Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: a systematic review of the literature


CRD summary
The authors concluded that the evidence for the effectiveness of pharmacological and non-pharmacological interventions to relieve cough in adults with non-malignant respiratory conditions was limited. Many trials had conflicting results and were hindered by variable quality scores and small sample sizes. The authors' conclusion is likely to be reliable.

Authors' objectives
To evaluate the effectiveness of pharmacological and non-pharmacological interventions to relieve cough in adults with non-malignant respiratory or non-respiratory conditions.

Searching
MEDLINE, EMBASE, CINAHL, BNI, PsycINFO, Science Citation Index, AMED, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Cochrane Pain, Palliative and Supportive Care Trials Register, DARE, PEDRO, Index to Scientific and Technical Proceedings, Conference Papers Index, NRR and SIGLE were searched for articles in English. Dates ranged from 1966 to April 2009. Search terms were reported and reference was made to the full search strategy. Reference lists were scanned and authors were contacted to retrieve further unpublished or grey literature.

Study selection
Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of pharmacological or non-pharmacological interventions (classified by the EU directive 2001/83/EEC and defined in the paper) administered in any clinical setting to adult patients with acute, subacute or chronic cough due to non-malignant respiratory and non-respiratory diseases with a high prevalence of cough were eligible for inclusion. The primary outcomes of interest were subjective measures of cough frequency, severity or distress using validated and reliable methods (such as visual analogue, numeric rating or categorical scales). Secondary outcomes of interest were objective improvement of cough, quality of life, side-effects and patient withdrawal from trials. Patients with upper respiratory tract infection and cough reflex sensitivity studies were excluded.

Most of the included studies were conducted in patients with asthma or chronic obstructive pulmonary disease (COPD). Studies were conducted worldwide (10 were in UK). Pharmacological treatments included a range of corticosteroids, leukotriene receptor antagonists, mast cell stabilisers, ipratropium bromide, netileneexine, iodinised glycerol, lidocaine, and codeine. Non-pharmacological treatments included biological targeted imagery, SMS text messaging, ayurverdic herbs and speech pathology training. Control groups included placebo, other active treatment or different regimen and standard care. Most studies did not include cough as the primary outcome and used unvalidated measurement methods.

Two reviewers selected the studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed using the Jadad scale of randomisation, blinding and withdrawals/drop-outs. Scores could range from zero to a maximum 5 (highest quality).

One reviewer carried out the quality assessment and agreement on all studies was reached with a second reviewer. For consistency, a third reviewer checked a random sample of studies.

Data extraction
Data were extracted on the outcomes of interest. Numerous measures of effect were presented.

One reviewer extracted data. A second reviewer independently checked a sample of papers to reach agreement. For
consistency, a third reviewer checked a random sample.

**Methods of synthesis**
A narrative synthesis was presented by disease type.

**Results of the review**
Seventy-five trials (11,738 participants, range eight to 5,887) were included in the review. Mean sample size was 156 (78 when the largest trial was excluded). Jadad scores were: seven trials scored 5, 17 scored 4, 24 scored 3, 19 scored 2 and eight scored 1. Fifty-six trials were double-blind.

**Asthma (23 trials):** All trials that evaluated steroids showed positive effects on cough outcomes, particularly beclomethasone (four trials) and budesonide (one trial). Mast cell stabilisers, notably disodium cromoglycate (one trial) and lodoxadine (one trial) were effective. Two trials found nedocromil sodium to be effective, but no significant improvements were reported in two large trials. Leukotriene receptor antagonists (two trials), and Th2 cytokine inhibitor (one trial) showed positive effects. Also effective were the ayurvedic herbs deriphylline (with salbutamol) (one trial) and ginger (one trial) and SMS text messaging (one trial). There was no significant difference in one trial of theophylline.

**COPD (18 trials):** Three trials of neltenexine and single trials of fenspiride, fluticasone, formoterol, oxtriphyllyne, high-dose N-acetylcysteine (1,200μg) and the biological extract helicidine were effective. The largest trial in this analysis (5,887 participants) evaluated a smoking cessation programme that led to a significant decrease in cough symptoms. Treatment effects were non-significant in single trials of budesonide, codeine, nesosteine, and inhaled oxitropium bromide (in addition to theophylline).

**Bronchitis (eight trials):** Effective treatments were epinastine (one trial), ipratropium bromide compared with fenspiride (one trial), theophylline (one trial) and iodinised glycerol (two trials). Non-significant treatment effects were found for low-dose N-acetylcysteine (two trials) and budesonide (one trial).

**Reflux disease (five trials):** Proton pump inhibitors were evaluated in all trials. Lansoprazole (one trial) and omeprazole (two trials) were effective. Single trials of omeprazole and of esomeprazole showed no significant effect.

**Speech pathology training (one trial) and morphine (one trial) were effective for idiopathic cough. Other results for singular and combined respiratory diseases evaluated by three or fewer studies were reported in the paper.**

**Authors' conclusions**
The authors stated that the evidence was limited. Many trials had conflicting results and were hindered by variable quality scores and small sample sizes.

**CRD commentary**
The review was broad in scope with regard to the interventions of interest, but the inclusion criteria were more focused in terms of study design, participants and outcomes. Most outcomes were reported to be unvalidated measures, which conflicted with the inclusion criteria. The search strategy was extensive and included several relevant electronic databases. Attempts were made to minimise publication bias. Language bias was a possibility.

The chosen quality assessment tool was appropriate for the included study designs. More than half of the trials indicated a reasonable quality standard, but presentation of composite scores limits further interpretation. Some attempts were made to minimise error and bias in the review process. Sufficient study details were available to enable judgement about wide clinical variation, and thus the appropriateness of the chosen method of synthesis.

Despite the conflict with inclusion criteria, the authors' conclusion is likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future research was needed into cough management, with cough measured as the primary outcome using validated subjective and objective methods. Clinical heterogeneity should be minimised.
Further evaluation of speech therapy as an adjunct to pharmacological treatments was warranted.

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