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## Respiratory Medicine CME

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## CME Article

Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature<sup>☆</sup>A. Molassiotis<sup>a,\*</sup>, G. Bryan<sup>a</sup>, A. Caress<sup>a</sup>, C. Bailey<sup>b</sup>, J. Smith<sup>c</sup><sup>a</sup> School of Nursing, Midwifery & Social Work, University of Manchester, University Place, Manchester M13 9PL, UK<sup>b</sup> School of Health Sciences, University of Southampton, UK<sup>c</sup> Respiratory Research Group, School of Translational Medicine, University of Manchester, UK

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## SUMMARY

The management of cough in adults with respiratory and non-respiratory illnesses is suboptimal and based mostly on clinical opinions rather than evidence. A systematic review was carried out assessing all trials in adult patients with respiratory and non-respiratory diseases (excluding cancer) that had chronic cough as primary or secondary outcome. A total of 1177 trials were retrieved and 75 met the criteria for inclusion in the review. The vast majority were in patients with asthma and chronic obstructive pulmonary disease (COPD). Cough was the primary outcome in less than one-quarter of the studies. The measurement of cough was variable, mostly using unvalidated scales or being part of an overall 'symptoms' score. Positive results were overall seen with the use of corticosteroids, leukotriene receptor antagonists, mast cell stabilizers, ipratropium bromide, neltexine, iodinated glycerol and lidocaine. Speech pathology training and symptom monitoring through SMS messages (accompanied by treatment adjustments) have also shown promise. Evidence for established anti-tussive agents such as codeine was scarce, with positive studies from the 1960s, whilst more recent studies showed no effect in patients with COPD. Many studies had conflicting results. It is imperative that the management of cough and its evidence base be improved, using higher quality research designs and with cough being the primary outcome of trials.

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## Introduction

Cough is a common and often difficult problem seen by primary care physicians and other clinicians. Perhaps if we had an easy answer and a treatment that always or even usually worked we would not find chronic cough so frustrating. This literature review provides a summary of the 75 papers found to deal with chronic cough therapy. It will not be a surprise to many that antitussives have limited value in controlling chronic cough but read on to see what else is available and in what situations they may work.

## Educational aims

- To present the most common mechanisms for chronic cough.
- To review the evidence for the efficacy and effectiveness of the most commonly used classes of drugs to treat chronic cough.
- To present evidence for each type of therapy by disease e.g. COPD, asthma, acute respiratory infections.

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## 1. Background

Cough is a common symptom in respiratory (non-malignant) diseases<sup>1</sup> and related non-respiratory conditions, such as nasal disease or gastro-oesophageal reflux disease (GORD/GERD)]. Cough may either be productive (wet) producing purulent or mucoid sputum or non-productive (dry). Cough can be further divided into three categories based on duration: acute, lasting less than three weeks; sub-acute, lasting three to eight weeks; and chronic, lasting more than eight weeks.<sup>2,3</sup> Common causes of non-malignant cough include viral upper respiratory tract infections (the commonest by far), airway disease, including asthma and chronic obstructive pulmonary disease; gastro-oesophageal reflux disease (GORD), nasal disease, bronchiectasis and chronic infections. Persistent cough can be distressing to patients, leading to depression (in up to 53% of patients),<sup>4,5</sup> insomnia, vomiting, exhaustion and rib fractures.<sup>6,7</sup> Cough has a significant human and socioeconomic burden, as it is linked with absenteeism from work, impaired quality of life and effects in daily activities.<sup>8</sup> A number of reviews outlining management options<sup>1–3,8,9</sup> exist, but there is limited comprehensive systematic synthesis and assessment of effective management strategies currently available in adult patients, as most systematic

reviews (a significant number being Cochrane reviews) are focusing on children, whooping cough or antibiotic use in adults with prolonged cough. Furthermore, the management of cough is highly variable in clinical practice, and some of the reasons for this may include the unsystematic evaluation of causes of cough, the frequent use of non-specific cough treatments and the clinicians' insufficient knowledge in cough management.<sup>10</sup> A synthesis of evidence could assist in addressing some of these issues.

Hence there is a need to examine the existing evidence in cough research in respiratory and non-respiratory illnesses in order to highlight areas needing further research development, provide an understanding of the level of evidence for interventions used to manage cough and aid clinicians in their clinical decision-making.

### 1.1. Objective

The objective of this review was to determine the effectiveness of pharmacological and non-pharmacological/non-invasive interventions in the relief of cough in non-malignant respiratory and non-respiratory conditions in adult patients experiencing chronic cough.

### 1.2. Types of studies

Randomised Controlled Trials (with blinding)  
Controlled Clinical Trials (quasi randomised trials, trials with or without blinding and randomisation not mentioned, trials with a comparative arm).

### 1.3. Types of participants

Adult patients described as experiencing either acute, sub-acute or chronic cough; presence of cough (either productive (wet) cough producing purulent or mucoid sputum or non-productive (dry) cough without purulent or mucoid sputum) due to non-malignant respiratory and non-respiratory diseases with a high prevalence of cough, including interstitial lung disease (ILD), bronchiectasis; Chronic Obstructive Pulmonary Disease (COPD)/Chronic Obstructive Airways Disease (COAD); pulmonary oedema; lung abscess; emphysema; asthma; bronchitis; cardiac disease, including congestive heart failure (CHF), chronic heart failure and dilated cardiomyopathy; extra thoracic causes of cough including reflux disease, nasal disease and ACE-inhibitor related cough. Patients included in the studies could be treated in any clinical setting. Interventions should have a comparator group (placebo, another substance or usual care). Studies designed to examine effects on cough directly or as a proxy for improvement of an underlying disorder would be included.

### 1.4. Exclusion criteria

The following disease types were excluded:

Upper respiratory tract infection – bacterial and viral/chest infections; common cold; post infection cough, habitual cough; enlarged uvula; stress; acute sinusitis, lung cancer. Cough reflex sensitivity studies and animal studies were also excluded. Paediatric studies were also excluded, unless there was a mixed sample of children and adults.

### 1.5. Types of intervention

Pharmacological interventions: Any medicinal product or substance as classified by the EU directive 2001/83/EEC "any substance or combination of substances which may be

administered to human beings or animals with a view to making a diagnosis or to restoring, correcting or modifying physiological function in human beings or animals is likewise considered a medicinal product."

Non-pharmacological interventions were defined according to EU Directive 2001/83/EEC as 'any interventions that are not classified as medicinal products' and invasive and non-invasive interventions, such as complementary therapies, physiotherapy, education, behavioural approaches and self-management.

### 1.6. Types of outcome measures

The primary outcome was subjective measures of cough frequency, severity or distress on validated and reliable scales such as visual analogue scales, numerical rating scales, and categorical scales.

*Secondary outcomes:* Objective improvement in cough; Quality of life measured by validated and reliable instruments; Side-effects; Patient withdrawal from trials.

### 1.7. Search methods for identification of studies

A scoping search using broad terms and several databases, as well as consultation with clinicians contributed to the development of the search terms for this review. The electronic databases searched included:

MEDLINE (1966–April 2009)  
EMBASE (1980–April 2009)  
CINAHL (1980–April 2009)  
British Nursing Index (1985–April 2009)  
PsychINFO (1985–April 2009)  
Science Citation Index Expanded (1985–April 2009)  
AMED (Allied and Complementary Medicine) (1985–April 2009)  
Cochrane Pain, Palliative and Supportive Care Trails Register (Winter 2009 issue) Cochrane Database of Systematic Reviews (CDSR) (Winter 2009 issue)  
The Cochrane Central Register of Controlled Trials (CENTRAL) (Winter 2009 issue)  
Database of Abstracts of Reviews of Effectiveness (DARE) (Winter 2009 issue)  
PEDRO (physiotherapy) database (to April 2009)  
The Index to Scientific and Technical Proceedings (to January 2009)  
Conference Papers Index (to April 2009)  
National Research Register (to April 2009)  
SIGLE (System for Information on Grey Literature) (1980–April 2009)

### 1.8. Search strategy

The search terms included cough, respiratory illnesses (as a general term and with specific diagnoses), generic classes of drugs (anti-tussives, cough suppressants, opioids, topical anaesthetics, NMDA receptor antagonists, antihistamines, bronchodilators, steroids, antimuscarinics, aromatic inhalations) followed by specific drugs identified in the scoping exercise, complementary therapies (with individual therapies also included), physiotherapy, exercise movement technique, self-management, self-care, respiratory therapy, non-pharmacological interventions. In total, 108 terms were combined together with cough and respiratory disease diagnoses alongside with a published strategy for identifying randomised controlled trials.<sup>11</sup> A complete search strategy is available from the authors.

### 1.9. Hand searching, grey literature and personal contact

The reference lists of all relevant studies were checked for further relevant studies. Authors of main studies were contacted to find out about any unpublished or grey literature. The Index to Scientific and Technical Proceedings, the Conference Papers index and the National Research Register were additionally searched for grey literature.

### 1.10. Language

Studies in English language or with an available English translation were included.

### 1.11. Methods of the review

#### 1.11.1. Selection of studies

Titles and abstracts of identified studies were reviewed for relevance by two reviewers. The full text of all potentially relevant studies was assessed by two reviewers. Any disagreements were resolved after discussion with the rest of the reviewing team.

#### 1.11.2. Assessment of methodological quality

Methodological quality was assessed independently by two reviewers. A Jadad score (Oxford Quality Index) was assigned for each study.<sup>12</sup> This is a score ranging from 0 to 5, with points assigned for randomisation, blinding and withdrawals/dropouts, with a higher score representing a higher quality trial.

#### 1.11.3. Data extraction

A data extraction form was designed. One reviewer extracted the data from each paper, and a second reviewer evaluated the data extracted from all papers, reaching agreement in relation to the quality of the data and the Jadad score assigned. Agreement was achieved with each assessor assessing a small number of papers independently and then comparing the data extraction and scores with the other assessor, discussing also ways of being consistent in data extraction. A third reviewer checked a random sample for consistency. The following details were included: Publication details; Study aim; Study design; Sample size and patient characteristics; Adverse events; Method of assessing cough; Type of intervention; Outcome measures; Withdrawals and dropouts; Handling of missing data; Study results; Follow-up data; Any economic data; and any patient narrative comments.

#### 1.11.4. Data analysis

Reviewed studies were grouped into disease types and the effectiveness of specific strategies within each disease population assessed. A narrative synthesis is used to analyse the data obtained.

## 2. Results

1177 articles were retrieved and assessed through the search strategy. These included primarily results from searches in the electronic databases ( $n = 1164$ ; 62 included) as well as 31 articles from hand searches (9 included) and 10 from additional sources (4 included). Approaching key authors in the field has resulted in no more articles. After excluding duplicates, articles related to acute chest infections, vaccines, malignancies, reviews and those which had no outcome related to cough, 75 trials were included in this review (see Table 1 for indicative studies and Online Table under Supplementary Material for detailed description of all studies reviewed).<sup>13–86</sup>

The 75 trials included in the review had a total sample of 11,738 adult patients (mean of 156 patients/trial), however if the very large single trial<sup>63</sup> on smoking cessation is excluded (as it skews the

results), the mean sample per trial was 78 subjects, ranging from 8 to 5887 subjects. The majority of studies were conducted in adult patients with asthma and COPD patients.

Twenty-three trials were identified in adult patients with asthma ( $n = 1508$ , mean sample size = 65, range 8–235). Steroids were the most common drug tested as a cough therapy, and all studies were positive, particularly with beclomethasone<sup>15,16,18,20</sup> and budesonide.<sup>30</sup> Mast cell stabilizers were also shown to be effective, including disodium cromoglycate,<sup>24</sup> lodoxadine<sup>87</sup> and nedocromil sodium (two trials with positive results<sup>26,28</sup>) and two larger trials with negative results.<sup>27,29</sup> Leukotriene receptor antagonists were also effective (2 trials) as was the use of a Th2 cytokine inhibitor (1 trial).<sup>25,32,35</sup> Two different ayurvedic herbs were equally effective with salbutamol and deriphylline used in one trial,<sup>33</sup> although the trial was of poor quality, as was another positive herbal trial using ginger.<sup>19</sup> Theophylline did not show any improvements in cough in one trial.<sup>34</sup> A study whereby patients reported PEF values to researchers daily through SMS messages and researchers subsequently contacted patients to adjust medication or arrange hospital appointments showed significantly lower cough scores than the control group in a small study of 16 patients.<sup>31</sup>

Eight trials were identified in relation to adult patients with bronchitis (total  $n = 731$ ). All but two trials had a sample size of less than 80 subjects. While the use of low dose N-acetylcysteine<sup>38,39</sup> and budesonide<sup>40</sup> were negative, effective treatments included epinastine,<sup>41</sup> ipratropium bromide over fenspiride<sup>42</sup> theophylline<sup>45</sup> and iodinated glycerol.<sup>43,44</sup>

Eighteen trials included adult patients with COPD ( $n = 8013$  subjects), with a mean of 125 subjects/trial (excluding the single very large smoking cessation trial). Negative studies included the use of budesonide,<sup>47</sup> codeine,<sup>48</sup> nesosteine<sup>61</sup> and oxitropium bromide (in addition to theophylline).<sup>62</sup> Positive results were shown with regards to fenspiride,<sup>50</sup> fluticasone,<sup>51</sup> formoterol,<sup>52</sup> neltexine,<sup>58–60</sup> helicidine (a biological extract prepared from the snail *Helix pomatia* L.),<sup>53</sup> oxtriphylline<sup>64</sup> and a high dose (1200 µg) N-acetylcysteine.<sup>56</sup> While lidocaine 4 ml had an equivalent effect to bronchodilators (but fewer side-effects)<sup>55</sup> and ipratropium bromide was also equivalent to another drug of the same class, that of metaproterenol.<sup>54</sup> In a large trial of 5887 smokers, a smoking cessation programme led to significant decreases in cough symptoms as well as in the use of inhaled ipratropium bromide.<sup>63</sup>

Five trials have tested a proton pump inhibitor in the management of cough in adult patients with reflux disease ( $n = 258$  subjects; mean of 52 patients/trial). While esoprazole and omeprazole showed negative results in one trial each,<sup>69,72</sup> lansoprazole<sup>70</sup> and omeprazole<sup>71,73</sup> have provided positive results over placebo. Morphine (5 mg) in one trial<sup>66</sup> and speech pathology training in another trial<sup>67</sup> were also effective treatments in relation to idiopathic cough. Allergic rhinoconjunctivitis was the focus of one trial only, in which the tested antihistamine (loratadine) in a small-scale study was shown to be effective.<sup>13</sup> Benzonatate was equivalent to a mixture that contained codeine in one trial of patients with asthmatic bronchitis and emphysema<sup>36</sup> as was codeine in a small trial of 10 patients.<sup>68</sup> Mogueistene and dextromethopran were shown to be equivalent in a trial of 124 patients.<sup>78</sup> A large trial of codeine was also effective in a dose of 60 mg<sup>46</sup> as was neltexine in two further trials.<sup>79,80</sup> Sinecod linctus, a common over-the-counter cough medication, was no more effective than a small dose of codeine in one trial.<sup>86</sup>

## 3. Discussion

Some of the key and overarching issues identified through this systematic review include the limited amount of research directed specifically to the management of chronic cough, the significant

**Table 1**  
Indicative interventions for non-malignant cough [for a description of all studies see Online Table under Supplementary material].

Author	Date	Country	Study Design	Sample, size	Treatment (dose)	Outcome Measures	Results	Conclusions/Comments	Jadad score
Ribeiro et al., 2007		Brazil <sup>18</sup>	RCT Double Blind	<i>N</i> = 64 (42M/22F)	Chlorofluorocarbon-beclomethasone (1500 µg/d) or placebo for 2 weeks.	Decrease in daily cough scores during the 2-week treatment period (Patient symptom, diary and visual analogue scale (Primary) Secondary outcomes: Duration of cough, respiratory questionnaire, bronchoprovocation testing (BPT) with methacholine and allergy testing	36/42 patients (82%) in active group had complete resolution of cough. 8 showed no improvement (18%). Cough cessation was observed in 3 patients (15%) in the placebo group, whilst cough persisted in 17 patients (85%).  Median duration of cough similar in both groups ( <i>P</i> = 0.9). Difference in cough diaries and VAS before and after beclomethasone compared with before and after placebo (difference of differences, 1.0 95% CI, 0.4–1.5; <i>P</i> < 0.002 for diaries, difference of differences 1.1, 95% CI 0.6–1.8, <i>P</i> < 0.01 for VAS). Comparison of symptom diaries with VAS data for the placebo and control groups at the end of the protocol ( <i>P</i> = 0.001) No correlation between cough diaries and questionnaires ( <i>r</i> = 0.12, <i>P</i> = 0.07) or BPT ( <i>r</i> = 0.23, <i>P</i> = 0.06).	Significant improvement in cough symptoms in patients treated with chlorofluorocarbon-beclomethasone compared with placebo.  Significant difference in numbers of patients experiencing resolution of cough when treated with chlorofluorocarbon-beclomethasone compared to placebo.	4
				Patients had cough > 8 weeks.  10 patients were smokers.					
Nicolis et al., 1962		Italy <sup>46</sup>	RCT Double Blind	<i>N</i> = 184 (No gender info)	Study 1: <b>Codeine</b> (30mg qid) or placebo for 5 days, crossed over after a 3 day washout period ( <i>n</i> = 43).	Cough (primary)	Study 1 and 2 failed to show any significant difference between placebo and codeine.	Statistically significant difference in number of coughs in patients treated with a single dose of codeine (60mg) compared to placebo. However, 2 studies with lower codeine dosages over longer timeframe failed to identify a significant effect on cough. Authors give no information about withdrawals or adverse events.	2
				<i>N</i> = 19 (14M/5F)	Study 2: <b>Codeine</b> (30mg qid) or placebo for 8 days crossed over every 3 days ( <i>n</i> = 56)  Study 3: <b>Codeine</b> (60mg) or placebo single application. (3 separate groups of patients).		Study 3 reported a significant difference in number of coughs in patients treated with codeine compared to placebo (group 1: 6.4 ± 1.2 V 11.7 ± 1.5, <i>P</i> < 0.001; group 2: 8.2 ± 1.9 V 13.5 ± 1.9, <i>P</i> < 0.001; Group 3: 9.8 ± 1.6 VS. 14.5 ± 1.9, <i>P</i> < 0.001). Authors also provide a graphical comparison of mean number of coughs/h at 3 different time-points for 33 patients (group3). Difference between codeine and placebo significant at 3 h and 4 h after codeine administration 2 h after administration = <i>P</i> > 0.05, 3 h after administration = <i>P</i> < 0.01, 4 h after administration = <i>P</i> < 0.001). Trend towards difference in the mean number of coughs in heavier coughing patients treated with codeine (NS).		

Smith et al., 2006 UK <sup>48</sup>	RCT Double blind, placebo controlled Cross-over trial	N = 19 (14M/5F)	<b>Codeine</b> (60 mg b.i.d.) or placebo.	Cough frequency (primary) Citric acid thresholds, subjective cough measures (VAS).	Median rate of cough (combined night and day scores) was lower during treatment with codeine (6.41 coughs/h, IQR 3.86–9.10, $P = 0.02$ compared with baseline) compared to placebo (7.22 c/h, IQR 4.42–10.40, $P = 0.03$ compared with baseline) and baseline (8.27 c/h, IQR 5.94–11.67). 4% reduction in cough rate was observed for codeine compared with placebo (mean difference = 1.1 cs/h, 95% CI, 0.89–1.25 cs/h). Log 10 transformed cough rates showed a sig. difference between baseline, placebo and codeine rates (repeat-measures ANOVA, $F = 4.97$ , $df = 2$ , $P = 0.02$ ). Differences between baseline, codeine and placebo treatments was seen in day cough scores ( $F = 3.72$ , $df = 2$ , $P = 0.05$ ), but not in night scores ( $F = 0.56$ , $df = 2$ , $P = 0.48$ ). Difference between subjective baseline cough scores and day and night scores NS ( $F = 0.453$ , $df = 2$ , $P = 0.59$ ; and $F = 0.68$ , $df = 2$ , $P = 0.50$ respectively). No SD between daytime codeine and baseline VAS scores $P = 0.11$ . Difference between codeine and placebo, $P = 0.96$ . No SD between baseline, placebo or codeine ( $P = 0.25$ ). No significant correlations between the change in time spent coughing and the change in cough score (day $r = -0.07$ , $P = 0.78$ , night = 0.17, $P = 0.48$ ) or change in VAS (day $r = -0.07$ , $P = 0.79$ , night $r = 0.30$ , $P = 0.24$ ). Improvement in cough severity scores in both groups 1 h post inhalation compared to baseline (Lidocaine score = 3 versus 8, $P < 0.01$ , Bronchodilator score = 3 versus 8, $P < 0.01$ ). $P = 0.44$ for difference between Lidocaine and bronchodilators.	No significant improvement in cough frequency in patients treated with codeine compared to placebo.	4
Chong et al., 2005 Taiwan <sup>55</sup>	RCT Double blind	N = 127 (85M/42F)	<b>Lidocaine</b> (4 ml N = 62) or Bronchodilator (N = 65)	Effectiveness (primary)  Cough severity score, comparison of adverse effects.	Improvement in cough severity scores in both groups 1 h post inhalation compared to baseline (Lidocaine score = 3 versus 8, $P < 0.01$ , Bronchodilator score = 3 versus 8, $P < 0.01$ ). $P = 0.44$ for difference between Lidocaine and bronchodilators.	Significant improvement in cough severity scores in patients treated with Lidocaine or Bronchodilators for short term cough suppression. 228 adverse events reported. Significantly more patients experienced tremors and palitations whilst using Bronchodilators compared to those Lidocaine. Significantly more patients using lidocaine reported oropharyngeal numbness and a bitter taste compared to bronchodilator patients ( $P < 0.01$ ).	5
Morice et al., 2007 UK <sup>46</sup>	RCT Double Blind	N = 27 (9M/18F) Patients had persistent cough > 3 months.	<b>Morphine</b> (5mg) b.i.d. or placebo for 4 weeks.	Change in Leicester Cough Questionnaire for Chronic Cough (primary), daily cough diary, citric cough challenges.	Daily cough diary showed a significant reduction in mean cough scores on morphine $P < 0.01$ compared with baseline.	Significant improvement in mean cough scores in patients treated with morphine.	4

AE: adverse reactions; NS: not significant; SD: significant differences; h = hour.

quality and methodological issues that exist with various studies, and the small samples used. Among the 75 studies reviewed, only about one-quarter ( $N = 20$ ) of the studies used 'cough' as a primary outcome. The vast majority of studies were focused on efficacy of treatment in relation to respiratory illnesses, with cough being a secondary outcome. Very few studies reported sample size calculations, hence it is not possible to ascertain whether negative results are due to a Type II error or not. Quality scores were also variable, although it is encouraging to see that more recent studies have been assigned higher Jadad scores in this review.

The measurement of cough in the reviewed studies has been particularly problematic. The vast majority of the trials have used patient diaries, cough counts, and patient self reports, largely unvalidated methods for measuring cough. Often cough has been only a small component of 'symptoms' and included as part of a number of other symptoms (such as dyspnoea) assessed together. Only a couple of trials have used a validated method of measuring cough, such as the Leicester Cough Questionnaire. Some studies assessed cough frequency, some others cough intensity and others cough distress/discomfort. While these data are important, each study describes a separate facet of the cough symptom experience: a better approach, arguably, would be to address all three parameters together as each provides a different and complementary perspective (a frequent mild and not distressing cough is a different experience, for example, compared with an occasional severe and distressing cough).

Nevertheless, some treatments have shown consistently positive results (with varying levels of effect) in specific patient groups, including corticosteroids, leukotriene receptor antagonists, mast cell stabilizers, ipratropium bromide, neltexine, ionised glycerol and lidocaine. In GORD, proton pump inhibitors may be effective in individual patients, but a relevant systematic review specific to GORD suggests that data are insufficient to support their use,<sup>88</sup> while for allergic rhinoconjunctivitis the use of antihistamines may be appropriate. The trials, however, often present mixed results that do not allow for firm conclusions to be drawn (such as the mast cell stabilizer nedocromil) or positive evidence comes from a single small study with no replication (such as Th2 cytokine inhibitor). Also, the example of codeine (by far one of the commonest prescriptions for cough) is interesting as it is generally considered to be the anti-tussive to which novel treatments should be compared. Early small scale and poor quality trials in the 1960s/70s show positive results, while more recent higher quality trials suggest no effect of codeine over placebo; whether codeine should be the comparator when designing trials of new medications is increasingly in question. Benzonatate, moguis-teine and dextromethophran (the latter often included in over-the-counter cough mixtures) also showed possible effects, but again the evidence base for these drugs is small.

Non-pharmacological trials are scarce, with only three trials identified, and only two (speech pathology training and use of SMS messages to monitor symptoms) showing positive results. Speech pathology training could be a useful adjunct to pharmacological treatments, particularly as coughing has the potential to traumatise the upper airways (i.e. the vocal cords). More work should be directed in this promising area. Monitoring symptoms through technology (mobile phones/internet) is another area that has shown improvements, and this is a method that can have important self-management and health service utilisation implications. This is an area of increasing research focus, and studies have already started demonstrating the potential of such applications.<sup>89,90</sup>

It is clear that the treatment options for cough are far from satisfactory, and have been described as an unmet need for the cough patient.<sup>91</sup> Future research should focus more appropriately in providing concrete evidence for the management of this common and distressing symptom. Cough should be measured as

the primary outcome with the use of validated methods that consider all dimensions of the cough experience. Both subjective and objective measures should be used, as they have the potential to capture both patient perception and independent evidence of efficacy.<sup>92</sup> Patients should be selected carefully for inclusion, avoiding heterogeneity in terms of concurrent respiratory disease, smoking status and other clinical characteristics that may affect the results (i.e. concurrent maintenance treatments). More research should explore the impact of cough on psychosocial status, quality of life and daily activities. Also, it is unclear from the trials reviewed what the duration of any treatment should be, as studies for the same drug have used different durations for the intervention. Many of the studies showing statistically significant positive effects have managed to change the cough by 15–20%; whether this is a clinically important difference and whether patients can notice such a small difference is unclear. This issue needs further exploration in the literature. There should also be a better balance between testing non-specific and specific anti-tussives in the future.

With the lack of clarity in the assessment and management of cough as described above and elsewhere,<sup>91,93</sup> it is not surprising that clinical guidelines have focused to date more on principles of treatment rather than on much needed explicit guidance for clinical decision-making, and are mostly based upon expert opinion rather than evidence base. Such difficulties have been highlighted in the latest updated guidelines from the American College of Chest Physicians.<sup>92</sup>

Idiopathic cough, accounting for a significant number of patients seen in secondary and tertiary care, has been the focus of only 3 trials with a total of 158 subjects enrolled. A 20% of patients with cough may present with more than one aggravating factor,<sup>94</sup> and this group of patients may need a more complex management regime before symptom resolution is achieved, but few trials have focused on this population. Combinations of treatments may need to be developed, including both pharmacological and non-pharmacological approaches. Furthermore, there is an urgent need for more high quality research to build the evidence base around the management of cough in respiratory illness, more attention from the physicians and higher investment from the industry. New preparations are in phase II or III trials (e.g. NOP1 agonists, bradykinin B2 or GABA receptor antagonists, among others).<sup>93</sup> Amitryptiline, gabapentin and carbamazepine are experimental options that could have a role in the management of cough<sup>91</sup> supported by case study reports. It is to be hoped that some better tested and improved cough medications will enter the market in the next few years.

#### Conflict of interest statement

None of the authors has any conflict of interest in relation to this paper that would inadvertently influence the work.

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#### Appendix. Supplementary material

Supplementary material associated with this article can be found in the online version, at [doi:10.1016/j.rmed.2010.02.010](https://doi.org/10.1016/j.rmed.2010.02.010).

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### Educational questions

Answer the following questions:

1. Chronic cough is defined as daily coughing of which duration?
  - a. Cough lasting at least three weeks
  - b. Cough lasting eight weeks or more
  - c. Cough lasting three months or more
  - d. Cough lasting three months or more in two consecutive years.
2. Chronic cough affects which of the following?
  - a. sleep
  - b. absenteeism
  - c. changes in daily activities
  - d. quality of life
  - e. all of the above
3. Which of the following medications have been shown to be helpful in decreasing cough across several conditions?
  - a. Codeine
  - b. Inhaled corticosteroids
  - c. Antihistamines
  - d. Theophyllines
4. Cough is easily measured using standardized, well validated and commonly used measures.
  - a. True
  - b. False

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