80%. (Grade A = high quality)
5. While only the allocation concealment quality assessments are displayed in the meta-analysis figures, all assessments are included in the 'Characteristics of included studies' table. Inter-review author reliability for the identification of high quality studies for each component is measured by the Kappa statistic.

### Data synthesis

For the dichotomous outcome variables of each individual study, odds ratio was calculated using a modified intention-to-treat (ITT) analysis. This analysis assumed that participants not available for outcome assessment had not improved (and probably represented a conservative estimate of effect). The summary weighted odds ratio and 95% confidence interval (CI) (fixed-effect model) was calculated using Review Manager (version 5). Number needed to treat to benefit (NNTB) was calculated from the pooled odds ratio (OR) and its 95% CI, applied to a specified baseline risk using an online calculator (Cates 2003).

The cough indices were assumed to be normally distributed continuous variables so that the mean difference in outcomes could be estimated (mean difference). If studies had reported outcomes using different measurement scales, the standardised mean difference would have been estimated.

### Subgroup analysis and investigation of heterogeneity

An a priori subgroup analysis was planned for:

(a) children (14 years and younger) versus adolescents and adults (older than 14 years);

(b) hospitalised versus ambulatory settings;

(c) classes of OTC cough medications:

(i) antitussives (codeine and derivatives);

(ii) expectorants;

(iii) mucolytics;
(iv) antihistamine-decongestant combinations;
(v) antihistamines alone;
(vi) other drug combinations;
(vii) males versus females in adults.

### Sensitivity analysis

It was planned that sensitivity analyses be carried out to assess the impact of potentially important factors on the overall outcomes:
(a) study quality;
(b) study size;
(c) variation in the inclusion criteria;
(d) differences in the medications used in the intervention and comparison groups;
(e) differences in outcome measures;
(f) analysis using random-effects model;
(g) analysis by 'treatment received';
(h) analysis by 'intention to treat';
(i) analysis by study design, parallel and crossover studies.

## RESULTS

## Description of studies

### Results of the search

In the first version of this review (Chang 2007), the search identified 238 potentially relevant titles. After reviewing the abstracts, 21 full-text papers were obtained; 17 were excluded (details are provided in the 'Characteristics of excluded studies' table), most on the basis of being non-randomised, with no placebo. A review article (Ida 1997) described three studies of dimemorfan, (a dextromethorphan analogue), which were not found by the search. One of these was described as a placebo controlled trial (the other two were not), but we could not obtain it, and nor were sufficient details provided in the review article (Ida 1997). Another paper described three studies, of which one appeared to include patients with acute lower respiratory tract infection (specified as acute bronchitis or bronchoalveolitis but which may have included patients with pneumonia) (Mancini 1996). We attempted to contact the study authors but were not able to extract data on the subgroup of patients with pneumonia, and thus we excluded the trial from further analysis.
In this 2009 update, we identified two studies on erdosteine (a mucolytic agent) but these were excluded as they are available only on medical prescription in countries with tight regulatory control of medications such as USA, Australia and the UK (Balli 2007; Titti 2000).

### Included studies

Four studies were included, as described in the 'Characteristics of included studies' table; all were available in English. However, data specific for pneumonia were only available in two papers (Principi 1986; Roa 1995). Authors of three papers did not respond to our correspondence requesting for further pneumonia-specific data.
Of the included studies, one study was exclusively in children (Principi 1986), two were exclusively in adults (Aquilina 2001; Azzopardi 1964) and one included adolescents and adults (Roa 1995). One study utilised an antitussive (Dimyril) (Azzopardi 1964) and three of the studies examined the efficacy of different formulations of mucolytics (bromhexine (Roa 1995), neltenexine (Aquilina 2001) and ambroxol (Principi 1986)). In two of these studies, the concomitant antibiotics used were reported (Principi 1986; Roa 1995). Two studies were multi-centre studies (Principi 1986; Roa 1995) of which the funding was unspecified. Two studies were single-centre studies (Aquilina 2001; Azzopardi 1964). One study was a controlled non-placebo study (Roa 1995) and the rest utilised a randomised placebo-control design (Aquilina 2001; Azzopardi 1964; Principi 1986). All but one study (Azzopardi 1964) used a parallel design. The inclusion and exclusion criteria (that is, including the definition of pneumonia) varied between the studies; only one study was exclusively in patients with pneumonia (Principi 1986). In Roa (Roa 1995), bacterial pneumonia was defined as the presence of recent productive phlegm, fever or leucocytosis (> 10,000 $mm^3$) and pulmonary infiltrates on radiographic examination. In Principi (Principi 1986) inclusion required either a positive blood culture for a well-defined bacterium or a chest X-ray (CXR) showing lobar or sub lobar involvement together with raised inflammatory markers, erythrocyte sedimentation rate $\geq$ 30 mm/h and reactive C protein $\geq$ 25 $\mu$g/mL. The two smaller papers (Aquilina 2001; Azzopardi 1964) which contributed rather fewer numbers to the analysis did not clearly define pneumonia.
The outcomes of the studies also varied and none utilised a validated scale for cough. The larger trials, Roa and Principi, were performed and published 12 and 21 years ago, respectively, and so were not methodologically as robust as one would expect of current-day trials (Principi 1986; Roa 1995). The Roa 1995 trial evaluated clinical response, bacteriological response and each clinical symptom by a visual analogue scale. Both clinical and bacteriological responses had clearly defined definitions; they defined cure as complete disappearance of pre-treatment signs and symptoms, improvement as an improvement on the visual analogue scale but less than cure. Principi 1986 evaluated clinical and radiological signs and used absolute numbers and severity scores to evaluate clinical symptoms and signs, including cough. The Aquilina 2001 trial used severity scores on pre-specified examination days and at the end of therapy, the investigator expressed an overall assessment of the therapeutic efficacy. The Azzopardi 1964 trial was more obviously subjective in its evaluation.

### Excluded studies

As described above, 17 trials were excluded (details are provided in the 'Characteristics of excluded studies' table), most on the basis of being non-randomised, with no placebo.

## Risk of bias in included studies

On the quality assessment scale, two studies scored high quality on two assessments (Principi 1986; Roa 1995) and the remaining two had only one high-quality point (Aquilina 2001; Azzopardi 1964). Agreement between the review authors for the scores was good: weighted Kappa score for the quality assessment scale was 0.63.

### Allocation

See 'Characteristics of included studies' table.

### Blinding

See 'Characteristics of included studies' table.

### Incomplete outcome data

See 'Characteristics of included studies' table.

## Effects of interventions

See: **Summary of findings for the main comparison**

In one study (Azzopardi 1964) the number of participants with pneumonia was not specified. In the other three included studies (Aquilina 2001; Principi 1986; Roa 1995) the total number of randomised participants was 555, of which 224 had pneumonia. The total number who completed the trials was 518, of which 219 had pneumonia. Given the lack of data, meta-analysis could not be performed on any outcome when children and adults were considered separately and, thus, sensitivity analysis was irrelevant. Single study results and the data and analysis section are described below.

#### Paediatric

#### Mucolytics

Principi reported that cough disappeared more rapidly in children treated with ambroxol than in the placebo group (Principi 1986). However, in the data and analysis section for the primary outcome (Analysis 1.1) of 'not cured or not improved' (defined on CXR), there was no significant difference between groups, OR 0.40, 95% CI 0.10 to 1.62. There was also no difference between groups for the secondary outcome of 'no improvement' (Analysis 1.2), OR 0.40, 95% CI 0.10 to 1.62. However, for the secondary outcome of clinically 'not cured' there was a significant difference between groups (defined on CXR) as presented in the data and analysis section (Analysis 1.3), favouring the ambroxol group. The OR was 0.36, 95% CI 0.16 to 0.77 and the NNTB was 5, 95% CI 3 to 16.

For the outcome of cough scores Principi reported a significant difference between groups, favouring the ambroxol group from day three onwards (Principi 1986). The data and analysis section for mean cough scores on days 3 and 10 are shown in Analysis 2.1 and Analysis 2.2. For day 3, the mean difference was -0.25, 95% CI -0.33 to -0.17. For day 10, the mean difference was -0.15, 95% CI -0.17 to -0.13.

The trial authors reported no significant adverse events in either group (Principi 1986).

#### Other OTCs

There were no studies on any other type of OTC medication for cough associated with pneumonia in children.

#### Adults

#### Antitussives

The Azzopardi study on 34 adults (total number assumed based on study design, see the 'Characteristics of included studies' table) included adults with pneumonia (number unknown) in addition to other lower respiratory tract infection aetiologies (Azzopardi 1964). Data on those with pneumonia alone were not available and are not described here.

#### Mucolytics

The Roa study reported that for the total group (that is, adults with pneumonia and bronchitis) the differences between cough frequency on days three, five and seven and baseline were significantly larger in the bromhexine group compared to the control group (Roa 1995). There was also a difference between groups (favouring bromhexine) for cough discomfort and ease of expectoration on days three and five, but not on day seven, as well as sputum volume on day three, but not on days five or seven. There was no difference between the groups for difficulty in breathing or chest pain on any day. At final evaluation significantly more participants were 'cured' (46%) in the bromhexine group compared to the control group (34%) (Roa 1995).

Data specifically described for pneumonia was available only for global 'clinical response' and this is presented in the data and analysis section (Analysis 3). For the primary outcome of clinically 'not cured or not improved' (Analysis 3.1) there was no significant difference between groups, OR 1.21, 95% CI 0.48 to 3.04. There was also no significant difference between groups for the secondary outcome 'not improved', OR 1.21, 95% CI 0.48 to

3.04 (Analysis 3.2). However, like the results for children treated with a mucolytic, there was a significant difference between groups for the secondary outcome 'not cured', OR 0.32, 95% CI 0.13 to 0.75; NNTB 5, 95% CI 3 to 19, favouring those on bromhexine (Analysis 3.3). The authors reported a total of 11 adverse events, six in the active treatment group and five in the control group (Roa 1995).

In the study using neltenexine (a mucolytic), we could not obtain data specific for those with pneumonia (n = 3) (Aquilina 2001). The trial authors reported no significant adverse events in any of the groups (Aquilina 2001).

#### Other OTC cough medications

There were no studies on any other type of OTC medication for cough.

#### Combined data for children and adults

#### Mucolytics

In post hoc analysis, data on children and adults were combined. There was no significant statistical heterogeneity in any of the outcomes (Analysis 4.1 to Analysis 4.3). In the combined data, meta-analysis showed no significant difference between groups for the primary outcome (Analysis 4.1) of 'not cured or not improved', OR 0.85, 95% CI 0.40 to 1.80. There was also no significant difference between groups for the secondary outcome 'not improved' (Analysis 4.2), OR 0.80, 95% CI 0.38 to 1.67. However, Analysis 4.3 showed a significant difference between groups for the outcome 'not cured', OR 0.34, 95% CI 0.19 to 0.60); NNTB 4, 95% CI 3 to 8, favouring those on a mucolytic.

#### Sensitivity analyses

The only appropriate sensitivity analysis that could be performed was that for Analysis 4, Combined children and adults. Statistical heterogeneity was absent but given the clinical heterogeneity a random-effects model was used to re-examine the results. This revealed that there was still no significant difference between groups for Analysis 4.1 ('not cured or not improved') but the OR was altered with a wider confidence interval, OR 0.79, 95% CI to 0.27 to 2.29. For Analysis 4.2 ('not improved'), the non-significant difference was also unaltered but OR changed to 0.72, 95% CI 0.21 to 2.24. For Analysis 4.3 ('not cured'), the significant difference between groups was also preserved and there was no difference in the OR or 95% CI: OR 0.34, 95% CI 0.19 to 0.60); NNTB 4, 95% CI 3 to 8, favouring those on a mucolytic.

## DISCUSSION

Only a few studies have examined OTC medications for cough related to pneumonia.

### Summary of main results

Although four studies were included in this review, only data from two studies could be used (Principi 1986; Roa 1995). Both of these studies examined the efficacy of a mucolytic as an adjunct to the management of pneumonia and used cough as the principle outcome. In the primary outcome of 'not cured or not improved', there was no difference between groups when children and adults were considered separately, or when data were combined in a post hoc analysis. However, in one of the secondary outcomes ('not cured') the use of a mucolytic increased the cure rate similarly in both children and adults (NNTB = 5). Therefore, we cannot be confident of its efficacy. Nevertheless, based on Analysis 2.1, if a mucolytic is tried then the time to response, (that is, the 'expected timeframe to which a significant improvement is seen' (Chang 2006)), is three days. However, these data come from only a single study.

### Overall completeness and applicability of evidence

OTC medications for cough consist of a variety of drugs used as sole agents or in combination. These drugs include antitussives (such as codeine derivatives), antihistamines and non-pharmaceutical medications (for example, menthol) (Eccles 2002). However, it is also possible that non-pharmaceutical additives used (such as sugar, alcohol) may have a therapeutic effect, such that the placebo effect of medications for cough has been reported to be as high as 85% (Eccles 2002). Thus, it is not surprising that although the total sample size for the combined studies was not small (number = 224), there was no effect seen for the primary outcome. Given that there was a significant difference between groups, further evaluation on mucolytics using more robust outcomes (as outlined in the 'Implications for research') is certainly warranted.

Although adverse events were uncommon in the clinical trials identified in this study, there are case reports of severe adverse events, including severe morbidity and even death (Kelly 2004).

### Quality of the evidence

On the quality assessment scale, two studies scored high quality on two assessments (Principi 1986; Roa 1995) and the remaining two had only one high-quality point (Aquilina 2001; Azzopardi 1964). Thus, the quality of the evidence is low as shown on the Summary of findings for the main comparison.

### Potential biases in the review process

This systematic review is limited to four studies (with only two with extractable data) and in these studies only a single type of OTC for cough was examined. Thus, there is a clear lack of studies in this area. Also, the inclusion criteria and outcomes varied among trials.

## AUTHORS' CONCLUSIONS

### Implications for practice

With the lack of evidence, the routine use of OTC cough medications in treating children or adults with troublesome cough associated with pneumonia cannot be recommended. Of those tested, mucolytics are the only type of OTC medication that has been shown to be possibly efficacious. The 'time to response' (subjective cough severity) is three days when used in adjunct to an appropriate antibiotic. In current practice it is recommended that young children are not given OTC cough medications containing codeine derivatives and antihistamines because of the known adverse events of these medications.

### Implications for research

RCTs of OTC medications to determine their effectiveness in treating cough associated with pneumonia are clearly needed. Current guidelines advocate that studies of antitussives should take place in patients with a clearly defined clinical entity, such as pneumonia. Trials should be parallel studies and double blinded given the known problems in studying cough, specifically the large placebo and time period effects. Clinical, radiological and bacteriological responses should be objectively evaluated. Based on the above data, a short trial of seven days would suffice. Outcome measures for the clinical studies on cough should be clearly defined using validated subjective data and supported by objective data, if possible.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

### Aquilina 2001

| | |
|---|---|
| Methods | Single-centre double blind parallel placebo controlled RCT. Method of recruitment was not specified.<br>Concomitant antitussives, mucolytics and beta-2 agonist disallowed. Clinical evaluation performed on baseline, days 3, 7 and final. Subjects assessed for signs and symptoms relevant to diagnosis of acute or chronic lung disease including sputum volume and characteristics, dyspnoea, cough, pulmonary auscultation, difficulty in expectorating<br>Compliance not mentioned. Inclusion and exclusion criteria described in next column<br>Description of withdrawals or dropouts not mentioned.<br>Assessment of quality<br>1. Allocation concealment: Grade B<br>2. Blinding: Grade A<br>3. Reporting of participants by allocation group: Grade B<br>4. Follow up: Grade C |
| Participants | 14 subjects allocated to neltenexine, 14 to placebo. Three within group had pneumonia but data specific to pneumonia was unavailable. Mean age of total group was 57.5 years (SD 3.04).<br>Inclusion criteria: Adults (aged > 18 years) with acute and chronic lung disease.<br>Exclusion criteria: Pulmonary tuberculosis, lung cancer, allergy to neltenexine, severe bronchospasm (requiring beta-2 agonist, corticosteroids or aminophylline), or pregnant or lactating women |
| Interventions | Neltenexine (a mucolytic), 37.4 mg tds or placebo (one tablet tds) for 10 to 12 days |
| Outcomes | Overall physicians' assessment of efficacy scored; excellent, good, moderate, not satisfactory. Exact quantification unspecified.<br>Sputum volume, sputum characteristics (1 = serous to 5 = very purulent), and 5-point scores for dyspnoea, cough, pulmonary auscultation, difficulty in expectorating, from 0 (absent) to 4 very severe |
| Notes | Wrote to authors with no response.<br>Data for pneumonia alone not available. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Azzopardi 1964**

| | |
|---|---|
| Methods | Single-centre double blind placebo controlled RCT. Subjects recruited from inpatients in the geriatric unit of Barnet General Hospital, England. The method of randomisation and allocation was not described. When the medication (active or placebo) was considered ineffective, the pharmacist was asked to change to alternate treatment. Data card and observation record prepared for each subject, other medications recorded and authors indicated that these factors were taken into account when assessing response to trial drugs (but did not specify how). Inclusion and exclusion criteria not described. Description of withdrawals or dropouts not mentioned<br>Assessment of quality<br>1. Allocation concealment: Grade B<br>2. Blinding: Grade A<br>3. Reporting of participants by allocation group: Grade B<br>4. Follow up: Grade C |
| Participants | Total randomised unknown. Total described in group unclear as some subjects could have been counted twice given potential crossover methodology. If assumed crossover was undertaken for all, total randomised would be 34. Age of subjects not given. Subjects had variety of aetiological factors for cough (pneumonia, acute and chronic bronchitis, bronchiectasis, carcinoma, cardiac failure, cor pulmonale, nervous cough, coryza, influenza)<br>Inclusion and exclusion criteria not described. |
| Interventions | Dimyril (active ingredient = isoaminile citrate, a codeine derivative) or placebo in identical bottles. Dose used varied. Initially 3 to 4 times/day followed by 'as necessary' dosing of up to 5 times a day (1 to 2 g) |
| Outcomes | Outcomes not clearly specified.<br>Paper stated:<br>"The evidence of the patient, the several observers (day and night nurses, physician, and medico-social worker), the number of doses per 24 hours, and (when recorded) the actual cough frequencies were considered in deciding whether or not the nuisance and frequency of cough had been reduced" |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Principi 1986**

| | |
|---|---|
| Methods | Multi-centre double blind parallel placebo controlled RCT. Children recruited from 3 hospitals in Italy<br>Potential subjects admitted into hospital for symptoms of pneumonia screened for inclusion criteria (next column). Double blinded study and all subjects were treated as inpatients and re-evaluated daily for heart rate, respiratory rate, maximal rectal body temperature. Cough, dyspnoea and chest pathological scores also recorded daily. CXR on admission and end of treatment. Compliance not mentioned but presumed excellent given inpatient study<br>All children given antibiotics (see column on intervention). Other co-treatment (e.g. anti-pyretic agents) not mentioned. Inclusion and exclusion criteria described in next column<br>Description of withdrawals or dropouts not mentioned. As children were inpatients, assumed most followed up. CXR follow-up rate 115/120 = 95.8%<br>Assessment of quality<br>1. Allocation concealment: Grade B<br>2. Blinding: Grade A<br>3. Reporting of participants by allocation group: Grade B<br>4. Follow up: Grade A |
| Participants | Total of 120 children randomised - 60 in each arm. Outcome measure available for 115 children (57 active arm, 58 controls), 95.8%<br>Antibiotic with ambroxol group: mean age not given, 11 aged < 1 year, 9 aged 1 to 2 years, 19 aged 2 to 5 years, 21 aged 5 to 12 years. Gender - M: 28; F: 32. Mean body weight 17.1 kg (SD 1.08).<br>Antibiotic with placebo: Mean age not given, 12 children aged < 1 year, 11 aged 1 to 2 years, 20 aged 2 to 5 years, 17 aged 5 to 12 years. Gender - M: 38; F:22. Mean body weight 16.2 kg (SD 1.06)<br>Inclusion criteria: Children admitted into hospital for pneumonia. Have had blood culture performed before commencement of antibiotics and positive for well defined bacterium or a CXR showing lobar and sub lobar involvement, with ESR $\geq$ 30 mm/h and C-reactive protein $\geq$ 25 $\mu$g/mL<br>Exclusion criteria: Taken antibiotics, mucolytics or mucoregulatory drugs in the preceding week |
| Interventions | Trial medications consisted of ambroxol (1.5 to 2 mg/kg/day in two divided doses) or placebo for 10 days. All children also given antibiotics, chosen on basis of microbiological data or in accordance with literature on most probable aetiology for each age, for 7 to 10 days. Children aged < 5 years given oral amoxil or intramuscular ampicillin (50 mg/kg in 3 to 4 divided doses). Older children had oral erythromycin ethylsuccinate (50 mg/kg/day in 4 doses) |
| Outcomes | Cough, dyspnoea and chest pathological signs scored, ranging from 0 (absent) to 3 (very severe). CXR findings at the end of treatment was compared to pre-treatment CXR and expressed as normalised, improved or unchanged |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

**Roa 1995**

| | |
|---|---|
| Methods | Multi-centre double blind parallel RCT comparing amoxicillin plus bromhexine versus amoxycillin alone.<br>Subjects recruited from 22 centres involving internalists or pulmonologists in the Philippines<br>Potential subjects evaluated for inclusion criteria by history, examination, CXR, laboratory tests (blood counts, sputum). The method of randomisation and allocation was not described. Double blinded study and all subjects were treated as outpatients and re-evaluated on days 3, 5, 7 and 10. Compliance monitored by pill counting<br>Subjects allowed to receive medications for fever and constitutional symptoms but not any other cough expectorants or antimicrobials. Inclusion and exclusion criteria described in next column<br>Description of withdrawals or dropouts mentioned for entire group. Maximum follow-up rate 375/407 = 92% but less for other aspects<br>Assessment of quality<br>1. Allocation concealment: Grade B<br>2. Blinding: Grade A<br>3. Reporting of participants by allocation group: Grade A<br>4. Follow up: Grade B |
| Participants | Total of 407 subjects randomised - 201 in active Rx and 206 in control group. 392 completed study (192 active, 200 controls). Compliance of 80% in active group and 85% in control group<br>Amoxil with bromhexine group: Mean age 32 (SD 13) years, gender - 117 M: 75 F; 51 with pneumonia, 141 with bronchitis.<br>Amoxil alone: Mean age 32 (SD 12), gender - 130 M: 70 F; 50 with pneumonia, 150 with bronchitis<br>Inclusion criteria: Adolescents and adults aged 15 to 60 years with uncomplicated community acquired lower respiratory tract infection (pneumonia or bronchitis), clinically assessed to be bacterial in aetiology. Pneumonia defined as presence of cough < 2 weeks, purulent phlegm, fever and/or leucocytosis (> 10, 000 $mm^3$), and pulmonary infiltrates on CXR. Acute bronchitis defined as presence of cough < 2 weeks, purulent phlegm, fever and/or leucocytosis (> 10,000 $mm^3$). Sputum culture had to be sensitive to amoxil or if organism resistant, subject included if clinical response at Day 3 occurred on amoxil<br>Exclusion criteria: Frank respiratory failure, coexistent chronic disease (diabetes, renal failure, liver or renal impairment, terminal illness such as cancer, active tuberculosis, healed tuberculosis with bronchiectasis, chronic bronchitis or emphysema, heavy smokers (undefined)), pregnant or lactating, hypersensitivity to study drugs, or recent (< 2 weeks) treatment with antibiotics |
| Interventions | Active Rx = amoxil 240 mg and bromhexine 8 mg, both 4 times/day for 7 days<br>Control group: amoxil alone, 250 mg 4 times/day for 7 days. |
| Outcomes | Days 3, 5, 7 and 10. Subjects evaluated for clinical response, bacteriological response, subjective symptom scores, adverse events, compliance, complete blood count<br>Clinical response:<br>Cured = complete disappearance of pre-treatment symptoms and signs<br>Improvement = pre-treatment symptoms and signs improved but not cured<br>Failure = pre-treatment symptoms and signs did not improve or worsened<br>Indeterminate = clinical response could not be determined.<br>Clinical symptoms:<br>10 mm visual analog scale of symptoms of cough frequency, cough discomfort, difficulty breathing not related to cough, chest pain not related to cough, ease of expectoration<br>Bacteriologic response:<br>Eradication = absence of pre-treatment pathogen or no more culturable material could be expectorated<br>Persistence = presence of pre-treatment pathogen<br>Super-infection = appearance of resistant pathogen after starting treatment |

**Roa 1995** (*Continued*)

| | |
|---|---|
| | Indeterminate = bacteriologic response could not be reliably assessed |
| Notes | Wrote to authors with no response.<br>Data for pneumonia alone available only for global clinical response outcome |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment? | Unclear risk | B - Unclear |

tds: three times a day
CXR: chest X-ray
Rx: treatment

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

| Study | Reason for exclusion |
|---|---|
| Aliprandi 2004 | Non-placebo trial. Study involves comparing levodropropizine, codeine and cloperastine to levocloperastine |
| Balli 2007 | Erdosteine is not legally available as an over-the-counter medication in countries such as Australia, UK and USA. Study compared amoxil plus erdosteine to amoxil-placebo in children with acute lower respiratory tract infections |
| Barberi 1993 | Non-placebo study comparing nimesulide to lysine-aspirin in children |
| Bartolucci 1981 | Non-controlled study in 40 adults using anti-phlogistic-balsamic compound (in Italian) |
| Caporalini 2001 | Non-placebo study comparing neltenexine against N-acetylcysteine |
| Dotti 1970 | Randomised controlled study but subjects did not have pneumonia (in Italian) |
| Finiguerra 1981 | A double blind study in adults with acute and chronic bronchitis (not pneumonia) |
| Forssell 1966 | Non-placebo study comparing drops to syrup formulation of an antitussive in infants and young children (in German) |
| Hargrave 1975 | Study examined role of bromhexine in prevention of post-operative pneumonia |
| Ida 1997 | A review article describing three studies on dimemorfan, a dextromethorphan analogue. Of the three cited studies, one was a placebo-controlled trial. Insufficient details were included in the text and further data were not available from the author, who was unable to be contacted |
| Jayaram 2000 | Non-placebo study comparing two cough formulations |

(*Continued*)

| | |
|---|---|
| Mancini 1996 | The paper summarises 3 studies which were not referenced. The first of the 3 studies described a RCT in children with "acute lower respiratory affections (e.g. acute bronchitis, bronchoalveolitis)". Unknown if children with pneumonia included and results stated reduction in cough scores with no specific data given. We wrote to authors and no response was received<br>The other two studies described were in adults with '"superinfected chronic bronchitis" and "hypersecretory chronic obstructive bronchopneumopathies" |
| Pelucco 1981 | Non-randomised, non-placebo study in 26 adults (in Italian) |
| Titti 2000 | Erdosteine is not legally available as an over-the-counter medication in countries such as Australia, UK and USA. Multi-centre RCT compared ampicillin plus erdosteine to ampicillin-placebo in children with acute lower respiratory tract infections |
| Turrisi 1984 | Non-randomised, non-placebo study using fenspiride in 20 adults (in Italian) |
| Wang 2005 | Study used Fuxiong plaster (i.e. not an OTC). Randomised controlled study in children with pneumonia |
| Wieser 1973 | Placebo but non-randomised study comparing placebo to prenodiazine in 84 adults (in German) |
| Zhang 2005 | Study used Toubiao Qingfei (an externally applied therapy, i.e. not an OTC). Randomised controlled study in children with fever from pneumonia |
| Zurcher 1966 | Non-placebo, double blind study comparing Sinecod-Hommel to a codeine based antitussive in 95 adults (in German) |

OTC: Over-the-counter

## DATA AND ANALYSES

### Comparison 1. Children - global assessment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Not cured or not improved | 1 | 120 | Odds Ratio (M-H, Fixed, 95% CI) | 0.40 [0.10, 1.62] |
| 2 Not improved | 1 | 120 | Odds Ratio (M-H, Fixed, 95% CI) | 0.40 [0.10, 1.62] |
| 3 Not cured | 1 | 120 | Odds Ratio (M-H, Fixed, 95% CI) | 0.36 [0.16, 0.77] |

### Comparison 2. Children - cough score

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mean cough score at day 3 | 1 | 120 | Mean Difference (IV, Fixed, 95% CI) | -0.25 [-0.33, -0.17] |
| 2 Mean score at day 10 | 1 | 120 | Mean Difference (IV, Fixed, 95% CI) | -0.15 [-0.17, -0.13] |

### Comparison 3. Adults - global assessment

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Not cured or not improved | 1 | 101 | Odds Ratio (M-H, Fixed, 95% CI) | 1.21 [0.48, 3.04] |
| 2 Not improved | 1 | 101 | Odds Ratio (M-H, Fixed, 95% CI) | 1.21 [0.48, 3.04] |
| 3 Not cured | 1 | 101 | Odds Ratio (M-H, Fixed, 95% CI) | 0.32 [0.13, 0.75] |

### Comparison 4. Combined children and adults

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Not cured or not improved | 2 | 221 | Odds Ratio (M-H, Fixed, 95% CI) | 0.85 [0.40, 1.80] |
| 2 Not improved | 2 | 221 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.38, 1.67] |
| 3 Not cured | 2 | 221 | Odds Ratio (M-H, Fixed, 95% CI) | 0.34 [0.19, 0.60] |

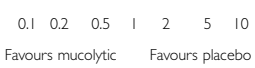
### Analysis 1.1. Comparison 1 Children - global assessment, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 1 Not cured or not improved

| Study or subgroup | Mucolytic (Ambroxol) n/N | Placebo n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 3/60 | 7/60 | | 100.0 % | 0.40 [ 0.10, 1.62 ] |
| **Total (95% CI)** | **60** | **60** | | **100.0 %** | **0.40 [ 0.10, 1.62 ]** |
| Total events: 3 (Mucolytic (Ambroxol)), 7 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.29 (P = 0.20) | | | | | |




### Analysis 1.2. Comparison 1 Children - global assessment, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 2 Not improved

| Study or subgroup | Mucolytic (ambroxol) n/N | Placebo n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 3/60 | 7/60 | | 100.0 % | 0.40 [ 0.10, 1.62 ] |
| **Total (95% CI)** | **60** | **60** | | **100.0 %** | **0.40 [ 0.10, 1.62 ]** |
| Total events: 3 (Mucolytic (ambroxol)), 7 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.29 (P = 0.20) | | | | | |

### Analysis 1.3. Comparison 1 Children - global assessment, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 3 Not cured

| Study or subgroup | Mucolytic (ambroxol) n/N | Placebo n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 15/60 | 29/60 | | 100.0 % | 0.36 [ 0.16, 0.77 ] |
| **Total (95% CI)** | **60** | **60** | | **100.0 %** | **0.36 [ 0.16, 0.77 ]** |
| Total events: 15 (Mucolytic (ambroxol)), 29 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.62 (P = 0.0089) | | | | | |

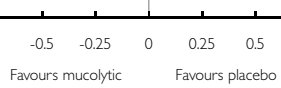

### Analysis 2.1. Comparison 2 Children - cough score, Outcome 1 Mean cough score at day 3.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 2 Children - cough score

Outcome: 1 Mean cough score at day 3

| Study or subgroup | Mucolytic (ambroxol) N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Principi 1986 | 60 | 1.2 (0.2) | 60 | 1.45 (0.25) | | 100.0 % | -0.25 [ -0.33, -0.17 ] |
| **Total (95% CI)** | **60** | | **60** | | | **100.0 %** | **-0.25 [ -0.33, -0.17 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 6.05 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



### Analysis 2.2. Comparison 2 Children - cough score, Outcome 2 Mean score at day 10.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 2 Children - cough score

Outcome: 2 Mean score at day 10

| Study or subgroup | Mucolytic (ambroxol) N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Principi 1986 | 60 | 0.1 (0.05) | 60 | 0.25 (0.05) | | 100.0 % | -0.15 [ -0.17, -0.13 ] |
| **Total (95% CI)** | **60** | | **60** | | | **100.0 %** | **-0.15 [ -0.17, -0.13 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 16.43 (P < 0.00001)

Test for subgroup differences: Not applicable


### Analysis 3.1. Comparison 3 Adults - global assessment, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 1 Not cured or not improved

| Study or subgroup | Mucolytic - bromhexi n/N | Placebo n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Roa 1995 | 13/51 | 11/50 | | 100.0 % | 1.21 [ 0.48, 3.04 ] |
| **Total (95% CI)** | **51** | **50** | | **100.0 %** | **1.21 [ 0.48, 3.04 ]** |

Total events: 13 (Mucolytic - bromhexi), 11 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.41 (P = 0.68)

### Analysis 3.2. Comparison 3 Adults - global assessment, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 2 Not improved

| Study or subgroup | Mucolytic - bromhexi n/N | Placebo n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Roa 1995 | 13/51 | 11/50 | | 100.0 % | 1.21 [ 0.48, 3.04 ] |
| **Total (95% CI)** | **51** | **50** | | **100.0 %** | **1.21 [ 0.48, 3.04 ]** |
| Total events: 13 (Mucolytic - bromhexi), 11 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | | |

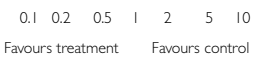

### Analysis 3.3. Comparison 3 Adults - global assessment, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 3 Not cured

| Study or subgroup | Treatment n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Roa 1995 | 27/51 | 39/50 | | 100.0 % | 0.32 [ 0.13, 0.75 ] |
| **Total (95% CI)** | **51** | **50** | | **100.0 %** | **0.32 [ 0.13, 0.75 ]** |
| Total events: 27 (Treatment), 39 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.60 (P = 0.0094) | | | | | |



### Analysis 4.1. Comparison 4 Combined children and adults, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 1 Not cured or not improved

| Study or subgroup | Mucolytic n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 3/60 | 7/60 | | 44.5 % | 0.40 [ 0.10, 1.62 ] |
| Roa 1995 | 13/51 | 11/50 | | 55.5 % | 1.21 [ 0.48, 3.04 ] |
| **Total (95% CI)** | **111** | **110** | | **100.0 %** | **0.85 [ 0.40, 1.80 ]** |
| Total events: 16 (Mucolytic), 18 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 1.69, df = 1 (P = 0.19); $I^2$ =41% | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | |

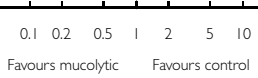

### Analysis 4.2. Comparison 4 Combined children and adults, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 2 Not improved

| Study or subgroup | Mucolytic n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 3/60 | 8/60 | | 47.9 % | 0.34 [ 0.09, 1.36 ] |
| Roa 1995 | 13/51 | 11/50 | | 52.1 % | 1.21 [ 0.48, 3.04 ] |
| **Total (95% CI)** | **111** | **110** | | **100.0 %** | **0.80 [ 0.38, 1.67 ]** |
| Total events: 16 (Mucolytic), 19 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 2.25, df = 1 (P = 0.13); $I^2$ =56% | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | |



### Analysis 4.3. Comparison 4 Combined children and adults, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 3 Not cured

| Study or subgroup | Mucolytic n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Principi 1986 | 15/60 | 29/60 | | 54.0 % | 0.36 [ 0.16, 0.77 ] |
| Roa 1995 | 27/51 | 39/50 | | 46.0 % | 0.32 [ 0.13, 0.75 ] |
| **Total (95% CI)** | **111** | **110** | | **100.0 %** | **0.34 [ 0.19, 0.60 ]** |
| Total events: 42 (Mucolytic), 68 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.04, df = 1 (P = 0.84); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 3.68 (P = 0.00023) | | | | | |


# APPENDICES

## Appendix 1. Embase.com search strategy

1. 'coughing'/exp
2. cough*:ti,ab
3. #1 OR #2
4. 'pneumonia'/exp
5. pneumon*:ti,ab
6. #4 OR #5
7. 'antitussive agent'/exp
8. antitussiv*:ti,ab
9. 'expectorant agent'/exp
10. expectorant*:ti,ab
11. 'cholinergic receptor blocking agent'/exp
12. 'cholinergic antagonist':ti,ab OR 'cholinergic antagonists':ti,ab
13. 'histamine h1 receptor antagonist'/exp
14. 'histamine h1 antagonist':ti,ab OR 'histamine h1 antagonists':ti,ab
15. 'mucolytic agent'/exp
16. mucolytic*:ti,ab
17. 'drug combination'/exp
18. 'drug combination':ti,ab OR 'drug combinations':ti,ab
19. 'non prescription drug'/exp
20. 'non prescription drug':ti,ab OR 'non prescription drugs':ti,ab OR 'non-prescription drug':ti,ab OR 'non-prescription drugs':ti,ab

21. 'over the counter':ti,ab OR 'over-the-counter':ti,ab OR otc:ti,ab
22. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23. #3 AND #6 AND #22

## WHAT'S NEW

Last assessed as up-to-date: 9 July 2009.

| Date | Event | Description |
|---|---|---|
| 9 September 2010 | Amended | Contact details updated. |

## HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2007

| Date | Event | Description |
|---|---|---|
| 10 July 2009 | New search has been performed | Searches conducted. No new included studies found. Two new studies excluded |
| 21 February 2008 | Amended | Summary of Findings table added. |
| 30 January 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

The protocol was written by Christina C Chang (CCC), Anne B Chang (ABC) and Allen C Cheng (ACC) based on previous protocols on cough in children.

For the review: CCC and ABC selected articles from search, performed the data extraction, data analysis and wrote the review.

ACC was the adjudicator if disagreement occurred and contributed to writing the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT


### Internal sources

- No sources of support supplied

### External sources

- NHMRC, Australia.

Salary support for ABC

- Queensland Health Smart State Funds, Australia.

Salary support for ABC


## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Antitussive Agents [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Cough [*drug therapy; etiology]; Drug Therapy, Combination [methods]; Expectorants [therapeutic use]; Nonprescription Drugs [*therapeutic use]; Pneumonia [complications; *drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

### MeSH check words

Adolescent; Adult; Child; Humans