Effective Health Care Program

Comparative Effectiveness Review
Number 100

Assessment and Management of Chronic Cough

Agency for Healthcare Research and Quality
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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10066-I

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AHRQ Publication No. 13-EHC032-EF
January 2013
Errata March 2014

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested Citation: McCrory DC, Coeytaux RR, Yancy WS Jr., Schmit KM, Kemper AR, Goode A, Hasselblad V, Heidenfelder BL, Irvine RJ, Musty MD, Gray R, Sanders GD. Assessment and Management of Chronic Cough. Comparative Effectiveness Review No. 100. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC032-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2013. Errata March 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Errata

Table A in the Executive Summary and Tables 6, 11, and 12 in the full report have been updated to reflect the following changes:

1. CQLQ--corrected sample size and correlation coefficients for French 2002 paper for Internal Consistency.
2. CQLQ--corrected sample size and correlation coefficients for French 2002 paper for Repeatability.
3. PC-QOL--added data from Newcombe 2010 study for Repeatability.

The text and conclusions remain unchanged.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors thank Megan von Isenburg, M.S.L.S., for help with the literature search and retrieval.

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Assessment and Management of Chronic Cough

Structured Abstract

Objectives. Cough is the most common complaint for patients seeking medical attention in the United States. Although the most common cause of cough is acute self-limited viral infections, chronic cough (cough that lasts more than 4 weeks in children <14 years of age or more than 8 weeks in adolescents and adults) has a significant impact on quality of life and is responsible for up to 38 percent of pulmonary outpatient visits. Furthermore, a treatable cause is absent in up to 46 percent of patients with chronic cough despite a thorough diagnostic investigation. The comparative value of tools for assessing cough and the comparative effectiveness of treatments for unexplained or refractory cough are uncertain.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (June 4, 2012) for relevant English-language comparative studies.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded evidence. Random-effects models were used to compute summary estimates of effects. We supplemented the meta-analysis of direct comparisons with a mixed treatment meta-analysis that incorporated data from placebo comparisons and head-to-head comparisons.

Results. To evaluate instruments for assessing cough, we considered the dimensions of cough frequency, cough severity, and cough-specific quality of life (QOL). We sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. Seventy-eight studies (5,927 subjects) evaluated instruments for assessing cough. The Leicester Cough Questionnaire (LCQ) and Cough-specific Quality of Life Questionnaire (CQLQ) were the most widely studied instruments in adults; there is moderate strength of evidence (SOE) to support both the LCQ's and the CQLQ's validity in assessing severity/QOL of cough. For pediatric populations, there is moderate SOE to support the Parent Cough-specific Quality of Life questionnaire's (PC-QOL) validity in assessing severity/QOL of cough. Electronic recording devices are accurate for assessing cough frequency, but show variable correlation with other tools. Although visual analog scales (VAS) are easy to administer and have face validity, we did not identify any studies to formally validate their accuracy in assessing cough. We identified no studies exploring the impact of cough assessment instruments on therapeutic efficacy or patient outcome efficacy.

Forty-eight studies (2,923 patients) evaluated 67 therapeutic comparisons for patients with chronic cough. Classes of drugs evaluated included opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics. The opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing chronic cough in adults. In particular, codeine and dextromethorphan reduced cough severity and frequency. Relative to placebo, the effect of dextromethorphan on cough severity was 0.54 (95% confidence interval [CI], 0.27 to 0.80; p=0.0008), and the effect of opiates was 0.63 (95% CI, 0.40 to 0.86; p<0.0001). Relative to placebo, the effect of dextromethorphan on cough frequency was 0.40 (95% CI, 0.18 to 0.85; p=0.0248), and the effect of codeine was 0.57 (95% CI, 0.36 to 0.91; p=0.0260). However, due to inconsistency and imprecision of results, and small numbers

of direct comparisons, the overall SOE is insufficient to draw firm conclusions about the comparative effectiveness of these agents. Very few studies evaluated nonpharmacological therapies (two studies) or the management of cough in children (three studies).

Conclusions. Several instruments for assessing cough severity, frequency, and impact on cough-specific quality of life show good internal consistency but variable correlation with other cough measurement tools, meaning that a number of instruments are precise but their accuracy is less clear. Although the evidence is sparse, the opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough in adults. Our review highlights the need for further studies in patient populations with unexplained or refractory chronic cough as determined by current diagnostic and empiric treatment recommendations. Further, it shows the need for more systematic design and reporting of these studies and assessment of their patient-centered outcomes. This is in contrast to the more extensive literature on the management of acute cough.

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Executive Summary

Background

In the United States, cough is the most common complaint for which patients seek medical attention and is the second most common reason for a general medical examination, accounting for more than 26 million office visits annually.[1] Cough often results from an acute, self-limited, viral upper respiratory tract infection; however, there are multiple causes of cough beyond this, including both respiratory tract and nonrespiratory tract-related etiologies. Cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older is considered to be chronic by the American College of Chest Physicians (ACCP).[2,3] Cough serves a potentially beneficial purpose by clearing the airways of excessive mucus, irritants, or abnormal substances such as edema fluid or pus. But while cough may serve a useful function, it can also lead to a variety of problems, including exhaustion (57%), feeling self-conscious (55%), insomnia (45%), changes in lifestyle (45%), musculoskeletal pain (45%), hoarseness (43%), excessive perspiration (42%), and urinary incontinence (39%).[4] These problems are more likely to be prominent in the setting of chronic versus acute cough. As a consequence, chronic cough is responsible for up to 38 percent of pulmonary outpatient visits.[5,6]

To effectively assess cough and monitor response to treatment, it is essential to have valid measurement tools. Currently there are many different tools used to assess cough frequency and severity, including quality-of-life questionnaires, visual analog scales, electronic recordings, and human counts. It is important to determine whether the tools currently in use accurately assess cough and response to treatment. While no universally accepted gold standard exists for comparison, data regarding the validity, consistency, reliability, and responsiveness of these tools are needed. The purpose of this review is to evaluate the effectiveness of instruments to evaluate cough and the comparative effectiveness of treatments for the symptom of cough in patients with either unexplained or refractory chronic cough.

In patients with no identifiable cause of cough (unexplained or idiopathic) or no response to specific treatment (unresponsive, refractory, or intractable), chronic cough poses a particularly challenging problem. The differential diagnosis for chronic cough has a different list of etiologies compared with acute cough. Treatment for chronic cough contrasts with acute cough in that acute cough treatment may focus on curing the underlying etiology (e.g., bacterial bronchitis or pneumonia) or suppressing symptoms for the short period of time needed for the etiology to resolve spontaneously (e.g., viral etiologies). Cough becomes chronic if it persists, often due to an underlying etiology that is difficult to diagnose or treat. Therefore, treatments for cough may have differential effectiveness depending on whether the cough is acute versus chronic. Side effects of medication may also become more salient in the setting of chronic cough given that treatment duration is longer, allowing more opportunity for side effects to occur. Chronic cough also differs from acute cough in that quality of life may be affected more severely and in different ways than with acute cough. Recent studies from the United Kingdom, United States, and Japan evaluating patients with chronic cough have estimated that up to 46 percent of patients have idiopathic cough despite a thorough diagnostic investigation.[7]

The management of nonspecific acute or chronic cough in young children can be especially difficult because of the risks associated with pharmacotherapy. In 2008, manufactures voluntarily removed over-the-counter infant (<2 years of age) cough and cold products (e.g., those containing ephedrine, pseudoephedrine, phenylephrine, diphenhydramine,

brompheniramine, or chlorpheniramine) because of many reports of serious adverse events. Later that year, manufactures relabeled cough and cold products to warn against use in children <4 years of age.[8] This position is supported by the American Academy of Pediatrics.

The diagnosis and management of cough has been the subject of several guideline efforts, two aimed at assessment of cough in adults,[9,10] and one focused on children.[11] Guidelines from ACCP, last updated in 2006, are the most comprehensive resource and will be the subject of a future update.[10]

Identifying the underlying etiology is the most important step in the successful management of chronic cough.[10] If, however, no cause can be identified, or if treatment of the underlying etiology fails to resolve the cough, then the cough may be treated symptomatically. In the majority of cases, symptomatic treatment consists of antitussive therapy to decrease cough frequency and severity. Antitussive treatments vary in mechanism of action. Nonspecific antitussives such as dextromethorphan and codeine appear to act in the brain stem to reduce the cough reflex. Other nonspecific antitussives, such as benzonatate, act to anesthetize respiratory passages and thus reduce the stimulus to cough. Other agents aim to decrease the volume of respiratory tract secretions and thus the need to cough. These latter antitussive agents are also used to treat certain common underlying etiologies and include antihistamines, corticosteroids, antibiotics, decongestants, and mast cell stabilizers. Nonpharmacological antitussives are few but may include, for example, honey. Recently, speech therapy interventions have been used to treat chronic cough in patients suspected of upper airway hypersensitivity.[12]

In a limited number of situations where cough provides a useful function (such as in bronchiectasis, pneumonia, or atelectasis), protussive therapy may be used in an attempt to increase cough effectiveness without increasing its frequency. Protussive treatments aim to change the characteristics of mucus in such a way that it can be cleared more effectively by mucociliary action or cough. Such effective clearing can subsequently lessen the severity and frequency of a patient's cough. Protussive pharmacological agents include expectorants, mucolytics, and mucus-modifying agents. Examples of these include guaifenesin, hypertonic saline, and acetylcysteine. In addition, physical maneuvers such as chest physical therapy, flutter valves, or pneumatic jackets may be used, especially in patients with respiratory muscle weakness.

Scope and Key Questions

This comparative effectiveness review (CER) was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the comparative effectiveness of measurement tools for assessing cough and of symptomatic treatments for chronic cough.

With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The KQs considered in this review were:

KQ 1: In adults and adolescents (≥14 years of age) and children (<14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough?

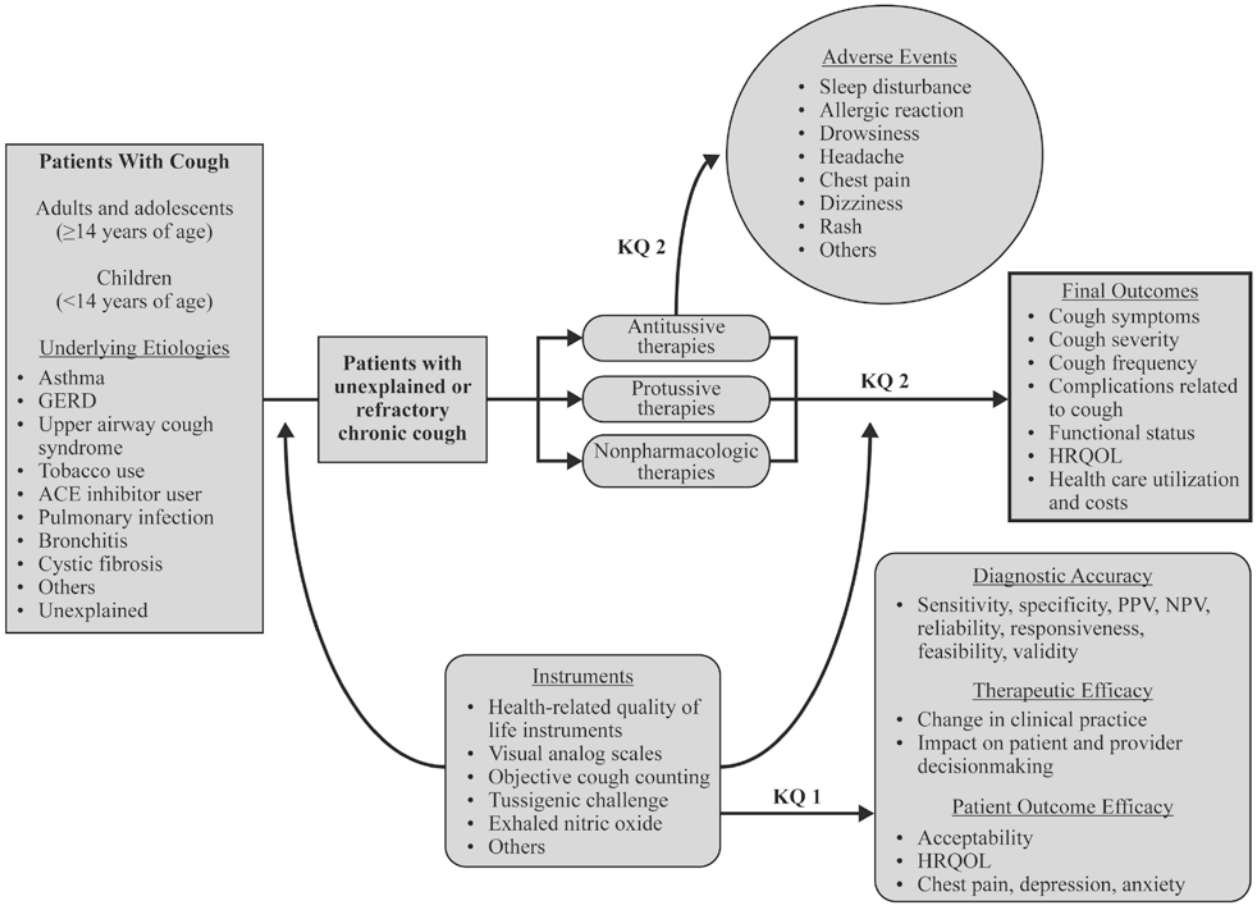
KQ 2: In adults and adolescents (≥14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?

a. In patients with unexplained chronic cough

b. In patients with refractory cough with a known underlying etiology

Figure A depicts the KQs within the context of the PICOTS.

Figure A. Analytic framework



ACE = angiotensin-converting enzyme; GERD = gastroesophageal reflux disease; HRQOL = health-related quality of life; KQ = Key Question; NPV = negative predictive value; PPV = positive predictive value

Methods

The methods for this CER follow those suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide)[13] and Methods Guide for Medical Test Reviews (hereafter referred to as the Medical Test Guide).[14]

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing clinicians (adult and pediatric pulmonology, otolaryngology, school nursing, respiratory medicine, primary care), patients, scientific experts, and payers, to help define the KQs. The KQs were then posted for public comment in September 2011 for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened the Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the

TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report.

Literature Search Strategy

To identify the relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR; last search date for all three sources June 4, 2012). Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of references from a set of key primary and systematic review articles. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used several approaches to identify relevant grey literature, including a request for scientific information packets submitted to drug and device manufacturers and a search of U.S. Food and Drug Administration (FDA) device registration studies and new drug applications. We also searched study registries and conference abstracts for relevant articles from completed studies. Grey literature databases searched included ClinicalTrials.gov (July 18, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (July 18, 2012); and ProQuest COS Conference Papers Index (January 18, 2012).

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2 of the main report. For KQ 1, the search focused on English-language evaluative studies that compared qualitative and/or quantitative instruments used to assess cough in patients (inpatients or outpatients) with cough of any duration and considering the following outcomes: diagnostic accuracy (e.g., sensitivity, validity, reliability, among others); therapeutic efficacy (e.g., impact on patient or provider decisionmaking); and patient outcome efficacy (e.g., acceptability, quality of life). For KQ 2, the search focused on English-language, prospective (randomized controlled trial [RCT] or cohort studies), comparative assessments of pharmacological and nonpharmacological therapies aimed at treating the symptom of cough in patients with chronic cough, in particular, patients with unexplained chronic cough or refractory cough of known etiology. We accepted as chronic any cough described as such, or that exceeded 8 weeks in adults and adolescents or 4 weeks in children $\leq$14 years of age. Because determination of whether an individual's chronic cough was truly unexplained or refractory was often difficult or impossible given available descriptions in the published article, we did not exclude articles based on diagnostic evaluation or empiric therapeutic trials, but rather described such information in an attempt to infer to what extent study populations could be considered unexplained or refractory according to current criteria. Articles were excluded if the therapy was directed at an underlying etiology rather than the symptom of cough, if cough resulted from invasive respiratory tract instrumentation, or if the intervention tested was not available in the United States. The following outcomes were considered: cough symptoms and severity, complications related to coughing, functional status, health-related quality of life, health care utilization and costs, and adverse effects of therapy.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were reviewed independently by two investigators for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Extraction

The research team created data abstraction forms and evidence table templates for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We gave particular attention to describing the details of the treatment, patient characteristics, and study design that were related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the study period. The safety outcomes were framed to help identify adverse events from drug therapies and nonpharmacological therapies. Data necessary for assessing quality and applicability were also abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included articles and revised as necessary.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[13] To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies, additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding were considered. We used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting.

For studies of diagnostic tests (KQ 1), we used the QUality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2[15] to assess quality in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias and concerns regarding applicability, with associated signaling questions to help with these bias and applicability judgments.

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ.

For KQ 1 we considered the three dimensions of (1) cough frequency, (2) cough severity (which might include quantity and characteristics of sputum, difficulty of expectoration, dyspnea, between cough sensations, or pain), and (3) cough-specific quality of life (QOL). We then sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. For cough frequency, we evaluated validity by concurrence with measures of other constructs (e.g., cough severity, cough-specific QOL, tussigenic challenge (or cough reflex sensitivity), and exhaled nitrous oxide), and we assessed reliability using intermethod reliability (e.g., manual cough counts vs. electronic recording device cough counts) and test-retest reliability. Although we consider cough severity and cough-specific QOL to be separate dimensions of cough, most of the standardized questionnaires included in this report measured aspects of both of these dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL together to be "severity/QOL" instruments. Within this report, we did not identify any validated instruments that focused purely on cough severity. For these severity/QOL instruments, we evaluated validity by looking at concurrence with measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability, as well as internal consistency. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough.

For KQ 2, we determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons where at least three studies reported the same outcome. We considered measures of cough frequency, regardless of the scale used, to be similar enough to combine using effect sizes (standardized mean differences); similarly, measures of cough severity that used different measurement scales were considered similar enough to combine using effect sizes.

When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics). We present summary estimates, standard errors, and confidence intervals in our data synthesis.

We supplemented the meta-analysis of direct comparisons with a mixed treatment meta-analysis that incorporated data from placebo comparisons and head-to-head comparisons, including multi-armed trials (i.e., trials that included more than one comparison). The general strategy for analysis was to construct a random-effects model that was comparable to the standard random-effects models used in the meta-analysis of effect sizes. This model, which was

fitted using SAS® PROC NLMIXED (2009; SAS Institute Inc., Cary, NC), estimated the effect sizes (relative to placebo) for each treatment.

Strength of the Body of Evidence

We rated the strength of evidence for each KQ and outcome using the general approach described in the Methods Guide.[13,16] and Medical Test Guide.[14] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned.

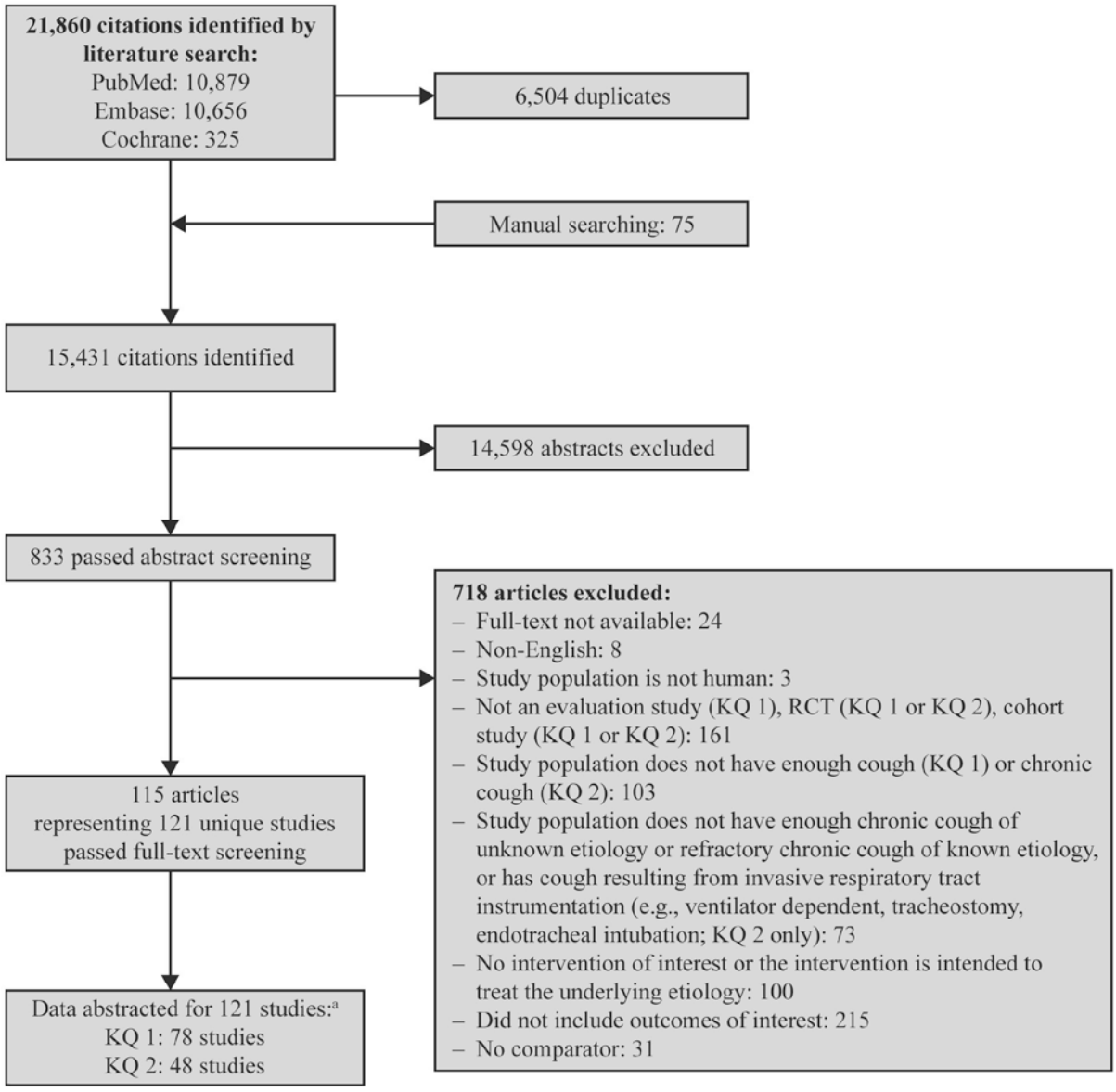
Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.[13,17] In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We used checklists to guide the assessment of applicability. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Results

Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 21,860 citations, 6,504 of which were duplicate citations. Manual searching identified 75 additional citations, for a total of 15,431 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 833 full-text articles were retrieved and screened. Of these, 718 were excluded at the full-text screening stage, leaving 115 articles for data abstraction. Overall, we included 121 studies represented by these 115 publications: 78 studies were relevant to KQ 1, 48 to KQ 2 (5 studies were relevant to both KQs). Studies were conducted in Europe (54%); the United States or Canada (23%); Australia or New Zealand (11%); Asia (8%); and other locations (8%). Nineteen studies in KQ 1 (23%) and 3 studies in KQ 2 (6%) included children. Forty-five studies (37%) were published before 2000. No additional information was found through our grey literature search.

Figure B. Literature flow diagram



KQ = Key Question; RCT = randomized controlled trial
[a]Five studies were relevant to both KQ 1 and KQ 2.

Key Question 1. Instruments Used To Assess Cough

Key points from the Results chapter are:

- Electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with instruments that measure other dimensions of cough.
- The Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ) are the most widely studied cough-specific quality-of-life questionnaires in adult populations. Both have demonstrated validity and reliability, with emerging evidence available on responsiveness.

- There is moderate strength of evidence to support the validity and responsiveness of the Parent Cough-specific Quality of Life Questionnaire (PC-QOL) in assessing the severity/QOL of cough among children.
- Emerging data support the responsiveness of recording devices, cough-related questionnaires, and tussigenic challenge tests, but further research is needed to accurately estimate the minimally important difference (MID) of these assessment instruments.
- Although diaries and visual analog scales are based on face validity, assess a wide variety of different cough outcomes, and are widely used both in research and practice, there is little data to validate their accuracy in assessing cough, and what data exist show inconsistent correlations with other cough measurement tools. These tools are usually simple and easy to use, but more data are needed to determine their reliability and validity in assessing cough frequency or severity/QOL.
- While all of the included studies evaluated aspects of the comparative diagnostic accuracy of the various cough measurement tools, none evaluated the comparative therapeutic efficacy or patient outcome efficacy of these tools.

Cough can be assessed along several dimensions, the most of important of which may be frequency, severity, and cough-specific QOL. Cough frequency is objective and relatively easy to measure but may not necessarily correlate with severity or cough-specific QOL, whereas cough severity and cough-specific QOL may be closely interrelated. Most of the standardized questionnaires included in this report measured aspects of both of these latter dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL together to be "severity/QOL" instruments. In this CER we evaluate the available data that support the validity and reliability of instruments to measure one of two dimensions of cough: (1) cough frequency; or (2) the severity/QOL impact of cough (including assessments of the impact of cough on sleep, work, general well-being, health-related quality of life, etc.). We also evaluate the available data that support these instruments' ability to measure potentially meaningful clinical change over time (responsiveness).

To be eligible for inclusion in this report, a study had to either (1) compare a cough frequency or severity/QOL assessment instrument with one or more cough assessment, health-related quality of life, or clinical change instrument; or (2) report data on changes in the instrument score over time in response to treatment for cough or the underlying etiology of the cough. For the purposes of this report, we consider tussigenic challenge tests and exhaled nitric oxide tests as severity/QOL assessments.

A total of 78 studies met the inclusion criteria for this KQ. Of these, 67 (86%) were judged to have a low risk of bias and 11 (14%) were judged to have a high risk of bias. In most cases, the funding source was not reported or was unclear. Seven studies were RCTs, and the remaining 71 were observational studies. A total of 5,927 participants were included across studies; sample sizes of individual studies ranged from 1 to 671 subjects. Thirty-three studies (42%) enrolled patients with chronic cough of mixed, unknown, or unspecified etiology; 18 (23%) enrolled patients with acute cough or cough of unspecified duration, and 27 (35%) focused on specific clinical conditions such as chronic bronchitis, asthma, or lung cancer. Fifty-nine studies included adults and adolescents (≥14 years of age), 15 included only children (<14 years of age), and 4 included adults, adolescents, and children.

Table A summarizes the findings of our review and the strength of evidence[16] for the available outcomes of validity, internal consistency, reliability, and responsiveness for the main instruments. Details about the specific components of these ratings (risk of bias, consistency,

directness, and precision) are available in the main report. We did not identify any studies evaluating the comparative therapeutic efficacy or patient outcome efficacy of these tools; therefore, the current evidence base is insufficient for us to draw any conclusions about these outcomes.

Table A. Summary of strength of evidence (SOE) and effect estimate for KQ 1[a]

Instrument (Dimension[s] Assessed)	Validity (Correlation With Other Measures of Cough)	Reliability		Responsiveness
		Internal Consistency (Cronbach's Alpha)	Repeatability	
Leicester Cough Questionnaire (LCQ) (Severity/QOL)	**Moderate SOE** 15 studies; 1,058 subjects Range of r = 0.26–0.93	**High SOE** 4 studies; 430 subjects Range of r = 0.77–0.93	**High SOE** 2 studies; 256 subjects Range of r = 0.86–0.92	**Moderate SOE** 8 studies; 659 subjects Range of ES = 0.84–19.5
Cough-specific Quality of Life Questionnaire (CQLQ) and Adverse Cough Outcome Survey (ACOS)[b] (Severity/QOL)	**Moderate SOE** 5 studies; 336 subjects Range of r = 0.24–0.56	**Insufficient SOE** 1 study; 184 subjects Range of r = 0.63–0.92	**Insufficient SOE** 1 study; 52 subjects Range of r = 0.75–0.93	**Moderate SOE** 7 studies; 460 subjects Range of MID = 10.6–21.9
Parent Cough-specific Quality of Life questionnaire (PC-QOL) (Severity/QOL)	**Moderate SOE** 4 studies; 593 subjects Range of r = 0.01–0.70	**Moderate SOE** 3 studies; 247 subjects Range of r = 0.56–0.91	**Insufficient SOE** 1 study; 43 subjects Range of r = 0.40–0.51	**Moderate SOE** 3 studies; 247 subjects Range of ES = 0.32–0.41
Electronic recording devices (Frequency)	**High SOE** 17 studies; 546 subjects Range of r = 0.89–0.99	**NA**	**Moderate SOE** 5 studies; 185 subjects Range of r = 0.8–1.0	**Insufficient SOE** 1 study; 67 subjects Detected change with treatment
Visual analog scales (Severity/QOL)	**Insufficient SOE** 9 studies; 410 subjects No summary measure	**NA**	**NA**	**Insufficient SOE** 1 study; 21 subjects Sensitivity of 0.81–0.95 for detecting clinically important change

ACOS = Adverse Cough Outcome Survey; CQLQ = Cough-specific Quality of Life Questionnaire; ES = effect size; KQ = Key Question; LCQ = Leicester Cough Questionnaire; MID = minimal important difference; NA = not applicable; PC-QOL = Parent Cough-specific Quality-of-Life questionnaire; r = correlation coefficient; SOE = strength of evidence

[a]All strength of evidence ratings of "Insufficient" or "NA" (not applicable) are shaded in grey.

[b]The ACOS has been revised and replaced by the CQLQ.

Key Question 2. Nonspecific Therapies for Chronic Cough

Key points from the Results chapter of the full report are:

- A wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough, including opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics.
- Patients with unexplained or refractory chronic cough are not well defined as a population in the evidence base, restricting the applicability of many studies.
- Of the agents reviewed, the opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough in adults.

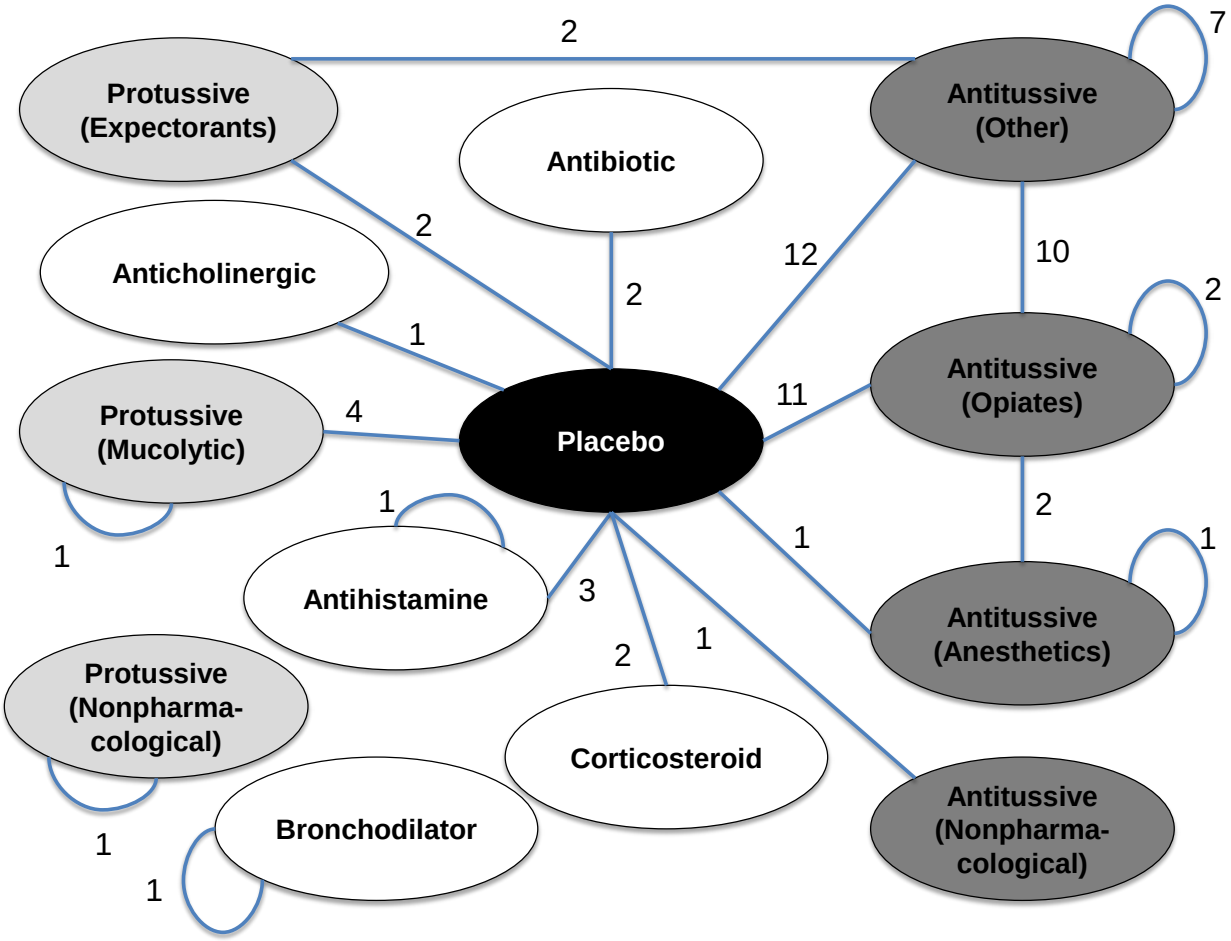
- There were several important quality limitations in the literature, including (1) too few good-quality studies focusing on chronic cough; (2) relatively short durations of followup (3) a diversity of outcomes measured across studies, which limited between-study comparisons; and (4) when similar outcomes were assessed across studies, the instruments used were diverse and inconsistent, making comparison and interpretation difficult.
- Data on nonpharmacological therapies for chronic cough were sparse.
- Studies evaluating management of unidentified or refractory chronic cough in children are extremely limited.
- All preparations appeared to be well-tolerated, but side effects and adverse events were uncommonly reported; underreporting side effects and adverse events could limit the assessment of effectiveness of these drugs.

Sixty-seven comparisons from 48 studies evaluated therapies in patients with chronic cough and met our inclusion criteria. The 48 studies were described in 42 publications. Thirty-three of the 48 studies were parallel-group RCTs, and 12 were randomized crossover studies. The range of years of publication was 1953 to 2012; 76 percent of the articles were published before 2000. Only three studies were performed in children.

A total of 2,923 participants were included across trials; sample sizes were relatively small, ranging from 8 to 214 participants. Duration of followup was relatively short in most studies, ranging from 1 hour to 115 days. Thirty-three (33) studies (69 percent) had a followup duration of 2 weeks or less. The majority of studies were rated fair in quality (n=29, or 60%); 11 studies were good in quality, and 8 were poor in quality. Fair- and poor-quality studies had the following limitations: limited description of study entry criteria, randomization, and patient population; incomplete followup; less valid statistical analyses (not intention-to-treat, post hoc subgroup analyses); and/or inadequate reporting of methods and findings.

A variety of agents were studied and could be broadly categorized into antitussives, protussives, and nonantitussive/nonprotussive agents. Antitussives were further categorized as opiates, anesthetics, nonpharmacological, or “other” types. Protussives included expectorants, mucolytics, and nonpharmacological therapies. Nonantitussive/nonprotussive pharmacotherapies included antihistamines, antibiotics, anticholinergics, and bronchodilators. Figure C represents the various categories of agents and the comparisons among these agents represented in the included studies. The 48 studies represented 67 different comparisons within or between treatment classes and included studies of 59 individual agents. There were 39 comparisons (58%) with placebo. The most common class comparisons were between other antitussives and placebo (12 comparisons, 18%), followed by comparisons between antitussive opiates and placebo (11 comparisons, 16%) and comparisons between antitussive opiates and other antitussives (10 comparisons, 15%). Fourteen different class comparisons were evaluated by only one or two studies. Only two studies evaluated nonpharmacological interventions.

Figure C. Overview of intervention class comparisons



The heterogeneity of the included studies in terms of the interventions and comparators, combined with the lack of three or more studies reporting the same outcome where there were multiple comparisons, precluded us from performing meta-analyses on almost all outcomes. Even when similar outcomes were assessed across studies, the instruments used were diverse and inconsistent, making comparison and interpretation difficult. Therefore the evidence from head to head trials is insufficient to draw conclusions about relative benefit.

We were, however, able to evaluate the relative effects on cough severity for four classes of treatments for chronic cough: antitussive opiates, antitussive dextromethorphan, antitussive moguisteine, and protussive mucolytics. This analysis included 11 studies and 700 patients. Most of the studies compared the treatment with placebo, but one compared opiates with dextromethorphan and placebo. Because each study used a different measure of severity, we converted all results to effect sizes (standardized mean differences). Relative to placebo, the effect of dextromethorphan on cough severity was 0.54 (95% confidence interval [CI], 0.27 to 0.80; p=0.0008), the effect of opiates was 0.63 (95% CI, 0.40 to 0.86; p<0.0001), the effect of moguisteine was 0.62 (95% CI, 0.04 to 1.16, p=0.0366), and the effect of mucolytics was 0.14 (95% CI -0.20 to 0.49; p=0.384). The studies showed significant heterogeneity (p=0.0023). The effects of dextromethorphan, moguisteine, and opiates compared with placebo on cough severity support a benefit of these therapies, but the evidence is insufficient to determine relative benefit among these therapies.

We performed a similar meta-analysis for cough frequency, including 7 studies and 396 patients. Relative to placebo, the effect of dextromethorphan on cough frequency was 0.40 (95% CI, 0.18 to 0.85; p=0.0248), the effect of codeine was 0.57 (95% CI, 0.36 to 0.91; p=0.0260), and the effect of moguisteine was 0.60 (95% CI, 0.31 to 1.17, p=0.1117). Again, the studies showed significant heterogeneity (p=0.0231). The effects of dextromethorphan and codeine compared with placebo on cough frequency support a benefit of these therapies, although the estimates are too imprecise to determine if one is superior to another. The effect of moguisteine was too imprecise to draw conclusions about is efficacy.

Tables B and C summarize the strength of evidence for the most commonly used classes of therapies and evaluated outcomes. Details about the specific components of these ratings (risk of bias, consistency, directness, and precision) are available in the main report. Across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias, the findings were inconsistent; the evidence, when available, was indirect (i.e., based on mixed treatment meta-analysis); and the findings, when available, were imprecise. There was insufficient evidence to support conclusions about comparative effectiveness of the interventions for any of our key outcomes. Evidence for other comparisons was too sparse to construct such summary tables.

Table B. Summary of strength of evidence (SOE) and effect estimate for KQ 2—active treatment comparisons[a]

Treatment Comparison	Cough Severity	Cough Frequency	Adverse Effects
Antitussive (anesthetic) vs. antitussive (opiate)	**Insufficient SOE** 1 study; 45 subjects Imprecise results	**Insufficient SOE** 2 studies; 105 subjects Imprecise results	**Insufficient SOE** 1 study; 60 subjects Imprecise results
Antitussive (opiate) vs. antitussive (other)	**Insufficient SOE** 16 studies; 958 subjects Opiates, dextromethorphan, and moguisteine had significant effect sizes vs. placebo in MTM (ranging from 0.54–0.63), but wide and overlapping CIs are too imprecise to (determine equivalence or noninferiority or) draw conclusions about relative effectiveness	**Insufficient SOE** 8 studies; 655 subjects Both codeine and dextromethorphan had significant ES vs. placebo in MTM, but wide and overlapping CIs are too imprecise to draw conclusions about relative effectiveness	**Insufficient SOE** 5 studies/273 subjects No summary measure
Protussive (mucolytic) vs. antitussive (other)	**Insufficient SOE** 4 studies; 274 subjects Mucolytics had much smaller effect size vs. placebo, p=NS, in MTM compared with dextromethorphan	**Insufficient SOE** 1 study; 24 subjects No summary measure	**Insufficient SOE** 0 studies/subjects
Protussive (mucolytic) vs. antitussive (opiate)	**Insufficient SOE** 4 studies; 274 subjects Mucolytics had much smaller effect size vs. placebo, p=NS, in MTM compared with codeine	**Insufficient SOE** 1 study; 24 subjects No summary measure	**Insufficient SOE** 0 studies/subjects

CI = confidence interval; ES = effect size; KQ = Key Question; MTM = mixed treatment meta-analysis; NS = not statistically significant;
SOE = strength of evidence
[a]All strength of evidence ratings of "Insufficient" are shaded in grey.

Table C. Summary of strength of evidence (SOE) and effect estimate for KQ 2—comparisons with placebo[a]

Treatment Comparison	Cough Severity	Cough Frequency	Adverse Effects
Codeine/opiates—Antitussive (opiates) vs. placebo	**Low SOE** 11 studies; 396 subjects[b] 0.63 (95% CI, 0.40 to 0.86; p<0.0001), from MTM	**Low SOE** 7 studies; 700 subjects[b] 0.57 (95% CI, 0.36 to 0.91; p=0.0260), from MTM	**Insufficient SOE** Imprecise results
Dextromethorphan—Antitussive (other) vs. placebo	**Low SOE** 11 studies; 396 subjects[b] 0.54 (95% CI, 0.27 to 0.80; p=0.0008), from MTM	**Low SOE** 7 studies; 700 subjects[b] 0.40 (95% CI, 0.18 to 0.85; p=0.0248), from MTM	**Insufficient SOE** No summary measure
Protussive (mucolytic) vs. placebo	**Insufficient SOE** 11 studies; 396 subjects[b] 0.14 (95% CI -0.20 to 0.49; p=0.384) from MTM	**Insufficient SOE** No summary measure	**Insufficient SOE** No summary measure
Moguisteine—Antitussive (other) vs. placebo	**Low SOE** 11 studies; 396 subjects[b] 0.62 (95% CI, 0.04 to 1.16, p=0.0366), from MTM	**Insufficient SOE** 7 studies; 700 subjects[b] 0.60 (95% CI, 0.31 to 1.17, p=0.1117), from MTM	**Insufficient SOE** No summary measure

CI = confidence interval; KQ = Key Question; MTM = mixed treatment meta-analysis; SOE = strength of evidence
[a]All strength of evidence ratings of "Insufficient" are shaded in grey.
[b]Total number of studies/patients from mixed treatment meta-analysis

Discussion

Key Findings

We reviewed 78 studies involving 5,927 patients that evaluated instruments used to assess cough. Our findings suggest that selected cough-specific quality-of-life instruments are valid and reliable for assessing cough. The LCQ and the CQLQ along with its predecessor, the Adverse Cough Outcome Survey [ACOS]), are the most widely studied cough-specific quality-of-life questionnaires in adults, with several studies showing fair to moderate correlation with other cough measurement tools such as cough frequency logs, tussigenic challenges, electronic recordings, or other quality-of-life questionnaires. Electronic recording devices are reliable for assessing cough frequency, but they show variable correlation with other cough measurement tools. This may be because cough frequency is unidimensional, whereas the impact that cough may have on an individual's functional status, quality of life, or sense of wellbeing may depend on many other factors. Multidimensional quality-of-life assessments such as the LCQ, CQLQ, and other cough-specific instruments may therefore be more useful than simple cough frequency in assessing meaningful impact of cough. Visual analog scales, although widely used both in research and practice, have little to no data to validate their accuracy in assessing cough, and inconsistent correlations with other cough measurement tools.

We reviewed 48 studies involving 2,923 patients that evaluated nonspecific (or symptomatic) therapies to treat patients with chronic cough. Our review found that a wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough. The opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise for managing the symptom of chronic cough. In particular, codeine (with dose response and placebo-controlled data) and dextromethorphan have reasonably good data for reducing cough frequency and severity. However, due to inconsistency and imprecision of results, and small numbers of head-to-head comparisons, the overall strength of evidence is insufficient to draw firm conclusions

about the comparative effectiveness of these agents. Finally, the evidence exploring the effectiveness of treatments in patients with truly unexplained cough was minimal. We considered the vast majority of study populations to have unresponsive chronic cough. Only three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough. Interestingly, therapy in each of these studies was associated with a reduction in cough severity, suggesting that chronic unexplained cough can respond to nonspecific therapies aimed at the symptom and not the underlying etiology.

Unfortunately, we identified only one study of a currently available (in the United States) treatment (amoxicillin clavulanate) in children with chronic cough, but the study's applicability was limited in terms of its sample size and the description of the diagnostic evaluation of cough. Given the lack of studies on treatment of chronic unexplained cough in children, it is not surprising that there were no data on harms in this population.

Applicability

It is reasonable to assume that the utility, performance, reliability, and validity of cough instruments may differ between children and adults, between acute and chronic cough conditions, and between underlying etiologies such as asthma, chronic bronchitis, acute rhinitis, lung cancer, and chronic refractory cough. More consistent reporting of patient characteristics such as age, underlying etiology, duration of symptoms and/or illness, overall medical comorbidity, and prior treatment would facilitate evaluations of various cough instruments in important subgroups. For our analysis of instruments for the assessment of cough (KQ 1), most of the studies were conducted in Europe (41 studies, 53%); 32 of these were conducted exclusively in the United Kingdom. Nineteen (24%) studies were conducted in the United States or Canada. Location of study was not, however, obviously related to design, patient, outcome, or analytical characteristics.

By restricting inclusion to trials of patients with unexplained or refractory cough, we improved the applicability of our findings to this population but also decreased the availability of evidence that could be reviewed. Expanding our evidence to include patients with acute cough would have substantially increased the evidence base but greatly reduced the applicability of the findings to the unexplained or refractory chronic cough population. Few studies directly reported assembling patients fitting our intended population of idiopathic or refractory chronic cough. More often patients were selected from persons with chronic cough (of variable duration) with a variety of diseases associated with cough. While we tried to apply criteria to improve applicability (e.g., excluding cystic fibrosis and bronchiectasis), the studies we ultimately included contained more diversity than we intended. In particular, studies with mixed etiologies of cough (including, e.g., patients with tuberculosis or lung cancer) and studies from different eras and geographic locations challenge the usefulness of data on treatment. The majority of studies took place in Europe, with 9 in the United Kingdom and 17 in other countries in Europe (total of 54%); only 9 (19%) took place within the United States or Canada.

For the studies focusing on the adult population, many of the drug treatment trials we identified included drugs that are not currently available in the United States (12 studies, 30 percent). The applicability of the included studies was also reduced given the age of much of the evidence, and therefore of the corresponding interventions and underlying clinical management of the patients. Publication dates ranged from 1953 to 2012, with 32 (76%) of the articles being

published before 2000. Given the changes in both available therapies and the diagnosis and treatment of underlying etiologies, more recent studies of contemporary therapies are needed.

Limitations of the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include: (1) few studies exploring the clinical population of interest (unexplained or refractory chronic cough) and in specific patient subgroups of interest (e.g., children, women, immunocompromised patients); (2) variable definitions of chronic cough; (3) diverse etiologies of cough that might respond differently to different therapies; (4) incomplete reporting of patient characteristics, study design, or outcomes; (5) small sample sizes and short duration of followup; (6) lack of gold standard outcomes to assess efficacy and tolerability; and (7) inconsistent reporting of comparative statistical analyses. In addition, most of the studies were comparatively old, and as such the evidence base suffers from age because of advances in clinical trial methodology, improved diagnostic evaluation of cough, and development of valid and reliable measures for cough and cough-specific quality of life.

Our review methods also had limitations. Our study was limited to English-language publications. In addition, even within patients with chronic cough, the target population of patients with unexplained chronic cough or refractory chronic cough with a known underlying etiology was difficult to identify. Rarely was a thorough negative diagnostic evaluation performed to assemble a group with unexplained chronic cough; in the case of studies of patients with a known underlying etiology, seldom was previously tried therapy described well enough to determine whether patients were treatment-refractory. In general, we considered use of a symptomatic treatment in a population with a known underlying etiology to imply refractory cough unless patients were noted to be treatment-naïve; certain etiologies, however, were considered differently. For example, most studies of cough-variant asthma, a common cause of chronic cough in children, which is usually highly responsive to appropriate asthma management, were excluded.

It is possible that our a priori definition of chronic cough in childhood (i.e., persisting at least 4 weeks if <14 years of age, or 8 weeks if 14 years or older) was too long and did not reflect care delivery. However, our decision to include studies that described their population as suffering with chronic cough regardless of time cut-off may have mitigated this problem. Focusing on nonspecific or symptomatic treatments to the exclusion of treatments aimed at specific causes of chronic cough proved more complicated to implement than we had anticipated. Certain therapies that we classified as specific (e.g., antihistamines and decongestants for upper airway cough syndrome) are sometimes referred to as nonspecific.[18] Furthermore, some other specific treatments were occasionally tested as nonspecific treatments in populations that did not meet diagnostic criteria for conditions for which the specific treatment would be appropriate. Finally, we grouped antitussive and protussive drugs into subsets that sometimes included pharmacologically diverse agents or separate drugs with certain similarities.

Research Gaps

We found sufficient evidence to suggest that the LCQ and CQLQ (for adults) and the PC-QOL (for children) may be valid instruments for assessing severity/QOL of cough, and that electronic recording devices, in general, appear to be valid assessments of cough frequency

compared with human cough counts. Unfortunately, however, the current evidence base is insufficient to provide conclusive findings related to the comparative effectiveness of available therapies for patients with unexplained or refractory chronic cough. There are, therefore, numerous areas of evidence gaps and areas for potential future research. We used the framework recommended by Robinson et al. to identify gaps in evidence and describe why these gaps exist.[19] This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies gaps as due to (1) insufficient or imprecise information, (2) biased information; (3) inconsistency or unknown consistency, and (4) not the right information. Results are as follows:

KQ 1—Instruments used to assess cough:

- Evidence establishing the responsiveness, validity, reliability, and consistency of available assessment instruments other than the LCQ and CQLQ, and building on available evidence for the LCQ and CQLQ instruments
- Additional validation or measurement studies focusing on the pediatric population in addition to the limited studies that report on the PC-QOL
- Development and validation of child/patient-completed, cough-specific quality-of-life instruments (as opposed to parent/proxy instruments such as the PC-QOL)
- Feasibility of cough assessment instruments in usual care (outside of RCTs or validation studies)
    - Insufficient evidence curently exists; could be explored through observational studies
- Uncertainty about the effects of patient self-reporting, parent reporting, or provider reporting in use of cough assessment tools
    - Insufficient evidence curently exists; could be explored through observational studies
- Incomplete evidence regarding the minimally important difference of cough frequency or severity/QOL instruments
- Impact of measurement tools on therapeutic efficacy or patient outcome efficacy

KQ 2—Nonspecific therapies for chronic cough:

- Comparative effectiveness of pharmacological therapies in the adult population
    - Current evidence is both imprecise and inconsistent. Additional comparative RCTs of contemporary and available agents are needed.
- Comparative effectiveness of pharmacological therapies in the pediatric population
    - Current evidence is insufficient and does not reflect available therapies. Comparative RCTs of contemporary and available agents specific to the pediatric population are needed.
- Comparative effectiveness of nonpharmacological therapies in both adult and pediatric populations
    - Current evidence is insufficient. Comparative RCTs of contemporary and available agents specific in both adult and pediatric populations are needed.
    - Additional RCTs or potentially patient-level meta-analyses of existing and future RCTs focusing on subpopulations of interest including women, pregnant women, patients with specific underlying etiologies, immunocompromised patients, and patients with a history of substance abuse

- Comparative effectiveness of available therapues in impacting health utilization and costs
    - Insufficient evidence curently exists; could be explored through observational studies
- Comparative effectiveness of available therapies in impacting cough severity, frequency, and quality of life
    - Current evidence is both imprecise and inconsistent. Additional comparative RCTs using standardized instruments are needed.

Conclusions

There is no established gold standard for assessing either frequency or severity/QOL of cough, thereby making it difficult to quantitatively assess test accuracy for cough instruments. Validity of severity/QOL questionnaires was generally demonstrated in the published literature by correlation with other cough assessment instruments, whereas validity of cough recording devices was generally demonstrated using human cough counts as the reference standard. Reliability of questionnaires was generally demonstrated by test-retest correlation and by demonstrating internal consistency. Several instruments, including the LCQ, CQLQ, and the PC-QOL, show good internal consistency but variable correlation with other cough measurement tools. This suggests that these tools may be reliable but demonstrate variable validity. The lack of validated reference tests and the diverse number of instruments used among treatment evaluations also complicates comparisons across studies. We identified no evidence exploring the impact of cough assessment instruments on therapeutic efficacy or patient outcome efficacy.

A wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough, including opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics. There were relatively few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough. The opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough compared with placebo, but there were insufficient data to draw conclusions between therapies. Data on nonpharmacological therapies for chronic cough are extremely limited, as are data on the management of unidentified or refractory chronic cough in children.

Our systematic review highlights the clear need for further studies in patient populations with unexplained or refractory chronic cough as determined by current diagnostic and empiric treatment recommendations. Further, it shows the need for more systematic design and reporting of these studies and assessment of patient-centered outcomes.

References

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. www.cdc.gov/nchs/ahcd.htm.
2. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-283S. PMID: 16428719.
3. Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):59S-62S. PMID: 16428693.
4. Irwin RS, Curley FJ. The treatment of cough. A comprehensive review. Chest. 1991;99(6):1477-84. PMID: 2036833.
5. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis. 1981;123(4 Pt 1):413-7. PMID: 7224353.
6. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7. PMID: 2178528.
7. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371(9621):1364-74. PMID: 18424325.
8. U.S. Food and Drug Administration. Special Features: An Important FDA Reminder for Parents: Do Not Give Infants Cough and Cold Products Designed for Older Children.www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm263948.htm.
9. Pratter MR, Brightling CE, Boulet LP, et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):222S-231S. PMID: 16428715.
10. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S. PMID: 16428686.
11. Finnish Medical Society Duodecim. Chronic cough in a child. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007. www.guideline.gov/content.aspx?id=12798.
12. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22(2):159-62. PMID: 19061964.
13. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318.
14. Agency for Healthcare Research and Quality. Methods Guide for Medical Test Reviews. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct.
15. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-536. PMID: 22007046.
16. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63(5):513-23. PMID: 19595577.

17. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.

18. Chang AB. Therapy for cough: where does it fall short? Expert Rev Respir Med. 2011;5(4):503-13. PMID: 21859270.

19. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Introduction

Background

Chronic Cough

In the United States, cough is the most common complaint for which patients seek medical attention and is the second most common reason for a general medical examination, accounting for over 26 million office visits annually.[1] Cough often results from an acute, self-limited, viral upper respiratory tract infection; however, there are multiple causes of cough beyond this, including both respiratory tract and nonrespiratory tract-related etiologies. Cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older is considered to be chronic by the American College of Chest Physicians (ACCP).[2,3] Such chronic cough is responsible for up to 38 percent of pulmonary outpatient visits.[4,5] The purpose of this review is to evaluate the effectiveness of instruments to evaluate cough and the comparative effectiveness of treatments for the symptom of cough in patients with either unexplained or refractory chronic cough. Recent studies from the UK, United States, and Japan evaluating patients with chronic cough have estimated that up to 46 percent of patients have idiopathic cough despite a thorough diagnostic investigation.[6]

Although cough is a troublesome symptom that causes discomfort to patients, it serves a potentially beneficial purpose by clearing the airways of excessive mucus, irritants, or abnormal substances such as edema fluid or pus. But while cough may serve a useful function, it can also lead to a variety of problems, including exhaustion (57%), feeling self-conscious (55%), insomnia (45%), changes in lifestyle (45%), musculoskeletal pain (45%), hoarseness (43%), excessive perspiration (42%), and urinary incontinence (39%).[7] These problems are more likely to be prominent in the setting of chronic versus acute cough.

This review focuses on chronic cough because of the significant adverse effects that chronic cough has been shown to have on the quality of patients' lives; if the cause of chronic cough can be identified and properly treated, these adverse effects can be markedly improved.[8]

Patient Population

Across all ages, there are many causes of chronic cough, of which more than one may affect any particular patient. The three most common causes of chronic cough in adult nonsmokers who seek medical attention for their cough are upper airway cough syndrome (UACS, formerly known as postnasal drip syndrome), asthma, and gastroesophageal reflux disease (GERD).[4,5,9-11] Several prospective studies[4-6,10-12] suggest that chronic cough is due to multiple causes 18 to 62 percent of the time. Even in patients for whom the underlying cause of cough has been identified and treated, the symptom of cough may persist and cause continued distress.

In patients with no identifiable cause of cough (unexplained or idiopathic) or no response to specific treatment (unresponsive, refractory, or intractable), chronic cough poses a particularly challenging problem. The differential diagnosis for chronic cough has a different list of etiologies compared with acute cough. Treatment for chronic cough contrasts with acute cough in that acute cough treatment may focus on curing the underlying etiology (e.g., bacterial bronchitis or pneumonia) or suppressing symptoms for the short period of time needed for the etiology to resolve spontaneously (e.g., viral etiologies). Cough becomes chronic if it persists, often due to an underlying etiology that is difficult to diagnose or treat. Therefore, treatments for

cough may have differential effectiveness depending on whether the cough is acute versus chronic. Side effects of medication may also become more salient in the setting of chronic cough given that treatment duration is longer, allowing more opportunity for side effects to occur. Chronic cough also differs from acute cough in that quality of life may be affected more severely and in different ways than with acute cough.

For adult patients in whom a specific cause of chronic cough is not easily identified, ACCP 2006 guidelines recommend an empiric approach to diagnosis and treatment.[13] This approach begins with a trial of an antihistamine (first-generation) and decongestant (for presumed UACS), followed by an assessment for cough-variant asthma by bronchoprovocation challenge (BPC), followed by a trial of asthma treatment or, if BPC is not available, an empiric trial of antiasthma therapy. If the BPC is negative or an empiric trial of antiasthma treatment is ineffective, then an assessment for nonasthmatic eosinophilic bronchitis (NAEB) is recommended, by induced sputum test for eosinophils. If this test is positive, or if it cannot be performed, then a trial of inhaled corticosteroids is recommended. Finally, if the induced sputum for eosinophils is negative or a trial of corticosteroids is negative, then empiric treatment for GERD is recommended.

Assessment and management of chronic cough in children results in additional uncertainties and concerns. Limitations and possible harms in extrapolating evidence from adults to children are well documented.[2,14,15] However, the lack of clinical studies specific to children also limits the available evidence and therefore possible evidence-based options for treating children.[14] Within cough specifically, there are both similarities but also clear physiological differences between children and adults and the underlying etiologies. Responses to certain medications have been shown to vary in terms of both their effectiveness and morbidity between adults and children.[16-19] Children are therefore an important and distinct population of interest for the management of unexplained or refractory chronic cough.

Patients with a chronic cough in whom an underlying etiology is not defined despite a thorough diagnostic workup are considered to have unexplained chronic cough. Patients in whom an underlying etiology has been identified, but in whom treatment fails to resolve the chronic cough, are considered to have refractory cough. How best to manage and treat patients with refractory cough and patients with unexplained chronic cough is uncertain and is the target of this systematic review.

Measuring Cough

Accurate, precise measurement of the frequency, severity, quality, and health problems caused by cough, therefore, is important if researchers and clinicians are to better understand the impact of chronic cough, make treatment decisions, and assess efficacy of treatments. Treatment of chronic cough is most successful when therapy can be directed at the underlying etiology; a systematic review has been performed producing a consensus guideline and algorithm to assist with this important process.[20] Therapies for the cough symptom (i.e., not specific to the underlying etiology), however, are often used when an etiology is not found or when cough persists despite therapies aimed at underlying etiologies. The purpose of this review is to evaluate the effectiveness of instruments to evaluate cough and the comparative effectiveness of treatments for the symptom of cough for patients with either unexplained or refractory chronic cough.

Measurement methods to formally evaluate cough severity/QOL have had limited acceptance within the broader clinical community. A recent review of treatments for respiratory diseases

with cough found that cough was seldom a primary outcome and was most frequently measured using unvalidated scales or as part of an overall symptom score.[21] If accurate and reproducible measurement methods can be identified, this may lead to more widespread use of more clinically relevant outcomes in research studies. Such measurement methods could also be useful to practicing clinicians when evaluating the efficacy of chosen treatments or assessing the severity/QOL of a patient's chronic cough.

Current Treatment Strategies

The diagnosis and management of cough has been the subject of several guideline efforts, two aimed at assessment of cough in adults,[13,22] and one focused on children.[23] Guidelines from the ACCP, last updated in 2006, are the most comprehensive resource and will be the subject of a future update.[13] According to these guidelines, initial clinical evaluation is aimed at determining the cause or underlying etiology of cough based on history, physical examination, and—if the cough is chronic—chest x-ray. Several measurement methods exist to evaluate cough severity, including health-related quality-of-life (HRQOL) instruments, visual analog scales, cough counts (using real-time wearable computerized equipment), and tussigenic challenge. These methods, however, have had limited acceptance within the broader clinical community, and their current use and subsequent impact on clinical decisionmaking and patient outcomes are small.

Identifying the underlying etiology of chronic cough is the most important step of successful management.[13] If, however, no cause can be identified, or if treatment of the underlying etiology fails to resolve the cough, then the cough may be treated symptomatically (Table 1), although the efficacy/effectiveness of some of these nonspecific treatments is unclear. In the majority of cases, symptomatic treatment consists of antitussive therapy to decrease cough frequency and severity. Antitussive treatments vary in mechanism of action. Nonspecific antitussives such as dextromethorphan and codeine appear to act in the brain stem to reduce the cough reflex. Other nonspecific antitussives, such as benzonatate, act to anesthetize respiratory passages and thus reduce the stimulus to cough. Other agents aim to decrease the volume of respiratory tract secretions and thus the stimulus and need to cough. These latter antitussive agents are also used to treat certain common underlying etiologies (e.g., UACS, NAEB) and include antihistamines, corticosteroids, antibiotics, decongestants, and mast cell stabilizers. Nonpharmacological antitussives are few but may include, for example, honey. Recently, speech therapy interventions have been used to treat chronic cough in patients suspected of upper airway hypersensitivity.[24]

In a limited number of situations where cough provides a useful function (such as in bronchiectasis, pneumonia, or atelectasis), protussive therapy may be used in an attempt to increase cough effectiveness without increasing its frequency. Protussive treatments aim to change the characteristics of mucus in such a way that it can be cleared more effectively by mucociliary action or cough. Such effective clearing can subsequently lessen the severity and frequency of a patient's cough. Protussive pharmacological agents include expectorants, mucolytics, and mucus-modifying agents. Examples of these include guaifenesin, hypertonic saline, and acetylcysteine. In addition, physical maneuvers such as chest physical therapy, flutter valves, or pneumatic jackets may be used, especially in patients with respiratory muscle weakness.

Managing the symptom of chronic cough, regardless of whether the etiology is known, is a challenge to even the most experienced health care provider. Several special considerations apply to children (<14 years of age). Duration of treatment, especially in asthmatic children, is

not clearly specified in existing guidelines. The benefits of antihistamines in young children (primarily under 12 years of age) with chronic cough are also not clearly understood. Because of the risk of adverse events, the U.S. Food and Drug Administration (FDA) recommends that cough and cold medicines not be used for children under 6 years of age, and the industry has voluntarily withdrawn these medicines for children under 2 years of age. In adults and adolescents (≥14 years of age), management of chronic cough is also challenging, and the appropriate role of the most commonly used antitussive and protussive treatments remains unclear. A review that covers older trials of these commonly used agents, as well as recent trials using newer agents and methodologies, may add significantly to the evidence base for guiding treatment.

Table 1. Commonly used therapies available in the United States for symptomatic treatment of chronic cough

Broad Category	Medication/Therapy Class	Therapy Name
Nonspecific pharmacological antitussives (cough suppressants)	Anesthetics	Benzonatate
	Opiates	Codeine, hydrocodone
	Other	Dextromethorphan
Nonpharmacological antitussives	Foods	Honey, tea, lemon, liquor
	Psychological	Cognitive behavioral therapy
	Alternative	Acupuncture, tai chi, yoga, meditation
	Multidimensional	Speech therapy
Protussives	Expectorants	Guaifenesin
	Mucolytic or mucus modifying	Acetylcysteine, dornase alfa inhaled
Nonpharmacological protussives	Physical	Chest physical therapy

Scope and Key Questions

Scope of the Review

This comparative effectiveness review (CER) was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the effectiveness of measurement tools for assessing cough (KQ 1) and the effectiveness of symptomatic treatments for chronic cough (KQ 2).

For KQ 1, the search focused on evaluative studies that compared qualitative and/or quantitative instruments used to assess cough in patients with cough of any duration. The goal was to assess the usefulness of the instruments by considering their diagnostic accuracy and their ability to impact treatment decisions and patient outcomes.

For KQ 2, the search focused on prospective, comparative assessments of pharmacological and nonpharmacological therapies aimed at treating the symptom of cough in patients with chronic cough. Articles were not included if the therapy was directed at an underlying etiology rather than the symptom of cough, if cough resulted from invasive respiratory tract instrumentation, or if the intervention was not available in the United States. A number of patient-oriented outcomes were considered, including cough symptoms and severity, complications related to coughing, functional status, health-related quality of life, and adverse effects of therapy. In addition, studies examining health care utilization and costs were included.

Key Questions

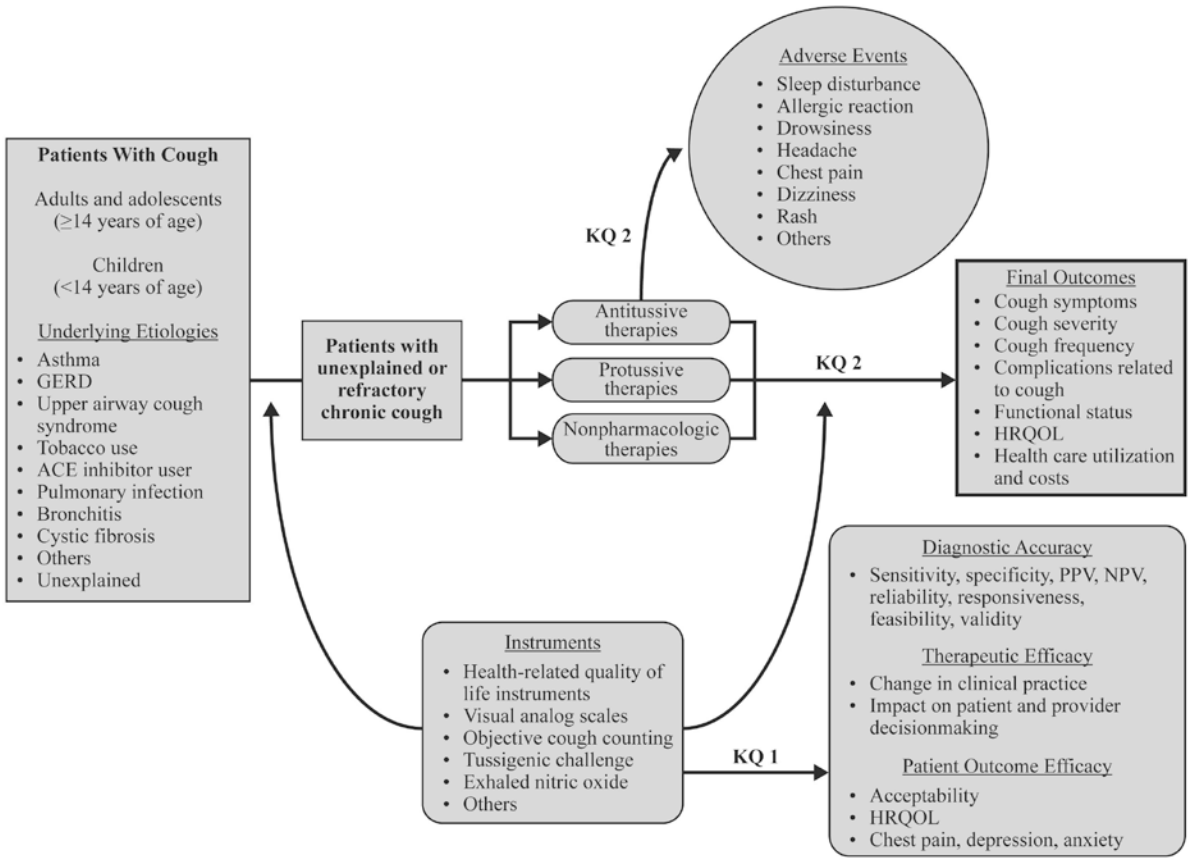
With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods chapter for details). The KQs considered in this review were:

- **KQ 1:** In adults and adolescents (≥ 14 years of age) and children (<14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough?
- **KQ 2:** In adults and adolescents (≥ 14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?
    a. In patients with unexplained chronic cough
    b. In patients with refractory cough with a known underlying etiology

Analytic Framework

Figure 1 depicts the KQs within the context of the PICOTS.

Figure 1. Analytic framework



ACE = angiotensin-converting enzyme; GERD = gastroesophageal reflux disease; HRQOL = health-related quality of life; KQ = Key Question; NPV = negative predictive value; PPV = positive predictive value

This figure depicts the KQs within the context of the PICOTS described above, In general, this figure shows that this CER compares the diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments to assess the severity, frequency, and impact of cough on patient-centered outcomes (KQ 1), and then the morbidity, adverse events, and health care utilization for patients with unidentified or refractory chronic cough receiving various treatments. Subgroups considered include children 14 years and younger (including exploration of children under 6 years of age, children under 2 years of age, and infants), and patients with differing underlying cough etiologies. Adverse events considered are sleep disturbance, allergic reaction, drowsiness, headache, chest pain, dizziness, and rash. Patient-centered final outcomes include: cough symptoms, cough severity, cough frequency, complications related to cough, functional status, general and cough-specific health-related quality of life, and health care utilization and costs.

Methods

The methods for this comparative effectiveness review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide)[25] and Methods Guide for Medical Test Reviews (hereafter referred to as the Medical Test Guide).[26] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[27] All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (adult and pediatric pulmonology, otolaryngology, school nursing, respiratory medicine, primary care), patients, scientific experts, and payers, to help define the Key Questions (KQs). The KQs were then posted for public comment in September 2011 for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. We next drafted a protocol for the review applying the input received from both the Key Informants and the TEP panel.

Literature Search Strategy

Search Strategy

To identify the relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (CDSR; last search date for all three sources June 4, 2012). Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed). An experienced search librarian guided all searches. Exact search strings are included in Appendix A. We supplemented the electronic searches with a manual search of references from a set of key primary and systematic review articles. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used several approaches to identify relevant grey literature including a request for scientific information packets submitted to drug and device manufacturers and a search of U.S. Food and Drug Administration (FDA) device registration studies and new drug applications. We also searched study registries and conference abstracts for relevant articles from completed studies. Grey literature databases searched included ClinicalTrials.gov (July 18, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (July 18, 2012); and ProQuest COS Conference Papers Index (January 18, 2012). Search terms used for these sources are provided in Appendix A. We planned to search ClinicalStudyResults.org, but that Web site is no longer available.

Inclusion and Exclusion Criteria

The PICOTS (population, interventions, comparators, outcomes, timing, and settings) criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Populations	• Humans • KQ 1: Patients with cough (any duration) • KQ 2: o Patients with chronic cough (persisting 4 weeks if <14 years of age or 8 weeks if ≥ 14 years of age, or as stated by study authors) o Patients with unexplained or idiopathic, unresponsive, refractory, intractable, or uncertain chronic cough • Subgroups of potential interest include: o Age (the elderly, children <6 years of age, children <2 years of age) o Pregnant women o Women o Underlying etiologies (asthma, GERD, UACS, tobacco use, ACE inhibitor use, pulmonary infection, bronchitis, cystic fibrosis, others) o Immunocompromised patients o Patients with a history of substance abuse	KQ 2: • Patients with chronic cough of known etiology undergoing specific therapy • Patients with cough resulting from invasive respiratory tract instrumentation (e.g., ventilator dependent, tracheostomy, endotracheal intubation)
Interventions	• KQ 1: Qualitative and quantitative instruments used to assess cough (e.g., general and cough-specific HRQOL instruments, visual analog scales, objective cough counting, tussigenic challenge, exhaled nitric oxide) • KQ 2: Nonspecific symptomatic treatment of cough with: o Antitussive medications such as opiates (codeine, hydrocodone), dextromethorphan, and respiratory anesthetics (benzonatate) o Protussive medications such as expectorants (guaifenesin) and mucolytic or mucus-modifying agents (acetylcysteine, dornase alfa inhaled) o Nonpharmacological treatments such as chest physiotherapy, herbal remedies, aroma therapy, acupuncture, humidifiers, medicated vapors, alcohol, honey, speech therapy	KQ 2: • Medications that are not commercially available globally or have been pulled from the market worldwide. Note that we did *not* exclude medications that are not commercially available within the United States but are available elsewhere
Comparators	• KQ 1 (instruments): Other instruments; the proposed reference standard will be cough counts • KQ 2 (interventions): All of the above-listed interventions compared both within class and across classes, and including placebo for mixed meta-analysis	None

Table 2. Inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	• KQ 1: Study assesses an outcome of interest: o Diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value, validity, reliability, responsiveness, feasibility) o Therapeutic efficacy (e.g., change in clinical practice, impact on patient or provider decisionmaking) o Patient outcome efficacy (e.g., acceptability, quality of life, chest pain, depression, or anxiety) • KQ 2: Study assesses an outcome of interest: o Cough symptoms o Cough severity o Cough frequency o Complications related to coughing o Functional status o Health-related quality of life (generic or cough-specific) o Health care utilization and costs o Adverse effects of antitussive, protussive, and nonpharmacological interventions including sleep disturbance, allergic reaction, drowsiness, headache, chest pain, dizziness, rash	KQ 2: • Study assesses outcomes only using induced sputum (relevant only to patients with wet or productive cough), or BPC (measures hyperresponsiveness relevant to measuring lower airway reactivity to diagnose asthma)
Timing	• Timing of followup was not limited[a]	None
Setting	• Inpatient and outpatient	None
Study design	• KQ 1 (instruments): Evaluation studies • KQ 2 (interventions): RCTs, cohort studies • All sample sizes	• Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series) • KQ 2: Case-control studies
Publications	• English-language only • Peer-reviewed articles • Relevant systematic review, meta-analysis, or methods article (used only for background and as potential sources of additional relevant material)	• Non-English-language publications[b]

ACE = angiotensin-converting enzyme; BPC = bronchoprovocation challenge; GERD = gastroesophageal reflux disease; HRQOL = health-related quality of life; KQ = Key Question; RCT = randomized controlled trial; UACS = upper airway cough syndrome

[a]For all included studies, we indicate the total number of patients enrolled and longest length (weeks or months) of followup, if relevant.

[b]Given the high volume of potentially relevant literature available in English-language publications, the planned focus of our review on therapies actively used within the United States, and the scope of our current KQs, non-English-language articles were excluded.

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 2, titles and abstracts were reviewed independently by two investigators for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the two reviewers arrived at different decisions

about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching.

For citations retrieved by searching the grey literature, the above-described procedures were modified such that a single screener initially reviewed all citations; final eligibility for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc, Manotick, ON, Canada).

Data Extraction

The research team created data abstraction forms and evidence table templates for abstracting data for each KQ. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus, or by obtaining a third reviewer's opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project with the DistillerSR database.

We designed the data abstraction forms to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We gave particular attention to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of nonpharmacological therapies), patient characteristics (e.g., underlying etiology of chronic cough, age of patient), and study design (e.g., randomized controlled trial [RCT] versus observational) that were related to outcomes. In addition, we described comparators carefully, as treatment standards may have changed during the study period. The safety outcomes were framed to help identify adverse events, including those from drug therapies (sleep disturbance, allergic reaction, drowsiness, headache, chest pain, dizziness, and rash) and those associated with nonpharmacological therapies. Data necessary for assessing quality and applicability, as described in the Methods Guide,[25] were abstracted. Before the data abstraction form templates were used, they were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency/reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Appendix B provides a detailed listing of the elements included in the data abstraction forms.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in the Methods Guide.[25] To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. We applied criteria for each study type derived from core elements described in the Methods Guide. Criteria of interest for all studies included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. Criteria specific to RCTs included methods of randomization and allocation concealment. For observational studies,

additional elements such as methods for selection of participants, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding were considered.

To indicate the summary judgment of the quality of individual studies, we used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting (Table 3).

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

For studies of diagnostic tests (KQ 1), we used the QUality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2[28] to assess quality. QUADAS-2 describes risk of bias in four key domains: patient selection, index test(s), reference standard, and flow and timing. The questions in each domain are rated in terms of risk of bias and concerns regarding applicability, with associated signaling questions to help with these bias and applicability judgments.

Study design was considered when grading quality. RCTs were graded as good, fair, or poor. Observational studies were graded separately, also as good, fair, or poor.

Data Synthesis

We began our data synthesis by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes.

KQ 1—Test Performance Measures

For KQ 1 we considered the three dimensions of (1) cough frequency, (2) cough severity (which might include quantity and characteristics of sputum, difficulty of expectoration, dyspnea, between cough sensations, or pain), and (3) cough-specific quality of life (QOL). While cough frequency is a unidimensional measure (although it is sometimes broken down into daytime and nighttime cough frequency), we considered cough severity and cough-specific QOL to be separate (and often multidimensional) dimensions of cough. Most of the standardized questionnaires included in this report measured aspects of both of these dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL

together to be "severity/QOL" instruments. Within this report, we did not identify any validated instruments which focused purely on cough severity.

We sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. For cough frequency, we evaluated validity by concurrence with measures of other constructs (e.g., cough severity, cough-specific QOL, tussigenic challenge (or cough reflex sensitivity), and exhaled nitrous oxide), and we assessed reliability using inter-method reliability (e.g., manual cough counts versus electronic recording device cough counts) and test-retest reliability. For severity/QOL instruments, we evaluated validity by looking at concurrence with measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability, as well as internal consistency. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough.

KQ 2—Overall Approaches and Meta-Analyses for Direct Comparisons

We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons where at least three studies reported the same outcome. We considered measures of cough frequency, regardless of the scale used, to be similar enough to combine using effect sizes (standardized mean differences); similarly, measures of cough severity that used different measurement scales were considered similar enough to combine using effect sizes.

When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ). We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We reported p-values for Q statistics as follows: $0.15 > p > 0.05$ as some evidence of heterogeneity, $0.05 > p > 0.0001$ as evidence of heterogeneity, and $p<0.0001$ as evidence of extreme heterogeneity. The degree of heterogeneity was reflected in our strength of evidence conclusions. For comparison, we also performed fixed-effect meta-analyses. We present summary estimates, standard errors, and confidence intervals in our data synthesis.

KQ 2—Indirect Comparisons With Mixed Treatment Comparisons Techniques

We supplemented the meta-analysis of direct comparisons with a mixed treatment meta-analysis that incorporated data from placebo comparisons and head-to-head comparisons, including multi-armed trials (i.e., trials that included more than one comparison). The general strategy for analysis was to construct a random-effects model that was comparable with the standard random-effects models used in the meta-analysis of effect sizes.

This model, which was fitted using SAS® PROC NLMIXED (2009; SAS Institute Inc., Cary, NC), estimated the effect sizes (relative to placebo) for each treatment. For some treatments that could not be included in the mixed treatment meta-analysis, we calculated effect sizes from data reported in the studies (raw data, means and variances, or test statistics) to present results in comparable terms.

Strength of the Body of Evidence

We rated the strength of evidence for each KQ and outcome using the general approach described in the Methods Guide[25,29] and Medical Test Guide;[26] we note, however, that the latter does not specifically address responsiveness or other psychometric properties of a test. In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision (Table 4).

Table 4. Strength of evidence—required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Based on study design (RCT vs. observational study), number of studies, and aggregate study quality; for KQ 1, assessed using the QUADAS-2 instrument.[28]
Consistency	Consistent Inconsistent Unknown/not applicable	Based on whether effect sizes are generally on the same side of "no effect" and on the overall range of effect sizes. Note that diverse results alone would not necessarily reduce consistency ratings if different study designs, methodological quality of studies, diversity in subject characteristics, and/or study context appear to explain the observed heterogeneity.
Directness	Direct Indirect	Based on whether the evidence involves direct comparisons or indirect comparisons (e.g., through a mixed treatment meta-analysis), and on the degree to which the measured outcomes were related to final outcomes of interest.
Precision	Precise Imprecise	Based on the size of the confidence intervals of effect estimates and on whether those confidence intervals overlap with values needed to make management decisions.

KQ = Key Question; QUADAS-2 = QUality Assessment tool for Diagnostic Accuracy Studies-2; RCT = randomized controlled trial

Additional domains were used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Test studies (KQ 1) are generally indirect, as the link between the test intervention and outcome is mitigated by prognosis, management, and the effectiveness of treatments. As a rule of thumb, we considered correlation coefficients > 0.7 as strong evidence of association, 0.40–0.69 as moderate evidence, and <0.40 as weak evidence. In our summary SOE assessments for KQ 1,

lack of directness was weighed less heavily and risk of bias most heavily Thus, we allowed high SOE levels despite the lack of directness among these studies.

Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.[25,30] In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We used checklists to guide the assessment of applicability (see Appendix B, sections IV and VIII). We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in adult and pediatric pulmonology, respiratory medicine, and primary care, along with individuals representing stakeholder and user communities, were invited to provide external peer review of the draft report; AHRQ and an associate editor also provided comments. The draft report was posted on AHRQ's Web site for public comment for 4 weeks, from June 12, 2012, to July 10, 2012. We have addressed all reviewer comments, revising the text as appropriate, and have documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on AHRQ's Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.

Results

Introduction

In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each of the two KQs, we begin by listing the key points of the findings, followed by a brief description of included studies, followed by a more detailed synthesis of the evidence. The detailed syntheses under KQ 1 are organized by measures of cough frequency, cough severity, and responsiveness. The detailed syntheses under KQ 2 are organized by comparison drug classes (antitussives, protussives, other agents). We conducted quantitative syntheses where possible, as described in the Methods chapter.

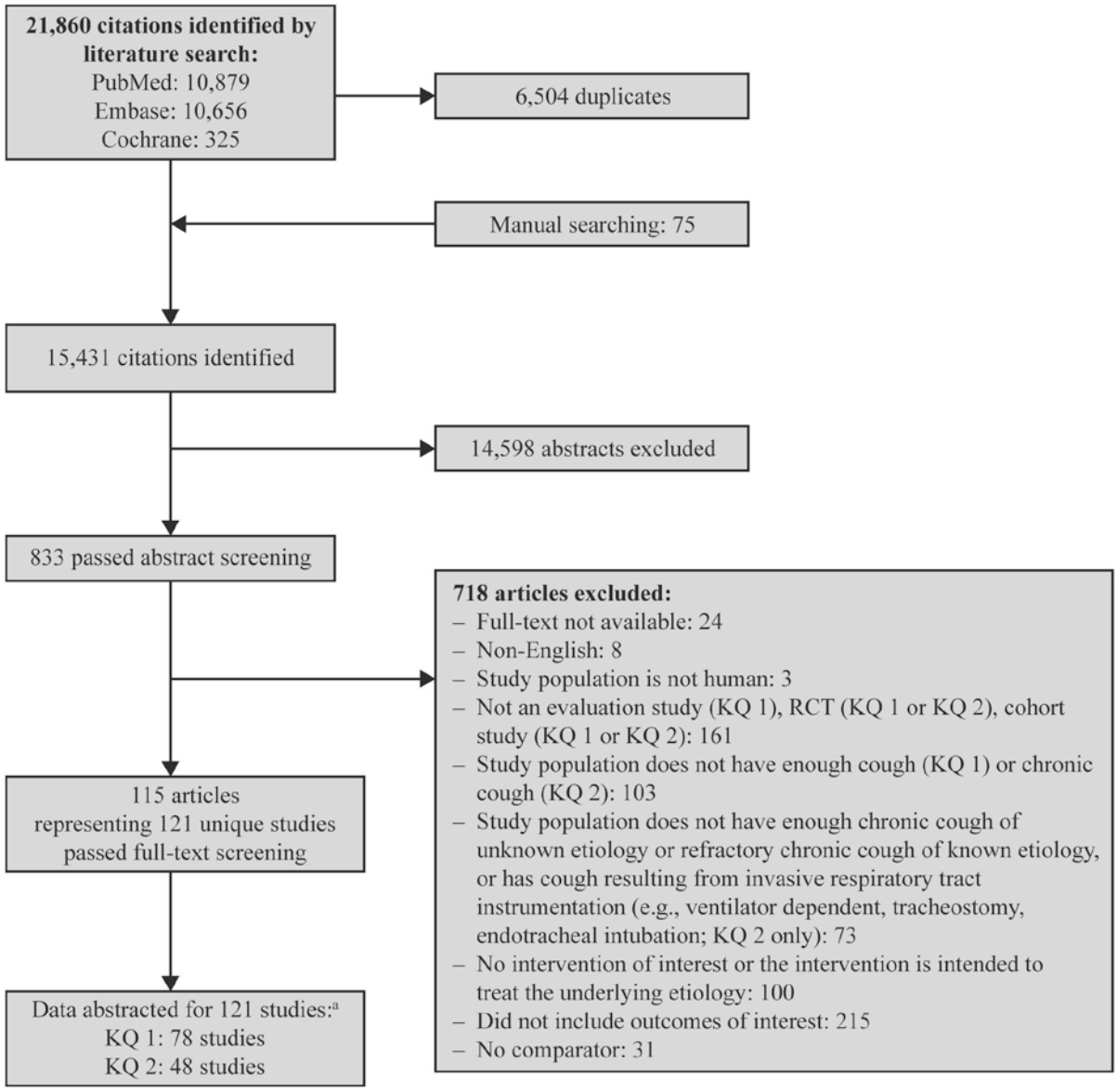
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed®, Embase®, and CDSR yielded 21,860 citations, 6,504 of which were duplicate citations. Manual searching identified 75 additional citations, for a total of 15,431 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 833 full-text articles were retrieved and screened. Of these, 718 were excluded at the full-text screening stage, leaving 115 articles for data abstraction. These 115 articles described 121 unique studies, 78 of which were relevant to KQ 1, and 48 of which were relevant to KQ 2 (5 studies were relevant to both KQs). No additional information was found through our grey literature search.

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Literature flow diagram



KQ=Key Question; RCT=randomized controlled trial
[a]Five studies were relevant to both KQ 1 and KQ 2.

Description of Included Studies

Overall, we included 121 studies represented by 115 publications: 78 studies were relevant to KQ 1, 48 to KQ 2. Studies were conducted in Europe (54%); the United States or Canada (23%); Australia or New Zealand (11%); Asia (8%); and other locations (8%). Nineteen studies in KQ 1 (23%) and 3 studies in KQ 2 (6%) included children. Forty-five studies (37%) were published before 2000.

Further details are provided in the relevant KQ results sections, below.

Key Question 1. Instruments Used To Assess Cough

KQ 1: In adults and adolescents (≥ 14 years of age) and children (<14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough?

Key Points

- Electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with instruments that measure other dimensions of cough.
- The Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ) are the most widely studied cough-specific quality-of-life questionnaires in adult populations. Both have demonstrated validity and reliability, with emerging evidence available on responsiveness.
- There is moderate strength of evidence to support the validity and responsiveness of the Parent Cough-specific Quality of Life Questionnaire (PC-QOL) in assessing the severity/QOL of cough among children.
- Emerging data support the responsiveness of recording devices, cough-related questionnaires, and tussigenic challenge tests, but further research is needed to accurately estimate the minimally important difference (MID) of these assessment instruments.
- Although diaries and visual analog scales are based on face validity, assess a wide variety of different cough outcomes, and are widely used both in research and practice, there are few data to validate their accuracy in assessing cough, and what data exist show inconsistent correlations with other cough measurement tools. These tools are usually simple and easy to use, but more data are needed to determine their reliability and validity in assessing cough frequency or severity/QOL.
- While all of the included studies evaluated aspects of the comparative diagnostic accuracy of the various cough measurement tools, none evaluated the comparative therapeutic efficacy or patient outcome efficacy of these tools.

Description of Included Studies

Cough can be assessed along several dimensions, the most of important of which may be frequency, severity, and cough-specific QOL. Cough frequency is objective and relatively easy to measure but may not necessarily correlate with severity or cough-specific QOL, whereas cough severity and cough-specific QOL may be closely interrelated. Most of the standardized questionnaires included in this report measured aspects of both of these latter dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL together to be "severity/QOL" instruments. In this CER we evaluate the available data that support the validity and reliability of instruments to measure one of two dimensions of cough: (1) cough frequency; or (2) the severity/QOL impact of cough (including assessments of the impact of cough on sleep, work, general well-being, health-related quality of life, etc.). We also evaluate the available data that support these instruments' ability to measure potentially meaningful clinical change over time (responsiveness).

To be eligible for inclusion in this report, a study had to either: 1) compare a cough frequency or severity/QOL assessment instrument with one or more cough assessment, health-related quality of life, or clinical change instrument; or 2) report data on changes in the instrument score over time in response to treatment for cough or the underlying etiology of the cough. For the purposes of this report, we consider tussigenic challenge tests and exhaled nitric oxide tests as severity/QOL assessments.

In what follows, we rely heavily on tabular presentation of information because of the large degree of heterogeneity with respect to patient populations, study design and objectives, index and reference tests, and the nature and content of the results reported in the individual studies. We summarize the findings of studies of adults and adolescents (≥14 years of age) separately from those of children (<14 years of age). Studies that include adults, adolescents, and children are listed only once in a given table (categorized as "Studies in Adults, Adolescents, and Children"). These studies are included in the study counts in both the "adult and adolescents" and the "children" sections in the text below. Note, however, that their findings are summarized in one or the other of these sections based on the mean age of the included patients and therefore the relevance of the findings to the overall adult or pediatric populations.

A total of 78 studies met the inclusion criteria for this KQ.[8,31-106] Seven were RCTs;[34,56,59,80,93,96,100] the remaining 71 were observational studies. Nineteen studies (24%) were conducted in the United States or Canada,[32,43,45,47,48,50,56,58,60,63,67,74,79,88,90,94,99,102,103] and 39 (50%) in Europe,[34,36-39,44,49,51-53,55,59,61,62,64,66,68,70-73,75,77,78,80,81,83,87,89,91,92,95-98,101,105-107] including 32 (41%) conducted exclusively in the UK.[36-38,44,49,51-53,55,59,61,62,64,68,70-73,77,78,80,81,83,89,91,92,95-98,101,107] Seven studies took place in Australia/New Zealand,[40-42,84-86,104] five in other locations,[57,69,76,82,93] and four in multiple locations.[46,54,65,100] Geographical location was not reported for four studies.[8,31,33,35] In most cases, the funding source was not reported or was unclear. Other study characteristics are summarized in Appendix F (Table F-1). A total of 5,927 participants were included across studies; sample sizes of individual studies ranged from 1 to 671 subjects. Of the 78 studies, 67 (86%) were judged to have a low risk of bias, and 11 (14%) were judged to have a high risk of bias (see Appendix E for details).

Thirty-three studies (42%) enrolled patients with chronic cough of mixed, unknown, or unspecified etiology; 18 (23%) enrolled patients with acute cough or cough of unspecified duration, and 27 (35%) focused on specific clinical conditions such as chronic bronchitis, asthma, or lung cancer. Fifty-nine studies included adults and adolescents (≥14 years of age), 15 included only children (<14 years of age), and 4 included adults, adolescents, and children.

Thirty-two studies (41%) identified a specific cough-related questionnaire as an index test, 22 studies (28%) reported on a specific electronic device designed to measure cough frequency, and 24 (31%) reported on instruments other than cough-related questionnaires or electronic recording devices. Most studies that included other instruments such as visual analog scales, symptom diaries, tussigenic challenges, or self-reported global change items utilized them as validation tools but did not evaluate them as index tests themselves. Few of the included studies provided information regarding previous validation of reference tests. While all of the included studies evaluated aspects of the comparative diagnostic accuracy of these measurement tools, none evaluated their comparative therapeutic efficacy or patient outcome efficacy.

Detailed Synthesis

Measures of Cough Frequency

Our search identified 42 studies that evaluated instruments designed to assess the frequency of cough (Table 5).[35-37,41,44,45,47,55,59,62,64,65,71,73-75,77,78,90,95,98,102] Of the 42 studies, 8 (19%) were conducted in the United States or Canada.[45-47,74,90,94,102,103] Thirty-seven studies (88%) were judged to have low risk of bias, and 5 (12%) had high risk of bias. A variety of reference standards were employed to validate these instruments, including human count, other electronic recording devices, video recording devices, quality-of-life questionnaires, subjective scoring, and laboratory tussigenic challenges.

Table 5. Results of studies of cough frequency assessment instruments

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents						
Barnabe, 1995[34]	VAS	NA	No	No	Yes	Mean VAS scores of cough frequency decreased over the 2 days of treatment.
Barry, 2006[35]	Hull Automatic Cough Counter	Cough count (by a human)	No	Yes	No	SN: 0.80 SP: 0.96 Reproducibility: 100%
Birring, 2008[36]	Leicester Cough Algorithm	Cough count (by a human)	No	Yes	No	Correlation: 0.9 (p<0.001) (stage 1); 0.93 (p<0.001) (stage 2) SN: 0.91 (stage1); 0.86 (stage 2) SP: 0.99 (stage 1); 0.99 (stage 2) Reliability: (ICC): 0.9
Birring, 2006[37]	Leicester Cough Monitor	Electronic cough recorder (sound or pressure)	No	Yes	No	Reliability (ICC): 0.8
		Leicester Cough Questionnaire	Yes	No	No	Correlation Total score: -0.6 (p=0.03) Physical: -0.6 (p=0.03) Psychological: -0.5 (p=0.08) Social: -0.7 (p=0.01)
		Capsaicin tussigenic challenge (C5)	Yes	No	No	Correlation: 0.9 (p=0.008)
		Capsaicin tussigenic challenge (C2)	Yes	No	No	Correlation: 0.8 (p≤0.05)
Coyle, 2005[45]	LifeShirt system	Video cough recorder	No	Yes	No	Overall (95% CI) SN: 78.1 (76.7 to 79.4) SP:99.6 (99.5 to 99.6) PPV: 84.6 (83.3 to 85.8) NPV: 99.4 (99.0 to 99.1) Comparison of nighttime with daytime: SN, SP, PPV, NPV=p<0.0001

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Crawford, 2008[46]	Electronic cough recorder	CASA-Q Cough symptoms	Yes	Yes	Yes	The cough symptom and sputum symptom domains did not correlate with cough recordings.
Decalmer, 2007[49]	Electronic cough recorder	VAS Cough challenge	Yes	Yes	No	"The repeatability of cough monitoring was excellent," both for day and night recordings. There was a significant inverse correlation between log10 daytime cough rates and log C5 (Pearson's r=20.45, p=0.001). Subjective cough measures tended to correlate more strongly with objective cough rates for overnight than for daytime recordings and the VAS correlated more strongly than cough scores.
Faruqi, 2011[55]	Hull Automated Cough Counter	NA	No	No	Yes	Median cough counts were significantly lower 8 weeks after baseline assessment.
		Leicester Cough Questionnaire	Yes	No	No	Correlation: -0.62 (p<0.001)
		SAS	Yes	No	No	Correlation: 0.54 (p<0.001)
		VAS	Yes	No	No	Correlation: 0.38 (p=0.007)
		C2	Yes	No	No	Correlation: -0.45 (p=0.001)
		C5	Yes	No	No	Correlation: -0.55 (p<0.001)
		Reproducibility	No	Yes	No	r=0.91, (p<0.001)
Fisman, 2001[57]	Cough frequency score	Cough severity score	No	No	Yes	Cough severity and cough frequency scores decreased, respectively, from 2.6 ± 1.1 to 0.7 ± 1.0 (p<0.001) and from 6.9 ± 2.2 to 2.1 ± 2.4 (p<0.001).

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Free-stone, 1997[59]	Electronic cough recorder	NA	Yes	No	Yes	Correlation: r=0.524 (95% CI, 0.32 to 0.68), p<0.0001 between cough frequency and CSPLs Responsiveness: Decrease in all 3 measures of cough (p<0.001)
		Score	Yes	No	No	Correlation: NS
		VAS	Yes	No	No	Correlation: NS
Hsu, 1994[65]	24-hour ambulatory recorder and EMG	Cough count	No	Yes	No	Correlation: 0.99, p<0.005
		Score	Yes	No	No	Correlation: 0.96, p<0.005
Kelsall, 2011[72]	24-hour cough recording	Cough counts VAS	Yes	Yes	Yes	Intraclass correlation: r=0.98 (p<0.001) Change in cough frequency did not correlate with the change in cough VAS scores or cough scores during the day (r=0.26; p=0.052, and r=0.23; p=0.08, respectively) and correlated only with cough VAS scores at night (r=0.45; p=0.001, and r=0.23; p=0.10, respectively).
Kelsall, 2009[70]	24-hour ambulatory recorder	Cough challenge	Yes	No	Yes	Log 2 and log 24-hr cough frequency and log overnight cough frequency correlated with cough reflex sensitivity to citric acid (logC5).

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Kelsall, 2008[71]	24-hour ambulatory recorder Parameters measured: cough epochs, explosive phases, cough seconds	Cough count (by a human)	No	Yes	No	Correlation: Cough epochs vs. cough seconds (r^2=0.84) Correlation: Cough epochs vs. explosive phases (r^2=0.80) Correlation: Cough seconds vs. explosive phases (r^2=0.98)
		Daytime VAS	Yes	No	No	Correlation: with explosive phases: r=0.45 (p≤0.001)
			Yes	No	No	Correlation: with cough seconds: r=0.44 (p≤0.001)
			Yes	No	No	Correlation: with cough epochs: r=0.40 (p=0.001)
		Nighttime VAS	Yes	No	No	Correlation: with explosive phases: r=0.67 (p≤0.001)
			Yes	No	No	Correlation: with cough seconds: r=0.64 (p≤0.001)
			Yes	No	No	Correlation: with cough epochs: r=0.60 (p≤0.001)
		Leicester Cough Questionnaire	Yes	No	No	Correlation: with explosive phases: r=-0.53 (p≤0.001)
			Yes	No	No	Correlation: with cough seconds: r=-0.53 (p≤0.001)
			Yes	No	No	Correlation: with cough epochs: r=-0.46 (p≤0.001)
Key, 2010[73]	Electronic cough recorder	Cough count (by a human)	No	Yes	No	Correlation: Mean difference 0.9 (±1.7)
		VAS	Yes	No	No	Correlation: Day r=0.80 (p<0.001) Night r=0.71 (p=0.001)
		Leicester Cough Questionnaire	Yes	No	No	Correlation Total score: -0.80 (p<0.001) Physical: -0.76 (p<0.001) Psychological: -0.76 (p<0.001) Social: 0.74 (p<0.001)

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Krahnke, 2004[74]	Audio cough recorder	NA	No	No	Yes	Cough counts decreased over 3 days of treatment for seasonal allergic rhinitis.
		Daytime score	Yes	No	No	Correlation: 0.54 (p<0.0001)
		Nighttime score	Yes	No	No	Correlation: 0.39 (p=0.0006)
		Daytime plus nighttime score	Yes	No	No	Correlation: 0.51 (p<0.001)
Krajnik, 2010[75]	Portable automatic cough analyzer	Daytime total cough incidents, score	Yes	No	No	Correlation: 0.63 (p=0.22)
		Daytime cough incidents per hour, score	Yes	No	No	Correlation: 0.60 (p=0.29)
		Time spent coughing per hour during the day, score	Yes	No	No	Correlation: 0.48 (p=0.1)
		Nighttime cough incidents per hour, score	Yes	No	No	Correlation: 0.29 (p=0.34)
		Time spent coughing per hour during the night, score	Yes	No	No	Correlation: 0.26 (p=0.4)
		Total time spent coughing per hour	Yes	No	No	Correlation: 0.37 (p=0.21)
		Total cough incidents per hour	Yes	No	No	Correlation: 0.52 (p=0.066)

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Leconte, 2011[105]	LR102 recording device	Video recorder	No	Yes	No	The cough meter was well tolerated by all but one patient who complained of itching at the electrode sites. The two recording methods produced cough frequencies that were closely correlated (r=0.87 for number of cough episodes per hour; r=0.89 for number of single coughs per hour). There was no systematic difference between the two measures across the spectrum of cough frequency. ICCs were also good (ICC=0.86 for episode [95% CI, 0.75 to 0.92] and 0.88 for single cough [95% CI, 0.78 to 0.93]). The number of coughs per hour measured by the cough meter was significantly higher than that measured by counting coughs on the video recording (number of cough episodes per hour 22.57 vs. 18.77, respectively; number of single coughs per hour 65.22 vs. 52.67, respectively). The mean difference between the two methods was 3.8 for cough episodes per hour (p=0.04) and 12.5 for single coughs per hour (p<0.01).
Marsden, 2008[77]	Electronic cough recorder	Tussigenic challenge (C5)	Yes	No	No	Correlation: 0.08 (p=0.65)
		Tussigenic challenge (C2)	Yes	No	No	Correlation: 0.39 (p=-0.03)
		Score	Yes	No	No	Correlation: 0.32 (p=0.45)
		Leicester Cough Questionnaire	Yes	No	No	Correlation Total score: 0.54 (p<0.001) Physical: -0.45 (p=0.001) Psychological: -0.48 (p≤0.001) Social: -0.55 (p<0.001)

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Matos, 2007[78]	Leicester Cough Monitor	Cough count (by a human)	No	Yes	No	SN: 97.8 (IQR, 88.1 to 99.1)
Ribeiro, 2007[93]	Diary VAS	NA	No	No	Yes	There was a significant difference in the cough diaries and VAS scores before and after beclomethasone treatment compared with before and after placebo use (difference of differences, 1.0; 95% CI, 0.4 to 1.5; p=0.002 for diaries; and difference of differences, 1.1; 95% CI, 0.6 to 1.8; p=0.01 for the VAS).
Shaheen, 2011[94]	Fisman cough frequency score	NA	No	No	Yes	Cough frequency score decreased from 6.2 (SD 1.8) to 3.0 (SD 1.8) in the PPI group and form 6.8 (SD 2.0) to 4.5 (SD 2.5), p=0.3.
Smith, 2006[98]	Video recorder	Cough count (by a human)	No	Yes	No	Manual counting of cough sounds from digital audio recordings has excellent agreement with simultaneous video recordings in laboratory conditions.
Smith, 2006[97]	Cough recorder	Cough score VAS	Yes	No	Yes	Correlation with day cough frequency: Change in cough score r=0.34, p=0.204 Change in VAS r=0.47, p=0.070 Correlation with night cough frequency: Change in cough score r=0.19, p=0.510 Change in VAS r=0.81, p=0.001
Smith, 2006[96]	Cough recorder	Cough challenge Cough score VAS	Yes	No	Yes	There were no significant correlations between the change in time spent coughing and the change in cough threshold (r=20.27; p=0.30), change in cough score (day r=20.07, p=0.78; night r=0.17, p=0.48), or change in VAS (day r=20.07, p=0.79; night r=0.30, p=0.24).

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Smith, 2006[95]	Cough recorder	Tussigenic challenge	Yes	No	No	Subjective measures of cough and cough reflex sensitivity are statistically related to time spent coughing in patients with COPD, but with low-to-moderate levels of correlation.
		Electronic recorder	Yes	No	No	
		Score	Yes	No	No	
		Cough-specific quality of life	Yes	No	No	
Thomas, 1978[102]	DATA recording system	Cough count (by a human)	No	Yes	No	Reliability (ICC): Coefficient of variation: 1.8% Reproducibility: Able to detect effect of codeine with a probability of <0.01 Accuracy: Group 1 correlation coefficient : 0.99; coefficient of determination=0.98 Group 2 correlation coefficient: -0.94; coefficient of determination=0.88
Wood-cock, 2010[100]	Lifeshirt cough recorder	NA	No	No	Yes	The intervention drug (SCH486757) was associated with reduced cough counts as measured by the Lifeshirt. On day 5, SCH486757 reduced cough counts by a median of 7.0 coughs/hour, codeine reduced counts by 13.8 coughs/hour, and placebo reduced counts by 7.8 coughs/hour over the first 4 hours.
Woolf 1964[103]	Human cough count Hospital room equipped with a recording system	Human cough count	No	Yes	Yes	There was nearly perfect correlation of cough counts between two human observers. Cough curves were constructed for each of the 4 treatment periods for this single-subject study. For the most part, the cough curves did not cross over the 24-hour study period.

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults, Adolescents, and Children						
Hamutcu, 2002[62]	Logan Research (LR 100) cough monitor	Electronic cough recorder	No	Yes	No	Correlation: 0.96, p<0.0001
Paul, 2006[90]	Accelerometer	Video recorder	No	Yes	No	Correlation: 0.997 (p<0.001)
Studies in Children Only						
Archer, 1985[31]	Cough recorder	Diary	Yes	No	No	There was no correlation between night cough counts and diary card scores for night-time wheeze, daytime wheeze, daytime activity or for 24 hour diary scores calculated for the 24 hour period beginning with, and the period ending with, the night recording.
Chang, 2003[42]	Ambulatory cough recording	Parent cough score Child cough score Cough challenge	Yes	No	No	Log cough frequency correlated with parent and child recorded log cough score (r(s)=0.42, p=0.02) and r(s)=0.44, p=0.01, respectively). Cough scores did not correlate with cough challenge test.
Chang, 1998[40]	Electronic cough monitor	Parent-completed diary Child-competed diary	Yes	No	No	The agreement adjusted for chance (Cohen's Kappa) between the subjective and objective presence of daytime cough for the subjects was 100%, and that for controls was 0.61 for child-completed cards and 0.44 for parent-completed cards. When both groups were considered together, the agreement was 0.67 and 0.47, respectively. For night-time cough, the agreement between the subjective and objective presence of cough was poor both in subjects and controls. In the subjects, there was no difference between the parent and child scores.
Chang, 1997[41]	Holter monitor cough meter	Electronic cough recorder (sound or pressure)	No	Yes	No	Mean difference of -0.3 coughs x h(-1), 95% CI (-0.7, 0.2); limits of agreement -2.2 to 1.7 coughs x h(-1).

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
Corrigan, 2003[44]	Logan Research (LR 100) cough monitor	Video cough recorder	No	Yes	No	SN: 81.00% PPV: 0.8
Dales, 1997[47]	Electronic cough recorder	Cough count (by a human)	No	Yes	No	SN: 80 SP: 95 Accuracy: 90
		Diary	Yes	No	No	Kappa: ≤0.10
Falconer, 1993[53]	Electronic cough recorder	Diary	Yes	No	No	Mean Kappa between reported and recorded cough was 3.0 (range: -0.17 to 1.0), representing poor agreement beyond chance.
Fuller, 1998[61]	Video recording	Parent questionnaire Parent diary	Yes	No	No	On the second night of recording the between-subject correlation coefficient for individual coughs and percentage of the night awake was 0.25, p=0.13 (n=37) and for individual coughs and percentage of the night awake and restless was 0.36, p=0.03 (n=37). The within-subject correlation coefficient log % awake time on log number of coughs was 0.26 (p=0.01; r=0.13, SE 0.036) with a residual coefficient of variation of 74%. The within-subject correlation coefficient (log % awake time + % restless) was 0.17 (p=0.02; r=0.016, SE 0.0071) with a residual co-efficient of variation of 17%.
Hoskyns, 1991[64]	Cough recorder	Parental night cough diary	Yes	No	Yes	Correlation: (r=0.588, p<0.02) during medication week; no correlation during placebo week

Table 5. Results of studies of cough frequency assessment instruments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
New-combe, 2010[86]	Digital voice recorder	PC-QOL psychological	Yes	No	No	Correlation, Time 1: -0.10 (p=0.521) Correlation, Time 2: -0.28 (p=0.089)
		PC-QOL physical	Yes	No	No	Correlation, Time 1: -0.21 (p=0.188) Correlation, Time 2: -0.46 (p=0.003)
		PC-QOL social	Yes	No	No	Correlation, Time 1: -0.11 (p=0.487) Correlation, Time 2: -0.51 (p=0.001)
		PC-QOL physical	Yes	No	No	Correlation, Time 1: -0.15 (p=0.329) Correlation, Time 2: -0.42 (p=0.008)
	Cough count/hour	NA	No	No	Yes	Effect size for responsiveness to change over time: 0.19
Zihlif, 2005[101]	LR100 cough recorder	Parent cough scores	Yes	No	No	There was significant correlation between parental scoring of day and night cough compared with actual number of recorded coughs (r=0.930, p<0.0001 for daytime cough; r=0.711 for nighttime cough, p=0.002).

CASA-Q = Cough and Sputum Assessment Questionnaire; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DATA = Discriminator and Accumulator of Tussive Activity; EMG = electromyogram; ICC = intraclass correlation coefficient; IQR = interquartile range; NA = not applicable; NPV = negative predictive value; NS = not statistically significant; PC-QOL = Parent Cough-specific Quality-of-Life questionnaire; PPV = positive predictive value; SE = standard error; SN = sensitivity; SP = specificity; VAS = visual analog scale

Twenty-four different cough frequency assessment tools were described in the 42 studies summarized above (Appendix F, Table F-2), not including humans counting coughs either during direct observation of patients or from recording devices. Of these 24 cough frequency assessments, all but one (the Fisman Cough Severity Frequency Score) are electronic recording devices.

Adults and Adolescents (≥14 Years of Age)

Of the 42 studies that evaluated instruments designed to assess the frequency of cough, 29 (69%) included adults and adolescents, and 2 (5%) included adults, adolescents, and children (Table 5). Most of these studies evaluated the performance of electronic recording devices for the purpose of counting the number of coughs in a given period of time.

Five studies comparing sound recording devices with human cough count or video recording[34,36,65,90,98] and one study comparing sound recording devices with another electronic recording device[62] showed strong correlation between the measures. Note that the studies by Paul and colleagues[90] and Hamutcu and colleagues[62] also included children under 14 in their studies, although the mean age of the patients was 28.1 ± 25 and 13.6 ± 2.6 years, respectively. One study comparing sound recording devices with the LCQ showed moderately strong correlation.[73] Other studies comparing sound recording devices with other cough measurement tools demonstrated only fair to moderate correlation.[37,55,59,70,74,75,77,95,97] In general, the results of studies that evaluated electronic recording devices demonstrated variable sensitivity, good PPV, high correlation coefficients, and excellent specificity and NPV when comparing the recording devices with human cough counts.[34-36,45,78]

Three studies estimated the sensitivity and specificity of three different cough recording devices to assess cough frequency, with human cough counting as the reference standard.[35,36,78] A fourth study[102] calculated a correlation coefficient between cough counts as measured by an electronic recording device and human cough count. In all four studies, recording devices and humans reported nearly identical counts. This suggests that recording devices are highly valid as cough-counting instruments, at least in controlled or laboratory settings. Correlation between recording devices and other cough assessment instruments, however, was generally poor to moderate, with reported Spearman coefficient values generally in the 0.30–0.60 range. These findings are consistent with an interpretation of limited validity of recording devices; it is also possible, however, that counting coughs with an electronic recording is a valid way to assess cough frequency, but that cough frequency correlates only moderately with cough severity or QOL, which are the constructs that were usually assessed by the instruments with which recording devices were compared.

Five studies assessed the reliability of recording devices.[35-37,55,102] Intraclass correlation coefficients were consistently ≥0.80, with reproducibility reported to be 100 percent in one study.[35]

Children (<14 Years of Age)

Of the 42 studies that evaluated instruments designed to assess the frequency of cough, 11 (26%) included only children under the age of 14, and 2 (5%) included adults, adolescents, and children (Table 5). All 13 of these studies reported on an electronic recording device. Reference tests included another electronic recording device (audio or video) in four studies,[41,44,62,90] parent-reported questionnaires, scores, or diaries in five studies,[40,42,61,64,101] child-reported scores or diaries in three studies,[40,42,47] diaries where it was uncertain whether the parent or child was

doing the reporting,[31,53] and the PC-QOL instrument in one study.[86] There was strong correlation ($r \geq 0.96$) between electronic devices, and variable correlation between self-reported or parent-reported instruments and electronic recording devices. Some studies reported no significant relationship between parent or child reporting of cough frequency and the number of coughs identified by recording devices, whereas some reported a significant correlation during daytime but not during nighttime. One study[64] reported a significant correlation ($r=0.588$, $p<0.02$) between cough frequency assessed by a cough recording device and a parental night cough diary during a week when medication for cough was administered to subjects, but no significant correlation during the placebo week.

Two studies estimated the sensitivity and specificity of two different cough recording devices to assess cough frequency, with human cough counting as the reference standard.[44,47] Both demonstrated a sensitivity of approximately 80 percent.

Measures of Cough Severity or Quality of Life

We identified 56 studies that reported on instruments designed or purported to assess the severity of cough or the quality of life impact of cough on sleep, work, or an aspect of health-related quality of life (Table 6).[8,31-34,37-40,42,43,46,48-52,54-61,63,66-69,71-73,76,77,79-86,88,91-97,99,100,104,106] A variety of reference standards were employed to validate these instruments, including electronic recording devices, quality-of-life questionnaires, subjective scoring, and laboratory tussigenic challenges. Of these studies, 14 (25%) were conducted in the United States or Canada.[32,43,46,48,50,56,58,60,63,67,79,88,94,99,107] Forty-seven studies (84%) were judged to have a low risk of bias, and the remaining 9 (16%) to have high risk of bias.

Table 6. Results of studies of cough severity or quality-of-life impact assessments

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents						
Au, 2005[32]	CBSAS	FEV1 prebronchodilator	Yes	No	No	Spearman coefficient: -0.38 (p<0.01)
		FEV1 postbronchodilator	Yes	No	No	Spearman coefficient: -0.32 (p<0.01)
		FVC prebronchodilator	Yes	No	No	Spearman coefficient: -0.44 (p<0.01)
		FVC postbronchodilator	Yes	No	No	Spearman coefficient: -0.40 (p<0.01)
		SGRQ Total	Yes	No	No	Spearman coefficient: 0.67 (p<0.01)
		SGRQ Symptoms	Yes	No	No	Spearman coefficient: 0.67 (p<0.01)
		SGRQ Activity	Yes	No	No	Spearman coefficient: 0.49 (p<0.01)
		SGRQ Impact	Yes	No	No	Spearman coefficient: 0.58 (p<0.01)
		San Diego Shortness of Breath Questionnaire	Yes	No	No	Spearman coefficient: 0.49 (p<0.01)
Baiardini, 2005[33]	CCIQ	NA	Yes	No	Yes	Spearman coefficient: 0.67 to 0.88 for each item on test-retest Responsiveness: A statistically significant difference was recorded in 16 of the 21 items after treatment
	CCIQ Sleep/con-centration	NA	Yes	No	No	Cronbach's α: 79.98
	CCIQ Relationship	NA	Yes	No	No	Cronbach's α: 86.98
	CCIQ Daily life impact	NA	Yes	No	No	Cronbach's α: 69.04
	CCIQ Mood	NA	Yes	No	No	Cronbach's α: 65.41
	CCIQ	SF-36	Yes	No	No	Low correlation, except for "daily life impact" item that correlated with 3 SF-36 domains

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Barnabe, 1995[34]	VAS	NA	Yes	No	Yes	VAS scores of sleep disturbance significantly correlated with the number of nocturnal cough recorded on the second day of treatment.
Berkhof, 2012[106]	LCQ	NA	No	No	Yes	11 of 49 patients perceived a significant improvement in cough. In these patients the mean change in the total LCQ score after 12 weeks was 4.3 ± 2.5.
		LCQ Domains --Physical --Psychological --Social --Total	No	Yes	No	Reliability: Cronbach's α for internal consistency: 0.67 0.75 0.74 0.86
		LCQ Domains --Physical --Psychological --Social --Total	No	Yes	No	Reliability: Intraclass correlation coefficients (95% CI) 0.93 (0.84 to 0.97) 0.79 (0.51 to 0.91) 0.88 (0.72 to 0.95) 0.92 (0.81 to 0.96)
		SRGQ-Total	Yes	No	No	Validity: Spearman correlation coefficients (p-value) LCQ-Total: -0.60 (0.001)
		SF-36 --Physical functioning --Role physical --Pain --General health --Vitality --Social functioning --Role emotional --Mental health	Yes	No	No	LCQ-Total: 0.28 (0.041) LCQ-Total: 0.22 (0.11) LCQ-Total: 0.47 (0.001) LCQ-Total: 0.37 (0.007) LCQ-Total: 0.50 (0.001) LCQ-Total: 0.43 (0.001) LCQ-Total: 0.10 (0.48) LCQ-Total: 0.44 (0.001)
Birring, 2006[37]	LCQ Total	Cough frequency	Yes	No	No	Spearman coefficient: 0.6 ($p<0.05$)
		Cough challenge	Yes	No	No	Spearman coefficient: -0.1 (NS)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Birring, 2003[38]	LCQ Total	Cough severity	Yes	Yes	Yes	Spearman coefficient: -0.72 Cronbach's α: 0.92 Repeatability (intraclass correlation): 0.96 Responsiveness (effect size based on clinical change score): 1.68
		SGRQ	Yes	No	No	Spearman coefficient: -0.54
		SF-36	Yes	No	No	Spearman coefficient: 0.46
	LCQ Physical	NA	No	Yes	Yes	Cronbach's α: 0.79 Repeatability (intraclass correlation): 0.93 Responsiveness (effect size based on clinical change score): 1
	LCQ Psychological	NA	No	Yes	Yes	Cronbach's α: 0.89 Repeatability (intraclass correlation): 0.9 Responsiveness (effect size based on clinical change score): 1.75
	LCQ Social	NA	No	Yes	Yes	Cronbach's α: 0.85 Repeatability (intraclass correlation): 0.88 Responsiveness (effect size based on clinical change score): 0.84
Braido, 2006[39]	CCIQ Daily life impact	SF-36 Physical functioning	Yes	No	No	Spearman coefficient: 0.281
		SF-36 Vitality	Yes	No	No	Spearman coefficient: 0.291
		SF-36 Physical summary	Yes	No	No	Spearman coefficient: 0.333
Chernecky, 2004[43]	LCCQ	NA	No	Yes	No	Cronbach's α: 0.98 ($p<0.001$)
	LCCQ	LCCQ-"How much coughing do you have?"	Yes	No	No	Spearman coefficient: 0.80 ($p=0.10$)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Crawford, 2008[46]	CASA-Q Cough symptoms	NA	No	Yes	Yes	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.77 Cronbach's α: 0.85 The mean CASA-Q cough symptom and sputum symptom domain scores indicated responsiveness towards both worse and improved symptoms.
		SGRQ Symptoms	Yes	No	No	Spearman coefficient: -0.17 (p=0.0003)
		SGRQ Impact	Yes	No	No	Spearman coefficient: -0.32 (p<0.0001)
		SGRQ Activities	Yes	No	No	Spearman coefficient: -0.04 (p=0.38)
		SGRQ Total	Yes	No	No	Spearman coefficient: -0.25 (p<0.0001)
	CASA-Q Cough impact	NA	No	Yes	No	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.88 Cronbach's α: 0.91
		SGRQ Symptoms	Yes	No	No	Spearman coefficient: -0.23 (p<0.0001)
		SGRQ Impact	Yes	No	No	Spearman coefficient: -0.54 (p<0.0001)
		SGRQ Activities	Yes	No	No	Spearman coefficient: -0.27 (p<0.0001)
		SGRQ Total	Yes	No	No	Spearman coefficient: -0.49 (p<0.0001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Crawford, 2008[46] (continued)	CASA-Q Sputum symptoms	NA	No	Yes	Yes	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.80 Cronbach's α: 0.80 The mean CASA-Q cough symptom and sputum symptom domain scores indicated responsiveness towards both worse and improved symptoms.
	CASA-Q Sputum impact	NA	No	Yes	No	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.82 Cronbach's α: 0.89
De Vito Dabbs, 2002[48]	QLTP Total	NA	Yes	Yes	No	Spearman coefficient: 0.7 Cronbach's α: 0.82 Repeatability (intraclass correlation): 0.9
	QLTP Respiratory symptoms	NA	No	Yes	No	Cronbach's α: 0.76 Repeatability (intraclass correlation): 0.8
	QLTP General symptoms	NA	No	Yes	No	Cronbach's α: 0.8 Repeatability (intraclass correlation): 0.9
	QLTP Activities of daily living	NA	No	Yes	No	Cronbach's α: 0.896 Repeatability (intraclass correlation): 0.89
	QLTP Total	MSFSD	Yes	No	No	Spearman coefficient: 0.5

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
De Vito Dabbs, 2002[48] (continued)	QLTP Respiratory symptoms	MSFSD	Yes	No	No	Spearman coefficient: 0.5
	QLTP General symptoms	MSFSD	Yes	No	No	Spearman coefficient: 0.51
	QLTP Activities of daily living	Functional Performance Inventory	Yes	No	No	Spearman coefficient: 0.7
	QLTP Shortness of breath	VAS	Yes	No	No	Spearman coefficient: 0.93
	QLTP Severity of cough	VAS	Yes	No	No	Spearman coefficient: 0.87
Decalmer, 2007[49]	LCQ Total	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.62 (p≤0.001)
	LCQ Physical	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.55 (p≤0.001)
	LCQ Psycholo-gical	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.59 (p≤0.001)
	LCQ Social	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.55 (p≤0.001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Dicpini-gaitis, 2006[50]	Cough severity score	CES-D	Yes	No	Yes	Improvement in cough score correlated with improvement in depression score (Spearman coefficient=0.323, p=0.003). There was a significant improvement in both cough and depression scores after 3 months (p<0.001).
Doherty, 2000[52]	Diary VAS	Capsaicin cough test	Yes	No	No	Capsaicin sensitivity was related to symptomatic cough as measured by the diary card score in both asthma and COPD (r=-0.38 and r=-0.44, respectively), but only in asthma and not COPD when measured using a VAS (r=-0.32 and r=-0.44, respectively).
Doherty, 2000[51]	Diary card VAS	Capsaicin cough test	Yes	No	Yes	Neither diary card scores nor VAS were related to C5 response rate.
Faruqi, 2011[55]	LCQ Total Cough counts VAS	Repeat LCQ score Cough challenge	Yes	No	Yes	Spearman coefficient: 0.91 (p<0.001) Cough counts correlated well with capsaicin sensitivity and subjective parameters, being strongest for LCQ (r=-0.6, p<0.001). The subjective parameters correlated moderately well amongst themselves (r=0.6, p=0.001) and weakly with capsaicin sensitivity.
		Hull Cough Counter	Yes	No	No	Spearman coefficient: -0.6 (p<0.001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Field, 2009[56]	CQLQ VAS	NA	Yes	No	Yes	The CQLQ scores were grouped by whether the cough disappeared, improved, or did not improve. The scores of patients whose cough did not improve did not change and were poorer than those whose cough resolved (p<0.0001) and those whose cough improved but did not disappear (p<0.0001). A VAS (0 [none] to 10 [very severe]) was used to determine the effects of CRE management on the severity of cough-associated symptoms. At 8 weeks, mean (± SD) chest pain, throat pain, nausea, and stress incontinence scores in women improved 1.7 ± 3.4 (p=0.0004), 0.9 ± 2.7 (p=0.04), 1.0 ± 2.5 (p=0.004), and 0.9 ± 2.3 (p=0.03), respectively.
Fisman, 2001[57]	Cough severity score	Cough frequency score	No	No	Yes	Overall, the cough frequency score method alone could identify a beneficial modification of cough in 17 (81%) patients and cough severity score method alone in 17 (76%). Using the combined cough frequency/severity scoring, a beneficial modification of cough could be identified in 20 (95%) of patients.
Fletcher, 2010[58]	CQLQ	GRC	No	No	Yes	Responsiveness: MID=10.58 (SD 10.63)
		Punum Ladder	No	No	Yes	Responsiveness: MID=21.89 (SD 15.38)
	GRC 6-month minus baseline score	CQLQ at 6 months	No	Yes	No	Spearman coefficient: 0.673
		CQLQ at 1 month	No	Yes	No	Spearman coefficient: 0.025
Freestone, 1997[59]	Cough severity score	Cough recorder	No	No	Yes	In both the codeine and placebo groups the median subjective score was 2.0 (IQR, 2.0 to 3.0). This decreased to 1.0 (IQR, 1.0 to 2.0) 90 minutes after treatment (p<0.0001).

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
French, 2002[60]	CQLQ Total	NA	No	No	Yes	Posttreatment cure scores were significantly lower (p<0.001) than pretreatment scores in 24 chronic coughers
		Repeat testing	No	Yes	No	Cronbach's α: 0.92 Repeatability (intraclass correlation):0.89 (p<0.001) Test-retest paired t-value: -1.39
	Physical complaints	NA	No	Yes	No	Cronbach's α: 0.85 Repeatability (intraclass correlation): 0.88 (p<0.001) Test-retest paired t-value: -0.92
	Psycho-social issues	NA	No	Yes	No	Cronbach's α: 0.83 Repeatability (intraclass correlation): 0.91 (p<0.001) Test-retest paired t-value: -0.19
	Functional abilities	NA	No	Yes	No	Cronbach's α: 0.86 Repeatability (intraclass correlation): 0.85 (p<0.001) Test-retest paired t-value: -1.21
	Emotional well-being	NA	No	Yes	No	Cronbach's α: 0.70 Repeatability (intraclass correlation): 0.77 (p<0.001) Test-retest paired t-value: -1.44
	Extreme physical complaints	NA	No	Yes	No	Cronbach's α: 0.70 Repeatability (intraclass correlation): 0.93 (p<0.001) Test-retest paired t-value: -0.24
	Personal safety fears	NA	No	Yes	No	Cronbach's α: 0.63 Repeatability (intraclass correlation): 0.75 (p<0.001) Test-retest paired t-value: -1.28
		EQ-5D	Yes	No	No	Spearman coefficient: r=-0.30 (p=0.23)
		EQ-VAS	Yes	No	No	Spearman coefficient: r=-0.24 (p=0.33)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
French, 1998[8]	ACOS	SIP Total	No	No	Yes	With successful treatment, the average number of ACOS complaints decreased from 8.6 to 1.9 (p<0.001)
	ACOS Exhaustion	SIP Total	Yes	No	No	Spearman coefficient: 0.58 (p<0.001)
	ACOS Lifestyle change	SIP Total	Yes	No	No	Spearman coefficient: 0.54 (p<0.001)
	ACOS Cannot sing in church	SIP Total	Yes	No	No	Spearman coefficient: 0.31 (p=0.05)
	ACOS Hoarseness	SIP Total	Yes	No	No	Spearman coefficient: 0.43 (p=0.006)
	ACOS Aching all over	SIP Total	Yes	No	No	Spearman coefficient: 0.36 (p<0.03)
	Number of ACOS events	SIP-body care and movement	Yes	No	No	Spearman coefficient: 0.31 (p=0.03)
		SIP-home management	Yes	No	No	Spearman coefficient: 0.33 (p=0.02)
		SIP-social interaction	Yes	No	No	Spearman coefficient: 0.46 (p=0.001)
		SIP-alertness behavior	Yes	No	No	Spearman coefficient: 0.45 (p=0.002)
		SIP-communication	Yes	No	No	Spearman coefficient: 0.38 (p=0.009)
		SIP-recreation	Yes	No	No	Spearman coefficient: 0.31 (p=0.04)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Huisman, 2007[66]	LCQ Total	NA	No	Yes	Yes	Cronbach's α: 0.93 Repeatability (intraclass correlation): 0.93 Responsiveness (average improvement score [95% CI]): 5.28 (4.41 to 6.15)
		Modified Borg score	Yes	No	No	Spearman coefficient: -0.41
		HADS	Yes	No	No	Spearman coefficient: -0.42
		SF-36 General Health	Yes	No	No	Spearman coefficient: 0.41
	LCQ Physical	NA	No	Yes	Yes	Cronbach's α: 0.77 Repeatability (intraclass correlation): 0.86 Responsiveness (average improvement score [95% CI]): 1.42 (1.14 to 1.71)
		Modified Borg score	Yes	No	No	Spearman coefficient: -0.37
		HADS	Yes	No	No	Spearman coefficient: -0.42
		SF-36 General Health	Yes	No	No	Spearman coefficient: 0.54
	LCQ Psycholo-gical	NA	No	Yes	Yes	Cronbach's α: 0.84 Repeatability (intraclass correlation): 0.93 Responsiveness (average improvement score [95% CI]):1.77 (1.47 to 2.06)
		Modified Borg score	Yes	No	No	Spearman coefficient: -0.38
		HADS	Yes	No	No	Spearman coefficient: -0.39
		SF-36 General Health	Yes	No	No	Spearman coefficient: 0.28

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Huisman, 2007[66] (continued)	LCQ Social	NA	No	Yes	Yes	Cronbach's α: 0.83 Repeatability (intraclass correlation): 0.93 Responsiveness (average improvement score [95% CI]): 2.10 (1.70 to 2.49)
		Modified Borg score	Yes	No	No	Spearman coefficient: -0.36
		HADS	Yes	No	No	Spearman coefficient: -0.46
		SF-36 General Health	Yes	No	No	Spearman coefficient: 0.3
Irwin, 2002[67]	ACOS VAS	NA	Yes	No	Yes	Before surgery (median, 23.7 days), VAS score was 73.1 ± 6.1, and ACOS score was 15.0 ± 1.1. After surgery (median, 41.2 days and 1 year), cough improved in all, VAS score decreased to 19.1 ± 8.3 and 22.6 ± 8.1 (p=0.001), respectively, and ACOS score decreased to 2.0 ± 1.3 and 3.6 ± 2.3, respectively (p=0.002). VAS scores decreased 75.7% ± 24.3% in the short term after surgery and 64.4% ± 37.7% at 1 year. ACOS scores decreased by 84% ± 29.6% in the short term after surgery and 78.9% ± 37.1% at 1 year. Over time, VAS and ACOS scores correlated significantly with each other (r=0.88, p=0.004).
Jones, 2011[68]	LCQ Total	Cough symptom score	Yes	No	No	Spearman coefficient: -0.86 (p<0.0001)
		Cough challenge	Yes	No	No	Spearman coefficient: -0.72 (p<0.0001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Kelsall, 2011[72]	VAS Cough score	24-hour cough recording Human cough counts	Yes	No	Yes	Cough scores were not significantly changed with the catheter during the day or at night. Average day and night scores did not show overall reduction. Cough VAS scores fell significantly with the catheter (p=0.002) but there were no differences in VAS scores at night. Averaging day and night cough, VAS scores showed a mean 9.5 mm (SD ± 35) reduction (p<0.001). 72% of subjects reported a decrease on the cough VAS with the catheter in situ. The change in cough frequency did not correlate with the change in cough VAS scores or cough scores during the day (r=0.26, p=0.52 and r=0.23, p=0.08, respectively) and correlated only with cough VAS scores at night (r=0.45, p=0.001 and r=0.23, p=0.10, respectively).
Kelsall, 2008[71]	LCQ Total	Time spent coughing	Yes	No	No	Spearman coefficient: r=0.36 (p=0.11)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Key, 2010[73]	LCQ Total	Total cough rates	Yes	No	No	Spearman coefficient: -0.76 (p<0.001)
	LCQ Physical	NA	Yes	No	No	Spearman coefficient: -0.76 (p<0.001)
	LCQ Psycholo-gical	NA	Yes	No	No	Spearman coefficient: -0.74 (p<0.001)
	LCQ Social	NA	Yes	No	No	Spearman coefficient: -0.80 (p<0.001)
	LCQ Total	Day cough rates	Yes	No	No	Spearman coefficient: -0.72 (p<0.001)
	LCQ Physical	NA	Yes	No	No	Spearman coefficient: -0.72 (p=0.001)
	LCQ Psycholo-gical	NA	Yes	No	No	Spearman coefficient: -0.71 (p=0.001)
	LCQ Social	NA	Yes	No	No	Spearman coefficient: -0.77 (p<0.001)
	LCQ Total	Night cough rates	Yes	No	No	Spearman coefficient: -0.46 (p=0.048)
	LCQ Physical	NA	Yes	No	No	Spearman coefficient: -0.46 (p=0.048)
	LCQ Psycholo-gical	NA	Yes	No	No	Spearman coefficient: -0.55 (p=0.016)
	LCQ Social	NA	Yes	No	No	Spearman coefficient: -0.46 (p=0.048)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Ma, 2009[76]	LCQ Total (post-treatment)	NA	No	No	Yes	Responsiveness: 14.2 to 19.5
	LCQ Physical (post-treatment)	NA	No	No	Yes	Responsiveness: 6.3 to 13.5
	LCQ Psycholo-gical (post-treatment)	NA	No	No	Yes	Responsiveness: 6.5 to 17.4
	LCQ Social (post-treatment)	NA	No	No	Yes	Responsiveness: 6.7 to 10.7
	LCQ Total	SF-36-physical	Yes	No	No	Spearman coefficient: 0.39 (p<0.0001)
		SF-36-mental	Yes	No	No	Spearman coefficient: 0.30 (p<0.001)
		Challenge-log C5	Yes	No	No	Spearman coefficient: 0.134 (p=0.25)
Marsden, 2008[77]	LCQ Total	Daytime spent coughing	Yes	No	No	Spearman coefficient: 0.54 (p<0.001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Monz, 2010[79]	CASA-Q Cough symptom	PGI-C response-"Very much better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 26.9 (21.30)
		PGI-C response-"Better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 19.4 (22.51)
		PGI-C response-"A little better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 19.8 (20.49)
	CASA-Q Cough impact	PGI-C response-"Very much better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 28.6 (21.28)
		PGI-C response-"Better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 22.9 (19.41)
		PGI-C response-"A little better"	Yes	No	Yes	Mean change in CASA-Q domain score (SD) between day 1 and 43: 19.2 (18.09)
	CASA-Q Cough and sputum domain scores	Diary	Yes	No	No	"Pearson correlation coefficients between the cough and sputum diary items and the respective CASA-Q symptom domain scores were moderate to high and ranged from 0.620 to 0.685 at day 8, 0.690 to 0.746 at day 15 and 0.599 to 0.801 at day 43. All correlations were statistically significant ($p<0.0001$)."
Morice, 2007[80]	LCQ Symptom diary	Cough challenge	Yes	No	Yes	The mean score for the LCQ was 12.3 (2.5) at baseline, 13.5 (2.7) on placebo (NS) and improving to 15.5 (2.7) on morphine ($p<0.01$ vs. baseline, $p<0.02$ vs. placebo). The physical, psychological, and social questions of the LCQ showed a significant improvement in all three subgroups. The daily cough diary showed a rapid and highly significant reduction in the cough score on morphine (3.4 [1.8], $p<0.01$), whereas placebo had no discernible effect over baseline.

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Murray, 2009[81]	LCQ	SGRQ	Yes	Yes	Yes	Spearman coefficient; -0.7 (p<0.0001) Cronbach's α: 0.96 (95% CI, 0.93 to 0.97) p<0.0001 Repeatability: Median score (IQR) baseline 11.3 (9.3 to13.7) and after 2-wk antibiotics 17.8 (15 to 18.8) p<0.0001. The LCQ had a significant inverse correlation with the SGRQ: Spearman rank correlation coefficient of -0.69 (95% CI, -0.53 to -0.81; p=0.0001).
Mwachari, 2007[82]	ABSS	NA	No	Yes	Yes	Responsiveness (effect sizes) of the ABSS Baseline, n=649 (mean score 6.3 ± SD 3.6), effect size=0.89 Baseline to 3 days, n=607 (3.0 ± 3.1), effect size=0.89 Baseline to 7 days, n=576 (2.1 ± 2.7) 1.14, effect size=0.89 Baseline to 14 days, n=530 (2.1 ± 2.9) 1.16, effect size=0.89 Item total correlation Dry cough, r=0.453 (p<0.05) Night cough, r=0.462 (p<0.05) The Cronbach's beta coefficient for the ABSS was 0.66, indicating moderate internal consistency based on the standard criterion of ≥0.70 to indicate high internal consistency. As expected, the ABSS for adjacent measurements had higher correlations in comparison with visits farther apart: baseline and 3-day visit (r=0.21), 3-day and 7-day visits (r=0.36), 7-day and 14-day visits (r=0.28) in comparison with baseline and 7-dayvisit (r=0.08), baseline and 14-day visit (r=0.09) and 3-day and 14-day visits (r=0.17).

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Nandha, 2000[83]	Diary	Patient recall Pharmacist assessment	Yes	No	Yes	There was no significant difference in patient recall of relief obtained from the medication and that actually recorded in the diary card for each of the 3 days. Statistically significant correlations were demonstrated between the two assessments obtained between diary cards and poststudy assessment scores of cough symptoms on days 2 and 3 only. The first day symptoms tended to be rated "better" on recall than that recorded in the diary card (p=0.033).
Novitsky, 2002[88]	ACOS	SIP Patient-graded outcomes of antireflux surgery	Yes	No	Yes	ACOS and SIP scores correlated with improved outcomes. Early improvement in postoperative cough severity and quality of life not only persisted but also improved over long-term followup (p<0.05). Over time, ACOS and SIP scores correlated significantly with each other (r=0.91, p<0.01).
Polley, 2008[91]	LCQ Total	CQLQ	Yes	No	No	Spearman coefficient: r=-0.56 (p<0.001)
		EQ-5D	Yes	No	No	Spearman coefficient: r=0.60 (p=0.008)
		EQ-VAS	Yes	No	No	Spearman coefficient: r=0.43 (p=0.07)
Raj, 2009[92]	LCQ Total	GCR Score	No	No	Yes	Responsiveness: MID=1.3 (SD 3.2)
	LCQ Physical	NA	No	No	Yes	Responsiveness: MID=0.2 (SD 0.8)
	LCQ Psycholo-gical	NA	No	No	Yes	Responsiveness: MID=0.2 (SD 1.1)
	LCQ Social	NA	No	No	Yes	Responsiveness: MID=0.8 (SD 1.5)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Ribeiro, 2007[93]	Diary VAS	Respiratory questionnaire	Yes	No	Yes	There was a significant difference in the cough diaries and VAS scores before and after beclomethasone treatment compared with before and after placebo use (difference of differences, 1.0; 95% CI, 0.4 to1.5; p=0.002 for diaries; and difference of differences, 1.1; 95% CI, 0.6 to 1.8; p=0.01 for the VAS). Neither cough diaries nor VAS scores correlated with questionnaire (r=0.12; p=0.07) or BPT (r=0.23; p=0 .06) findings.
Shaheen, 2011[94]	CQLQ FCSF	NA	No	No	Yes	Subjects in both the PPI and placebo arm experienced significant improvement in CQLQ over baseline scores, subjects in the PPI arm did not show a greater improvement in CQLQ scores compared with placebo (mean improvement 9.8 in the PPI group vs. 5.9 in the placebo group, p=0.3). Mean changes in FCSF scores were not significantly different between PPI and placebo (Severity: 1.0 vs. 0.8, p=0.7; Frequency: 3.2 vs. 2.3, p=0.3).

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Singapuri, 2008[107]	LCQ-Total	Mannitol challenge test C2	Yes	No	No	Spearman coefficient: r=-0.09 (p=0.77)
		Mannitol challenge test C5	Yes	No	No	Spearman coefficient: r=0.38 (p=0.2)
	VAS	Mannitol challenge test C2	Yes	No	No	Spearman coefficient: r=-0.09 (p=0.77)
		Mannitol challenge test C5	Yes	No	No	Spearman coefficient: r=-0.32 (p=0.29)
	Mannitol challenge test C2	NA	No	Yes	No	Repeatability (intraclass correlation): 0.53
	Mannitol challenge test C5	NA	No	Yes	No	Repeatability (intraclass correlation): 0.59
Smith, 2006[97]	Cough score VAS	Cough recording	Yes	No	Yes	Correlation with day cough frequency: Change in cough score r=0.34, p=0.204 Change in VAS r=0.47, p=0.070 Correlation with night cough frequency: Change in cough score r=0.19, p=0.510 Change in VAS r=0.81, p=0.001
Smith, 2006[96]	Cough score VAS	Cough challenge Ambulatory cough recording	Yes	No	Yes	There were no significant correlations between the change in time spent coughing and the change in cough threshold (r=20.27; p=0.30), change in cough score (day r=20.07, p=0.78; night r=0.17, p=0.48), or change in VAS (day r=20.07, p=0.79; night r=0.30, p=0.24).
Smith, 2006[95]	CQLQ Total	Time spent coughing	Yes	No	No	Spearman coefficient: r=0.36 (p=0.06)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Vernon, 2010[99]	CSD	LCQ SF-36 WPAI MOS-SS GRC	Yes	Yes	Yes	CSD total score: Internal consistency (a) on day 1 was 0.89, and on day 8 was 0.96 Reproducibility (intraclass correlation coefficients [ICC]) was 0.68 on day 1 to day 8 and 0.94 on day 8 to day 15 CSD total scores correlated with the VAS (r=0.84, p<0.0001), LCQ total (r=-0.62, p<0.0001) and subscale scores (r=-0.43, p<0.01 to -0.60, p<0.0001), and WPAI subscale scores (r=0.27 [NS] to 0.51, p<0.01). No significant relationships with SF-36 or MOS-SS were found.
	LCQ Total	NA	Yes	No	No	Spearman coefficient: r=-0.62 (p<0.0001)
	LCQ Physical	NA	Yes	No	No	Spearman coefficient: r=-0.43 (p<0.01)
	LCQ Psycholo-gical	NA	Yes	No	No	Spearman coefficient: r=-0.56 (p<0.001)
	LCQ Social	NA	Yes	No	No	Spearman coefficient: r=-0.60 (p<0.0001)
	CSD Total	Patient VAS severity rating	Yes	No	No	Spearman coefficient: r=0.84 (p<0.0001)
		Clinician VAS severity rating	Yes	No	No	Spearman coefficient: r=0.35 (p<0.05)
		LCQ Total	Yes	No	No	Spearman coefficient: r=-0.62 (p<0.0001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults and Adolescents (continued)						
Woodcock, 2010[100]	Cough score VAS	Cough recording	No	No	Yes	There was no significant difference in change in average cough severity scores from baseline to treatment between SCH486757 and placebo (SCH486757 mean baseline=1.98, mean change during treatment=-0.57 (-30.1%); placebo mean baseline=2.01, mean change=-0.49 (-19.7%), p=0.56). Nor were there significant changes in cough severity score for codeine compared with placebo [codeine mean baseline=2.15, mean change=-0.72 (-33.2%), p=0.07compared with placebo).
Studies in Adults, Adolescents, and Children						
Hartnick, 2009[63]	PCQ	NA	No	No	Yes	Authors concluded that "the PCQ is a valid and reliable instrument with which to follow children with chronic cough longitudinally"
		Time point 1	No	Yes	No	Cronbach's α: 0.914 (p<0.001) Repeatability: Test-retest correlation (stable patients)
		Time point 2	No	Yes	No	Cronbach's α: 0.951 (p<0.001) Repeatability: Q1=0.5 (p<0.001)
		Time point 3	No	Yes	No	Cronbach's α: 0.953 (p<0.001) Repeatability: Q2=0.38 (p<0.001) Q3=0.42 (p<0.001) Q4=0.53 (p<0.001) Q5=0.5 (p<0.001)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Adults, Adolescents, and Children (continued)						
Kalpaklio-glu, 2005[69]	LCQ Total	NA	No	No	Yes	The effect size of each specific quality-of-life questionnaire was 1 or higher after treatment, whereas it was much lower in the SF-36.
		Audio recording device	Yes	No	No	Spearman coefficient Log explosive phases, 24-hr: -0.53 (p<0.001) Log cough seconds, 24-hr: -0.53 (p<0.001) Log explosive epochs, 24-hr: -0.46 (p<0.001)
	LCQ	CQLQ SF-36	Yes	No	No	Pretreatment symptom scores were significantly correlated with the CQLQ and LCQ scores (beta=.415 and beta=-0.272, respectively, p=0.008) but not with either component of the SF-36.
	LCQ CQLQ	SF-36	Yes	No	No	Authors state: "we showed that specific questionnaires are more effective in assessing the impact of chronic cough on HRQoL" than the SF-36.
Studies in Children Only						
Archer, 1985[31]	Diary	Cough recorder	Yes	No	No	There was no correlation between night cough counts and diary card scores for night-time wheeze, daytime wheeze, daytime activity, or for 24-hour diary scores calculated for the 24-hour period beginning with, and the period ending with, the night recording.
Chang, 2012[104]	PC-QOL Cough diary	PedsQL	Yes	No	No	Correlation between PC-QOL and duration of cough: -0.01 (p=0.92)
Chang, 2003[42]	Parent cough score Child cough score	Ambulatory cough recording Cough challenge	Yes	No	No	Log cough frequency correlated with parent and child recorded log cough score (r(s)=0.42, p=0.02) and r(s)=0.44, p=0.01, respectively). Cough scores did not correlate with cough challenge test.

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
Chang, 1998[40]	Parent-completed diary Child-competed diary	Electronic cough monitor	Yes	No	No	The agreement adjusted for chance (Cohen's Kappa) between the subjective and objective presence of daytime cough for the subjects was 100%, and that for controls was 0.61 for child-completed cards and 0.44 for parent-completed cards. When both groups were considered together, the agreement was 0.67 and 0.47, respectively. For night-time cough, the agreement between the subjective and objective presence of cough was poor both in subjects and controls. In the subjects, there was no difference between the parent and child scores.
Faniran, 1999[54]	New (unnamed) question-naire	NA	Yes	Yes	No	3-week test-retest revealed a Kappa statistic >0.6 for most of the items. Questions on cough not associated with cold or flu tended to have better test-retest reliability than questions on cough associated with cold or flu.
Fuller, 1998[61]	Parent question-naire Parent diary	Video recording Sleep assessment Worries expressed by parents	Yes	No	Yes	On the second night of recording, the between-subject correlation coefficient for individual coughs and percentage of the night awake was 0.25, p=0.13 (n=37), and for individual coughs and percentage of the night awake and restless was 0.36, p=0.03 (n=37). The within-subject correlation coefficient log % awake time on log number of coughs was 0.26 (p=0.01; r=0.13, SE 0.036) with a residual coefficient of variation of 74%. The within-subject correlation coefficient (log % awake time + % restless) was 0.17 (p=0.02; r=0.016, SE 0.0071) with a residual coefficient of variation of 17%. The regression coefficients imply that halving the number of coughs will reduce the percentage awake time on average by 9% (95% CI, 4 to 15%) and percentage awake and restless time by 1% (95% CI, 0 to 2%).

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
Newcombe, 2011[84]	PC-QOL Total	NA	No	No	Yes	An anchor-based approach resulted in an MID estimate of 0.9 for overall PC-QOL change and ranged from 0.71 to 0.95 for individual domain PC-QOL change.
		VCD	Yes	Yes	No	Spearman coefficient: p=-0.70 (p<0.001) Cronbach's α: 0.84
	PC-QOL Physical	NA	Yes	No	No	Spearman coefficient: p=-0.65 (p<0.001)
	PC-QOL Psycholo-gical	NA	Yes	No	No	Spearman coefficient: p=-0.64 (p<0.001)
	PC-QOL Social	NA	Yes	No	No	Spearman coefficient: p=-0.55 (p=0.001)
Newcombe, 2010[86]	PC-QOL Total	VCD	Yes	Yes	Yes	Spearman coefficient: r=-0.55 (p=0.001) Cronbach's α: 0.94 at Time 1; 0.97 at Time 2 Effect size based on clinical change score: 0.39
		VAS	Yes	No	No	Spearman coefficient: r=-0.55 (p=0.001)
		Cough counts	Yes	No	No	Spearman coefficient: r=-0.32 (p=0.074)
		PedsQL (total score)	Yes	No	No	Spearman coefficient: r=0.46 (p<=0.034)
	PC-QOL Physical	NA	Yes	No	Yes	Effect size based on clinical change score: 0.41
	PC-QOL Psycholo-gical	NA	Yes	No	Yes	Effect size based on clinical change score: 0.32
	PC-QOL Social	NA	Yes	No	Yes	Effect size based on clinical change score: 0.32

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
Newcombe, 2008[85]	PC-QOL	NA	No	No	Yes	All subscales from the psychometric analysis showed significant improvement in parent-reported quality of life following the intervention (all p<0.001).
		Cough score	Yes	No	No	Spearman correlation coefficient: r=0.15
		PedsQL-psychosocial	Yes	Yes	No	Cronbach's α: r=0.81; Spearman coefficient: r=-0.33
		PedsQL-physical	Yes	Yes	No	Cronbach's α: r=0.84; Spearman coefficient: r=-0.47 (p<0.01)
		PedsQL-emotional	Yes	Yes	No	Cronbach's α: r=0.71; Spearman coefficient: r=-0.16 (p=NS)
		PedsQL-social	Yes	Yes	No	Cronbach's α: r=0.70; Spearman coefficient: r=-0.18 (p<0.01)

Table 6. Results of studies of cough severity or quality-of-life impact assessments (continued)

Study	Index Test	Comparator(s)	Validity Assessed?	Reliability Assessed?	Responsiveness Assessed?	Results
Studies in Children Only (continued)						
		PedsQL-school	Yes	Yes	No	Cronbach's α: r=0.70; Spearman coefficient: r=-0.51 (p<0.05)
		SF-12-physical	Yes	Yes	No	Cronbach's α: r=0.83; Spearman coefficient: r=-0.14 (p=NS)
		SF-12-role physical	Yes	Yes	No	Cronbach's α: r=0.87; Spearman coefficient: r=-0.33 (p=NS)
		SF-12-role emotional	Yes	Yes	No	Cronbach's α: r=0.91; Spearman coefficient: r=-0.31 (p<0.05)
		SF-12-mental health	Yes	Yes	No	Cronbach's α: r=0.56; Spearman coefficient: r=-0.06 (p=NS)

ABSS = Acute Bronchitis Severity Score; ACOS = Adverse Cough Outcome Survey; AUC = area under the curve; BPT = bronchoprovocation testing; CASA-Q = Cough and Sputum Assessment Questionnaire; CBSAS = Chronic Bronchitis Symptoms Assessment Scale; CCIQ = Chronic Cough Impact Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CQLQ = Cough-specific Quality of Life Questionnaire; CRE = certified respiratory educator; Cronbach's α = Cronbach's alpha coefficient; CSD = Cough Severity Diary; EQ-5D = EuroQol five dimension component index; EQ-VAS = EuroQol visual analog scale; EuroQol = European Quality of Life questionnaire; FCSF = Fisman Cough Severity/Frequency; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GRC = Global Rating of Change; HADS = Hospital Anxiety and Depression Scale; IQR = interquartile range; LCCQ = Lung Cancer Cough Questionnaire; LCQ = Leicester Cough Questionnaire; MID = minimally important difference; MOS-SS = Medical Outcomes Study Sleep Scale; MSFSD = Modified Symptom Frequency/Symptom Distress scale; NA = not applicable; NS = not statistically significant; PC-QOL = Parent Cough-Specific Quality-of-Life questionnaire; PedsQL = Pediatric Quality of Life Inventory; PGI-C = Patient Global Impression of Change; PPI = proton pump inhibitor; QLTP = Questionnaire for Lung Transplant Patients; ROC = receiver operating characteristic; SD = standard deviation; SE = standard error; SF-36/SF-12 = Medical Outcomes Study 36-Item/12-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire; SIP = Sickness Impact Profile; Spearman coefficient = Spearman correlation coefficient; VAS = visual analog scale; VCD = verbal category descriptive scale; WPAI = Work Productivity Index

Of the many cough frequency assessment tools described in the 56 studies summarized above, 14 were cough-related questionnaires (Table 7). Some of these are cough-specific (Leicester Cough Questionnaire [LCQ], Chronic Cough Impact Questionnaire [CCIQ], Cough-specific Quality of Life Questionnaire [CQLQ], Pediatric Cough Questionnaire [PCQ], Parent Cough-specific Quality-of-Life Questionnaire [PC-QOL], Adverse Cough Outcome Survey [ACOS]), while others focus on disease states for which cough is a predominant symptom (Chronic Bronchitis Symptoms Assessment Scale [CBSAS], Cough and Sputum Assessment Questionnaire [CASA-Q], Lung Cancer Cough Questionnaire [LCCQ], Punum Ladder, and Cough Severity Diary [CSD], and the Questionnaire for Lung Transplant Patients [QLTP]). Other instruments are general assessments, such as the Global Rating of Change (GRC) scale. The ACOS has been revised and replaced by the CQLQ. Twelve of the 14 questionnaires were developed and studied in adult populations, and 2 (the PCQ and PC-QOL) were designed for use in pediatric populations.

Table 7. Description of cough severity or quality-of-life impact instruments

Measure	Type of Scale	Population Derived	Domains	No. of Items	Scoring
Adult Populations					
Adverse Cough Outcome Survey (ACOS)[a]	Self-completed HRQOL	Adults with persistent troublesome cough	Psychosocial Physical	29	Each item scored as yes or no No information on total score provided
Chronic Bronchitis Symptoms Assessment Scale (CBSAS)	Self-completed Disease-specific	Outpatient adults with stable chronic bronchitis	Symptoms Activity Impact	15	Morning -6 items (0-25) Evening -9 items (0-36) Lower scores indicate less severe symptoms
Chronic Cough Impact Questionnaire (CCIQ)	Self-completed HRQOL	Outpatient adults with chronic cough	Sleep/ concentration Relationship Daily Life Impact Mood	21	Each item individually scored 5 point scale (1=not at all, 2=a little, 3=enough, 4=much, 5=very much)
Cough and Sputum Assessment Questionnaire (CASA-Q)	Self-completed Condition-specific	Adults with chronic bronchitis, COPD with and without sputum	Cough Symptoms Cough Impact Sputum Symptom Sputum Impact	25	Each item scored 0-4 (total score 100) Each domain totaled Higher scores associated with fewer symptoms
Cough Severity Diary (CSD)	Self-completed Condition-specific	Adults with chronic or subacute cough	Frequency Intensity Disruptiveness	7	11-point scale ranging from 0 to 10 with anchors on each end (e.g., never to constantly) Higher scores indicate greater severity
Cough-specific Quality of Life Questionnaire (CQLQ) [a]	Self-completed Condition-specific	Adult smokers	Physical Complaints Psychosocial Issues Functional Abilities Emotional Well-Being Extreme Physical Complaints Personal Safety Fears	28	Each item scored on 4-point Likert scale Total score 28-112 Low scores indicate no adverse effect of cough on quality of life
Leicester Cough Questionnaire (LCQ)	Self-completed HRQOL	Outpatient adults with chronic cough	Physical Psychological Social	19	7-point Likert Scale Range 3 to 21 Higher scores indicate better health

Table 7. Description of cough severity or quality-of-life impact instruments (continued)

Measure	Type of Scale	Population Derived	Domains	No. of Items	Scoring
Adult Populations (continued)					
Lung Cancer Cough Questionnaire (LCCQ)	Self-completed Condition-specific	Adult women with lung cancer	Not reported	8	Scores range from 0-32 Higher scores indicate greater symptom severity
Lung Cancer Wheezing Questionnaire	Self-completed Condition-specific	Adult women with lung cancer	Not reported	7	Scores range from 0-18 Higher scores indicate greater symptom severity
Questionnaire for Lung Transplant Patients (QLTP)	Self-completed Condition-specific	Adult single, double or heart/lung transplant	Respiratory symptoms General symptoms Activity of daily living	48	Each subscale is summed for a total score of 48 Higher scores indicate greater symptoms
Pediatric Populations					
Pediatric Cough Questionnaire (PCQ)	Self-/parent-completed Condition-specific	Children aged 6 to 12 years	Cough questions Cough associated with cold or flu (wet cough) Cough not associated with cold or flu (dry cough)	12	Each item scored as yes or no. Information on total score not provided
Parent Cough-specific Quality-of-Life Questionnaire (PC-QOL)	Self-/parent-completed Condition-specific	Children <18 years old with chronic cough	Frequency (emotions, interference, and annoyance) Worry (fragility and serious illness)	26	7-point Likert scale for each item Information on total score not provided

ACOS = Adverse Cough Outcome Survey; CASA-Q = Cough and Sputum Assessment Questionnaire; CBSAS = Chronic Bronchitis Symptoms Assessment Scale; CCIQ = Chronic Cough Impact Questionnaire; CSD = Cough Severity Diary; COPD = chronic obstructive pulmonary disease; CQLQ = Cough-specific Quality of Life Questionnaire; e; HRQOL = health-related quality of life; LCQ = Leicester Cough Questionnaire; LCCQ = Lung Cancer Cough Questionnaire; PCQ = Pediatric Cough Questionnaire; PC-QOL = Parent Cough-Specific Quality-of-Life questionnaire; QLTP = Questionnaire for Lung Transplant Patients

[a]The ACOS has been revised and replaced by the CQLQ.

Adults and Adolescents (≥14 Years of Age)

Forty-five (80%) of the 56 studies that reported on instruments to assess the severity or quality of life impact of cough included adults and adolescents, and 2 (4%) included adults, adolescents, and children (Table 6). Note that the two studies which included adults, adolescents, and children[63,69] had populations with a mean age of 38.3 and 6.8 years, respectively; therefore, the latter study by Hartnick and colleagues[63] is discussed in more detail in the children only section, below, while the study by Kalpaklioglu[69] is included here.

Of the cough-specific questionnaires, the LCQ was the most widely studied, with 19 studies. Four studies demonstrated strong correlation between the LCQ and other cough measurement tools such as electronic recording devices, subjective symptom scores, cough frequency scores, other questionnaires, and tussigenic challenges,[38,68,73,81] while most of the remaining studies showed only fair to moderate correlation with a variety of other cough measurement tools, both objective and subjective.[8,37,38,49,66,69,76,77,107] The LCQ was developed based on an outpatient adult population with chronic cough, and no studies evaluated its measurement accuracy in the pediatric population. The LCQ has the advantage of ease of administration and interpretation, which is ideal for an ambulatory clinic setting.

Data on the CQLQ were reported in 7 of the 55 studies on cough severity or quality of life impact.[56,58,60,69,91,94,95] An additional three studies[8,67,68] reported on the ACOS, which represents a prior generation of the CQLQ. The CQLQ, which includes six domains, has been shown to correlate with the LCQ, both of which appear to be better at assessing the impact of chronic cough than the SF-36.[69] The CQLQ offers an advantage over the LCQ in its ability to capture sex differences in chronic cough because the LCQ, unlike the CQLQ, does not have an item that assesses urinary incontinence as an important side effect of cough.

The other cough-specific questionnaires have been less extensively studied, and although most report good internal correlation, results correlating these instruments with other cough measures or assessing responsiveness have been variable or lacking.

There is no universally accepted reference standard for the assessment of either cough severity or the impact of cough on health-related quality of life. Most studies of disease-specific or general quality-of-life questionnaires evaluate an instrument's validity by correlation of total scores or domain subscores with other cough or respiratory symptom measurement tools. Reliability of questionnaires in adult populations with cough was most commonly assessed by test-retest correlation and measures of internal consistency. Cronbach's alpha was generally high, with values > 0.80 reported for the majority of questionnaires. Repeatability was also generally good, with high intraclass coefficients reported for most of the questionnaires. In the absence of a single reference standard, however, and with application among a wide variety of patient populations, Spearman coefficients in the 0.2–0.8 range do not necessarily suggest that a given instrument is not a valid assessment tool. Nor is the Spearman coefficient an appropriate point of comparison between two different instruments. These findings may best be interpreted as providing evidence that some questionnaires are valid assessments of cough severity or the impact of cough in health-related quality of life, but that there is insufficient evidence to precisely characterize the validity of most of these instruments.

Children (<14 Years of Age)

Nine of the 56 studies (16%) that reported on instruments to assess the severity or quality of life impact of cough included only children under the age of 14, and 2 (4%) included adults, adolescents, and children (Table 6). The vast majority of subjects in the one of these latter two

studies were under the age of 14 (mean age was 6.8 years);[63] we therefore consider this study to be primarily among children <14 years of age and discuss it below.

Only two named cough-related questionnaires (PC-QOL and PCQ) were evaluated by these 8 studies. In a series of three studies,[84-86] Newcomb and colleagues compared the PC-QOL and the PedsQL (a generic quality-of-life instrument), a cough score, the SF-36, VAS, and VCD instruments, and cough counts. Variable correlation was demonstrated with domains of the PedsQL and SF-36. Robust correlation was demonstrated with VAS and VCD scores ($r=-0.55$ and $r=-0.70$, $p<0.001$) but not with cough counts ($r=-0.32$, $p=0.074$). Chang et al.[104] administered the PC-QOL, the PedsQL (a generic quality-of-life instrument), and a cough diary to 346 children to assess the burden and etiologies associated with chronic cough, and found that the PC-QOL did not correlate with duration of cough ($r=-0.01$, $p=0.92$).

A single study evaluated the PCQ. In this study,[63] Hartnick et al. performed validation exercises by administering the 5-item PCQ to the parents of 120 children with chronic cough on 3 different occasions. The first two administrations were conducted within 2 weeks of each other, prior to initiating treatment. The third administration was conducted 3 weeks after the second one to determine if the PCQ would accurately reflect parents' perception of how their child's cough had changed following treatment, as assessed by a parent-reported global assessment of change. This study demonstrated test-retest reliability for each of the five PCQ questions, and provided evidence to confirm the PCQ's internal consistency, discriminant validity, and convergent validity.

Three other studies conducted in pediatric populations did not evaluate a named questionnaire. Two compared diaries or cough severity/QOL scores completed by parents and children to an electronic cough monitor,[40,42] and one compared a parent questionnaire and parent diary with video recordings and an assessment of children's sleep.[61] The results of these three studies suggest that the frequency of children's cough is variably related to parents' self-reported assessments, with a generally stronger relationship between cough frequency and parents' assessment of cough severity or QOL impact during the daytime than at nighttime.

Instrument Responsiveness

Of the 78 studies pertinent to KQ 1 identified by our literature search, 36 (46%) provided information on at least one instrument's responsiveness. For this section of the report, we included studies that estimated an instrument's effect size or minimally important difference (MID), or that otherwise commented on the apparent ability of an instrument to assess change over time in cough frequency, cough severity, or response to a tussigenic challenge test. We also included studies that provided comparative data on two or more cough assessments before and after treatment for cough or its underlying etiology. We did not include efficacy, effectiveness, or safety trials of cough treatment strategies that did not directly or indirectly compare two or more cough assessments; such studies comprise essentially the entire published literature of interventions for cough and its underlying etiologies, as well as much of the literature on interventions with cough as a known side effect. Without a comparative analysis of two or more cough assessments as reported by individual study authors, it is difficult or impossible to determine whether a given instrument failed to detect clinical change or whether there was an absence of clinical change resulting from a given intervention.

Adults and Adolescents (≥14 Years of Age)

Thirty (83%) of the 36 studies that provided information on at least one instrument's responsiveness included adults and adolescents, and 2 studies (6%) studies included adults, adolescents, and children. Of these, eight studies reported on the LCQ, seven on the CQLQ or ACOS, and two on the CASA-Q. Three studies assessed responsiveness of tussigenic challenge tests. The remaining studies in adult and adolescent populations included information pertaining to responsiveness for a variety of different instruments, including generic health-related quality-of-life instruments, recording devices, unnamed questionnaires, and VAS and diary instruments. Below, we summarize the literature for the studies that reported responsiveness data on the LCQ, CQLQ, ACOS, and CASA-Q.

There is compelling evidence in support of the LCQ's potential ability to detect clinical change over time. Berkhof et al.[106] demonstrated that the mean change in total LCQ score after 12 weeks of treatment was 4.3 (SD 2.5) among the 11 (of 49) patients who reported improvement in cough over the course of the 12 weeks. Murray et al.[81] reported a change in total LCQ score from 11.3 (95% CI, 9.3 to 13.8) to 17.8 (95% CI, 14.2 to 18.8) associated with a course of antibiotic treatment for exacerbations of bronchiectasis believed to be due to a pulmonary infection. The LCQ demonstrated significant correlation with the St. George Respiratory Questionnaire over the same time period with that same group of bronchiectasis patients. Similar findings were reported by Morice et al.,[80] with total LCQ scores increasing from 12.3 (SD 2.5) to 15.5 (SD 2.7) among patients whose cough was treated with morphine. Significant score increases were also noted for all three LCD domains among patients treated with morphine. Patients treated with morphine in this study also demonstrated significant reductions in cough scores as assessed by a daily cough diary, but no significant change over time was noted among patients in the placebo group. Four studies[38,66,76,92] in adults and adolescents, and one study in adults, adolescents, and children[69] estimated responsiveness indices for the LCQ and its domains; the values of estimates varied across the studies, in part because of different methods and reference tests.

There is also compelling evidence that suggests that the related CQLQ and ACOS instruments are responsive to clinical change. Irwin et al.[67] reported strong correlation between VAS and ACOS scores over time and demonstrated that both ACOS and VAS scores changed soon after patients underwent antireflux surgery. French et al.[8] demonstrated that with successful treatment of chronic cough, the average number of ACOS complaints decreased from 8.6 to 1.9 ($p<0.001$), and Novitsky et al.[88] demonstrated that both ACOS and Symptom Inventory Profile scores correlated with improved outcomes and with each other. Field et al.[56] demonstrated that mean CQLQ scores differed between patients whose cough scores (as assessed by a VAS) had disappeared, improved, or did not improve. Fletcher et al.[58] demonstrated the CQLQ's responsiveness relative to a global rating of change instrument and the Punum Ladder, an instrument that allows patients to rate change in both their overall health-related quality of life associated with their cough and on six domains of quality of life associated with the six subscales of the CQLQ. French et al.[60] also demonstrated that total and subscale CQLQ scores were significantly lower post-treatment when patients were no longer reporting cough as a complaint. Of the seven studies we identified that reported responsiveness-related information for the CQLQ, only one had ambiguous findings; in a 12-week RCT of proton pump inhibitors versus placebo in patients with chronic cough,[94] CQLQ scores demonstrated similar changes in both treatment groups. It is possible, however, that the treatment with proton pump inhibitors was not effective, as opposed to the CQLQ not being a responsive instrument.

Two studies reported on responsiveness of the CASA-Q. Crawford et al. developed this questionnaire and validated it among patients with COPD or chronic bronchitis in Germany, France, and the U.S., using German, French, and English language versions of the questionnaire.[46] This study demonstrated the responsiveness of the CASA-Q among patients who reported both worsening or improvement of cough symptoms over an unspecified period of time. Monz et al.[79] estimated the mean change in CASA-Q scores over a 6-week period relative to self-reported clinical change as assessed by the Patient Global Impression of Change (PGI-C) instrument. If one considers self-reported clinical change of "a little better" (as assessed by the PGI-C) to indicate a minimally important difference (MID), the estimated MID for the CASA-Q, is 19.8 (SD 21.28). Other MID estimates for the CASA-Q among this patient population can be derived by the data reported in the paper by Monz et al.

Children (<14 Years of Age)

Four studies (11%) reported on responsiveness of standardized cough questionnaires among children aged 14 years or younger, and two studies included adults, adolescents, and children. Three of these studies were conducted by Newcombe and colleagues[84-86] on the PC-QOL. These studies included children with chronic cough and their parents. They provide compelling evidence in support of the PC-QOL's responsiveness. All subscales from the psychometric analysis showed significant improvement in parent-reported quality of life following the treatment for cough (all $p<0.001$), and all improvements in PC-QOL scores derived by clinical impact were significant at $p<0.001$. Those parents whose children had not ceased coughing reported significantly greater frequency of concern and worries on the CASA-Q than those whose children had ceased coughing. The trend for change scores were found to increase with higher VCD change ratings for the overall CASA-Q scores, as well as for its three subscales. These investigators estimated effect sizes based on clinical change scores as assessed by a VCD.

A fourth study by Fuller and colleagues[61] compared parent's perception of their child's cough and sleep disturbance with cough counts through video recording. At the end of the study, 82 percent of parents correctly perceived whether their child's cough was better or worse. Most parents could not, however, comment on whether their child's sleep was disturbed.

A single study reported on responsiveness for the PCQ in children and adolescents (up to 18 years, mean age 6.8 years ± 5.1). Hartnick et al.[63] developed this 5-item questionnaire and administered it to the parents of 120 children who presented to a pediatric pulmonology clinic with a chief complaint of cough. The PCQ was administered three times: prior to the first visit; within 2 weeks of the first administration but before any treatment had been instituted so that test-retest reliability could be assessed; and 3 weeks after the second administration to determine if it would accurately reflect the parent's perception of how the child's cough had changed following treatment. The authors found that mean PCQ at posttreatment was significantly different from the mean at pretreatment in cases in which parents reported that their child's cough had either improved ($p<0.001$) or worsened ($p=0.003$), whereas mean scores at these two time points were unchanged in cases in which parents reported that their child's cough was unchanged after treatment ($p=0.19$)

Key Question 2. Nonspecific Therapies for Chronic Cough

KQ 2: In adults and adolescents (≥14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?

a. In patients with unexplained chronic cough

b. In patients with refractory cough with a known underlying etiology

Key Points

Key points from the Results chapter are:

- A wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough, including opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics.
- Patients with unexplained or refractory chronic cough are not well-defined as a population in the evidence base, restricting the applicability of many studies.
- Of the agents reviewed, the opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough in adults.
- There were several important quality limitations in the literature, including (1) too few good-quality studies focusing on chronic cough; (2) relatively short durations of followup 3) a diversity of outcomes measured across studies, which limited between-study comparisons; and 4) when similar outcomes were assessed across studies, the instruments used were diverse and inconsistent, making comparison and interpretation difficult.
- Data on nonpharmacological therapies for chronic cough were sparse.
- Studies evaluating management of unidentified or refractory chronic cough in children are extremely limited.
- All preparations appeared to be well-tolerated, but side effects and adverse events were uncommonly reported; underreporting side effects and adverse events could limit the assessment of effectiveness of these drugs.

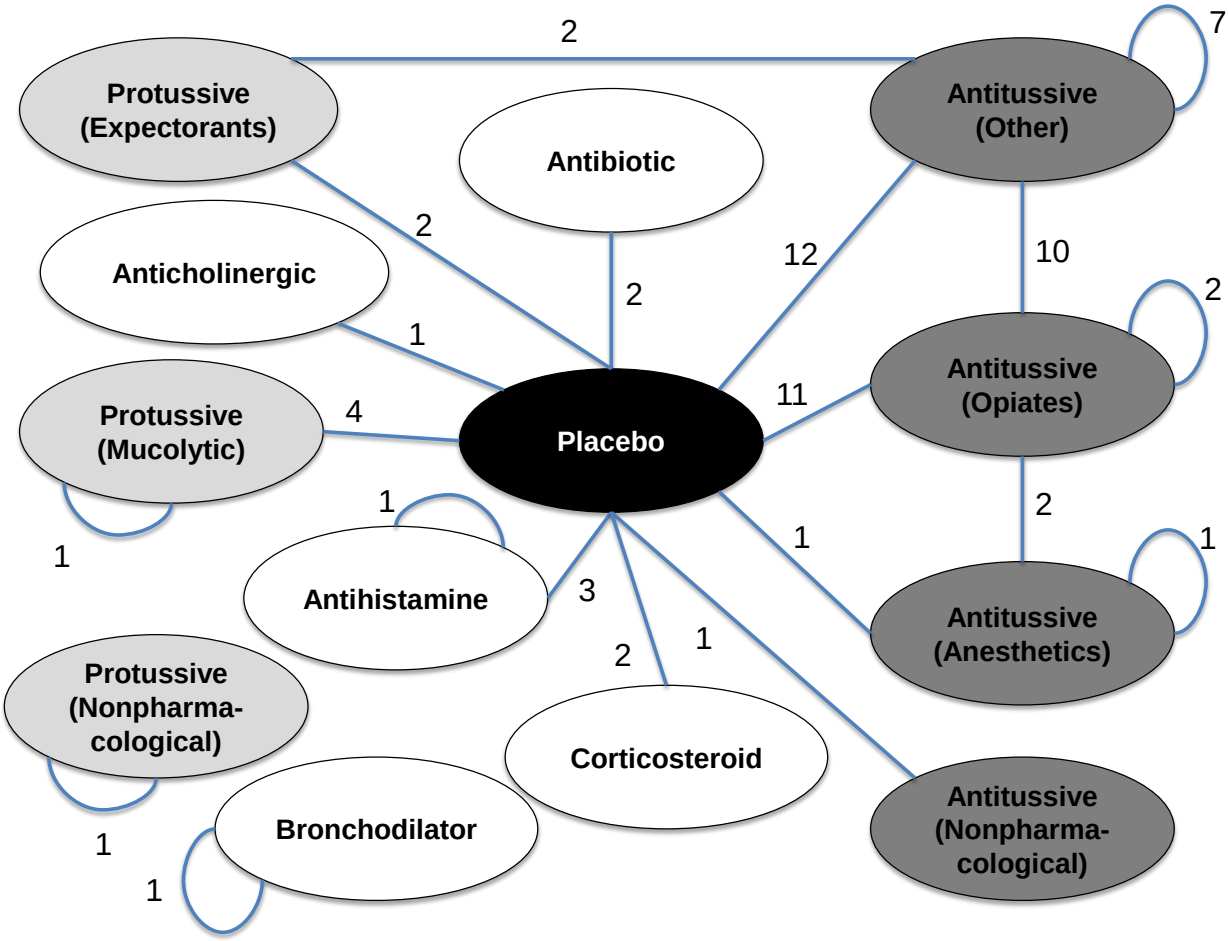
Description of Included Studies

Sixty-seven (67) comparisons from 48 studies evaluated therapies in patients with chronic cough and met our inclusion criteria. The 48 studies were described in 42 publications.[34,80,93,96,103,108-144] Thirty-three of the 48 studies were parallel-group RCTs,[34,80,93,108,109,112,115,117-120,122-125,128,130,132-135,137-144] and 12 were randomized crossover studies.[96,110,111,113,114,116,121,126,127,129,131,136] The range of years of publication was 1953 to 2012; 32 (76%) of the articles were published before 2000. Only three studies[130,138,144] were performed in children. The majority of studies took place in Europe, with 9 in the UK[80,96,113,114,118,122,126,129,143] and 17 in other countries in Europe[34,108,109,115,116,119,124,125,131,132,139,142] (total of 54%); 8 studies took place in the United States,[103,110-112,123,133-135] 7 in Asia,[117,127,128,136,137,141] 5 in Australia/New Zealand,[121,130,138,140,144]1 in Canada,[120] and 1 in South America.[93] A total of 2923 participants were included across trials; sample sizes were relatively small, ranging from 8 to 214

participants. Duration of followup was relatively short in most studies, ranging from 1 hour to 115 days. Thirty-three studies (69%) had a followup duration of 2 weeks or less. Other study characteristics are summarized in Appendix F (Table F-3). The majority of studies were rated fair in quality (n=29, or 60%); 11 studies were good in quality, and 8 were poor in quality. Fair- and poor-quality studies had the following limitations: limited description of study entry criteria, randomization, and patient population; incomplete followup; less valid statistical analyses (not intention-to-treat, post hoc subgroup analyses); and/or inadequate reporting of methods and findings.

A variety of interventions were studied; these can be broadly categorized into antitussives, protussives, and nonantitussive/nonprotussive interventions. Antitussives were further categorized as opiates, anesthetics, nonpharmacological, or "other" types. Protussives included expectorants, mucolytics, and nonpharmacological therapies. Nonantitussive/nonprotussive pharmacotherapies included antihistamines, antibiotics, anticholinergics and bronchodilators. Figure 3 represents the various classes of interventions and the comparisons among these represented in the included studies. The 48 studies represented 67 different comparisons within or between treatment classes and included studies of 59 individual agents. There were 39 comparisons (58%) with placebo. The most common class comparisons were between other antitussives and placebo (12 comparisons, 18%), followed by comparisons between antitussive opiates and placebo (11 comparisons, 16%) and comparisons between antitussive opiates and other antitussives (10 comparisons, 15%). Fourteen different class comparisons were evaluated by only one or two studies. Only two studies evaluated nonpharmacological interventions.

Figure 3. Overview of intervention class comparisons



Within the included studies, a variety of causes for chronic cough were represented, including bronchitis, chronic obstructive pulmonary disease (COPD), asthma, upper airway cough syndrome (UACS), fibrosis, neoplasm, tuberculosis, cystic fibrosis, gastroesophageal reflux disease (GERD), and unexplained cough, among others (Appendix F, Table F-3).

Table 8 details the specific agents used within the different class comparisons. It also lists the categories of outcomes assessed. The most frequent outcomes studied were cough severity/QOL (57 comparisons, 85%) and cough frequency (37 comparisons, 55%). However, even within these outcome categories, the instruments used to measure similar outcomes varied widely across studies. Other outcomes included functional status, tussigenic challenge, global assessment, and adverse effects, among others.

Table 8. Interventions and outcomes assessed

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antibiotic vs. Placebo	2	Yousaf, 2010[143]	Erythromycin	Placebo	X	X		X	X						
		Marchant, 2012[144]*	Amoxicillin	Placebo	X	X									
Anticholinergic vs. Placebo	1	Holmes, 1992[121]	Ipratropium bromide inhaler	Placebo	X										X
Antihistamine vs. Antihistamine	1	Lilienfield, 1976[123]	Diphenhydramine	Diphenhydramine		X								X	
Antihistamine vs. Placebo	3	Reid, 1989[130]*	Ketotifen	Placebo	X			X							
		van Asperen, 1992[138]*	Ketotifen	Placebo	X										
		Tanaka, 1996[136]	Loratadine	Placebo					X						
Antitussive (anesthetics) vs. Antitussive (anesthetics)	1	Simon, 1957[134]	Benzonatate	Linctussal (bencantyl)	X										
Antitussive (anesthetics) vs. Antitussive (opiates)	2	Simon, 1960[135]	Benzonatate	Dihydrocodeinone	X	X					X				
		Diwan, 1982[117]	Isoaminile citrate	Clophedianol HCl		X							X		
Antitussive (anesthetics) vs. Placebo	1	Simon, 1960[135]	Benzonatate	Placebo	X	X					X				

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antitussive (nonpharmacological) vs. Placebo	1	Vertigan, 2006[140]	SPEICH-C	Placebo	X							X			
Antitussive (opiates) vs. Antitussive (opiates)	2	Sevelius, 1971[133]	Codeine	Codeine		X									
		Sabot, 1977[132]	Viminol p-OHB	Viminol p-OHB	X										
Antitussive (opiates) vs. Antitussive (other)	10	Cass, 1953[110]	Codeine	Dextromethorphan	X								X	X	
		Cass, 1954[111]	Codeine	Dextromethorphan	X								X	X	
		Cass, 1956[112]	Codeine	Dextromethorphan	X										
		Dierckx, 1981[116]	Codeine	Glaucine	X	X									
		Matthys, 1983[125]	Codeine	Dextromethorphan	X	X					X				
		Gastpar, 1984[119]	Codeine	Glaucine	X	X									

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antitussive (opiates) vs. Antitussive (other) (continued)	10	Barnabe, 1995[34]	Codeine	Moguisteine	X	X									
		Luporini, 1998[124]	Dihydrocodeine rhodanate	Levodropropizine	X		X					X		X	
		Aliprandi, 2004[108]	Codeine	Levocloperastine	X	X	X								
		Aliprandi, 2004[108]	Codeine	Levocloperastine	X	X	X								
Antitussive (opiates) vs. Placebo	11	Cass, 1953[110]	Codeine	Placebo	X								X	X	
		Cass, 1954[111]	Codeine	Placebo	X								X	X	
		Cass, 1956[112]	Codeine	Placebo	X										
		Simon, 1960[135]	Dihydrocodeinone	Placebo	X	X					X				
		Woolf, 1964[103]	Codeine	Placebo		X									
		Sevelius, 1971[133]	Codeine	Placebo	X	X									
		Sabot, 1977[132]	Viminol p-OHB	Placebo	X										

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antitussive (opiates) vs. Placebo (continued)	11	Dierckx, 1981[116]	Codeine	Placebo	X	X									
		Matthys, 1983[125]	Codeine	Placebo	X	X					X				
		Smith, 2006[96]	Codeine	Placebo	X	X			X				X	X	
		Morice, 2007[80]	Morphine sulfate	Placebo	X			X	X				X		
Antitussive (other) vs. Antitussive (other)	7	Cass, 1956[112]	Dextromethorphan	Dextromethorphan	X										
		Ruhle, 1984[131]	Glaucine	Dextromethorphan	X	X							X		
		Del Donno, 1994[115]	Moguisteine	Dextromethorphan	X	X							X		
		Aliprandi, 2004[108]	Levocloperastine	Levodropropizine	X	X	X								
		Aliprandi, 2004[108]	Levocloperastine	Levodropropizine	X	X	X								
		Aliprandi, 2004[108]	Levocloperastine	Levodropropizine	X	X	X								
		Aliprandi, 2004[108]	Levocloperastine	DL-cloperastine	X	X							X		

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antitussive (other) vs. Placebo	12	Cass, 1953[110]	Dextromethorphan	Placebo	X								X		
		Cass, 1954[111]	Dextromethorphan	Placebo	X								X		
		Cass, 1956[112]	Dextromethorphan	Placebo	X										
		Vakil, 1966[137]	Pipazethate	Placebo		X									
		Wojcicki, 1975[142]	Duopect	Placebo	X										
		Dierckx, 1981[116]	Glaucine	Placebo	X	X									
		Matthys, 1983[125]	Dextromethorphan	Placebo	X	X					X				
		Ruhle, 1984[131]	Glaucine	Placebo	X	X							X		
		Ruhle, 1984[131]	Dextromethorphan	Placebo	X	X							X		
		Aversa, 1993[109]	Moguisteine	Placebo		X									
		Ramsay, 2008[129]	Dextromethorphan	Placebo	X			X	X				X		
		Mukaida, 2011[127]	Bakumondoto	Placebo	X	X									

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Antitussive (other) vs. Protussive (expectorants)	2	Wojcicki, 1975[142]	Duopect	Glycerol	X										
		Matts, 1977[126]	Diphenhydramine	Guaifenesin							X				
Bronchodilator vs. Bronchodilator	1	Wei, 2010[141]	Diprophylline	Methoxyphenamine	X	X		X							
Corticosteroid vs. placebo	2	Chaudhuri, 2004[113]	Fluticasone	Placebo	X										
		Ribeiro, 2007[93]	Beclomethasone	Placebo	X	X	X								
Protussive (expectorants) vs. Placebo	2	Wojcicki, 1975[142]	Glycerol	Placebo	X										
		Parvez, 1996[128]	Guaifenesin	Placebo	X	X									

Table 8. Interventions and outcomes assessed (continued)

Comparison	No. of Studies	Study	Intervention	Comparator	Cough Severity	Cough Frequency/ Resolution	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Clearance/ Retention	Patient Preference	Global Assessment	Adverse Events*	Drowsiness	Dyspnea
Protussive (mucolytic) vs. Placebo	4	Jackson, 1984[122]	N-acetylcysteine	Placebo	X							X			
		Guyatt, 1987[120]	Ambroxol	Placebo	X										
		Dueholm, 1992[118]	N-acetylcysteine	Placebo	X			X							X
		Parvez, 1996[128]	Bromhexine	Placebo	X	X									
Protussive (mucolytic) vs. Protussive (mucolytic)	1	Clarke, 1979[114]	2-mercapto-ethane-sulphonate	Hypertonic saline		X				X					
Protussive (nonpharmacological) vs. Protussive (nonpharmacological)	1	van Hengstum, 1988[139]	Positive expiratory pressure mask	Forced expiration						X					

*Three studies included only children.

Detailed Synthesis

Table 9 summarizes the patient-centered outcomes data collected for each study.

Studies Involving Opiate Antitussives

Among the studies reviewed, we found 29 comparisons within 17 studies involving opiate antitussives: 11 comparisons were with placebo,[80,96,103,110-112,116,125,132,133,135] 2 comparisons were of different doses of the same opiates,[132,133] 2 comparisons were with anesthetic antitussives,[117,135] and 10 comparisons were with nonopioid/nonanesthetic antitussives.[34,108,110-112,116,119,124,125] In the 11 comparisons of opiates with placebo,[80,96,103,110-112,116,125,132,133,135] opiates were more effective for improving cough frequency, cough severity, and/or quality of life (LCQ) in 8 of the studies.[80,103,110-112,116,125,133] The effective regimens in these studies were codeine 7.5–60 mg or morphine 5 mg. In one study, the opioid morphine resulted in significant rates of constipation and drowsiness but was not discontinued due to tolerability issues.[80] No one opioid was found to be superior to another in within-class comparisons, although codeine had a dose-response improvement in cough severity and frequency in a study comparing the following doses: 7.5 mg, 15 mg, 30 mg and 60 mg.[133] A study of another opiate, viminol, found a higher dose (140 mg) to be effective at reducing cough severity, but a lower dose (70 mg) was no different from placebo.[132]

When compared with anesthetic antitussives, opiates were not more effective for cough in the two studies making this comparison.[117,135] Opiates (only codeine derivatives in these studies) were compared with a variety of nonopioid/nonanesthetic antitussives. Codeine had comparable efficacy for reducing cough frequency, but was less effective than dextromethorphan for improving cough severity in one study.[125] In another study, the two agents were comparable for cough severity.[112] Two studies showed codeine 15–17 mg 3–4 times a day was more effective at reducing cough severity than low-dose dextromethorphan (4-6 mg 3–4 times a day).[110,111] Two studies comparing codeine with glaucine reported conflicting results; one noted significantly better improvement in cough severity and frequency with glaucine,[119] while the other noted no significant differences in cough frequency over 8 hours of followup; codeine did result in lower frequency of cough over the final 2 hours of the 8-hour duration.[116] Codeine or dihydrocodeine were similar in effectiveness for cough to moguisteine,[34] levodropropizine,[124] and levocloperastine[108] in studies making these comparisons.

In terms of tolerability, 2 of 39 patients taking codeine 30 mg in one study discontinued the study medication due to side effects: dry mouth and asthenia in one patient, nausea in the other patient.[34] In another study, the percentage of patients experiencing somnolence while taking dihydrocodeine was significantly higher (22%) than in in the group receiving levodropropizine (8%).[124] In two studies, side effects of nausea, constipation, and/or drowsiness were more frequent with codeine than with dextromethorphan.[110,111]

Studies Involving Anesthetic Antitussives

Anesthetic antitussives were examined in three studies resulting in four comparisons: one comparison was with placebo,[135] two were with opioids,[117,135] and one study compared two anesthetic antitussives.[134] Benzonatate was not superior to placebo in the one study making this comparison.[135] Clophedianol and benzonatate were not more effective for cough than opiates in the two studies making these comparisons.[117,135] The two anesthetic antitussives, benzonatate and

Becantyl® (sodium 2.6 ditertiarybutylnaphtalene monosulphonate; also named Becantex® or L.1633), had comparable effects on cough severity in one study.[134]

Studies Involving Other Antitussives

We found 31 comparisons in 21 studies involving other (i.e., nonopioid/nonanesthetic) antitussives: 12 were comparisons with placebo,[109-112,116,125,127,129,131,137,142] 7 were comparisons between 2 nonopioid/nonanesthetic antitussives,[108,112,115,131] 1 was a comparison of a combined antitussive/expectorant with the expectorant alone,[142] and 10 were comparisons with opioids[34,108,110-112,116,119,124,125] (see the section on "Studies Involving Opiate Antitussives" for a summary of these studies). Six studies compared dextromethorphan with placebo,[110-112,125,129,131] with 5 of these supporting the efficacy of dextromethorphan for treatment of cough.[110-112,125,129] In one study,[125] dextromethorphan 20 mg twice a day was more effective than placebo for reducing both cough frequency and severity. In another study,[129] dextromethorphan 30 mg three times a day was more effective than placebo at reducing cough in response to citric acid tussigenic challenge but not for cough severity, sleep disturbance, or cough-specific quality of life (LCQ). In three studies, dextromethorphan 4–20 mg 3–4 times a day were better than placebo for improvement of cough severity.[110-112] In the one negative study,[131] dextromethorphan 30 mg once was no better than placebo for impacting cough frequency or severity. A study examining glaucine 30 mg compared with placebo noted improvements in a 6-hour subset of 8-hour nocturnal cough frequency, but not in the full 8-hour duration of followup.[131] Another study of glaucine 30 mg noted lower cough frequency than placebo after 4 hours.[116] A Chinese herbal medicine consisting of extracts from six crude herbs called bakumondoto (3 g of powder before each meal) reduced cough severity and frequency compared with no treatment control over 8 weeks by participant self-report in diaries and on a visual analog scale.[127] Moguistene 200 mg 3 times a day was more effective than placebo for reducing cough frequency over 4 days.[109] Pipazethate 20 mg did not reduce cough frequency compared with placebo.[137]

In seven studies, none of the "other" antitussives was found to be superior to another in comparisons made among them,[108,115,131] nor were different doses of the same agent.[112]

One study compared the combination antitussive/expectorant Duopect® (narcotine/glycerol) 17 mg/120 mg 3 times a day, narcotine 17 mg, glycerol 120 mg 3 times a day, and placebo. More participants taking Duopect or narcotine than glycerol alone or placebo reported moderate to marked improvement in cough severity (n=28 vs. 24 vs. 13 vs. 3, respectively, of 32 patients in each arm, $p<0.01$ for Duopect and narcotine vs. glycerol and placebo).[142] Expectoration was "easier and freer" in a higher percentage of patients taking Duopect or glycerol than narcotine or placebo. In a multi-arm study, dextromethorphan 10 mg and 20 mg were similarly better than placebo for improvement of cough severity.[112]

Studies Involving Protussives

There were 10 comparisons involving protussives: two were comparisons of an expectorant with placebo,[128,142] two were comparisons of an expectorant with an 'other' antitussive,[126,142] four were comparisons of a mucolytic with placebo,[118,120,122,128] and one study compared a mucolytic with another mucolytic.[114] Compared with placebo, the expectorant bromhexine did not reduce cough frequency in one study.[128] In another study, guaifenesin reduced cough intensity (on 1 of 4 days that were analyzed over 2 weeks), increase sputum volume (on 1 of the 4 days), and improved subjective "ease of expectoration" in a subgroup of high-volume sputum patients.[128] Another study compared the combination antitussive/expectorant Duopect

(narcotine/glycerol) 17 mg/120 mg 3 times a day, narcotine 17 mg, glycerol 120 mg 3 times a day, and placebo. More participants taking Duopect or narcotine than glycerol alone or placebo reported moderate to marked improvement in cough severity (n=28 vs. 24 vs. 13 vs. 3, respectively, of 32 patients in each arm, $p<0.01$ for Duopect and narcotine vs. glycerol and placebo).[142] Expectoration was "easier and freer" in a higher percentage of patients taking Duopect or glycerol than narcotine or placebo. The following regimens did not improve cough frequency, severity, and/or quality of life compared with placebo: N-acetylcysteine 200 mg 3 times a day,[122] N-acetylcysteine 4 mg inhaled via metered-dose inhaler 4 times a day,[118] bromhexine 16 mg 4 times a day.[128] or ambroxol 60 mg twice a day.[120] In a comparison of inhaled aerosols, 2-mercapto-ethane sulfonate was not more effective than hypertonic saline at improving tracheobronchial clearance.[114]

Studies Involving Nonantitussive and Nonprotussive Pharmacotherapies

We identified four studies examining the effect of antihistamine medication on cough[123,130,136,138] Two of these studies were in children[130,138] and are discussed separately below. In the adult studies, one compared diphenhydramine 50 mg with diphenhydramine 25 mg to placebo, all preparations scheduled 4 times a day.[123] The two doses of diphenhydramine did not differ in efficacy for cough frequency, but both doses were superior to placebo. Higher dose diphenhydramine resulted in a greater frequency of drowsiness than the lower dose, which was comparable with placebo. In a placebo-controlled study,[136] loratadine 10 mg reduced the number of coughs following tussigenic challenge with ultrasonically nebulised distilled water in patients with nasal disease or unexplained chronic cough but not in normal patients.

One study examined the effect of the antibiotic erythromycin at a dose of 250 mg once a day and found no difference in cough severity, cough frequency, cough-specific quality of life or response to tussigenic challenge compared with placebo.[143] A study compared ipratroprium bromide 20 mcg inhaler, 4 puffs 4 times a day, with placebo and found improvements in cough severity and dyspnea associated with cough.[121] A study comparing two bronchodilators (diprophylline 200 mg 3 times a day vs. methoxyphenamine 2 capsules 3 times a day) did not find differences in their effects on cough frequency or cough-specific quality of life.[141] Two studies evaluated inhaled corticosteroids in patients with chronic cough of unknown etiology and found that cough severity was reduced[113] or cough more frequently resolved[93] compared with placebo.

Studies Involving Nonpharmacological Therapies

We identified only two studies that evaluated the comparative safety and effectiveness of nonpharmacological interventions for chronic cough.[139,140] Van Hengstum et al.[139] compared 20 minutes of positive expiratory pressure (PEP) physiotherapy with 30 minutes of a forced expiratory technique (FET) and no treatment using a randomized crossover trial involving eight adult patients (age range, 48–73 years) with chronic bronchitis. FET was found to be more effective than either PEP or no treatment in enhancing the primary outcome of tracheobronchial clearance, but there was no evidence that either treatment was effective in improving cough frequency or severity. This study was rated as fair quality because of the small sample size and nonblinded study design. Applicability is limited due to incomplete reporting of the interventions and the use of short-term, surrogate outcomes.

The second study was a randomized, placebo-controlled trial that compared speech pathology management with placebo among 87 adult patients with refractory chronic cough of at least 2 months in duration.[140] Patients in both study arms participated in four individual 30-minute intervention sessions with a speech pathologist with experience in treating voice disorders. The active intervention included targeted education and training in strategies to reduce cough and laryngeal irritation. The placebo intervention consisted of healthy lifestyle education, stress management, exercise, and diet. Patients in the intervention arm demonstrated greater reduction in cough ($p=0.003$) and limitation of symptoms on everyday activity ($p=0.011$) symptom scores relative to those in the placebo arm. The active treatment was also associated with greater reduction in breathing, voice, and upper airways symptom scores relative to the placebo intervention. This study was rated as fair quality because of the single-blind study design and the lack of a validated outcome measure. Applicability is limited by an intervention that requires a level of training or proficiency that is not widely available.

Studies Involving Children

Three studies addressed the treatment of chronic cough in children less than 14 years of age. Two of these evaluated ketotifen, an H1-antihistimine and mast-cell stabilizer.[130,138] In the United States, ketotifen is currently not available in oral form but is available as an eye drop for allergic conjunctivitis. The oral form is, however, available internationally, including from Canada. Both studies were RCTs of ketotifen versus placebo for children with chronic cough and/or wheeze. One evaluated 113 children between 6 and 36 months of age over 16 weeks,[138] and the other 214 children between 2 and 6 years of age over 12 weeks.[130] In the study of younger children, ketotifen was not more efficacious than placebo. However, the study of older children reported that the number of exacerbations of cough and wheeze lasting 3 or more days was reduced in the group treated with ketotifen compared with placebo. In addition, there was a decrease in the proportion of children taking beta-agonists and methylxanthines. The study of younger children was rated as good quality. The study of older children was rated fair because there was no allocation concealment, the primary outcome measure was unclear with multiple comparisons, and the study was industry funded. These two studies have low applicability to the management of children with chronic cough. In both studies, all subjects likely had asthma as their source of chronic cough. These studies were published over 20 years ago (in 1989 and 1992). The management of asthma has significantly changed since these studies were conducted, with greater emphasis on the role of controller medicines (e.g., inhaled corticosteroids, leukotriene inhibitors) to reduce the chronic symptoms associated with poorly controlled asthma. It is unclear whether findings regarding ketotifen are generalizable to the other available medications in its class.

The third study was a randomized, placebo-controlled trial of an antibiotic, amoxicillin clavulanate, in children with more than 3 weeks of wet cough.[144] Children were randomized to 14 days of antibiotic or placebo, and outcomes were measured with a cough diary using the verbal category descriptive score. The primary outcome was cough resolution, based on at least 75 percent reduction in cough score on average during the 2 days following treatment or 3 days within a the trial period. Fifty children were enrolled. The mean age in the treatment group was 1.75 years (range, 0.9 to 4.6 years) and 2.8 years (range, 0.95 to 5.25 years) in the control group. Cough resolution was 48 percent in the treatment group and 16 percent in the placebo group ($p=0.0016$), with a number needed to treat of 4. This study was rated as good quality, and

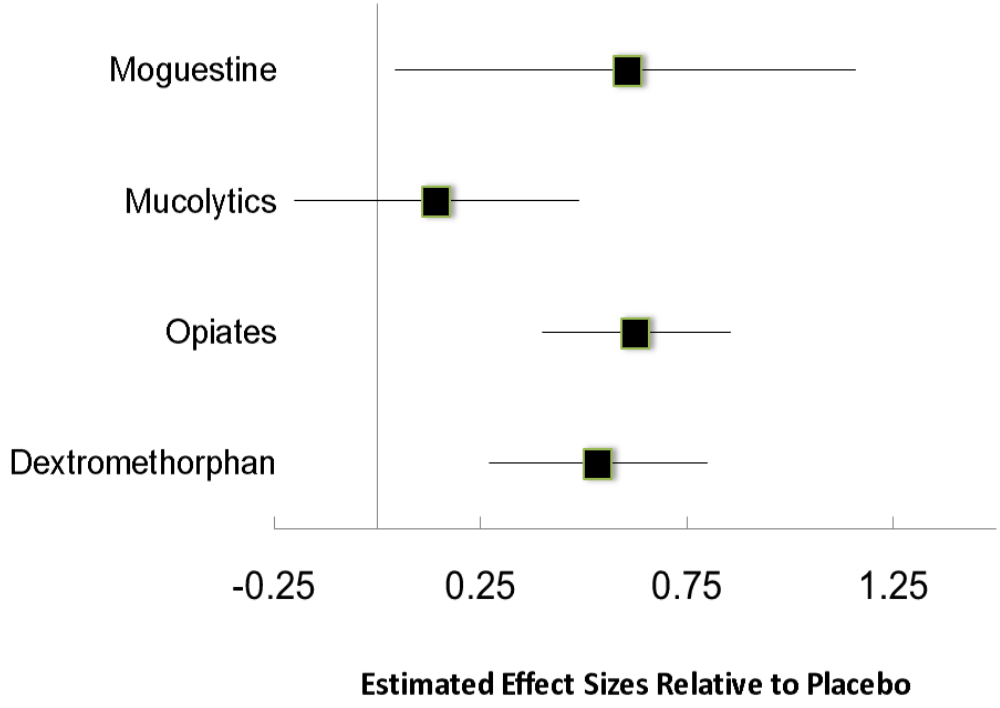
although it had a small sample size and the description of diagnostic evaluation of cough was minimal, it otherwise had good applicability.

Quantitative Synthesis

The heterogeneity of the included studies in terms of the interventions and comparators (Figure 3), combined with the lack of three or more studies reporting the same outcome where there were multiple comparisons (Table 8), precluded us from performing meta-analyses on almost all outcomes.

We were, however, able to evaluate the relative effects on cough severity for four classes of treatments for chronic cough: antitussive opiates, antitussive dextromethorphan, antitussive moguisteine, and protussive mucolytics. Thirteen studies reported results for cough severity, but two of these[116,131] did not provide sufficient information to estimate effect sizes. Of the remaining 11 studies (n=396 patients), 4 provided information on mucolytics, 3 provided information on dextromethorphan, 2 provided information on moguisteine, and 4 provided information on opiates. Most of the 11 studies compared the treatment with placebo,[34,80,115,118,120,122,125,128,129,132,135] but one compared opiates with dextromethorphan and placebo.[125] Methods used to measure cough severity differed widely amongst the studies, from studies looking at the proportion of patients receiving good or excellent cough relief after treatment,[134] to those evaluating a mean cough severity score using various Likert scores or VAS instruments,[34,80,115,120,122,129,132] to those measuring the median or mean change in intensity of cough.[118,125,128] Because each study used a different measure of severity, we converted all results to effect sizes (standardized mean differences). Relative to placebo, the effect of dextromethorphan on cough severity was 0.54 (95% confidence interval [CI], 0.27 to 0.80; p=0.0008), the effect of opiates was 0.63 (95% CI, 0.40 to 0.86; p<0.0001), the effect of moguisteine was 0.62 (95% CI, 0.04 to 1.16, p=0.0366), and the effect of mucolytics was 0.14 (95% CI -0.20 to 0.49; p=0.384; Figure 4). The studies showed heterogeneity (p=0.0023). The effects of dextromethorphan, moguisteine, and opiates compared with placebo on cough severity support a benefit of these therapies, but the evidence is insufficient to determine relative benefit among these therapies.

Figure 4. Meta-analysis of data on cough severity



We performed a similar meta-analysis for cough frequency, including 7 studies (n=700 patients).[34,109,115,116,125,133,135] Relative to placebo, the effect of dextromethorphan on cough frequency was 0.40 (95% CI, 0.18 to 0.85; p=0.0248), the effect of codeine was 0.57 (95% CI, 0.36 to 0.91; p=0.0260), and the effect of moguisteine was 0.60 (95% CI, 0.31 to 1.17, p=0.1117; Figure 5). The studies showed significant heterogeneity (p=0.0231). The effects of dextromethorphan and codeine compared with placebo on cough frequency support a benefit of these therapies, although the estimates are too imprecise to determine if one is superior to another. The effect of moguisteine was too imprecise to draw conclusions about is efficacy.

Figure 5. Meta-analysis of data on cough frequency

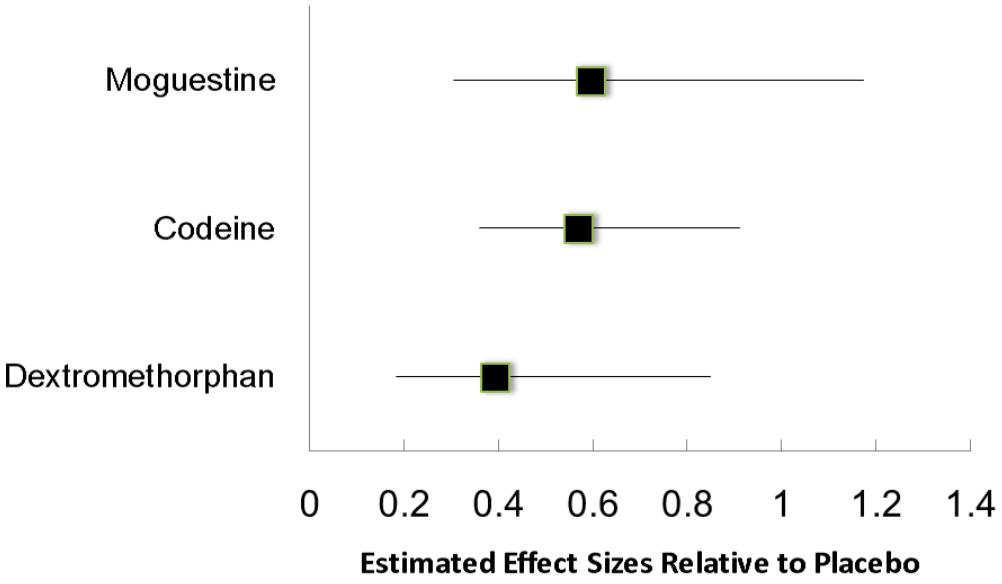


Table 9. Patient-centered outcomes data

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antibiotic vs. Placebo	Yousaf, 2010[143]	Mean change in cough VAS from baseline to post treatment at 12 wk: Erythromycin=-12 (SD 33) Placebo=2 (SD 29) Difference=10 (-11 to 33)	Geometric mean (log SD) fold change in coughs/24 hr from baseline to post treatment at 12 wk: Erythromycin=0.67 (SD 0.29) Placebo=0.73 (SD 0.66) Difference=1.1 (0.7 to 1.5)	NR	Mean change in LCQ from baseline to post treatment at 12 wk: Erythromycin=1.8 (SD 3.8) Placebo=1.8 (SD 3.8) Difference=0.0 (-2 to 2)	Geometric mean (log SD) fold change in tussigenic citric acid cough challenge test (C2): Erythromycin=1.6 (SD 0.06) Placebo=1.1 (SD 0.4) Difference=0.7 (0.4 to 1.3)	NR	NR
	Marchant, 2012[144]	Median verbal category descriptive score at 2 wk: Amoxicillin=0.5 (IQR, 0 to 2) Placebo=2.25 (IQR, 1.15 to 2.9) P=0.02	% patients with self-reported cough resolution at 2 wk: Amoxicillin=48 Placebo=16 P=0.015	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Anticholinergic vs. Placebo	Holmes, 1992[121]	Mean daily score for day-time cough over 3 wk of treatment: Ipratropium bromide=1.29 (SD 0.72) Placebo=1.66 (SD 0.74) p<0.05 Mean daily score for nighttime cough over 3 wk of treatment: Ipratropium bromide=0.82 (SD 0.68) Placebo=1.24 (SD 0.87) p<0.05	NR	NR	NR	NR	NR	Mean daily score for dyspnea associated with coughing bouts over 3 wk of treatment: Ipratropium bromide=0.25 (SD 0.49) Placebo=0.54 (SD 0.67) p<0.05
Antihistamine vs. Antihistamine	Lilienfield, 1976[123]	NR	16-hr cough count assessed at day 3: Diphenhydramine 50 mg: 163.8 (SEM 24.2) Diphenhydramine 25 mg: 175.8 (SEM 27.9)	NR	NR	NR	NR	There was little or no apparent correlation between antitussive effectiveness and incidence of drowsiness

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antihistamine vs. Placebo	Reid, 1989[130]	Mean day symptom score (0-3) rated by parent after 4 mo: Ketotifen=0.34 (SD 0.48) Placebo=0.37 (SD 0.50) Mean night symptom score (0-3) rated by parent after 4 mo: Ketotifen=0.26 (SD 0.43) Placebo=0.30 (SD 0.48)	NR	NR	Reduction in the number of housebound days due to respiratory symptoms: Ketotifen: p=0.036 Placebo: p=NS	NR	NR	NR
	van Asperen, 1992[138]	Mean daytime cough severity (0-3) 20 wk after start of trial: Ketotifen=0.99 Placebo=0.76 Mean nighttime cough severity (0-3) 20 wk after start of trial: Ketotifen=0.94 Placebo=0.76	NR	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antihistamine vs. Placebo (continued)	Tanaka, 1996[136]	NR	NR	NR	NR	No. of coughs induced by ultrasonically nebullised distilled water inhalation: Loratadine=25.3 (baseline), 14.3 (1 hr after treatment) Placebo=26.4 (baseline), 25.1 (1 hr after treatment) p<0.05	NR	NR
Antitussive (anesthetics) vs. Antitussive (anesthetics)	Simon, 1957[134]	No. of patients with excellent or good relief at least 2 wk from treatment: Benzonatate=43/52 Linctussal (bencantyl)=22/41 p<0.05	NR	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (anesthetics) vs. Antitussive (opiates)	Simon, 1960[135]	No. of patients with severity lessened: Benzonatate=28/45 Dihydrocodeinone=29/45	No. of patients with frequency lessened: Benzonatate=32/45 Dihydrocodeinone=30/45	NR	NR	NR	NR	Patient preference: Benzonatate=27% Dihydrocodeinone=49% p<0.05
	Diwan, 1982[117]	NR	Mean 24-hr cough count: Isoaminile citrate=52.5 (SEM 4.01) (baseline), 13.70 (SEM 2.84) (14 days after treatment) Chlophedianol hydrocholaride=63.3 (SEM 3.64) (baseline), 14.2 (SEM 2.66)	NR	NR	NR	Side effects were not troublesome and did not require a reduction in dose or withdrawal of treatment	NR
Antitussive (anesthetics) vs. Placebo	Simon, 1960[135]	No. of patients with severity lessened: Benzonatate=28/45 Placebo=26/45	No. of patients with frequency lessened: Benzonatate=32/45 Placebo=30/45	NR	NR	NR	NR	Patient preference: Benzonatate=27% Placebo=18% p<0.05

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (nonpharma-cological) vs. Placebo	Vertigan, 2006[140]	Mean score based on cough severity symptoms over last week assessed after 2 mo: Speech therapy=8.8 (SD 2.8) (baseline), 4.9 (SD 3.0) (post intervention) Placebo=7.5 (SD 3.6) (baseline), 6.3 (SD 3.5) (post intervention) p=0.003	NR	NR	NR	NR	NR	Mean score based on total cough, respiratory, voice, and upper airway symptoms over last week assessed after 2 mo: Speech therapy=35.4 (SD 16.0) (baseline), 22.7 (SD 18.0) (post intervention) Placebo=29.9 (SD 13.5) (baseline), 28.8 (SD 16.5) (post intervention) p<0.001
Antitussive (opiates) vs. Antitussive (opiates)	Sevelius, 1971[133]	NR	Average reduction in 6-hr posttreatment cough count: Codeine (7.5mg)=29% Codeine (15mg)=42% Codeine (30mg)=56% Codeine (60mg)=67% p<0.005 among doses.	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (opiates) (continued)	Sabot, 1977[132]	Mean cough severity (scale 0-3) assessed over 3 hours, 1 hour after dose: Viminol (70 mg)=3.57 Viminol (140 mg)=2.04 p=0.906	NR	NR	NR	NR	NR	NR
Antitussive (opiates) vs. Antitussive (other)	Cass, 1953[110]	Days of cough-suppressing effectiveness over 45 d Dextromethorphan has about 44% of the effectiveness of codeine	NR	NR	NR	NR	No of patients recorded as having side effect sduring 5d study period: Codeine (17 mg)=126 Dextromethor-phan (4 mg)=19	NR
	Cass, 1954[111]	Intensity of cough (based on Likert scale 0-4) after 35 d: Dextromethorphan =1.28 Codeine=1.26	NR	NR	NR	NR	Number of patients with side effects after 35 d: Nausea: Dex=3, codeine=13 Vomiting: Dex=0, codeine=3 Constipation: Dex=1, codeine=3 Drowsiness: Dex=1, codeine=18 Sleepiness: Dex=1, codeine=1	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other) (continued)	Cass, 1956[112]	Mean daily cough score (0-4) over the 10 days: Codeine=0.78 Dextromethorphan =0.86	NR	NR	NR	NR	NR	NR
	Dierckx, 1981[116]	Patient judgment on efficacy of treatment 8 hr after single dose (1-5): Codeine=2.45 Glaucine=2.76	Nocturnal cough counts 8 hr after single treatment Codeine=201.9 (SEM 29.9) Glaucine=241.8 (SEM 29.9) 0.1<P<0.2	NR	NR	NR	NR	NR
	Matthys, 1983[125]	Cough intensity on scale of 0-10: Codeine=4.6 (SD 1.5) (baseline), 4.5 (SD 1.6) (after 8 hr) Dextromethorphan =4.4 (SD 1.5) (baseline), 2.9 (SD 1.9) (after 8 hr) p<0.0008	Nocturnal night counts per hr: Codeine=9.8 (SD 7.5) (baseline), 4.9 (SD 4.3) (after 8 hr) Dextromethor-phan=9.5 (SD 6.9) (baseline), 3.4 (SD 3.4) (after 8 hr)	NR	NR	NR	NR	Patient preference (% patients rating) Codeine=12.5% (Best), 12.5% (Worst) Dextromethor-phan=87.5% (Best), 6.25% (Worst) p<0.001

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other) (continued)	Gastpar, 1984[119]	Physician score between 0-3: Codeine=3.0 (baseline), 2.00 (SEM 0.03) (3 days), 1.10 (SEM 0.07) (7 days) Glaucine=3.0 (baseline), 1.60 (SEM 0.07) (3 days), 0.47 (SEM 0.07) (7 days) p<0.001 VAS score between 0-100: Codeine=83.3 (SEM 0.7) (baseline), 50.1 (SEM 1.2) (3 days), 16.9 (SEM 1.6) (7 days) Glaucine=85.2 (SEM 0.5) (baseline), 38.6 (SEM 1.6) (3 days), 7.1 (SEM 0.7) (7 days) p<0.001	No. of patients with cough absent at day 7: Codeine=0 Glaucine=24 p<0.01	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other) (continued)	Barnabe, 1995[34]	VAS score between 0-100: Codeine=57.9 (baseline), 35.6 (2 days after treatment) Moguisteine=54.8 (baseline), 37.6 (2 days after treatment)	Morning coughs during 6 hr: Codeine=203 (SD 281) (baseline), 137 (SD 196) (3 days after first dose) Moguisteine=243 (SD 248) (baseline), 192 (SD 237) (3 days after first dose) Nocturnal coughs per hr: Codeine=16 (SD 14) (baseline), 8 (SD 10) (3 days after first dose) Moguisteine=27 (SD 32) (baseline), 16 (SD 18) (3 days after first dose) VAS score between 0-100: Codeine=54.8 (baseline), 39.0 (2 days after treatment) Moguisteine=61.8 (baseline), 34.6 (2 days after treatment)	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other) (continued)	Luporini, 1998[124]	Patient-reported score between 1-5: Dihydrocodeine=3.7 (SEM 0.6) (baseline), 2.47 (SEM 0.12) (7 days) Levodropropizine=3.7 (SEM 0.6) (baseline), 2.50 (SEM 0.12) (7 days)	NR	Nighttime awakenings: Dihydrocodeine=1.1 (SD 1.5) (baseline), 0.6 (SD 1.1) (7 days) Levodropro-pizine=1.4 (SD 1.9) (baseline), 1.2 (SD 1.7) (7 days)	NR	NR	NR	Drowsiness: Dihydrocodeine=15/69 (22%) Levodropropizine=5/66 (8%) p<0.05 No severe somnolence was recorded after treatment with either drug Global Assessment (Clearance): Dihydrocodeine=12% (patient assessment) =7% (physician assessment) Levodropropizine=11% (patient assessment) =7% (physician assessment) Global Assessment (Improvement): Dihydrocodeine=76% (patient assessment) =83% (physician assessment) Levodropropizine=67% (patient assessment) =73% (physician assessment)

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other) (continued)	Aliprandi, 2004[108]	Mean score between 0-4: Codeine=2.57 (baseline), 0.30 (end of treatment mean 15.6 days) Levocloperastine= 2.00 (baseline), 0.13 (end of treatment mean 15.6 days)	Mean score between 0-4: Codeine=2.77 (baseline), 0.37 (end of treatment mean 15.6 days) Levocloperastine= 2.55 (baseline), 0.12 (end of treatment mean 15.6 days)	Mean score between 0-4: Codeine=2.07 (baseline), 0.12 (end of treatment mean 15.6 days) Levocloperastine=2. 03 (baseline), 0.02 (end of treatment mean 15.6 days)	NR	NR	NR	NR
	Aliprandi, 2004[108]	Mean score between 0-4: Codeine=2.53 (baseline), 0.23 (end of treatment mean 10.2 days) Levocloperastine= 2.37 (baseline), 0.13 (end of treatment mean 9.8 days)	Mean score between 0-4: Codeine=2.63 (baseline), 0.23 (end of treatment mean 10.2 days) Levocloperastine= 2.50 (baseline), 0.10 (end of treatment mean 9.8 days)	Mean score between 0-4: Codeine=1.97 (baseline), 0.13 (end of treatment mean 10.2 days) Levocloperastine=1. 60 (baseline), 0.07 (end of treatment mean 9.8 days)	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Placebo	Cass, 1953[110]	Mean intensity of cough after 5 days of treatment: Codeine (17 mg)=1,1 Placebo=1.52	NR	NR	NR	NR	No. of patients recorded as having side effects during 5d study period: Codeine (17 mg)=126 Placebo=17	NR
	Cass, 1954[111]	Intensity of cough (based on Likert scale 0-4) after 35 d: Codeine=1.26 Placebo=1.49	NR	NR	NR	NR	Number of patients with side effects after 35 d: Nausea: codeine=13, placebo=3 Vomiting: codeine=3, placebo=0 Constipation: codeine=3, placebo=0 Drowsiness: codeine=18, placebo=2 Sleepiness: codeine=1, placebo=0	NR
	Cass, 1956[112]	Mean daily cough score (0-4) over the 10 days: Codeine=0.78 Placebo=1.15	NR	NR	NR	NR	NR	NR
	Simon, 1960[135]	No. of patients with severity lessened: Dihydrocodeinone =29/45 Placebo=26/45	No. of patients with frequency lessened: Dihydrocodeinone =30/45 Placebo=30/45	NR	NR	NR	NR	Patient preference: Dihydrocodeinone =49% Placebo=18% p<0.05

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Placebo (continued)	Woolf, 1964[103]	NR	Average number of daily cough counts over 4d Codeine=359 Placebo=513 Average number of 2-hour post-treatment coughs Codeine=27 Placebo=51	NR	NR	NR	NR	NR
	Sevelius, 1971[133]	NR	Average reduction compared with placebo in diurnal cough counts: Codeine (7.5mg)=29% Codeine (15mg)=42% Codeine (30mg)=56% Codeine (60mg)=67% p<0.005	NR	NR	NR	NR	NR
	Sabot, 1977[132]	Mean score (0-3) assessed over 3-hr period 1 hr after dose: Placebo=3.66 Viminol p-OHB (140 mg)=2.04; p<0.05 Viminol p-OHB (70 mg)=3.57; p=0.91	NR	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Placebo (continued)	Dierckx, 1981[116]	Patient judgment on efficacy of treatment 8 hr after single dose (1-5): Codeine=2.45 Placebo=2.66	Nocturnal cough counts 8 hr after single treatment Codeine=201.9 (SEM 29.9) Placebo=269.3 (SEM 31.3) P<0.05	NR	NR	NR	NR	NR
	Matthys, 1983[125]	Cough intensity on scale of 0-10: Codeine=4.6 (SD 1.5) (baseline), 4.5 (SD 1.6) (after 8 hr) Placebo=6.5 (SD 2.0) (baseline), 6.8 (SD 2.7) (after 8 hr) p<0.0001	Nocturnal night counts per hr: Codeine=9.8 (SD 7.5) (baseline), 4.9 (SD 4.3) (after 8 hr) Placebo=9.6 (SD 8.1) (baseline), 15.2 (SD 11.6) (after 8 hr) p<0.0001	NR	NR	NR	NR	Patient preference (% patients rating) Codeine=12.5% (Best), 12.5% (Worst) Placebo=0% (Best), 81.25% (Worst) p<0.001
	Smith, 2006[96]	Mean day cough symptom score (0-5) after 10d: Codeine=2.8 (SD 1.0) Placebo=2.7 (SD 0.6) P=0.59	Median day cough frequency (time spent coughing in coughs/hour) after 10d: Codeine=10.7 (IQR, 6.2 to14.6) Placebo=11.1 (IQR, 7.7 to 16.4)	NR	NR	Log median tussigenic citric acid cough challenge test (C2) after 10d: Codeine=-0.90 (IQR, -1.2 to -0.6) Placebo=-0.60 (IQR, -1.5 to -0.9)	Two subjects complained of drowsiness, one on both study days, the other on the codeine study day	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Placebo (continued)	Morice, 2007[80]	Mean difference of daily score (0-9) after 28 days: Morphine=3.45 (SD 1.76) Placebo=4.98 (SD 1.68)	NR	NR	LCQ change in score after 28 days: Morphine=15.5 (SD 2.7) Placebo=13.5 (SD 2.7) p<0.02	Mean tussigenic citric acid cough challenge test (C2) after 28 days: Morphine=220 (SD 344) Placebo=127 (SD 160)	Morphine was well tolerated and no patient dropped out because of adverse events. The most common side effects noted were constipation (40%) and drowsiness (25%)	NR
Antitussive (other) vs. Antitussive (other)	Cass, 1956[112]	Mean daily cough score (0-4) over the 10 days: Dextromethorphan (20 mg)=0.92 Dextromethorphan (10 mg)=0.86	NR	NR	NR	NR	NR	NR
	Ruhle, 1984[131]	Mean patient score (1-5) 8 hr after dose: Glaucine=2.9 Dextromethorphan =3.1	Nocturnal number of coughs after three treatments: Glaucine=511 Dextromethor-phan=540	NR	NR	NR	Incidence of side effects after three treatments: Glaucine=1 Dextromethor-phan=8 p<0.05	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Antitussive (other) (continued)	Del Donno, 1994[115]	Reduction in mean VAS score of morning cough troubleness: Moguisteine=47.6 (SD 25.1) (baseline), 24.3 (SD 19.3) (2 days) Dextromethorphan =47.2 (SD 23.9) (baseline), 28.0 (SD 20.8) (2 days)	Percentage reduction in number of coughs during 6-hr period after last dose vs. at baseline: Moguisteine=29.4 % Dextromethor-phan=30%	NR	NR	NR	Reduction in mean VAS score of sleep disturbance: Moguisteine=48.0 (SD 29.2) (baseline), 30.1 (SD 27.8) (2 days) Dextromethor-phan=44.5 (SD 26.4) (baseline), 27.2 (SD 22.5) (2 days)	NR
	Aliprandi, 2004[108]	Mean score between 0-4: Levocloperastine= 2.68 (baseline), 1.2 (end of treatment mean 9.5 days) Levodropropizine= 2.56 (baseline), 0.32 (end of treatment mean 9.3 days)	Mean score between 0-4: Levocloperastine= 2.60 (baseline), 0.12 (end of treatment mean 9.5 days) Levodropropizine =2.28 (baseline), 0.36 (end of treatment mean 9.3 days)	Mean score between 0-4: Levocloperastine=2. 5 (baseline), 0.12 (end of treatment mean 9.5 days) Levodropro-pizine=1.84 (baseline), 0.12 (end of treatment mean 9.3 days) p<0.05 at baseline	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Antitussive (other) (continued)	Aliprandi, 2004[108]	Mean score between 0-4: Levocloperastine= 2.60 (baseline), 0.17 (end of treatment mean 9.0 days) Levodropropizine= 2.43 (baseline), 0.67 (end of treatment mean 8.5 days)	Mean score between 0-4: Levocloperastine= 2.67 (baseline), 0.17 (end of treatment mean 9.0 days) Levodropropizine =2.67 (baseline), 0.83 (end of treatment mean 8.5 days)	Mean score between 0-4: Levocloperastine=2. 07 (baseline), 0.07 (end of treatment mean 9.0 days) Levodropro- pizine=1.80 (baseline), 0.40 (end of treatment mean 8.5 days) p<0.05	NR	NR	NR	NR
	Aliprandi, 2004[108]	Mean score between 0-4: Levocloperastine= 2.45 (baseline), 0.10 (end of treatment mean 9.2 days) Levodropropizine= 2.50 (baseline), 0.65 (end of treatment mean 9.2 days)	Mean score between 0-4: Levocloperastine= 2.70 (baseline), 0.10 (end of treatment mean 9.2 days) Levodropropizine =2.20 (baseline), 0.75 (end of treatment mean 9.2 days)	Mean score between 0-4: Levocloperastine=2. 10 (baseline), 0.10 (end of treatment mean 9.2 days) Levodropro- pizine=1.75 (baseline), 0.30 (end of treatment mean 9.2 days)	NR	NR	NR	NR
	Aliprandi, 2004[108]	Mean score between 0-4: Levocloperastine= 2.65 (baseline), 0.15 (end of treatment mean 13.3 days) DL- cloperastine=2.58 (baseline), 0.72 (end of treatment mean 13.6 days) p<0.001	Mean score between 0-4: Levocloperastine= 2.60 (baseline), 0.13 (end of treatment mean 13.3 days) DL- cloperastine=2.48 (baseline), 0.62 (end of treatment mean 13.6 days) p<0.001	Mean score between 0-4: Levocloperastine=2. 15 (baseline), 0.05 (end of treatment mean 13.3 days) DL- cloperastine=2.15 (baseline), 0.48 (end of treatment mean 13.6 days) p<0.001	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Placebo	Cass, 1953[110]	Mean intensity of cough after 5 d of treatment: Dextromethorphan (4 mg)=1,38 Placebo=1.52	NR	NR	NR	NR	No. of patients recorded as having side effect during 5 d study period: Dextromethor-phan (4 mg)=19 Placebo=17	NR
	Cass, 1954[111]	Intensity of cough (based on Likert scale 0-4) after 35 d: Dextromethorphan =1.28 Placebo=1.49	NR	NR	NR	NR	No. of patients with side effects after 35 d: Nausea: Dex=3, placebo=3 Vomiting: Dex=0, placebo=0 Constipation: Dex=3, placebo=0 Drowsiness: Dex=1, placebo=2 Sleepiness: Dex=1, placebo=0	NR
	Cass, 1956[112]	Mean daily cough score (0-4) over the 10 days: Dextromethorphan =0.86 Placebo=1.15	NR	NR	NR	NR	NR	NR
	Vakil, 1966[137]	NR	Average of 3 hourly cough counts: Pipazethate=53.2 Placebo=52.6	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Placebo (continued)	Wojcicki, 1975[142]	No. of patients with marked or moderate relief: Duopect=28/32 Placebo=3/32 p<0.05	NR	NR	NR	NR	NR	NR
	Dierckx, 1981[116]	Patient judgment on efficacy of treatment 8 hr after single dose (1-5): Glaucine=2.76 Placebo=2.66	Nocturnal cough counts 8 hr after single treatment Glaucine=241.8 (SEM 29.9) Placebo=269.3 (SEM 31.3) P<0.05	NR	NR	NR	NR	NR
	Matthys, 1983[125]	Cough intensity on scale of 0-10: Dextromethorphan =4.4 (SD 1.5) (baseline), 2.9 (SD 1.9) (after 8 hr) Placebo=6.5 (SD 2.0) (baseline), 6.8 (SD 2.7) (after 8 hr) p<0.0001	Nocturnal night counts per hr: Dextromethor-phan=9.5 (SD 6.9) (baseline), 3.4 (SD 3.4) (after 8 hr) Placebo=9.6 (SD 8.1) (baseline), 15.2 (SD 11.6) (after 8 hr) p<0.0001	NR	NR	NR	NR	Patient preference (% patients rating) Dextromethor-phan=87.5% (Best), 6.25% (Worst) Placebo=0% (Best), 81.25% (Worst) p<0.001
	Ruhle, 1984[131]	Mean patient score (1-5) 8 hr after dose: Dextromethorphan =3.1 Placebo=2.9	Nocturnal number of coughs after three treatments: Dextromethor-phan=540 Placebo=689	NR	NR	NR	Incidence of side effects after three treatments: Dextromethor-phan=8 Placebo=2 p<0.05	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Placebo (continued)	Ruhle, 1984[131]	Mean patient score (1-5) 8 hr after dose: Glaucine=2.9 Placebo=2.9	Nocturnal number of coughs after three treatments: Glaucine=511 Placebo=689 p<0.05	NR	NR	NR	Incidence of side effects after three treatments: Glaucine=1 Placebo=2	NR
	Aversa, 1993[109]	NR	Reduction in number of coughs in the interval 8-10am on day four vs. day one: Moguisteine: 42% Placebo: 14% p=0.028	NR	NR	NR	NR	NR
	Ramsay, 2008[129]	Mean VAS score (1-5) at day 5: Dextromethorphan =1.39 Placebo=1.66 Difference=-0.26 (CI -0.99 to 0.46)	NR	NR	LCQ (physical): Dextromethorphan=43.9 Placebo=43.7 LCQ (psychological): Dextromethorphan=42.1 Placebo=42.1 LCQ (social): Dextromethorphan=23.6 Placebo=23.2	Mean tussigenic citric acid cough challenge test (C2) 1 hr post dose: Dextromethor-phan=3.04 Placebo=1.71 p<0.05	Mean VAS score (or sleep disturbance (1-5) at day 5: Dextromethor-phan=0.75 Placebo=0.75	NR
	Mukaida, 2011[127]	VAS score for cough intensity: Bakumondoto vs. Placebo, p=0.055, 0.387 in two treatment periods	VAS score for cough frequency: Bakumondoto vs. Placebo=0.007, 0.055 in two treatment periods	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Protussive (expectorants)	Wojcicki, 1975[142]	No. of patients with marked or moderate relief: Duopect=28/32 Glycerol=13/32 p<0.05	NR	NR	NR	NR	NR	NR
	Matts, 1977[126]	NR	NR	NR	NR	NR	NR	Patient preference for treatment: Diphenhydramine =36/49 patients Guaifenesin=13/49 patients
Bronchodilator vs. Bronchodilator	Wei, 2010[141]	Mean cough symptom score: Diprophylline=3.0 (SD 0.81) (baseline), 1.49 (SD 0.44) (4 wk) Methoxyphenamine=3.0 (SD 0.85) (baseline), 1.48 (SD 0.51) (4 wk)	No. of patients with cough resolution at 16 wk: Diprophylline=72.6% Methoxyphenamin=74.1%	NR	Mean LCQ: Diprophylline=14.27 (SD 3.16) (baseline), 5.48 (SD 3.58) (4 wk) Methoxyphen-amine=14.32 (SD 3.19) (baseline), 5.58 (SD 3.23) (4 wk)	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Corticosteroid vs. Placebo	Chaudhuri, 2004[113]	Change in VAS scale (0-10) after 14 d: Fluticasone compared with before and after placebo (difference of differences, 1.0; 95% CI, 0.4 to 1.5; P<0.001) Mean percentage change in VAS was 22.3% (95% CI, -3.5% to 48.2%)	NR	NR	NR	NR	NR	NR
	Ribeiro, 2007[93]	No. of patients with no cough after 2 wk: Beclomethasone=35/44 Placebo=4/20 p<0.05	No. of patients with resolution of cough after 2 wk: Beclomethasone=34/44 Placebo=3/20 p<0.05	NR	NR	NR	No. of patients with no sleep disturbance after 2 wk: Beclomethasone=42/44 Placebo=19/20	NR
Protussive (expectorants) vs. Placebo	Wojcicki, 1975[142]	No. of patients with marked or moderate relief: Glycerol=13/32 Placebo=3/32 p<0.05	NR	NR	NR	NR	NR	NR
	Parvez, 1996[128]	Median change in average cough intensity on day 14: Guaifenesin=-0.03 (range -0.22 to 0.19) Placebo=-0.03 (range -0.4 to 0.1)	Median change in 3-hr cough count on day 14: Guaifenesin=-27.5 (range -219 to 157) Placebo=-37 (range -155 to 350)	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Protussive (mucolytic) vs. Placebo	Jackson, 1984[122]	Patient-reported score 0-3: N-acetylcysteine=1.75 (SD 0.79) (baseline), 1.38 (SD 0.76) (1 mo), 1.3 (SD 0.85) (2 mo), 1.23 (SD 0.74) (3 mo) Placebo=1.98 (SD 0.77) (baseline), 1.48 (SD 0.81) (1 mo), 1.5 (SD 0.75) (2 mo), 1.5 (SD 0.83) (3 mo) P<0.01	NR	NR	NR	NR	NR	Physician-reported global assessment over 3 mo period: N-acetylcysteine=85% patients/change Placebo=68% patients/change p=0.063
	Guyatt, 1987[120]	Cough interfering with daily activities (1-7 scale): Ambroxol=4.67 (baseline), 4.18 (4 wk) Placebo=4.76 (baseline), 5.37 (4 wk) Net Benefit=-0.09 (CI -0.67 to 0.50)	NR	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Protussive (mucolytic) vs. Placebo (continued)	Dueholdm, 1992[118]	Intensity of coughing, median change from baseline at 16 wk: N-acetylcysteine=0.02 (CI -0.52 to 0.47) Placebo=-1.03 (CI -1.31 to 0.12) p<0.05	NR	NR	VAS score between 0-10 on well-being, median change from baseline at 16 wk: N-acetylcysteine=0.14 (CI -0.47 to 0.56) Placebo=-0.02 (CI -0.82 to 1.21)	NR	NR	Morning dyspnea, median change from baseline at 16 wk: N-acetylcysteine=0.48 (CI -0.03 to 1.13) Placebo=-0.01 (CI -0.29 to 0.31) Exercise dyspnea, median change from baseline at 16 wk: N-acetylcysteine=0.10 (CI -0.34 to 0.65) Placebo=-0.45 (CI -1.24 to 0.22)
	Parvez, 1996[128]	Median change in average cough intensity on day 14: Bromhexine=0.15 (SD 10.00) Placebo=-3.21 (SD 9.7)	Median change in 3-hr cough count on day 14: Bromhexine=-9.11 (SD 67.5) Placebo=-44 (SD 94.1)	NR	NR	NR	NR	NR

Table 9. Patient-centered outcomes data (continued)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Protussive (mucolytic) vs. Protussive (mucolytic)	Clarke, 1979[114]	NR	Mean number of coughs, 6 hr after inhalation: 2-mercapto-ethane sulphonate=99 (SD 154) hypertonic saline=91 (SD 116)	NR	NR	NR	NR	NR
Protussive (nonpharma-cological) vs. Protussive (nonpharma-cological)	van Hengstum, 1988[139]	NR	NR	NR	NR	NR	NR	Retention after therapy: Positive expiratory pressure=70 (SD 14) Forced expiration technique=46 (SD 15) p<0.02

CI = confidence interval; d = day(s); hr = hour(s); LCQ = Leicester Cough Questionnaire; mo = month(s); No. = Number; NR = not reported; NS = not statistically significant; SD = standard deviation; SEM = standard error of the mean; VAS = visual analog scale; wk = week(s)

[a]If p value is not listed, the comparison was not statistically significant ($p \geq 0.05$).

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 78 studies involving 5927 patients that evaluated instruments used to assess cough (Key Question [KQ] 1) and 48 studies involving 2923 patients that evaluate nonspecific (or symptomatic) therapies to treat patients with chronic cough (KQ 2). We hoped to evaluate the comparative effectiveness of these instruments and treatments both in adults and in children (< 14 years of age). The evidence—especially related to the effectiveness of nonpharmacological therapies and to children—was very limited.

KQ 1. Instruments Used To Assess Cough

Our findings suggest that selected cough-specific quality-of-life instruments are valid and reliable for assessing cough. The Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ, along with its predecessor, the Adverse Cough Outcome Survey [ACOS]), are the most widely studied cough-specific quality-of-life questionnaires in adults, with several studies showing fair to moderate correlation with other cough measurement tools such as cough frequency logs, tussigenic challenges, electronic recordings, or other quality-of-life questionnaires. The Parent Cough-specific Quality-of-Life questionnaire (PC-QOL) has been validated in the pediatric population and shows good internal consistency and strong correlation with other subjective and objective cough measurement tools. Other cough-specific quality-of-life questionnaires, such as the Chronic Cough Impact Questionnaire (CCIQ) and the Cough and Sputum Assessment Questionnaire (CASA-Q) show good internal consistency but have not been compared extensively with objective cough measures. Other disease-specific, health-related quality-of-life questionnaires may include questions about cough, but also assess noncough symptoms, and their focus on multiple symptoms leads them to be less valuable tools specifically for assessing cough.

Electronic recording devices correlate well with human cough counts. This suggests that recording devices are reliable for assessing cough frequency. Electronic recording devices, however, demonstrate variable and generally weak correlation with other cough measurement tools, and the validation studies of devices that recorded cough events for 24 hours or longer were validated against human cough counts for only a portion of the overall recording period. Furthermore, we did not identify studies that confirmed that recording devices and human counters identified exactly the same cough events. This may be because cough frequency is unidimensional, whereas the impact that cough may have on an individual's functional status, quality of life, or sense of wellbeing may depend on many other factors. Multidimensional quality-of-life assessments such as the LCQ, CQLQ, and other cough-specific instruments may therefore be more useful than simple cough frequency in assessing meaningful impact of cough.

Visual analog scales (VAS), on the other hand, can generally be considered to have face validity and are usually easy to administer, but we did not identify any formal validation studies of any cough-related VAS instrument. A variety of other cough scoring methods we identified used inconsistent scales and assessed diverse cough outcomes, making it difficult to draw comparisons. Such instruments, which include diaries and ordinal scales, show variable to poor correlation with other cough measurement tools when used as reference tests.

Tables 10–14 summarize the strength of evidence[29] for the available outcomes of validity, internal consistency, reliability, and responsiveness for the various instruments. We did not identify any studies evaluating the comparative therapeutic efficacy or patient outcome efficacy of these tools; therefore, the current evidence base is insufficient for us to draw any conclusions about these outcomes. Among the quality-of-life questionnaires evaluated, only the LCQ. CQLQ/ACOS, and the PC-QOL were represented by four or more published studies; as such, they are they only three questionnaires for which we generated strength of evidence tables.

Table 10. Summary of the strength of evidence for KQ 1—Leicester Cough Questionnaire (LCQ)—cough severity/QOL

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate
Validity (correlation with other measures of cough)					**Moderate SOE**
15 (1058)	Low	Consistent	Direct	Imprecise	Range of r=0.26–0.93
Internal consistency (Cronbach's alpha)					**High SOE**
4 (430)	Low	Consistent	Direct	Precise	Range of r=0.77–0.93
Reliability (repeatability)					**High SOE**
2 (256)	Low	Consistent	Direct	Precise	Range of r=0.86–0.92
Responsiveness					**Moderate SOE**
8 (659)	Moderate	Consistent	Direct	Imprecise	Range of ES=0.84–19.5

ES = effect size; KQ = Key Question; LCQ = Leicester Cough Questionnaire; r = correlation coefficient; SOE = strength of evidence

Table 11. Summary of the strength of evidence for KQ 1—Cough-specific Quality of Life Questionnaire (CQLQ) and Adverse Cough Outcome Survey (ACOS)—cough severity/QOL

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate
Validity (correlation with other measures of cough)					**Moderate SOE**
5 (336)	Low	Consistent	Direct	Imprecise	Range of r=0.24–0.56
Internal consistency (Cronbach's alpha)					**Insufficient SOE**
1 (184)	Low	Inconsistent	Direct	Imprecise	Range of r=0.63–0.92
Reliability (repeatability)					**Insufficient SOE**
1 (52)	Low	Inconsistent	Direct	Imprecise	Range of r=0.75–0.93
Responsiveness					**Moderate SOE**
7 (460)	Moderate	Consistent	Direct	Imprecise	Range of MID=10.6–21.9

ACOS = Adverse Cough Outcome Survey; CQLQ = Cough-specific Quality of Life Questionnaire; KQ = Key Question; MID = minimally important difference; NA = not applicable; r = correlation coefficient; SOE = strength of evidence

Table 12. Summary of the strength of evidence for KQ 1—Parent Cough-specific Quality-of-Life questionnaire (PC-QOL)—cough severity/QOL

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate
Validity (correlation with other measures of cough)					**Moderate SOE**
4 (593)	Moderate	Consistent	Direct	Imprecise	Range of r=0.01–0.70
Internal consistency (Cronbach's alpha)					**Moderate SOE**
3 (247)	Low	Consistent	Direct	Imprecise	Range of r=0.56–0.91
Reliability (repeatability)					**Insufficient SOE**
1 (43)	Low	Inconsistent	Direct	Imprecise	Range of r=0.40–0.51
Responsiveness					**Moderate SOE**
3 (247)	Moderate	Consistent	Direct	Imprecise	Range of ES=0.32–0.41

ES = effect size; KQ = Key Question; MID = minimally important difference; NA = not applicable; PC-QOL = Parent Cough-specific Quality-of-Life questionnaire

Table 13. Summary of the strength of evidence for KQ 1—electronic recording devices—cough frequency

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate
Validity (correlation with other measures of cough)					**High SOE**
17 (546)	Low	Consistent	Direct	Precise	Range of r=0.89–0.99
Internal consistency (Cronbach's alpha)					**Insufficient SOE**
0	NA	NA	NA	NA	NA
Reliability (repeatability)					**Moderate SOE**
5 (185)	Low	Consistent	Direct	Precise	Range of r=0.8–1.0
Responsiveness					**Insufficient SOE**
1 (67)	Low	Insufficient	Direct	Imprecise	Detected change with treatment

ES = effect size; KQ = Key Question; r = correlation coefficient; SOE = strength of evidence

Table 14. Summary of the strength of evidence for KQ 1—visual analog scales—cough severity/QOL

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate
Validity (correlation with other measures of cough)					**Insufficient SOE**
9 (410)	Low	Inconsistent	Indirect	Imprecise	No summary measure
Internal consistency (Cronbach's alpha)					**Insufficient SOE**
0	NA	NA	NA	NA	NA
Reliability (repeatability)					**Insufficient SOE**
0	NA	NA	NA	NA	NA
Responsiveness					**Insufficient SOE**
1 (21)	High	Insufficient	Insufficient	Insufficient	Sensitivity of 0.81–0.95 for detecting clinically important change

KQ = Key Question; NA = not applicable; SOE = strength of evidence

KQ 2. Nonspecific Therapies for Chronic Cough

Our review of studies of nonspecific therapies for chronic cough found that a wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough, including opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics. The opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise for managing the symptom of chronic cough. In particular, codeine (with dose response and placebo-controlled data) and dextromethorphan have reasonably good data for reducing cough frequency and severity. However, due to inconsistency and imprecision of results, and small numbers of head-to-head comparisons, the overall strength of evidence is insufficient to draw firm conclusions about the comparative effectiveness of these agents. There were few high-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough. Even when similar outcomes were assessed across studies, the instruments used were diverse and inconsistent, making comparison and interpretation difficult. Furthermore, tolerability was uncommonly reported; thus, although few adverse effects were identified in the included studies, these data likely reflect the observed underreporting rather than assurance about the safety of these agents. In addition, other outcomes of interest (e.g., number of emergency department visits) have been evaluated in relation to over-the-counter cold and cough products, and this type of downstream impact of nonspecific therapies was not assessed in our review.[145] Finally, the evidence exploring the effectiveness of treatments in patients with truly unexplained cough was minimal. We considered the vast majority of study populations to have unresponsive chronic cough.[146] Only three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough.[80,93,143] Interestingly, therapy in each of these studies was associated with a reduction in cough severity, suggesting that chronic unexplained cough can respond to nonspecific therapies aimed at the symptom and not the underlying etiology.

Controlled studies on nonpharmacological therapies for chronic cough were few. For all treatment categories, studies evaluating management of unidentified or refractory chronic cough in children were extremely limited. We identified two studies of one therapy (oral ketotifen)

which is not currently available in the United States.[130,138] A third study looked at an antibiotic, amoxicillin clavulanate, in children with more than 3 weeks of wet cough, but its applicability was limited in terms of its sample size and the description of the diagnostic evaluation of cough.

Tables 15–19 summarize the strength of evidence for the most commonly used classes of therapies and evaluated outcomes. Those comparisons for which evidence was based on mixed treatment meta-analyses were considered indirect. Evidence for other comparisons was too sparse to construct such summary tables.

Table 15. Summary of the strength of evidence for KQ 2—antitussive (anesthetic) versus antitussive (opiate)

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)
Cough severity					**Insufficient SOE**
1 (45)	RCTs/Low	Inconsistent	Direct	Imprecise	Imprecise results
Cough frequency					**Insufficient SOE**
2 (105)	RCTs/Low	Insufficient	Direct	Imprecise	Imprecise results
Adverse effects					**Insufficient SOE**
1 (60)	RCTs/Low	Insufficient	Direct	Imprecise	Imprecise results

CI = confidence interval; KQ = Key Question; RCTs = randomized controlled trials; SOE = strength of evidence

Table 16. Summary of the strength of evidence for KQ 2—antitussive (opiate) versus antitussive (other)

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)
Cough severity					**Insufficient SOE**
16 (958)	RCTs/Low	Inconsistent	Indirect	Imprecise	Opiates, dextromethorphan, and moguisteine had significant effect sizes vs. placebo in MTM (ranging from 0.54–0.63), but wide and overlapping CIs are too imprecise to (determine equivalence or noninferiority or) draw conclusions about relative effectiveness
Cough frequency					**Insufficient SOE**
8 (655)	RCTs/Low	Inconsistent	Indirect	Imprecise	Both codeine and dextromethorphan had significant ES vs. placebo in MTM, but wide and overlapping CIs are too imprecise to draw conclusions about relative effectiveness
Adverse effects					**Insufficient SOE**
5 (273)	RCTs/Low	Insufficient	Direct	Imprecise	No summary measure

CI = confidence interval; ES = effect size; KQ = Key Question; MTM = mixed treatment meta-analysis; RCTs = randomized controlled trials; SOE = strength of evidence

Table 17. Summary of the strength of evidence for KQ 2—protussive (mucolytic) versus antitussive (other)

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)
Cough severity					**Insufficient SOE**
4 (274)	RCTs/Low	Inconsistent	Indirect	Imprecise	Mucolytics had much smaller effect size vs. placebo, p=NS, in MTM compared with dextromethorphan
Cough frequency					**Insufficient SOE**
1 (24)	RCTs/Low	Inconsistent	Direct	Imprecise	No summary measure
Adverse effects					**Insufficient SOE**
0	NA	NA	NA	NA	NA

CI = confidence interval; KQ = Key Question; MTM = mixed treatment meta-analysis; NA = not applicable; NS = not statistically significant; RCTs = randomized controlled trials; SOE = strength of evidence

Table 18. Summary of the strength of evidence for KQ 2—protussive (mucolytic) versus antitussive (opiate)

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)
Cough severity					**Insufficient SOE**
4 (274)	RCTs/Low	Inconsistent	Indirect	Imprecise	Mucolytics had much smaller effect size vs. placebo, p=NS, in MTM compared with codeine
Cough frequency					**Insufficient SOE**
1 (24)	RCTs/Low	Inconsistent	Indirect	Imprecise	No summary measure
Adverse effects					**Insufficient SOE**
0	NA	NA	NA	NA	NA

CI = confidence interval; KQ = Key Question; NS = not statistically significant; MTM = mixed treatment meta-analysis; RCTs = randomized controlled trials; SOE = strength of evidence

Table 19. Summary of the strength of evidence for KQ 2—active therapies versus placebo

Comparison	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Cough Severity (11 Studies; 396 Subjects[b])					
Codeine/ opiates—Antitussive (opiates) vs. placebo	RCTs/Low	Consistent	Direct	Imprecise	**Low SOE** 0.63 (95% CI, 0.40 to 0.86; p<0.0001), from MTM
Dextromethor-phan—Antitussive (other) vs. placebo	RCTs/Low	Consistent	Direct	Imprecise	**Low SOE** 0.54 (95% CI, 0.27 to 0.80; p=0.0008), from MTM
Protussive (mucolytic) vs. placebo	RCTs/Low	Inconsistent	Direct	Imprecise	**Insufficient SOE** 0.14 (95% CI -0.20 to 0.49; p=0.384) from MTM
Moguisteine—Antitussive (other) vs. placebo	RCTs/Low	Consistent	Direct	Imprecise	**Low SOE** 0.62 (95% CI, 0.04 to 1.16, p=0.0366), from MTM
Cough Frequency (7 Studies; 700 Subjects[b])					
Codeine/ opiates—Antitussive (opiates) vs. placebo	RCTs/Low	Consistent	Direct	Imprecise	**Low SOE** 0.57 (95% CI, 0.36 to 0.91; p=0.0260), from MTM
Dextromethor-phan—Antitussive (other) vs. placebo	RCTs/Low	Consistent	Direct	Imprecise	**Low SOE** 0.40 (95% CI, 0.18 to 0.85; p=0.0248), from MTM
Protussive (mucolytic) vs. placebo	NA	NA	NA	NA	**Insufficient SOE** No summary measure
Moguisteine—Antitussive (other) vs. placebo	RCTs/Low	Inconsistent	Direct	Imprecise	**Insufficient SOE** 0.60 (95% CI, 0.31 to 1.17, p=0.1117), from MTM

Table 19. Summary of the strength of evidence for KQ 2—active therapies versus placebo (continued)

Comparison	Domains Pertaining to Strength of Evidence (SOE)				Strength of Evidence (SOE) Effect Estimate (95% CI)
	Risk of Bias	Consistency	Directness	Precision	
Adverse Effects					
Codeine/ opiates—Antitussive (opiates) vs. placebo	RCTs/Low	Inconsistent	Direct	Imprecise	**Insufficient SOE** Imprecise results
Dextromethor-phan—Antitussive (other) vs. placebo	NA	NA	NA	NA	**Insufficient SOE** No summary measure
Protussive (mucolytic) vs. placebo	NA	NA	NA	NA	**Insufficient SOE** No summary measure
Moguisteine—Antitussive (other) vs. placebo	NA	NA	NA	NA	**Insufficient SOE** No summary measure

CI = confidence interval; KQ = Key Question; NA = not applicable; MTM = mixed treatment meta-analysis; RCTs = randomized controlled trials; SOE = strength of evidence

These summary tables highlight that across outcomes and comparisons, although the included evidence was from RCTs with an overall low risk of bias, the findings were inconsistent; the evidence was indirect, being mostly based on placebo-controlled trials; and the findings, when available, were imprecise. There was insufficient evidence to support conclusions about comparative effectiveness of the interventions for any of our key outcomes.

Findings in Relationship to What Is Already Known

Our results are generally consistent with previous systematic reviews and clinical guidelines. A recent systematic review of cough measurement tools by Leconte et al.[147] analyzed some of the same data included in this CER. This previous review included 34 articles and also focused on electronic recording devices, quality-of-life questionnaires, and subjective cough measurements such as visual analog scales and cough diaries. In our review, we included additional studies that were excluded in the previous study, including studies that used human cough count as a reference test,[35,36,40,47,65,71,73-75,78,98,102] and studies that evaluated disease-specific, health-related quality-of-life questionnaires.[32] Our review summarized 60 studies involving 5,430 subjects and over 36 distinct instruments. The previous systematic review concluded that both quality-of-life scales and electronic recording devices were accurate and useful clinical tools. Our findings corroborate those from the previous systematic review, while providing additional, recently-published evidence that further supports the validity of the LCQ in adult populations. As in the previous review, we found no validation studies of visual analog scales and found enough variability in correlation of these scores with other cough measurement tools that no recommendation could be made regarding their usefulness as cough measurement tools. Our review included similar numbers of studies evaluating electronic recording devices

and subjective score scales, but included more studies evaluating quality-of-life questionnaires, specifically the LCQ, which allowed us to be more comprehensive in our evaluation of this widely used tool.

Previous reviews of the effectiveness of antitussive and protussive drugs for cough have been broader in scope, but have drawn conclusions similar to those reached in this review. A recent review of cough suppressant and protussive drug treatment in the American College of Chest Physicians (ACCP) 2006 clinical practice guideline on cough addressed acute as well as chronic cough;[146] our review identified a few more trials of codeine[116,125] and dextromethorphan,[125,129,131] as well as trials of other opiates,[80,132] glaucine[116,131] and benzonatate.[134,135] Recommendations in the ACCP guidelines for use of peripheral cough suppressants (levodropropizine and moguisteine, neither available in the United States) were based on reduced cough frequency relative to placebo; similarly, a recommendation of short-term use of central cough suppressants (codeine and dextromethorphan) in chronic bronchitis cited placebo-controlled studies. None of the few extant head-to-head comparisons were cited; neither were comparative effectiveness comparisons or recommendations in selecting between drug classes made. Another review from the same guideline evaluated nonpharmacological treatments, noting that most studies of these therapies were conducted exclusively in patients with cystic fibrosis.[148] The recommendations therefore focused exclusively on populations outside the scope of our review, namely on patients with respiratory muscle weakness, cystic fibrosis, and bronchiectasis.

Applicability

The effects of interventions, as determined in clinical trials, do not always translate well to usual practice, where patient characteristics, clinical training, diagnostic workup, and resources may differ importantly from trial conditions. In addition, the availability of interventions studied in our review may differ from those easily available to patients within the United States.

For our analysis of instruments for the assessment of cough (KQ 1), overall, the study instruments were generally adequately described. The main study reporting issue affecting applicability was the description of the study population. Sociodemographic and clinical characteristics of the study populations were often inadequately described. Of the studies with an adequate description of the study population, there was marked variability within and between studies in terms of the etiology and duration of cough symptoms, the age of patients, and severity of illness. It is reasonable to assume that the utility, performance, reliability, and validity of cough instruments may differ between children and adults, between acute and chronic cough conditions, and between underlying etiologies such as asthma, chronic bronchitis, acute rhinitis, lung cancer, and chronic refractory cough. More consistent reporting of patient characteristics such as age, underlying etiology, duration of symptoms and/or illness, overall medical comorbidity, and prior treatment would facilitate evaluations of various cough instruments in important subgroups. As far as geographical location of studies is concerned, 41 studies (53%) were conducted in Europe, with 32 of those conducted exclusively in the UK. Nineteen (24%) studies were conducted in the United States or Canada. Location of study was not, however, obviously related to design, patient, outcome, or analytic characteristics.

In terms of our evaluation of therapies for the treatment of unexplained or refractory chronic cough (KQ 2), by restricting inclusion to trials of patients with unexplained or refractory cough, we improved the applicability of our findings to this population but also decreased the availability of evidence that could be reviewed. Expanding our evidence to include patients with acute cough would have substantially increased the evidence base but greatly reduced the

applicability of the findings to the unexplained or refractory chronic cough population. We identified only 48 studies involving 2,923 patients (median number of patients per study=55). Few studies directly reported assembling patients fitting our intended population of idiopathic or refractory chronic cough. More often patients were selected from persons with chronic cough (of variable duration) with a variety of diseases associated with cough. While we tried to apply criteria to improve applicability (e.g., excluding cystic fibrosis and bronchiectasis), the studies we ultimately included contained more diversity than we intended. In particular, studies with mixed etiologies (including, e.g., patients with tuberculosis or lung cancer) and studies from different eras and geographic locations challenge the usefulness of data on treatment. The majority of studies took place in Europe, with 9 in the UK and 17 in other countries in Europe (total of 54%); only 9 (19%) took place within the United States or Canada. Location of study was not, however, obviously related to design, patient, outcome, or analytic characteristics.

We were only able to identify three studies of children eligible for inclusion in our review. Unfortunately, these studies have limited applicability to today's management of children with chronic cough. Two studies evaluated the same drug, oral ketotifen, which is not available in the United States and is used for children who likely had asthma in a manner inconsistent with current asthma management guidelines. The management of asthma has significantly changed since these studies were conducted (1989 and 1992), and today a greater emphasis is placed on the role of controller medicines (e.g., inhaled corticosteroids, leukotriene inhibitors) to reduce the chronic symptoms associated with poorly controlled asthma. In addition, it is unclear whether findings regarding ketotifen are generalizable to the other available medications in its class. A third study was a randomized, placebo-controlled trial of an antibiotic, amoxicillin clavulanate, in 50 children with more than 3 weeks of wet cough. Cough resolution was 48 percent in the treatment group and 16 percent in the placebo group (p=0.0016). This study was rated as good quality, although it had a small sample size and the description of diagnostic evaluation of cough was minimal. The strength of evidence based on these three studies regarding treatment of chronic cough in the pediatric population is insufficient.

For the studies focusing on the adult population, many of the drug treatment trials we identified included drugs that are not currently available in the United States (12 studies, 25%). While we excluded drugs that had been withdrawn from the U.S. market (e.g., for safety issues), we retained studies of drugs that were marketed elsewhere, in part because we believed that such studies would help with the assessment of the effect of a class of cough treatments. However, we believe that the within-class similarities were greater among opiate antitussives, compared with nonopiate antitussives or protussive mucolytic or protussive expectorant groupings. The applicability of the included studies was also reduced given the age of much of the evidence, and therefore of the corresponding interventions and underlying clinical management of the patients. Publication dates ranged from 1953 to 2012, with 32 (76%) of the articles being published before 2000. Given the changes in both available therapies and the diagnosis and treatment of underlying etiologies, more recent studies of contemporary therapies are needed.

Implications for Clinical and Policy Decisionmaking

The availability of strong evidence for validity of cough-related quality-of-life questionnaires is probably more important for future research than for clinical care. Despite some newer valid measures, evaluating the benefit from efficacy data in the clinical literature is based mostly on unvalidated symptom measurement tools for which the minimum clinically important benefit has not been well-defined. This deficiency in the literature complicates comparisons of efficacy and

evaluation of the net benefit of therapeutic alternatives; therefore, the further development, validation, and use of these measures would help with future evaluations of the comparative effectiveness of available therapies. Consensus amongst researchers in terms of a reference standard test would be helpful for filling existing evidence gaps and future research needs.

The relatively low strength of the evidence summarized in this CER related to treatment of chronic cough provides limited guidance to clinical or policy decisionmaking. Despite the clinical and economic burden of chronic cough, continued insufficient evidence suggests that little needs to be changed regarding recommendations for symptomatic treatment of chronic cough from the major clinical practice guideline for cough diagnosis and management (ACCP 2006[146]). Greater differentiation in guideline recommendations between patients with unexplained and refractory cough from known causes would not seem to be supportable. The subjective nature of cough symptoms, combined with uncertainty about benefits and low reporting of adverse events, makes determining the net benefit of treatment somewhat uncertain even for those symptomatic cough treatments in which relevant studies have been performed. The lack of well-controlled scientific studies in children prompted recommendations against use of codeine and dextromethorphan in children from the American Academy of Pediatrics,[149] as well as slightly broader recommendations against prescription cough suppressants and OTC cough-cold products by the ACCP. The U.S. Food and Drug Administration (FDA) issued a Public Health Advisory in January 2008 recommending against the use of over-the-counter cough-cold preparations in children under 2 years of age, citing poor data on efficacy in children as well as adverse event data from the FDA's Adverse Event Reporting database and recent data on the way these products have actually been used by parents and children.[150] This example illustrates how policymakers have dealt with low-quality evidence in children, concerns about the applicability of efficacy data from adults, and current data from adverse event reporting.

Similar challenges exist with applying data on short-term outcomes to longer term or frequent symptomatic treatment of chronic cough, and applying data from historical populations that may have undergone inadequate diagnostic evaluation to present-day patients. Although the current systematic review does not add much to aid clinical and policy decisionmaking, it does help identify numerous gaps in the evidence base and areas of needed future research.

Limitations of the Comparative Effectiveness Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include: (1) few studies exploring the clinical population of interest (unexplained or refractory chronic cough) and in specific patient subgroups of interest (e.g., children, women, immunocompromised patients); (2) variable definitions of chronic cough; (3) diverse etiologies of cough that might respond differently to different therapies; (4) incomplete reporting of patient characteristics, study design, or outcomes; (5) small sample sizes and short duration of followup; (6) lack of gold standard outcomes to assess efficacy and tolerability; and (7) inconsistent reporting of comparative statistical analyses.

In addition, most of the studies were comparatively old, and as such the evidence base suffers from age because of advances in clinical trial methodology, improved diagnostic evaluation of cough, and development of valid and reliable measures for cough and cough-specific quality of life. The relative lack of newer therapeutic trials in nonspecific or symptomatic treatment for chronic cough may reflect more focus on disease-specific treatment to the exclusion of nonspecific treatments. Specific to KQ 1, we found no studies evaluating the impact of cough

assessment instruments on therapeutic or patient outcome efficacy. In addition, many of the cough instrument validation studies were based on reference instruments not previously validated for cough, which may introduce measurement error and which decreases our confidence in the reported results. An analytical synthesis of the literature was not possible in the current study of cough instruments due to the heterogeneity of included study instruments and methods, but would be a useful goal for future research given additional evidence. For KQ 2, the variability in treatment class and specific drug comparisons, and the scarcity of studies that reported similar outcome measures, inhibited the quantitative synthesis of the evidence and limited our conclusions based on this evidence.

Our review methods also had limitations. Our study was limited to English-language publications. It was the opinion of the investigators and the Technical Expert Panel that the resources required to translate non-English articles were not justified. With this exclusion our search still returned over 15,000 citations. Unfortunately, although the literature on cough is quite large, much of it focuses on acute cough. In addition, much of the chronic cough literature relates to specific populations that were outside the scope of this CER: bronchiectasis and cystic fibrosis. In addition, even within patients with chronic cough, the target population of patients with unexplained chronic cough or refractory chronic cough with a known underlying etiology was difficult to identify. Few studies assembled populations consistent with these goals. Rarely was a thorough negative diagnostic evaluation performed to assemble a group with unexplained chronic cough; in the case of studies of patients with a known underlying etiology, seldom was previously tried therapy described well enough to determine whether patients were treatment-refractory. Many decisions regarding these criteria were resolved through investigator discussion. In general, we considered use of a symptomatic treatment in a population with a known underlying etiology to imply refractory cough unless patients were noted to be treatment-naïve; certain etiologies, however, were considered differently, for example, most studies of cough-variant asthma, a common cause of chronic cough in children, which is usually highly responsive to appropriate asthma management, were excluded.

It is possible that our a priori definition of chronic cough in childhood (i.e., persisting at least 4 weeks if < 14 years of age, or 8 weeks if 14 years or older) was too long and did not reflect care delivery. However, our decision to include studies that described their population as suffering with chronic cough regardless of time cut-off may have mitigated this problem.

Focusing on nonspecific or symptomatic treatments to the exclusion of treatments aimed at specific causes of chronic cough proved more complicated to implement than we had anticipated. Certain therapies that we classified as specific (e.g., antihistamines and decongestants for upper airway cough syndrome) are sometimes referred to as nonspecific.[151] Furthermore, some other specific treatments (e.g., corticosteroids for eosinophilic bronchitis, antibiotics for chronic bronchitis) were occasionally tested as nonspecific treatments in populations that did not meet diagnostic criteria for conditions for which the specific treatment would be appropriate.

Finally, we grouped antitussive and protussive drugs into subsets that sometimes included pharmacologically diverse agents (e.g., glaucine, moguisteine) or even separate drugs with certain similarities (e.g., codeine and dextromethorphan). A physiological classification such as that used by Bolser et al.[146] that classifies drugs as affecting mucociliary function, afferent limb of the cough reflex, and central mechanism for cough and efferent limb of the cough reflex, may be a better alternative; however, certain drugs that have pharmacological properties that span mechanisms still create uncertainty.

Research Gaps

Chronic cough is a common health problem that is associated with significant health complications and reduction in health-related quality of life. We found sufficient evidence to suggest that the LCQ and CQLQ (for adults) and the PC-QOL (for children) may be valid instruments for assessing severity/QOL of cough, and that electronic recording devices, in general, appear to be valid assessments of cough frequency compared with human cough counts. Unfortunately, however, the current evidence base is insufficient to provide conclusive findings related to the comparative effectiveness of available therapies for patients with unexplained or refractory chronic cough. There are, therefore, numerous areas of evidence gaps and areas for potential future research. We used the framework recommended by Robinson et al. to identify gaps in evidence and describe why these gaps exist.[152] This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies gaps as due to (a) insufficient or imprecise information, (b) biased information; (c) inconsistency or unknown consistency, and (d) not the right information. Results are as follows:

KQ 1—Instruments used to assess cough:

- Evidence establishing the responsiveness, validity, reliability, and consistency of available assessment instruments other than the LCQ and CQLQ, and building on available evidence for the LCQ and CQLQ instruments
- Additional validation or measurement studies focusing on the pediatric population in addition to the limited studies that report on the PC-QOL
- Development and validation of child/patient-completed, cough-specific quality-of-life instruments (as opposed to parent/proxy instruments such as the PC-QOL))
- Feasibility of cough assessment instruments in usual care (outside of RCTs or validation studies)
    - Insufficient evidence curently exists; could be explored through observational studies
- Uncertainty about the effects of patient self-reporting, parent reporting, or provider reporting in use of cough assessment tools
    - Insufficient evidence curently exists; could be explored through observational studies
- Incomplete evidence regarding the minimally important difference of cough frequency or severity/QOL instruments
- Impact of measurement tools on therapeutic efficacy or patient outcome efficacy

KQ 2—Nonspecific therapies for chronic cough:

- Comparative effectiveness of pharmacological therapies in the adult population
    - Current evidence is both imprecise and inconsistent. Additional comparative RCTs of contemporary and available agents are needed.
- Comparative effectiveness of pharmacological therapies in the pediatric population
    - Current evidence is insufficient and does not reflect available therapies. Comparative RCTs of contemporary and available agents specific to the pediatric population are needed.
- Comparative effectiveness of nonpharmacological therapies in both adult and pediatric populations

    - Current evidence is insufficient. Comparative RCTs of contemporary and available agents specific in both adult and pediatric populations are needed.
    - Additional RCTs or potentially patient-level meta-analyses of existing and future RCTs focusing on subpopulations of interest including women, pregnant women, patients with specific underlying etiologies, immunocompromised patients, and patients with a history of substance abuse
- Comparative effectiveness of available therapues in impacting health utilizationa and costs
    - Insufficient evidence curently exists; could be explored through observational studies
- Comparative effectiveness of available therapies in impacting cough severity, frequency, and quality of life
    - Current evidence is both imprecise and inconsistent. Additional comparative RCTs using standardized instruments are needed.

For KQ 1, the primary research gaps include a paucity of validation studies for the pediatric population across all cough instruments and the lack of studies that address the feasibility of adminstration of cough measurement tools in the clinical setting or the impact of cough instruments on therapeutic or patient outcome efficacy. A major limitation to research assessing cough is that there is no consensus gold (or reference) standard. As such, many of the instruments were validated by reference standards that may be insufficient or have not themselves been validated to measure cough. As a result, we suggest that future cough validation studies use a common reference standard such as a validated clinical change instrument or the LCQ or CQLQ in adult populations. Based on our strength of evidence findings, electronic recording devices demonstrated high strength of evidence as an assessment of cough frequency, and as such may be appropriate reference standards for future validity research; such devices are, however, impractical for use by clinicans in real-world clinical practice.

For KQ 2, existing research examining therapies for chronic cough has a number of limitations, including variable definitions of chronic cough, diverse etiologies of cough that might respond differently to different therapies, small sample sizes, lack of power analyses, short duration of followup, lack of gold standard outcomes to assess efficacy and tolerability, and inconsistent reporting of comparative statistical analyses. Several of these limitations (e.g., diverse etiologies, lack of gold standard outcomes) may prove difficult to address. Future research recommendations, however, include:

- Striving to employ commonly used definitions for chronic cough and report descriptive statistics on the duration of cough, as well as the etiology and pertinent comorbid conditions
- Explicitly stating whether the aim of therapy is to treat the symptom of chronic cough or an underlying etiology; this will help clinicians understand how the study results might generalize to their individual patients
- Using longer durations of followup (several weeks as opposed to a few hours or days)
- Using a combination of objective cough frequency and patient-oriented outcome measures to provide the most meaningful information regarding the efficacy and effectiveness of therapies.
- Assessing tolerability of therapies in order to improve comparisons among therapies.
- Given the low efficacy of a number of commonly used cough therapies, stronger research designs would be traditional (parallel-group) randomized controlled trials (RCTs) or

randomized crossover trials, and would include both an active comparator and a placebo. These studies should consider and report the sample size needed to detect differences in the primary outcome, and should use and report standard statistical techniques to examine for differences.

Over the past two decades there has been a marked increase in the medical literature on research of nonpharmacological interventions such as herbal remedies; dietary supplements; traditional approaches such as Ayurveda or traditional Chinese medicine; manual or energy-based interventions such as chiropractic and acupuncture; and mind-body approaches such as yoga, Tai Chi, and meditation, among others. This is especially true for clinical conditions that are characterized by symptoms such as low back pain, headache, fatigue, or gastrointestinal symptoms. Still, our systematic review of the literature identified only two studies of nonpharmacological interventions for chronic cough; one was published in 1988 and one in 2006, and neither involved complementary or alternative medical approaches that have recently garnered attention by patients, clinicians, researchers. Only one study included in our review involved such an approach.[127]

Specific to the evaluation of therapies for chronic cough in children, a future systematic review of studies of acute cough may be helpful. During the course of the review process, we observed more studies of acute than chronic cough in children, and we were only able to include three studies in our systematic review given our inclusion/exclusion criteria. A systematic review of the acute cough literature would be helpful in evaluating the comparative effectiveness of treatments for acute cough in children and might also provide some insight into the therapeutic options for chronic cough. It is likely, however, that our current limited findings reflect the general lack of high-quality evidence regarding medications in children.

Conclusions

Several instruments, including the LCQ, CQLQ, and the PC-QOL, show good internal consistency but variable correlation with other cough measurement tools. The lack of validated reference tests and the diverse number of instruments used among treatment evaluations also complicates comparisons across studies. We identified no evidence exploring the impact of cough assessment instruments on therapeutic efficacy or patient outcome efficacy.

A wide variety of pharmaceutical agents have been used to treat the symptom of chronic cough, including opioid, anesthetic, and nonopioid/nonanesthetic antitussives; expectorant and mucolytic protussives; antihistamines; antibiotics; inhaled corticosteroids; and inhaled anticholinergics. There were relatively few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough. The opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough compared with placebo, but there were insufficient data to draw conclusions between therapies. Data on nonpharmacological therapies for chronic cough are extremely limited, as are data on the management of unidentified or refractory chronic cough in children.

Our systematic review highlights the clear need for further studies in patient populations with unexplained or refractory chronic cough as determined by current diagnostic and empiric treatment recommendations. Further, it shows the need for more systematic design and reporting of these studies and assessment of patient-centered outcomes.

References

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. www.cdc.gov/nchs/ahcd.htm.
2. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-83S. PMID: 16428719.
3. Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):59S-62S. PMID: 16428693.
4. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis. 1981;123(4 Pt 1):413-7. PMID: 7224353.
5. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7. PMID: 2178528.
6. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371(9621):1364-74. PMID: 18424325.
7. Irwin RS, Curley FJ. The treatment of cough. A comprehensive review. Chest. 1991;99(6):1477-84. PMID: 2036833.
8. French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61. PMID: 9701100.
9. Holinger LD, Sanders AD. Chronic cough in infants and children: an update. Laryngoscope. 1991;101(6 Pt 1):596-605. PMID: 2041439.
10. Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. Ann Intern Med. 1993;119(10):977-83. PMID: 8214994.
11. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest. 1995;108(4):991-7. PMID: 7555175.
12. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med. 1996;156(9):997-1003. PMID: 8624180.
13. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S. PMID: 16428686.
14. Smyth RL. Research with children. Paediatric practice needs better evidence—gained in collaboration with parents and children. Br Med J. 2001;322(7299):1377-8. PMID: 11397728.
15. Sinaiko AR, Daniels SR. The use of short-acting nifedipine in children with hypertension: another example of the need for comprehensive drug testing in children. J Pediatr. 2001;139(1):7-9. PMID: 11445783.
16. Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. Arch Dis Child. 2002;86(3):170-5. PMID: 11861232.
17. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114(1):e85-90. PMID: 15231978.
18. Kelly LF. Pediatric cough and cold preparations. Pediatr Rev. 2004;25(4):115-23. PMID: 15060179.
19. Hestand HE, Teske DW. Diphenhydramine hydrochloride intoxication. J Pediatr. 1977;90(6):1017-8. PMID: 859051.

20. Irwin RS. Introduction to the diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):25S-7S. PMID: 16428688.

21. Molassiotis A, Bryan G, Caress A, et al. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. Respir Med. 2010;104(7):934-44. PMID: 20385478.

22. Pratter MR, Brightling CE, Boulet LP, et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):222S-31S. PMID: 16428715.

23. Finnish Medical Society Duodecim. Chronic cough in a child. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007. nowww.guideline.gov/content.aspx?id=12798.

24. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22(2):159-62. PMID: 19061964.

25. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318.

26. Agency for Healthcare Research and Quality. Methods Guide for Medical Test Reviews. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct.

27. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. PMID: 19621072.

28. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.

29. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63(5):513-23. PMID: 19595577.

30. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.

31. Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.

32. Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.

33. Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.

34. Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.

35. Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.

36. Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.

37. Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.

38. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.

39. Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.

40. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.

41. Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.

42. Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.

43. Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.

44. Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.

45. Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.

46. Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.

47. Dales RE, White J, Bhumgara C, et al. Parental reporting of childrens' coughing is biased. Eur J Epidemiol. 1997;13(5):541-5. PMID: 9258566.

48. De Vito Dabbs A, Hoffman LA, Dauber JH, et al. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. Prog Transplant. 2002;12(3):191-8; quiz 9-200. PMID: 12371045.

49. Decalmer SC, Webster D, Kelsall AA, et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.

50. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43. PMID: 17167006.

51. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax. 2000;55(12):1028-32. PMID: 11083888.

52. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.

53. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.

54. Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.

55. Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.

56. Field SK, Conley DP, Thawer AM, et al. Effect of the management of patients with chronic cough by pulmonologists and certified respiratory educators on quality of life: a randomized trial. Chest. 2009;136(4):1021-8. PMID: 19349387.

57. Fisman EZ, Shapira I, Motro M, et al. The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings. J Med. 2001;32(3-4):181-7. PMID: 11563816.

58. Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.

59. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.

60. French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.

61. Fuller P, Picciotto A, Davies M, et al. Cough and sleep in inner-city children. Eur Respir J. 1998;12(2):426-31. PMID: 9727796.

62. Hamutcu R, Francis J, Karakoc F, et al. Objective monitoring of cough in children with cystic fibrosis. Pediatr Pulmonol. 2002;34(5):331-5. PMID: 12357476.

63. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. Ear Nose Throat J. 2009;88(11):1213-7. PMID: 19924664.

64. Hoskyns EW, Thomson A, Decker E, et al. Effect of controlled release salbutamol on nocturnal cough in asthma. Arch Dis Child. 1991;66(10):1209-12. PMID: 1953004.

65. Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7(7):1246-53. PMID: 7925902.

66. Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.

67. Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest. 2002;121(4):1132-40. PMID: 11948043.

68. Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.

69. Kalpaklioglu AF, Kara T, Kurtipek E, et al. Evaluation and impact of chronic cough: comparison of specific vs generic quality-of-life questionnaires. Ann Allergy Asthma Immunol. 2005;94(5):581-5. PMID: 15945562.

70. Kelsall A, Decalmer S, McGuinness K, et al. Sex differences and predictors of objective cough frequency in chronic cough. Thorax. 2009;64(5):393-8. PMID: 19131447.

71. Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.

72. Kelsall A, Houghton LA, Jones H, et al. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569-75. PMID: 20864619.

73. Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4. PMID: 20565979.

74. Krahnke J, Gentile D, Angelini B, et al. Comparison of objective and subjective measurements of cough frequency in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2004;93(3):259-64. PMID: 15478386.

75. Krajnik M, Damps-Konstanska I, Gorska L, et al. A portable automatic cough analyser in the ambulatory assessment of cough. Biomed Eng Online. 2010;9:17. PMID: 20226089.

76. Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.

77. Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol. 2008;122(5):903-7. PMID: 18842290.

78. Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.

79. Monz BU, Sachs P, McDonald J, et al. Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. Respir Med. 2010;104(4):534-41. PMID: 19917525.

80. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.

81. Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31. PMID: 19196812.

82. Mwachari C, Nduba V, Nguti R, et al. Validation of a new clinical scoring system for acute bronchitis. Int J Tuberc Lung Dis. 2007;11(11):1253-9. PMID: 17958990.

83. Nandha D, Goodyer L, Woodruffe-Peacock C. Diary cards and the assessment of cough symptoms in community pharmacies. Pharm World Sci. 2000;22(1):17-20. PMID: 10815295.

84. Newcombe PA, Sheffield JK, Chang AB. Minimally important change in a Parent-Proxy Quality-of-Life questionnaire for pediatric chronic cough. Chest. 2011;139(3):576-80. PMID: 20947650.

85. Newcombe PA, Sheffield JK, Juniper EF, et al. Development of a parent-proxy quality-of-life chronic cough-specific questionnaire: clinical impact vs psychometric evaluations. Chest. 2008;133(2):386-95. PMID: 18252913.

86. Newcombe PA, Sheffield JK, Juniper EF, et al. Validation of a parent-proxy quality of life questionnaire for paediatric chronic cough (PC-QOL). Thorax. 2010;65(9):819-23. PMID: 20805179.

87. Nieto L, de Diego A, Perpina M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97(4):393-400. PMID: 12693800.

88. Novitsky YW, Zawacki JK, Irwin RS, et al. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc. 2002;16(4):567-71. PMID: 11972189.

89. O'Connell F, Thomas VE, Pride NB, et al. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994;150(2):374-80. PMID: 8049818.

90. Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.

91. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.

92. Raj AA, Pavord DI, Birring SS. Clinical cough IV: what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.

93. Ribeiro M, Pereira CA, Nery LE, et al. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. Ann Allergy Asthma Immunol. 2007;99(1):61-8. PMID: 17650832.

94. Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):225-34. PMID: 21083673.

95. Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.

96. Smith J, Owen E, Earis J, et al. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006;117(4):831-5. PMID: 16630941.

97. Smith JA, Owen EC, Jones AM, et al. Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis. Thorax. 2006;61(5):425-9. PMID: 16449266.

98. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.

99. Vernon M, Kline Leidy N, Nacson A, et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4(4):199-208. PMID: 20519373.

100. Woodcock A, McLeod RL, Sadeh J, et al. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung. 2010;188 Suppl 1:S47-52. PMID: 19937046.

101. Zihlif N, Paraskakis E, Lex C, et al. Correlation between cough frequency and airway inflammation in children with primary ciliary dyskinesia. Pediatr Pulmonol. 2005;39(6):551-7. PMID: 15806596.

102. Thomas JS, Lyons HA, Shepherd DA. D.A.T.A.—an advanced automated electronic cough counting system for the evaluation of antitussive agents. Curr Ther Res Clin Exp. 1978;23(1):66-77.

103. Woolf CR, Rosenberg A. Objective assessment of cough suppressants under clinical conditions using a tape recorder system. Thorax. 1964;19:125-30. PMID: 14128569.

104. Chang AB, Robertson CF, Van Asperen PP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest. 2012. PMID: 22459773.

105. Leconte S, Liistro G, Lebecque P, et al. The objective assessment of cough frequency: accuracy of the LR102 device. Cough. 2011;7(1):11. PMID: 22132691.

106. Berkhof FF, Boom LN, ten Hertog NE, et al. The validity and precision of the leicester cough questionnaire in COPD patients with chronic cough. Health and Quality of Life Outcomes. 2012;10.

107. Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.

108. Aliprandi P, Castelli C, Bernorio S, et al. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41. PMID: 15553659.

109. Aversa C, Cazzola M, Clini V, et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. Drugs Exp Clin Res. 1993;19(6):273-9. PMID: 8013271.

110. Cass LJ, Frederik WS. Evaluation of a new antitussive agent. N Engl J Med. 1953;249(4):132-6. PMID: 13063699.

111. Cass LJ, Frederik WS, Andosca JB. Quantitative comparison of dextromethorphan hydrobromide and codeine. Am J Med Sci. 1954;227(3):291-6. PMID: 13138597.

112. Cass LJ, Frederik WS. Quantitative comparison of cough-suppressing effects of romilar and other antitussives. J Lab Clin Med. 1956;48(6):879-85. PMID: 13376983.

113. Chaudhuri R, McMahon AD, Thomson LJ, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. J Allergy Clin Immunol. 2004;113(6):1063-70. PMID: 15208586.

114. Clarke SW, Lopez-Vidriero MT, Pavia D, et al. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol. 1979;7(1):39-44. PMID: 104724.

115. Del Donno M, Aversa C, Corsico R, et al. Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough. Drug Investigation. 1994;7(2):93-100.

116. Dierckx P, Leblanc G, Decoster A, et al. Double-blind study of glaucine in chronic cough. Int J Clin Pharmacol Ther Toxicol. 1981;19(9):396-9. PMID: 7028646.

117. Diwan J, Dhand R, Jindal SK, et al. A comparative randomized double-blind clinical trial of isoaminile citrate and chlophedianol hydrochloride as antitussive agents. Int J Clin Pharmacol Ther Toxicol. 1982;20(8):373-5. PMID: 6749701.

118. Dueholm M, Nielsen C, Thorshauge H, et al. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. Respir Med. 1992;86(2):89-92. PMID: 1615189.

119. Gastpar H, Criscuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. Curr Med Res Opin. 1984;9(1):21-7. PMID: 6373156.

120. Guyatt GH, Townsend M, Kazim F, et al. A controlled trial of ambroxol in chronic bronchitis. Chest. 1987;92(4):618-20. PMID: 3308343.

121. Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respir Med. 1992;86(5):425-9. PMID: 1462022.

122. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. J Int Med Res. 1984;12(3):198-206. PMID: 6376210.

123. Lilienfield LS, Rose JC, Princiotto JV. Antitussive activity of diphenhydramine in chronic cough. Clin Pharmacol Ther. 1976;19(4):421-5. PMID: 773581.

124. Luporini G, Barni S, Marchi E, et al. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. Eur Respir J. 1998;12(1):97-101. PMID: 9701421.

125. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. J Int Med Res. 1983;11(2):92-100. PMID: 6852361.

126. Matts SG. A trial of Lotussin and linctus diphenhydramine in patients wth an irritant cough. J Int Med Res. 1977;5(6):470-2. PMID: 338397.

127. Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. Phytomedicine. 2011;18(8-9):625-9. PMID: 21177084.

128. Parvez L, Vaidya M, Sakhardande A, et al. Evaluation of antitussive agents in man. Pulm Pharmacol. 1996;9(5-6):299-308. PMID: 9232667.

129. Ramsay J, Wright C, Thompson R, et al. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br J Clin Pharmacol. 2008;65(5):737-41. PMID: 18279476.

130. Reid JJ. Double-blind trial of ketotifen in childhood chronic cough and wheeze. Immunol Allergy Pract. 1989;11(4):143-50.

131. Ruhle KH, Criscuolo D, Dieterich HA, et al. Objective evaluation of dextromethorphan and glaucine as antitussive agents. Br J Clin Pharmacol. 1984;17(5):521-4. PMID: 6375709.

132. Sabot G, Bagnato A, Frigerio G. Controlled evaluation of the antitussive activity of viminol p-hydroxybenzoate. Int J Clin Pharmacol Biopharm. 1977;15(4):181-3. PMID: 323163.

133. Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. Clin Pharmacol Ther. 1971;12(3):449-55. PMID: 4936034.

134. Simon SW. A comparative study of two new non-narcotic antitussive drugs. Ohio Med. 1957;53(12):1426-7. PMID: 13493953.

135. Simon SW. Symptomatic treatment of asthmatic bronchitis. J Am Geriatr Soc. 1960;8:107-11. PMID: 14446944.

136. Tanaka S, Hirata K, Kurihara N, et al. Effect of loratadine, an H1 antihistamine, on induced cough in non-asthmatic patients with chronic cough. Thorax. 1996;51(8):810-4. PMID: 8795669.

137. Vakil BJ, Mehta AJ, Prajapat KD. Trial of pipazethate as an antitussive. Clin Pharmacol Ther. 1966;7(4):515-9. PMID: 5328471.

138. van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health. 1992;28(6):442-6. PMID: 1466940.

139. van Hengstum M, Festen J, Beurskens C, et al. The effect of positive expiratory pressure versus forced expiration technique on tracheobronchial clearance in chronic bronchitics. Scand J Gastroenterol Suppl. 1988;143:114-8. PMID: 3291088.

140. Vertigan AE, Theodoros DG, Gibson PG, et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065-9. PMID: 16844725.

141. Wei W, Yu L, Wang Y, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology. 2010;15(5):830-6. PMID: 20546197.

142. Wojcicki J, Samochowiec L, Szwed G, et al. The use of Duopect as expectorant–antitussive agent. Arch Immunol Ther Exp (Warsz). 1975;23(1):135-42. PMID: 1090275.

143. Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010;65(12):1107-10. PMID: 20965928.

144. Marchant J, Masters IB, Champion A, et al. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax. 2012. PMID: 22628120.

145. Kuehn BM. Withdrawal of infant cold medicines decreases ED visits by half, CDC finds. JAMA. 2010;304(24):2686. PMID: 21177501.

146. Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):238S-49S. PMID: 16428717.

147. Leconte S, Ferrant D, Dory V, et al. Validated methods of cough assessment: a systematic review of the literature. Respiration. 2011;81(2):161-74. PMID: 21079381.

148. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):250S-9S. PMID: 16428718.

149. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics. 1997;99(6):918-20. PMID: 9190557.

150. U.S. Food and Drug Administration. Public Health Advisory: FDA Recommends that Over-the-Counter (OTC) Cough and Cold Products not be used for Infants and Children under 2 Years of Age. Date of release 1/2008. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051137.htm.

151. Chang AB. Therapy for cough: where does it fall short? Expert Rev Respir Med. 2011;5(4):503-13. PMID: 21859270.

152. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Acronyms and Abbreviations

ABSS	Acute Bronchitis Severity Score
ACCP	American College of Chest Physicians
ACE	angiotensin-converting enzyme
ACOS	Adverse Cough Outcome Survey
AHRQ	Agency for Healthcare Research and Quality
BPC	bronchoprovocation challenge
CASA-Q	Cough and Sputum Assessment Questionnaire
CBSAS	Chronic Bronchitis Symptoms Assessment Scale
CCIQ	Chronic Cough Impact Questionnaire
CDSR	Cochrane Database of Systematic Reviews
CER	comparative effectiveness review
CES-D	Center for Epidemiologic Studies Depression Scale
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CQLQ	Cough-specific Quality of Life Questionnaire
CSD	Cough Severity Diary
EuroQol	European Quality of Life questionnaire
FDA	U.S. Food and Drug Administration
FET	forced expiratory technique
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GRC	Global Rating of Change
HADS	Hospital Anxiety and Depression Scale
HRQOL	health-related quality of life
KQ	Key Question
LCCQ	Lung Cancer Cough Questionnaire
LCQ	Leicester Cough Questionnaire
MSFSD	Modified Symptom Frequency/Symptom Distress scale
NAEB	nonasthmatic eosinophilic bronchitis
NPV	negative predictive value
PCQ	Pediatric Cough Questionnaire
PC-QOL	Parent Cough-specific Quality-of-Life questionnaire
PEP	positive expiratory pressure
PICOTS	population, interventions, comparators, outcomes, timing of outcomes, and settings
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QLTP	Questionnaire for Lung Transplant Patients
QUADAS-2	QUality Assessment tool for Diagnostic Accuracy Studies-2
RCT	randomized controlled trial
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SGRQ	St. George's Respiratory Questionnaire
SIP	Sickness Impact Profile

TEP	Technical Expert Panel
UACS	upper airway cough syndrome
VCD	verbal category descriptive scale
WHO	World Health Organization

Appendix A. Exact Search Strings

PubMed® search strategy (June 4, 2012)

KQ 1: Instruments used to assess cough

Set #	Terms
#1	cough[MeSH] OR cough[tiab]
#2	cough/diagnosis[mesh] OR pain measurement[mesh] OR severity of illness index[mesh] OR questionnaires[mesh] OR rate[tiab] OR rating[tiab] OR rates[tiab] OR rated[tiab] OR assess*[tiab] OR evaluat*[tiab] OR scale[tiab] OR scales[tiab] monitor*[tiab] OR frequency[tiab] OR frequent[tiab] OR score[tiab] OR scores[tiab] OR "visual analog"[tiab] OR "visual analogue"[tiab]OR severity[tiab] OR sound[tiab] OR sounds[tiab] OR register*[tiab] OR measure*[tiab] OR count*[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR instrument[tiab] OR instruments[tiab]OR (tussigenic[tiab] AND challenge[tiab]) OR "exhaled nitric oxide"[tiab] OR tools[tiab] OR tool[tiab] OR lcq[tiab] OR cqlq[tiab] OR lcm[tiab] OR lifeshirt[tiab] OR lr102[tiab] OR lr100[tiab]
#3	#1 AND #2
#4	#3 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mesh] NOT humans[mesh])
#5	#4, Limit English

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])
#2	Cough[mesh] OR cough[ti]
#3	#1 AND #2
#4	#3, Limit to English

Embase® search strategy (June 4, 2012)

Platform: Embase.com

KQ 1: Instruments used to assess cough

Set #	Terms
#1	coughing'/de OR cough:ti OR cough:ab
#2	'coughing'/dm_di OR 'pain assessment'/exp OR 'questionnaire'/exp OR 'instrument'/exp OR "severity of illness":ti OR "severity of illness":ab OR rate:ti OR rate:ab OR rating:ti OR rating:ab OR rates:ti OR rates:ab OR rated:ti OR rated:ab OR assess*:ti OR assess*:ab OR evaluat*:ti OR evaluat*:ab OR scale:ti OR scale:ab OR scales:ti OR scales:ab OR monitor*:ti OR monitor*:ab OR frequency:ti OR frequency:ab OR frequent:ti OR frequent:ab OR score:ti OR score:ab OR scores:ti OR scores:ab OR "visual analog":ti OR "visual analog":ab OR "visual analogue":ti OR "visual analogue":ab OR severity:ti OR severity:ab OR sound:ti OR sound:ab OR sounds:ti OR sounds:ab OR register*:ti OR register*:ab OR measure*:ti OR measure*:ab OR count*:ti OR count*:ab OR questionnaire:ti OR questionnaire:ab OR questionnaires:ti OR questionnaires:ab OR instrument:ti OR instrument:ab OR instruments:ti OR instruments:ab OR (tussigenic:ti AND challenge:ti) OR (tussigenic:ab AND challenge:ab) OR "exhaled nitric oxide":ti OR "exhaled nitric oxide":ab OR tools:ti OR tools:ab OR tool:ti OR tool:ab OR lcq:ti OR lcq:ab OR cqlq:ti OR cqlq:ab OR lcm:ti OR lcm:ab OR lifeshirt:ti OR lifeshirt:ab OR lr102:ti OR lr102:ab OR lr100:ti OR lr100:ab
#3	#1 AND #2
#4	#3 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#4 AND ([embase]/lim NOT [medline]/lim)
#6	#5, Limits: Human, English

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	'coughing'/de OR cough:ti
#2	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR cross NEAR/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer* OR 'clinical study'/exp OR “clinical trial”:ti OR “clinical trial”:ab OR “clinical trials”:ti OR “clinical trials”:ab OR 'evaluation'/exp OR “evaluation study”:ti OR “evaluation study”:ti OR “evaluation studies”:ti OR “evaluation studies”:ab OR “intervention study”:ti OR “intervention study”:ab OR “intervention studies”:ti OR “intervention studies”:ab OR “case control”:ti OR “case control”:ab OR 'cohort analysis'/exp OR cohort:ti OR cohort:ab OR longitudinal*:ti OR longitudinal*:ab OR prospective:ti OR prospective:ab OR prospectively:ti OR prospectively:ab OR retrospective:ti OR retrospective:ab OR 'follow up'/exp OR “follow up”:ti OR “follow up”:ab OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR “comparative study”:ti OR “comparative study”:ab OR “comparative studies”:ti OR “comparative studies”:ab OR 'evidence based medicine'/exp OR “systematic review”:ti OR “systematic review”:ab OR “meta-analysis”:ti OR “meta-analysis”:ab OR “meta-analyses”:ti OR “meta-analyses”:ab
#3	#1 AND #2
#4	#3 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#4 AND [embase]/lim NOT [medline]/lim
#6	#5, Limits: Human, English

Cochrane search strategy (June 4, 2012)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ 1: Instruments used to assess cough

Set #	Terms
#1	MeSH descriptor Cough explode all trees OR cough:ti,ab
#2	MeSH descriptor Cough explode all trees with qualifier: DI OR MeSH descriptor Pain Measurement explode all trees OR MeSH descriptor Severity of Illness Index explode all trees OR MeSH descriptor Questionnaires explode all trees OR rate:ti,ab OR rating:ti,ab OR rates:ti,ab OR rated:ti,ab OR assess*:ti,ab OR evaluat*:ti,ab OR scale:ti,ab OR scales:ti,ab OR monitor*:ti,ab OR frequency:ti,ab OR frequent:ti,ab OR score:ti,ab OR scores:ti,ab OR “visual analog”:ti,ab OR “visual analogue”:ti,ab OR severity:ti,ab OR sound:ti,ab OR sounds:ti,ab OR register*:ti,ab OR measure*:ti,ab OR count*:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR instrument:ti,ab OR instruments:ti,ab OR (tussigenic:ti,ab AND challenge:ti,ab) OR "exhaled nitric oxide":ti,ab OR tools:ti,ab OR tool:ti,ab OR lcq:ti,ab OR cqlq:ti,ab OR lcm:ti,ab OR lifeshirt:ti,ab OR lr102:ti,ab OR lr100:ti,ab
#3	#1 AND #2
#4	#3 in Clinical Trials, Systematic Reviews

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	MeSH descriptor Cough explode all trees OR cough:ti
#2	Limit #1 to Clinical Trials, Systematic Reviews

Grey Literature Searches

ClinicalTrials.gov (July 18, 2012)

Terms: Cough (as condition)

WHO: International Clinical Trials Registry Platform Search Portal (July 18, 2012)

Terms: Cough (in title)

ProQuest COS Conference Papers Index (January 18, 2012)

Set #	Terms
#1	cough[su] OR cough[all]
#2	Limit to 2010-

Appendix B. Data Abstraction Elements

I. Study Characteristics

- Study Dates
- Study Sites
- Geographical Location (Select all that apply)
- Funding Source (Select all that apply)
- Setting (Select all that apply)
- Enrollment Approach (Select all that apply)
    - Consecutive patients
    - Convenience sample (not explicitly consecutive)
    - Not reported/unclear
    - Other – Describe
- Inclusion Criteria: Copy/paste inclusion criteria as reported in the article.
- Exclusion Criteria: Copy/paste exclusion criteria as reported in the article.
- Applicability of Key Questions (Indicate whether the article is applicable to each key question below.)
    - Which populations are included in this study? (Select all that apply)
        - Adults and adolescents (≥14 yrs) with cough
        - Children (<14 years of age) with cough
        - Adults and adolescents (≥14 yrs) with chronic cough
        - Children (<14 years of age) with chronic cough
    - Underlying etiology of cough symptoms in the study population:
        - If Unexplained/idiopathic (Select all that apply)
            - Absence of signs of symptoms of an etiology (NEG S/SX) – Describe
            - Negative diagnostic evaluation (NEG DX) – Describe diagnostic evaluation
            - Lack of response to trial of empiric therapy (NEG EMP TX) – Describe empiric therapy trial and response
            - Other – Describe
        - If Unresponsive/Refractory/Intractable: (Select all that apply)
            - If Known/suspected etiology (Select an answer)
                - Chronic obstructive pulmonary disease (COPD)
                - GERD
                - Asthma
                - Cough-variant asthma
                - UACS (postnasal drip, allergic rhinitis)
                - Interstitial lung disease (sarcoid, etc.)
                - Chronic bronchitis
                - Bronchiectasis, Cystic Fibrosis
                - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc.)
                - Unexplained
                - Other – Describe

        - Positive signs/symptoms – Describe
        - Positive diagnostic evaluation – Describe
        - Other – Describe
        - Specific therapy trial(s) and response – Describe
    - Chronicity – Describe minimum duration required (in weeks)
    - Key Question 1 - In adults and adolescents (≥14 years of age) and children (<14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough? (Yes/No, This is not a KQ1 article)
    - Key Question 2 - In adults and adolescents (≥14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?
        - In patients with unexplained chronic cough
        - In patients with refractory cough with a known underlying etiology (Yes/No, This is not a KQ2 article)
- Study Enrollment/Study Completion
    - Assessed for eligibility (N)
    - Eligible (N)
    - Randomized (N)
    - Completed follow-up (N)
    - Included in primary outcome analysis (N)
- Comments

II. KQ 1 Instruments

- Author
- Year
- Total N
- Was there a longitudinal component to this study (Yes/No)
- Patient Population – Describe
- Instruments – Include each instrument only once, either under Index or Reference Tests.
    - Index Test/Instrument being evaluated
        - Cough count (by a human)
        - Electronic cough recorder (Sound or pressure)
        - Video cough recorder
        - Tussigenic challenge
        - Cough diaries
        - Score
        - VAS
        - Global Rating Scale
        - If Questionnaire(s) – Questionnaire(s) Name
            - Leicester Cough Questionnaire
            - Cough-specific QoL
            - Chronic Bronchitis Symptoms Assessment Scale
            - Chronic Cough Impact Questionnaire
            - Lung Cancer Cough Questionnaire

                - Cough & Sputum Assessment
                - (A predictive questionnaire)
                - Punum Ladders
                - Adverse Cough Outcome Survey
                - Pediatric Cough Questionnaire
                - Hull Airway Reflux Questionnaire
                - Parent Prox QoL Questionnaire (PC-QoL)
                - Disabkids Questionnaire subscale
                - Cough Severity Diary
            - Other – Describe
    - Reference Test/Comparator
        - Cough count (by a human)
        - Electronic cough recorder (Sound or pressure)
        - Video cough recorder
        - Tussigenic challenge
        - Cough diaries
        - Score
        - VAS
        - Global Rating Scale
        - If Questionnaire(s) – Questionnaire(s) Name
            - Leicester Cough Questionnaire
            - Cough-specific QoL
            - Chronic Bronchitis Symptoms Assessment Scale
            - Chronic Cough Impact Questionnaire
            - Lung Cancer Cough Questionnaire
            - Cough & Sputum Assessment
            - (A predictive questionnaire)
            - Punum Ladders
            - Adverse Cough Outcome Survey
            - Pediatric Cough Questionnaire
            - Hull Airway Reflux Questionnaire
            - Parent Prox QoL Questionnaire (PC-QoL)
            - Disabkids Questionnaire subscale
            - Cough Severity Diary
        - Other – Describe
- Results – Specify what is being compared along with results
- Comments

III. KQ 1 Quality Assessment

- QUADAS-2 Tool for Quality Assessment of Studies of Diagnostic Accuracy
- Rate each risk of bias item listed below as “Yes,” “No,” or “Unclear.” “Yes” indicates low risk of bias, and “No” indicates high risk of bias. After considering each of the quality items, give the study an overall rating of “High risk of bias,” “Low risk of bias,” or “Unclear.” Detailed instructions for each item are provided below. A user's guide

explaining each question and how to score your responses is available in the QUADAS-2 article here: www.bris.ac.uk/quadas/quadas-2/
    - Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)
    - Describe the index test and how it was conducted and interpreted
    - Describe the reference standard and how it was conducted and interpreted
    - Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard
    - Was a consecutive or random sample of patients enrolled?
    - Were the index test results interpreted without knowledge of the results of the reference standard?
    - Is the reference standard likely to correctly classify the target condition?
    - Was there an appropriate interval between index test(s) and reference standard?
    - Was a case-control design avoided?
    - If a threshold was used, was it pre-specified?
    - Were the reference standard results interpreted without knowledge of the results of the index test?
    - Did all patients receive a reference standard?
    - Did the study avoid inappropriate exclusions?
    - Did all patients receive the same reference standard?
    - Were all patients included in the analysis?
    - Could the selection of patients have introduced bias?
    - Could the conduct or interpretation of the index test have introduced bias?
    - Could the reference standard, its conduct, or its interpretation have introduced bias?
    - Could the patient flow have introduced bias?
    - Are there concerns that the included patients do not match the review question?
    - Are there concerns that the index test, its conduct, or interpretation differ from the review question?
    - Are there concerns that the target condition as defined by the reference standard does not match the review question?
- Overall study rating
    - Risk of bias is judged as “low”, “high”, or “unclear”. If the answers to all questions in a domain are “yes”, then risk of bias can be judged low. If any question is answered “no”, potential bias exists and previously determined guidelines must be used to make a judgment. The “unclear” category should only be used when insufficient data are reported to permit a judgment.
- Comments

IV. KQ 1 Applicability Assessment

- Population (P)
    - Study population poorly described
    - Inadequate diagnostic evaluation of cough
- Intervention (I)

    - Instrument not well described
    - Highly selected instrument or level of training/proficiency not widely available
    - Doses not reflected in current practice
    - Monitoring practices/visit frequency not in typical practice (e.g., frequent contact, incentives)
    - Older versions of an intervention no longer in common use
    - Cointerventions likely to modify effectiveness of treatment
- Comparator (C)
    - Inadequate comparison therapy
    - Comparator(s) not well described
    - Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
- Outcomes (O)
    - Composite outcomes that mix outcomes of different significance
    - Uses lab assessment such as tussigenic challenge as main outcome
    - Short-term or surrogate outcomes
- Setting (S)
    - Conducted outside of the US and practices not well described or widely divergent relative to US practices
    - Not widely accessible technology
- Comments

V. KQ 2 All Study Arms

- Study type
    - RCT
    - Cohort
    - Crossover
- Common Co-interventions – List common co-interventions across all arms
- Placebo or Control – Treatment Type
    - Placebo
    - No treatment control
    - If Usual care control
        - Is the planned usual care identical for the intervention arm(s) and the comparator arm?
    - Other – Describe
    - Not applicable
- Active Treatment Arm 1 – Treatment Type
    - Pharmacologic Antitussive
        - Anesthetics (e.g., benzonatate)
        - Opiates (e.g., codeine, hydrocodone)
        - Other (e.g., Dextromethorphan) – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Antitussive

        - Foods (e.g., honey, tea, lemon, liquor)
        - Psychological (e.g., cognitive behavioral therapy)
        - Alternative (e.g., acupuncture, tai chi, yoga, meditation)
        - Multidimensional (e.g., speech therapy)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Pharmacologic Protussive
        - Expectorants (e.g., guaifenesin)
        - Mucolytic or mucus modifying (e.g., acetylcysteine, dornase alfa inhaled)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Protussive
        - Physical
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Not applicable
- Active Treatment Arm 2 – Treatment Type
    - Pharmacologic Antitussive
        - Anesthetics (e.g., benzonatate)
        - Opiates (e.g., codeine, hydrocodone)
        - Other (e.g., Dextromethorphan) – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Antitussive
        - Foods (e.g., honey, tea, lemon, liquor)
        - Psychological (e.g., cognitive behavioral therapy)
        - Alternative (e.g., acupuncture, tai chi, yoga, meditation)
        - Multidimensional (e.g., speech therapy)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Pharmacologic Protussive
        - Expectorants (e.g., guaifenesin)

        - Mucolytic or mucus modifying (e.g., acetylcysteine, dornase alfa inhaled)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Protussive
        - Physical
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Not applicable
- Comments

VI. KQ 2 Baseline Characteristics

- Number of Subjects
    - Total
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs
            - Adults 18+
            - Adults ≥ 65 yrs
            - Other age category – Specify age category used
    - Active Treatment Arm 1 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs

- Adults 18+
- Adults ≥ 65 yrs
- Other age category – Specify age category used

- Active Treatment Arm 2 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
  - Gender N
    - Total
    - Female
    - Male
  - Age N
    - Infants <6 mo
    - Children 6mo - 2yrs
    - Children 3-6 yrs
    - Children 7-13 yrs
    - Adults/Adolescents 14-64 yrs
    - Adults 18+
    - Adults ≥ 65 yrs
    - Other age category – Specify age category used
- Placebo or Control – Choose one (Placebo/No treatment control/Usual treatment control/Other)
  - Gender N
    - Total
    - Female
    - Male
  - Age N
    - Infants <6 mo
    - Children 6mo - 2yrs
    - Children 3-6 yrs
    - Children 7-13 yrs
    - Adults/Adolescents 14-64 yrs
    - Adults 18+
    - Adults ≥ 65 yrs
    - Other age category – Specify age category used

- Total Population
  - Age in Years
    - Total
      - Mean
      - Variability – Fill in which type
      - Median
      - Min
      - Max
    - Active Treatment Arm 1 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)

        - Mean
        - Variability – Fill in which type
        - Median
        - Min
        - Max
    - Active Treatment Arm 2 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
        - Mean
        - Variability – Fill in which type
        - Median
        - Min
        - Max
    - Placebo or Control – Choose one (Placebo/No treatment control/Usual treatment control/Other)
        - Mean
        - Variability – Fill in which type
        - Median
        - Min
        - Max
- Ethnicity
    - Total
        - Hispanic or Latino
        - Not Hispanic or Latino
    - Treatment Arm 1
        - Hispanic or Latino
        - Not Hispanic or Latino
    - Treatment Arm 2
        - Hispanic or Latino
        - Not Hispanic or Latino
    - Placebo or Control
        - Hispanic or Latino
        - Not Hispanic or Latino
- Race
    - Total
        - Black/African American
        - American Indian or Alaska Native
        - Asian
        - Native Hawaiian or other Pacific Islander
        - White
        - Multiracial
        - Other – Describe
    - Treatment Arm 1
        - Black/African American

                - American Indian or Alaska Native
                - Asian
                - Native Hawaiian or other Pacific Islander
                - White
                - Multiracial
                - Other – Describe
            - Treatment Arm 2
                - Black/African American
                - American Indian or Alaska Native
                - Asian
                - Native Hawaiian or other Pacific Islander
                - White
                - Multiracial
                - Other – Describe
            - Placebo or Control
                - Black/African American
                - American Indian or Alaska Native
                - Asian
                - Native Hawaiian or other Pacific Islander
                - White
                - Multiracial
                - Other – Describe
- Baseline Characteristics
    - Baseline Characteristics
        - Total
            - Cough severity measure #1 – Describe
                - Mean
                - Median
                - SD
            - Cough severity measure #2 – Describe
                - Mean
                - Median
                - SD
            - Cough severity measure #3 – Describe
                - Mean
                - Median
                - SD
            - Cough frequency – Describe
                - Mean
                - Median
                - SD
            - Cough duration – Describe
                - Mean
                - Median
                - SD

- FEV1 – Describe
    - Mean
    - Median
    - SD
- Tussigenic Challenge #1 – Describe
    - Mean
    - Median
    - SD
- Tussigenic Challenge #2 – Describe
    - Mean
    - Median
    - SD
- Bronchoprovocation challenge – Describe
    - Mean
    - Median
    - SD

- Treatment Arm 1
    - Cough severity measure #1 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe

        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Treatment Arm 2
    - Cough severity measure #1 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe
        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Placebo or Control
    - Cough severity measure #1 – Describe

        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe
        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Patient Group Imbalance (Yes/No/Unclear)
- Causes of Chronic Cough
    - Unexplained – If so, describe and provide numbers in table below
    - Known etiology
        - Total
            - Chronic obstructive pulmonary disease (COPD)
                - N
                - %
            - GERD
                - N
                - %

    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N
        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %
    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Treatment Arm 1
    - Chronic obstructive pulmonary disease (COPD)
        - N
        - %
    - GERD
        - N
        - %
    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N

        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %
    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Treatment Arm 2
    - Chronic obstructive pulmonary disease (COPD)
        - N
        - %
    - GERD
        - N
        - %
    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N
        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %

    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Placebo or Control
    - Chronic obstructive pulmonary disease (COPD)
        - N
        - %
    - GERD
        - N
        - %
    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N
        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %
    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Comments

VII. KQ 2 Quality Assessment

- Study Type
  - If RCT
    - Was the assignment randomized? (Yes/No/Unclear)
    - Was the allocation to study groups, (and interventions) adequately concealed? (Yes/No/Unclear)
  - If Cohort
    - Any attempt to balance the allocation between the groups? (Yes/No/Unclear)
    - Were the criteria applied equally to all groups? (Yes/No/Unclear)
    - Was the selection of the comparison group appropriate? (Yes/No/Unclear)
    - Does the design or analysis control account for important confounding and modifying variables? (Yes/No/Unclear)
    - In cohort studies, is the length of follow-up the same between the groups? (Yes/No/Unclear)
    - Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Other – Describe
- All study types
  - Are baseline characteristics similar between groups? If not, did the analysis control for differences? (Yes/No/Unclear)
  - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Unclear)
  - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
  - Did variation from the study protocol compromise the conclusions of the study?
  - Was there a high rate of differential or overall attrition? (Yes/No/Unclear)
  - Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up? (Yes/No/Unclear)
  - Is the analysis conducted on an intention-to-treat (ITT) basis? (Yes/No/Unclear)
  - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
  - Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Were incomplete/missing outcome data adequately reported and the data managed by an accepted method? (Yes/No/Unclear)
  - Was the primary outcome pre-specified? Are all pre-specified outcomes reported? (Yes/No/Unclear)
  - Was there a substantive conflict of interest which posed a substantive, important threat to validity of the results? (Yes/No/Unclear)
- Overall study rating

- Please assign each study an overall quality rating of "Good," "Fair," or "Poor" based on the following definitions. "Fair" is the initial assumption for cohort studies, unless there is significant evidence to prove that it could be categorized as "Good".
- Quality Rating
    - Good
    - Fair
    - Poor
        - If "Fair" or "Poor," provide rationale for decision.

VIII. KQ 2 Applicability Assessment

- Population (P)
    - Study population poorly described
    - Inadequate diagnostic evaluation of cough
- Intervention (I)
    - Intervention not well described
    - Highly selected intervention team or level of training/proficiency not widely available
    - Doses not reflected in current practice
    - Monitoring practices/visit frequency not in typical practice (e.g., frequent contact, incentives)
    - Older versions of an intervention no longer in common use
    - Cointerventions likely to modify effectiveness of treatment
- Comparator (C)
    - Inadequate comparison therapy
    - Comparator(s) not well described
    - Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
- Outcomes (O)
    - Composite outcomes that mix outcomes of different significance
    - Uses lab assessment such as tussigenic challenge as main outcome
    - Short-term or surrogate outcomes
- Setting (S)
    - Conducted outside of the US and practices not well described or widely divergent relative to US practices
    - Not widely accessible technology
- Comments

Appendix C. Included Studies

Aliprandi P, Castelli C, Bernorio S, et al. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41. PMID: 15553659.

Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.

Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.

Aversa C, Cazzola M, Clini V, et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. Drugs Exp Clin Res. 1993;19(6):273-9. PMID: 8013271.

Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.

Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.

Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.

Berkhof FF, Boom LN ten Hertog NE, et al. The validity of the Leicester Cough Questionnaire in COPD patients with chronic cough. Health Qual Life Outcomes. 2012 Jan 9;10:4. PMID: 22230731.

Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.

Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.

Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.

Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.

Cass LJ, Frederik WS. Quantitative comparison of cough-suppressing effects of romilar and other antitussives. J Lab Clin Med. 1956;48(6):879-85. PMID: 13376983.

Cass LJ, Frederick WS, and Andosca JB. Quantitative comparison of dextromethorphan hydrobromide and codeine. American Journal of the Medical Sciences. 1954;227(3):291-6. PMID: 13138597.

Cass LJ and Frederik WS. Evaluation of a new antitussive agent. New England Journal of Medicine 1953;249(4):132-6. PMID: 13063699.

Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.

Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.

Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.

Chang AB, Robertson CF, Van Asperen PP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest 2012; Epub ahead of print. PMID: 22459773.

Chaudhuri R, McMahon AD, Thomson LJ, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. J Allergy Clin Immunol 2004;113(6):1063-70. PMID: 15208586.

Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.

Clarke SW, Lopez-Vidriero MT, Pavia D, et al. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol. 1979;7(1):39-44. PMID: 104724.

Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.

Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.

Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.

Dales RE, White J, Bhumgara C, et al. Parental reporting of childrens' coughing is biased. Eur J Epidemiol. 1997;13(5):541-5. PMID: 9258566.

De Vito Dabbs A, Hoffman LA, Dauber JH, et al. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. Prog Transplant. 2002;12(3):191-8; quiz 9-200. PMID: 12371045.

Decalmer SC, Webster D, Kelsall AA, et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.

Del Donno M, Aversa C, Corsico R, et al. Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough. Drug Investig. 1994;7(2):93-100.

Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43. PMID: 17167006.

Dierckx P, Leblanc G, Decoster A, et al. Double-blind study of glaucine in chronic cough. Int J Clin Pharmacol Ther Toxicol. 1981;19(9):396-9. PMID: 7028646.

Diwan J, Dhand R, Jindal SK, et al. A comparative randomized double-blind clinical trial of isoaminile citrate and chlophedianol hydrochloride as antitussive agents. Int J Clin Pharmacol Ther Toxicol. 1982;20(8):373-5. PMID: 6749701.

Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.

Doherty MJ, Mister R, Pearson MG, et al. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax 2000;55(12):1028-32. PMID: 11083888.

Dueholm M, Nielsen C, Thorshauge H, et al. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. Respir Med. 1992;86(2):89-92. PMID: 1615189.

Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.

Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.

Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.

Field SK, Conley DP, Thawer AM, et al. Effect of the management of patients with chronic cough by pulmonologists and certified respiratory educators on quality of life: a randomized trial. Chest 2009;136(4):1021-8. PMID: 19349387.

Fisman EZ, Shapira I, Motro M, et al. The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings. J Med. 2001;32(3-4):181-7. PMID: 11563816.

Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.

Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.

French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61. PMID: 9701100.

French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.

Fuller P, Picciotto A, Davis M, et al. Cough and sleep in inner-city children. Eur Respir J 1998;12(2):426-31. PMID: 9727796.

Gastpar H, Criscuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. Curr Med Res Opin. 1984;9(1):21-7. PMID: 6373156.

Guyatt GH, Townsend M, Kazim F, et al. A controlled trial of ambroxol in chronic bronchitis. Chest. 1987;92(4):618-20. PMID: 3308343.

Hamutcu R, Francis J, Karakoc F, et al. Objective monitoring of cough in children with cystic fibrosis. Pediatr Pulmonol. 2002;34(5):331-5. PMID: 12357476.

Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. Ear Nose Throat J. 2009;88(11):1213-7. PMID: 19924664.

Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respir Med. 1992;86(5):425-9. PMID: 1462022.

Hoskyns EW, Thomson A, Decker E, et al. Effect of controlled release salbutamol on nocturnal cough in asthma. Arch Dis Child. 1991;66(10):1209-12. PMID: 1953004.

Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7(7):1246-53. PMID: 7925902.

Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.

Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total near-total elimination of esophageal acid. Chest 2002;121(4):1132-40. PMID: 11948043.

Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. J Int Med Res. 1984;12(3):198-206. PMID: 6376210.

Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.

Kalpaklioglu AF, Kara T, Kurtipek E, et al. Evaluation and impact of chronic cough: comparison of specific vs generic quality-of-life questionnaires. Ann Allergy Asthma Immunol. 2005;94(5):581-5. PMID: 15945562.

Kelsall A, Decalmer S, McGuiness K, et al. Dex differences and predictors of objective cough frequency in chronic cough. Thorax 2009;64(5):393-8. PMID: 19131447.

Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.

Kelsall A, Houghton LA, Jones H, et al. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569-75. PMID: 20864619.

Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4. PMID: 20565979.

Krahnke J, Gentile D, Angelini B, et al. Comparison of objective and subjective measurements of cough frequency in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2004;93(3):259-64. PMID: 15478386.

Krajnik M, Damps-Konstanska I, Gorska L, et al. A portable automatic cough analyser in the ambulatory assessment of cough. Biomed Eng Online. 2010;9:17. PMID: 20226089.

Leconte S, Liistro G, Lebecque P, et al. The objective assessment of cough frequency: accuracy of the LR102 device. Cough 2011;7(1):11. PMID: 22132691.

Lilienfield LS, Rose JC, Princiotto JV. Antitussive activity of diphenhydramine in chronic cough. Clin Pharmacol Ther. 1976;19(4):421-5. PMID: 773581.

Luporini G, Barni S, Marchi E, et al. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. Eur Respir J. 1998;12(1):97-101. PMID: 9701421.

Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.

Marchant J, Masters IB, Champion A, et al. Randomised controlled trial of amoxicillin clavulanate in children with chroni wet cough. Thorax 2012;67(8):689-93. PMID: 22628120.

Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol. 2008;122(5):903-7. PMID: 18842290.

Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.

Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. J Int Med Res. 1983;11(2):92-100. PMID: 6852361.

Matts SG. A trial of Lotussin and linctus diphenhydramine in patients wth an irritant cough. J Int Med Res. 1977;5(6):470-2. PMID: 338397.

Monz BU, Sachs P, McDonald J, et al. Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. Respir Med. 2010;104(4):534-41. PMID: 19917525.

Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.

Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. Phytomedicine. 2011;18(8-9):625-9. PMID: 21177084.

Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31. PMID: 19196812.

Mwachari C, Nduba V, Nguti R, et al. Validation of a new clinical scoring system for acute bronchitis. Int J Tuberc Lung Dis. 2007;11(11):1253-9. PMID: 17958990.

Nandha D, Goodyer L, Woodruffe-Peacock C. Diary cards and the assessment of cough symptoms in community pharmacies. Pharm World Sci. 2000;22(1):17-20. PMID: 10815295.

Newcombe PA, Sheffield JK, Chang AB. Minimally important change in a Parent-Proxy Quality-of-Life questionnaire for pediatric chronic cough. Chest. 2011;139(3):576-80. PMID: 20947650.

Newcombe PA, Sheffield JK, Juniper EF, et al. Development of a parent-proxy quality-of-life chronic cough-specific questionnaire: clinical impact vs psychometric evaluations. Chest. 2008;133(2):386-95. PMID: 18252913.

Newcombe PA, Sheffield JK, Juniper EF, et al. Validation of a parent-proxy quality of life questionnaire for paediatric chronic cough (PC-QOL). Thorax. 2010;65(9):819-23. PMID: 20805179.

Nieto L, de Diego A, Perpina M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97(4):393-400. PMID: 12693800.

Novitsky YW, Zawacki JK, Irwin RS, et al. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc 2002;16(4):567-71. PMID: 11972189.

O'Connell F, Thomas VE, Pride NB, et al. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994;150(2):374-80. PMID: 8049818.

Parvez L, Vaidya M, Sakhardande A, et al. Evaluation of antitussive agents in man. Pulm Pharmacol. 1996;9(5-6):299-308. PMID: 9232667.

Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.

Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.

Raj AA, Pavord DI, Birring SS. Clinical cough IV: what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.

Ramsay J, Wright C, Thompson R, et al. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br J Clin Pharmacol. 2008;65(5):737-41. PMID: 18279476.

Reid JJ. Double-blind trial of ketotifen in childhood chronic cough and wheeze. Immunol Allergy Pract. 1989;11(4):143-50.

Ribeiro M, Pereira CA, Nery LE, et al. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. Ann Allergy Asthma Immunol. 2007;99(1):61-8. PMID: 17650832.

Ruhle KH, Criscuolo D, Dieterich HA, et al. Objective evaluation of dextromethorphan and glaucine as antitussive agents. Br J Clin Pharmacol. 1984;17(5):521-4. PMID: 6375709.

Sabot G, Bagnato A, Frigerio G. Controlled evaluation of the antitussive activity of viminol p-hydroxybenzoate. Int J Clin Pharmacol Biopharm. 1977;15(4):181-3. PMID: 323163.

Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. Clin Pharmacol Ther. 1971;12(3):449-55. PMID: 4936034.

Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. Aliment Pharmacol Ther 2011;33(2):225-34. PMID: 21083673.

Simon SW. A comparative study of two new non-narcotic antitussive drugs. Ohio Med. 1957;53(12):1426-7. PMID: 13493953.

Simon SW. Symptomatic treatment of asthmatic bronchitis. J Am Geriatr Soc. 1960;8:107-11. PMID: 14446944.

Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.

Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.

Smith J, Owen E, Earis J, et al. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol 2006;117(4):831-5. PMID: 16630941.

Smith JA, Owen EC, Jones, AM, et al. Objective measurement of cough during pulmonary esacerbations in adults with cystic fibrosis. Thorax 2006;61(5):425-9. PMID: 16449266.

Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.

Tanaka S, Hirata K, Kurihara N, et al. Effect of loratadine, an H1 antihistamine, on induced cough in non-asthmatic patients with chronic cough. Thorax. 1996;51(8):810-4. PMID: 8795669.

Thomas JS, Lyons HA, Shepherd DA. D.A.T.A.—an advanced automated electronic cough counting system for the evaluation of antitussive agents. Curr Ther Res Clin Exp. 1978;23(1):66-77.

Vakil BJ, Mehta AJ, Prajapat KD. Trial of pipazethate as an antitussive. Clin Pharmacol Ther. 1966;7(4):515-9. PMID: 5328471.

van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health. 1992;28(6):442-6. PMID: 1466940.

van Hengstum M, Festen J, Beurskens C, et al. The effect of positive expiratory pressure versus forced expiration technique on tracheobronchial clearance in chronic bronchitics. Scand J Gastroenterol Suppl. 1988;143:114-8. PMID: 3291088.

Vernon M, Kline Leidy N, Nacson A, et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4(4):199-208. PMID: 20519373.

Vertigan AE, Theodoros DG, Gibson PG, et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065-9. PMID: 16844725.

Wei W, Yu L, Wang Y, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology. 2010;15(5):830-6. PMID: 20546197.

Wojcicki J, Samochowiec L, Szwed G, et al. The use of Duopect as expectorant–antitussive agent. Arch Immunol Ther Exp (Warsz). 1975;23(1):135-42. PMID: 1090275.

Woodcock A, McLeod RL, Sadeh J, et al. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung 2010;188(Suppl 1):S47-52. PMID: 19937046.

Woolf CR and Rosenberg A. Objective assessment of cough suppressants under clinical conditions using a tape recorder system. Thorax 1964;19:125-30. PMID: 14128569.

Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010;65(12):1107-10. PMID: 20965928.

Zihlif N, Paraskakis E, Lex C, et al. Correlation between cough frequency and airway inflammation in children with primary ciliary dyslinesia. Pediatr Pulmonol 2005;39(6):551-7. PMID: 15806596.

Appendix D. Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Full text not available

Abramson MJ, Schattner RL, Holton C, et al. Spirometry and regular follow-up do not improve outcomes in children or adolescents with asthma. Respirology 2012;17:50.

Agondi R, Kalil J, and Giavina-Bianchi P. Gastroesophageal reflux in patients with chronic cough. Journal of Allergy and Clinical Immunology 2012;129(2):AB9.

Albloushi A, Simpson S, Stick S, et al. Feasibility and safety of mannitol challenge in pre-school children using forced oscilations. Respirology 2012;17:4.

Boom L. Vaessen D, Uil S, et al. The effects of montelukast in patients with chronic cough and bronchial hyperreactivity. Chest 2011;140(4).

Cheng CL, Kao YHY, and Lin SJ. Safety and cough and cold medicines in children in Taiwan. Pharmacoepidemiology and Drug Safety 2011;20:S318-319.

Dockry RJ, Sunger K, Marsden P, et al. Investigating patterns in 24 hours of coughing. Thorax 2011;66:A65.

Kerwin E, Tashkin DP, Matiz-Bueno CE, et al. Clinical efficacy and safety of combined mometasone furoate and formoterol in patients with moderate to very severe chronic obstructive pulmonary disease (COPD). Journal of Allergy and Clinical Immunology 2012;129(2):AB201.

Khalid S, Dockry R, Holt K, et al. Cough responses to tussive agents in health and disease. Thorax 2011;66:A64.

Kurasirikul S, Vichyanond P, Piboonpocanun O, et al. Efficacy of gentamicin nasal irrigation in chronic rhinosinusitis in children. Journal of Allergy and Clinical Immunology 2012;129(2):AB44.

Lake C, Briffa P, Munoz P, et al. Documentation of cough provoked during a mannitol challenge using acoustic respiratory monitoring compared to video surveillance monitoring. Repriology 2012;17:1.

Lee KK, Matos S, Evans DH, et al. Predictors of 24-H cough frequency in acute cough. Thorax 2011;66:A64.

Li Y, Wang H. 100 Cases of children cough and gasp treated by fire needling. Chinese Journal of Acupuncture and Moxibustion. 1991;4(2):117-118.

Maesen F, Smeets J, Hoogslag MA. Azipranone (RU 20.201), a new cough suppressant. A clinical trial using objective and subjective parameters. Tijdschrift voor Geneesmiddelenonderzoek. 1983;8(7):1941-1944.

Perrem LM and O'Neill MB. Can questionnaire completion, by parents, obviate the need for outpatient assessments of their children with respiratory diseases? Irish Journal of Medical Science 2011;180:S452.

Quittner A, Marciel K, Kimberg C. et al. Content validity of a disease-specific patient-reported outcome for bronchiectasis. Chest 2011;140(4).

Saini G, McKeever T, Johnson S, et al. Thalidomide as treatment for IPF associated cough. Thorax 2011;66:A103.

Smith SM, MacAuslan J, Goldhor R, et al. Using acoustic analysis of coughs to identify respiratory infections in the emergency department. Academic Emergency Medicine 2012;19:S302.

Spector S, Tan R, and Lee R. Cough vs wheezing during methacholine challenge. Chest 2011;140(4).

Usta Guc B, Asilsoy S and Durmaz C. Bronchial hyperactivity in children with chronic cough. Allergy: European Journal of Allergy and Clinical Immunology 2011;66:199.

Usta Guc B, Asilsoy S, and Durmaz C. Bronchial hyperactivity in patients with rhinitis who consulted due to chronic cough. Allergy: European Journal of Allergy and Clinical Immunology 2011;66:199.

Vertigan A, and Gibson P. Development of a brief speech pathology intervention for chronic refractory cough. Pulmonary Pharmacology and Therapeutics 2011;24(3):e5.

Willis C, Robertson CF, Van Asperen PP, et al. A multi-centre study on chronic cough: burden and etiologies based on a standardized management pathway. Respirology 2012;17:79.

Zanasi A, Lanata L, De Danieli G, et al. Cough incidence, impact on sleep, and antitussive treatment in the pediatric population. Chest 2011;140(4).

Zhang Y. The values of fractional exhaled nitric oxide in the diagnosis and treatment of chronic cough. Respirology 2011;16:213.

Non-English language

Adamko DJ, Majaesic CM, Skappak C, et al. A pilot on the treatment of gastroesophageal reflux-related cough in infants. Zhongguo Dang Dai Er Ke Za Zhi 2012;14(5):321-7.

Carrasquer A, Targarona EM, Mannello F, et al. Laparoscopic fundoplication results in the treatment of the non-gastrointestinal symptoms of gastroesophageal reflux. Cir Esp 2012;90(4):238-42.

Ghaffari J, Saffar M, Salehifar E, et el. Anti-cough effects of tramadol in patients with pertussis. Journal of Mazaridaran University of Medical Sciences 2011;21(84):106-111.

Ghodrati S, Hormati A, Mousavi NN, et al. Comparison of FEV1 and PEF values in cough variant asthma during methacholine challenge test. Journal of Zanjan University of Medical Sciences and Health Services 2011;19(77):3.

Ghodrati S, Mousavinasab SN, Pezeshki B, et al. Prevalence of cough variant asthma in patients with chronic cough attending to Vali-e Asr hospital of Zanjan, Iran, 2009. Journal of Zanjan University of Medical Sciences and Health Services. 2011;19(76).

Kardos P, Gebhardt T. Chronic persistent cough (CPH) in the medical practice: Diagnostics and treatment of 329 patients in 2 years. Pneumologie. 1996;50(6):437-441.

Pacheco A, Faro V, Cobeta I, et al. Chronic cough with limited response to treatment and incidence of gastroesophageal reflux. Archivos de Bronconeumologia 2012;48(6):197-201.

Zhang YM, Lin JT. The values of fractional exhaled nitric oxide for the diagnosis and treatment response evaluation of chronic cough. Respirology. 2011;16:219.

Study population is not human

Chakraborty D, Shah B. Antimicrobial, anti-oxidative and anti-hemolytic activity of Piper betel leaf extracts. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(SUPPL. 3):192-199.

Harsanyi K, Tardos L, Feher I, et al. Pharmacologic, clinico-pharmacologic and clinical effects of Libexin. Boll Chim Farm. 1973;112(10):691-9. PMID: 4782264.

Schneider CR, Everett AW, Geelhoed E, et al. Provision of primary care to patients with chronic cough in the community pharmacy setting. Ann Pharmacother. 2011;45(3):402-8. PMID: 21325099.

Not an evaluation study (KQ 1), RCT (KQ1 or KQ2), cohort study (KQ1 or KQ2)

Agrawal M. OTC cold, cough and allergy products: more choice or more confusion? J Hosp Mark. 1999;13(1):79-86. PMID: 10623197.

Allan GM, Korownyk C, Kolber M. Do cough suppressants or honey help pediatric cough? Can Fam Physician. 2011;57(4):435. PMID: 21490355.

Altman KW, Irwin RS. Cough: a new frontier in otolaryngology. Otolaryngol Head Neck Surg. 2011;144(3):348-52. PMID: 21493194.

Amdekar YK. Cough and asthma. Indian J Pediatr. 2001;68 Suppl 2:S20-5. PMID: 11411373.

Anderson-James S, Marchant Julie M, O'Grady K-A,

et al. Inhaled corticosteroids for sub-acute cough in children. 2010;(12)#008888.

Anonymous. Cough medications in children. Drug Ther Bull. 1999;37(3):19-21. PMID: 10563059.

Anonymous. Cough. Stud Anc Med. 2009;38:225-82. PMID: 20481150.

Anonymous. Cough medication evaluation. JAMA. 1966;197(7):581-2. PMID: 5952817.

Anonymous. Cough suppressants ineffective for children. Journal of Family Practice. 2004;53(10):770-772.

Anonymous. Prolonged cough and chronic cough. Respirology. 2006;11(Suppl 4):S141-S142.

Anonymous. Prolonged and chronic cough. Respirology. 2006;11(Suppl 4):S160-S174.

Anonymous. Evaluation of cough. Respirology. 2006;11(Suppl 4):S143-S148.

Anonymous. Acute cough. Respirology. 2006;11(Suppl 4):S152-S159.

Anonymous. Cough in specific populations (paediatric patients, elderly patients and patients with underlying disease). Respirology. 2006;11(Suppl 4):S175-S186.

Axelsson I. Honey, not dextromethorphan, was better than no treatment for nocturnal cough in children with upper respiratory infections: Commentary. Evidence-Based Medicine. 2008;13(4):106.

Bailey EJ, Chang AB, Thomas D. In children with prolonged cough, does treatment with antibiotics have a better effect on cough resolution than no treatment? Part A: Evidence-based answer and summary. Paediatrics and Child Health. 2008;13(6):512-513.

Banner AS. Cough: physiology, evaluation, and treatment. Lung. 1986;164(2):79-92. PMID: 3084882.

Barraclough K. Diagnosis in general practice: Chronic cough in adults. BMJ. 2009;338(7705):1267.

Belvisi MG, Hele DJ. Cough: Citric acid and nerves. Drug Discovery Today: Disease Models. 2006;3(3):237-241.

Berman BA. Habit cough in adolescent children. Ann Allergy. 1966;24(1):43-6. PMID: 5902120.

Betti JL, Mebere Yemefa'a SR. An ethnobotanical study of medicinal plants used in the Kalamaloue National Park, Cameroon. Journal of Medicinal Plant Research. 2011;5(8):1447-1458.

Bickerman HA, Rodgers JM. Principles of measurement of cough depressing effect. Eur J Respir Dis Suppl. 1980;110:93-100. PMID: 7011831.

Birring SS. New concepts in the management of chronic cough. Pulm Pharmacol Ther. 2011;24(3):334-8. PMID: 21255671.

Birring SS, Passant C, Patel RB, et al. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. Eur Respir J. 2004;23(2):199-201. PMID: 14979491.

Bjornsdottir I, Einarson TR, Gudmundsson LS, et al. Efficacy of diphenhydramine against cough in humans: a review. Pharm World Sci 2007;29(6):577-83. PMID: 17486423.

Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 Suppl):238S-249S. PMID: 16428717,

Bolser DC. Pharmacologic management of cough. Otolaryngol Clin North Am. 2010;43(1):147-55, xi. PMID: 20172264.

Bolser DC. Current and future centrally acting antitussives. Respir Physiol Neurobiol. 2006;152(3):349-55. PMID: 16517221.

Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. Lung. 2008;186 Suppl 1:S55-8. PMID: 17939003.

Brodlie M, Graham C, and McKean MC. Childhood Cough. BMJ 2012;344:e1177. PMID 22395925

Brunk SF. The evaluation of antitussive agents. J Clin Pharmacol. 1973;13(8):305-8. PMID: 4490005.

Burdon JG. Chronic cough: diagnosis and treatment. Aust Fam Physician. 1987;16(5):596-602. PMID: 3606497.

Burford JG, George RB. Respiratory physical therapy in the treatment of chronic bronchitis. Semin Respir Infect. 1988;3(1):55-60. PMID: 3283882.

Burns MW. Chronic cough. Diagnostic and management options. Aust Fam Physician. 1996;25(2):161-2, 166-7. PMID: 8839374.

Bye MR. The child with cough. Emergency and Office Pediatrics. 1996;9(1):14-16.

Catania MA, Cuzzocrea S. Pharmacological and clinical overview of cloperastine in treatment of cough. Ther Clin Risk Manag. 2011;7:83-92. PMID: 21445282.

Chalmers RK. Cough depressants. J Am Pharm Assoc. 1966;6(10):538-42. PMID: 5977022.

Chang AB. Pediatric cough: children are not miniature adults. Lung. 2010;188 Suppl 1:S33-40. PMID: 19672656.

Chang AB and Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 Suppl):260S-283S. PMID: 16428719.

Chang AB, Lasserson TJ, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and sults. Cochrane Databse of Systematic Reviews 2011;(1). CD004823.

Chang AB, Marchant JM, McKean MC, et al. Inhaled cromones for prolonged non-specific cough in children. Cochrane Database of Systematic Reviews 2004;(1). CD004436

Chang AB, McKean MC, and Morris PS. Anticholinergics for prolonged non-specific cough in children. Cochrane Database of Systematic Reviews 2003;(4). CD004358.

Chang AB, Winter D, and Acworth JP. Leukotriene receptore antagonist for prolionged non-specific cough in children. Cochrane Database of Systematic Reviews 2006;(2). CD005602.

Chung KF. Clinical cough VI: the need for new therapies for cough: disease-specific and symptom-related antitussives. Handb Exp Pharmacol. 2009;(187):343-68. PMID: 18825350.

Chung KF. Effective antitussives for the cough patient: an unmet need. Pulm Pharmacol Ther. 2007;20(4):438-45. PMID: 17161637.

Chung KF. Measurement of cough. Respir Physiol Neurobiol. 2006;152(3):329-39. PMID: 16530025.

Chung KF. Pathophysiology and therapy of chronic cough. Minerva Med. 2005;96(1):29-40. PMID: 15827540.

Chung KF. Assessment and measurement of cough: the value of new tools. Pulm Pharmacol Ther. 2002;15(3):267-72. PMID: 12099776.

Chung KF. Currently available cough suppressants for chronic cough. Lung. 2008;186 Suppl 1:S82-7. PMID: 17909897.

Chung KF. Methods of assessing cough and antitussives in man. Pulm Pharmacol. 1996;9(5-6):373-7. PMID: 9232680.

Chung KF. Clinical cough VI: The need for new therapies for cough: Disease-specific and symptom-related antitussives. 2009;187:343-368.

Chung KF, Lalloo UG. Diagnosis and management of chronic persistent dry cough. Postgrad Med J. 1996;72(852):594-8. PMID: 8977940.

Cohlan SQ, Stone SM. The cough and the bedsheet. Pediatrics. 1984;74(1):11-5. PMID: 6739203.

Cooreman J, Redon S, Perdrizet S. Aetiology of chronic coughing among school-children of the Bordeaux area: Methodology of the survey and the preliminary results. Bulletin of the International Union against Tuberculosis. 1982;57(3-4):262-269.

Cowcher K, Hanks GW. Long-term management of respiratory symptoms in advanced cancer. J Pain Symptom Manage. 1990;5(5):320-30. PMID: 2079581.

Dawson KP, Thorpe CW, Toop LJ. The spectral analysis of cough sounds in childhood respiratory illness. J Paediatr Child Health. 1991;27(1):4-6. PMID: 2043389.

De Blasio F, Dicpinigaitis PV, Rubin BK, et al. An observational study on cough in children, epidemiology, impact on wuality of sleep and treatment outcome. Cough 2012;8(1):1. PMID: 22269875.

De Blasio F, Virchow, JC, Polverino M, et al. Cough management: a practical approach. Cough 2011; 7(1):7. PMID: 21985340.

de Jongste JC, Shields MD. Cough . 2: Chronic cough in children. Thorax. 2003;58(11):998-1003. PMID: 14586058.

Dicpinigaitis PV. Currently available antitussives.

Pulm Pharmacol Ther. 2009;22(2):148-51. PMID: 18771744.

Dicpinigaitis PV. Experimentally induced cough. Pulm Pharmacol Ther. 2007;20(4):319-24. PMID: 17113801.

Dicpinigaitis PV. Inhalation cough challenge. Current Respiratory Medicine Reviews. 2010;6(2):142-147.

Dolansky G, Rieder M. What is the evidence for the safety and efficacy of over-the-counter cough and cold preparations for children younger than six years of age? Paediatr Child Health. 2008;13(2):125-7. PMID: 19183719.

Donnelly D, Everard MM, and Chang AB. Indoor air modification interventions for prolonged non-specific cough in children. Cochrane Database Syst Rev;3 CD005075.

du Mont A. Cough & cold preparation. Community Outlook. 1983;:296-9. PMID: 6557885.

Ebell MH. Inhaled beta agonists for chronic, nonspecific cough in children? Am Fam Physician. 2006;73(7):1191-2. PMID: 16625712.

Ebell MH. Diagnosis of chronic cough. J Fam Pract. 1996;43(3):231-2. PMID: 8797745.

Eddy NB. Codeine and its alternates for pain and cough relief. Ann Intern Med. 1969;71(6):1209-12. PMID: 5361414.

Fontana GA, Widdicombe J. What is cough and what should be measured? Pulm Pharmacol Ther. 2007;20(4):307-12. PMID: 17291801.

Fuller RW, Jackson DM. Physiology and treatment of cough. Thorax. 1990;45(6):425-30. PMID: 2203180.

Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22(2):159-62. PMID: 19061964.

Gilbert G. Single dose of honey effective for cough in kids. Journal of the National Medical Association. 2008;100(4):459.

Ginsberg DL. Paroxetine treatment of opioid-resistant, persistent dry cough. Primary Psychiatry. 2004;11(10):24-25.

Goyal M, Sasmal D, Nagori BP. Review on medicinal plants used by local community of jodhpur district of thar desert. International Journal of Pharmacology. 2011;7(3):333-339.

Gupta A, McKean M, Chang AB. Management of chronic non-specific cough in childhood: an evidence-based review. Arch Dis Child Educ Pract Ed. 2007;92(2):33-9. PMID: 17430858.

Haq F, Ahmad H, Alam M. Traditional uses of medicinal plants of Nandiar Khuwarr catchment (District Battagram), Pakistan. Journal of Medicinal Plant Research. 2011;5(1):39-48.

Harvey HP. Pharmaceutical benefits: disodium cromoglycate. Med J Aust. 1970;2(1):45. PMID: 5447849.

Hendeles L. Efficacy and safety of antihistamines and expectorants in nonprescription cough and cold preparations. Pharmacotherapy. 1993;13(2):154-8. PMID: 8097037.

Ing A. Chronic cough. Respirology. 1997;2(4):309-16. PMID: 9525303.

Irwin RS. Unexplained cough in the adult. Otolaryngol Clin North Am. 2010;43(1):167-80, xi-xii. PMID: 20172266.

Irwin RS. Assessing cough severity and efficacy of therapy in clinical research: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):232S-237S. PMID: 16428716.

Irwin RS, Curley FJ. The treatment of cough. A comprehensive review. Chest. 1991;99(6):1477-84. PMID: 2036833.

Irwin RS, French CT. Cough and gastroesophageal reflux: identifying cough and assessing the efficacy of cough-modifying agents. Am J Med. 2001;111 Suppl 8A:45S-50S. PMID: 11749924.

Irwin RS, Madison JM. The diagnosis and treatment of cough. N Engl J Med. 2000;343(23):1715-21. PMID: 11106722.

Irwin RS, French CT, Fletcher KE. Quality of life in coughers. Pulm Pharmacol Ther. 2002;15(3):283-6. PMID: 12099779.

Johnstone K, Fong Kwun M, Bowman R, et al. Inhaled corticosteroids for subacute and chronic cough in adults. 2011;(9) CD009305.

Karpa KD, Barnes M, Patel A. Treating kids with

cough and cold: Filling the void. Drug Topics. 2008;152(5)

Karthishwaran K, Mirunalini S. Therapeutic potential of Pergularia daemia (Forsk.): The ayurvedic wonder. International Journal of Pharmacology. 2010;6(6):836-843.

Kelly LF. Pediatric cough and cold preparations. Pediatr Rev. 2004;25(4):115-23. PMID: 15060179.

Kerrebijn KF, Hoogeveen-Schroot HC, van der Wal MC. A prospective study on chronic respiratory disease in children. I. Aim and methods, results of the first year. Scand J Respir Dis. 1973;54(1):3-15. PMID: 4690405.

Khoshoo V, Edell D, Mohnot S, et al. Associated factors in children with chronic cough. Chest. 2009;136(3):811-5. PMID: 19567488.

Kopriva F, Szotkowska J, Zapalka M. Bronchial asthma and Chlamydia pneumoniae antibodies in children aged 4-8 years in Olomouc district. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2005;149(2):289-91. PMID: 16601774.

Koskela HO, Purokivi MK, Romppanen J. Neurotrophins in chronic cough: association with asthma but not with cough severity. Clin Respir J. 2010;4(1):45-50. PMID: 20298417.

Kripke C. Inhaled beta agonists for chronic, nonspecific cough in children? American Family Physician. 2006;73(7):1193-1194.

Kwon NH, Oh MJ, Min TH, et al. Causes and clinical features of subacute cough. Chest. 2006;129(5):1142-7. PMID: 16685003.

Laukka MA, Cameron AJ, Schei AJ. Gastroesophageal reflux and chronic cough: which comes first? J Clin Gastroenterol. 1994;19(2):100-4. PMID: 7963352.

Lavigne JV, Davis AT, Fauber R. Behavioral management of psychogenic cough: alternative to the "bedsheet" and other aversive techniques. Pediatrics. 1991;87(4):532-7. PMID: 2011431.

Lavorini F, Fontana GA, Chellini E, et al. Respiratory expulsive efforts evoked by maximal lung emptying. Chest. 2011;140(3):690-6. PMID: 21106658.

Lavorini F, Pantaleo T, Geri P, et al. Cough and ventilatory adjustments evoked by aerosolised capsaicin and distilled water (fog) in man. Respir Physiol Neurobiol. 2007;156(3):331-9. PMID: 17134944.

Lee BJ, Jeung YJ, Lee JY, et al. Increased S-nitrosothiol levels in nonasthmatic eosinophilic bronchitis compared with cough variant asthma. Int Arch Allergy Immunol. 2011;156(1):99-103. PMID: 21447965.

Lee SY, Cho JY, Shim JJ, et al. Airway inflammation as an assessment of chronic nonproductive cough. Chest. 2001;120(4):1114-20. PMID: 11591547.

Lee SY, Kim MK, Shin C, et al. Substance P-immunoreactive nerves in endobronchial biopsies in cough-variant asthma and classic asthma. Respiration. 2003;70(1):49-53. PMID: 12584391.

Lim KG. Nitric oxide measurement in chronic cough. Lung. 2010;188 Suppl 1:S19-22. PMID: 19809852.

LoBuono C. Antitussive offers convenient twicedaily dosing. Drug Topics. 2004;148(14):16.

Loudon RG, Brown LC. Cough frequency in patients with respiratory disease. Am Rev Respir Dis. 1967;96(6):1137-43. PMID: 6057616.

Lurie A, Mestiri M, Huchon G, et al. Methods for clinical assessment of expectorants: a critical review. Int J Clin Pharmacol Res. 1992;12(1):47-52. PMID: 1526698.

Maliwichi-Nyirenda CP, Maliwichi LL, Franco M. Medicinal uses of Berberis holstii Engl. (Berberidaceae) in Malawi, the only African endemic barberry. Journal of Medicinal Plant Research. 2011;5(8):1367-1373.

Maranetra N, Chuaychoo B, Lertakyamanee J, et al. The cost-effectiveness of a questionnaire as a screening test for chronic obstructive pulmonary disease among the Bangkok elderly. J Med Assoc Thai. 2003;86(11):1033-41. PMID: 14696785.

Marchant JM, Morris P, Gaffney JT, et al. Antibiotics for prolonged moist cough in children. Cochrane Database Syst Rev 2005♋4), CD004822.

Marchesani F, Cecarini L, Pela R, et al. Causes of chronic persistent cough in adult patients: the results of a systematic management protocol. Monaldi Arch Chest Dis. 1998;53(5):510-4. PMID: 9861809.

Marshall S. Over-the-counter advice for coughs. Pharmaceutical Journal. 2007;278(7435):85-88.

Matsumoto H, Niimi A, Takemura M, et al. Features of cough variant asthma and classic asthma during methacholine-induced brochoconstriction: a cross-sectional study. Cough. 2009;5:3. PMID: 19272144.

McGarvey L, Morice AH. Clinical cough II: Therapeutic treatments and management of chronic cough. 2009;187:277-295.

McGarvey LP, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. Thorax. 1998;53(9):738-43. PMID: 10319055.

McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. Eur Respir J. 2000;15(5):833-8. PMID: 10853845.

McKenzie SA, Mylonopoulou M, Bridge PD. Bronchodilator responsiveness and atopy in 5-10-yr-old coughers. Eur Respir J. 2001;18(6):977-81. PMID: 11829105.

Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med. 1996;156(9):997-1003. PMID: 8624180.

Milla CE, Hansen LG, Warwick WJ. Different frequencies should be prescribed for different high frequency chest compression machines. Biomed Instrum Technol. 2006;40(4):319-24. PMID: 16941931.

Molassiotis A, Bryan G, Caress A, et al. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: a systematic review of the literature. Respir Med 2010;104(7):934-44. PMID: 20385478.

Morice AH, Fontana GA, Sovijarvi AR, et al. The diagnosis and management of chronic cough. Eur Respir J 2004;24(3):481-92. PMID: 15358710.

Mulholland S, and Chang AB. Honey and lozenges for children with non-specific cough. Cochrane Database Syst Rev 2009; (2), CD007523.

Murata A, Ohota N, Shibuya A, et al. New non-invasive automatic cough counting program based on 6 types of classified cough sounds. Intern Med. 2006;45(6):391-7. PMID: 16617191.

Okwu DE, Uchenna NF. Exotic multifaceted medicinal plants of drugs and pharmaceutical industries. African Journal of Biotechnology. 2009;8(25):7271-7282.

Patel SS, Mohamed Saleem TS, Ravi V, et al. Passiflora incarnata Linn: A phytopharmacological review. International Journal of Green Pharmacy. 2009;3(4):277-280.

Pavia D. The role of chest physiotherapy in mucus hypersecretion. Lung. 1990;168 Suppl:614-21. PMID: 2117171.

Priyashree S, Jha S, Pattanayak S. A review on Cressa cretica Linn.: A halophytic plant. Pharmacognosy Reviews. 2010;4(8):161-166.

Rafferty P. Antihistamines in the treatment of clinical asthma. J Allergy Clin Immunol. 1990;86(4 Pt 2):647-50. PMID: 1977784.

Raj AA, Birring SS. Clinical assessment of chronic cough severity. Pulm Pharmacol Ther. 2007;20(4):334-7. PMID: 17113330.

Ramanuja S, Kelkar P. Habit cough. Ann Allergy Asthma Immunol. 2009;102(2):91-5; quiz 95-7, 115. PMID: 19230457.

Rolfe MW, Alberts WM. The chronic persistent cough. Compr Ther. 1996;22(10):615-21. PMID: 8950077.

Sadoul P, Puchelle E, Girard F. Criteria for evaluating mucus functions and their disorders in chronic bronchitis. Ciba Found Symp. 1978;(54):277-95. PMID: 248016.

Sanda KA, Grema HA, Geidam YA, et al. Pharmacological aspects of Psidium guajava: An Update. International Journal of Pharmacology. 2011;7(3):316-324.

Saric-Kundalic B, Fritz E, Dobes C, et al. Traditional medicine in the pristine village of Prokosko lake on Vranica Mountain, Bosnia and Herzegovina. Scientia Pharmaceutica. 2010;78(2):275-290.

Sause RB, Mangione RA. Cough and cold treatment with OTC medicines. J Pract Nurs. 1991;41(3):15-25. PMID: 1716321.

Savo V, Giulia C, Maria GP, et al. Folk phytotherapy

of the Amalfi Coast (Campania, Southern Italy). Journal of Ethnopharmacology. 2011;135(2):376-392.

Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar--pediatric cough and cold medications. N Engl J Med. 2007;357(23):2321-4. PMID: 18057333.

Shaw EB. Over-the-counter cough mixtures. JAMA. 1969;208(8):1493. PMID: 4388776.

Shields MD, Bush A, Everard ML, et al. Recommendations for the assessment and management of cough in children. Thorax. 2008;63(SUPPL. 3):iii1-iii15.

Smith J. Monitoring chronic cough: current and future techniques. Expert Rev Respir Med. 2010;4(5):673-83. PMID: 20923344.

Smith J. Ambulatory methods for recording cough. Pulm Pharmacol Ther. 2007;20(4):313-8. PMID: 17161969.

Smith J, Woodcock A. New developments in the objective assessment of cough. Lung. 2008;186 Suppl 1:S48-54. PMID: 18066694.

Smith JA. Assessing efficacy of therapy for cough. Otolaryngol Clin North Am. 2010;43(1):157-66, xi. PMID: 20172265.

Spector S. Use of mannitol inhalation challenge in assessment of cough. Lung. 2010;188 Suppl 1:S99-103. PMID: 19756864.

Srivastava R, Ahmed H, Dixit R, et al. Crocus sativus L.: A comprehensive review. Pharmacognosy Reviews. 2010;4(8):200-208.

Subburaj S, Parvez L, Rajagopalan TG. Methods of recording and analysing cough sounds. Pulm Pharmacol. 1996;9(5-6):269-79. PMID: 9232663.

Tan RA, Spector SL. Chronic cough. Compr Ther. 1997;23(7):467-71. PMID: 9262921.

Tomerak AA, McGlashan JJ, Vyas HH, et al. Inhaled corticosteroids for non-specific chronic cough in children. Cochrane Database Syst Rev 2005; (4), CD004231.

Tomerak AA, Vyas HH, Lakenpaul M, et al. Inhaled beta2-agonists for treating non-specific chronic cough in children. Cochrane Database Syst Rev 2005;(3), CD005373.

Torres M. Nonprescription over-the-counter cough and cold medicines for children. International Pediatrics. 2008;23(4):217-218.

Ummarino D, Vandermeulen L, Roosens B, et al. Gastroesophageal reflux evaluation in adult patients affected by chronic cough: a comparison between two techniques. Journal of Pediatric Gastroenterology and Nutrition 2011;53:S71-72.

Vassilev ZP, Chu AF, Ruck B, et al. Adverse reactions to over-the-counter cough and cold products among children: the cases managed out of hospitals. J Clin Pharm Ther. 2009;34(3):313-8. PMID: 19646077.

Vertigan AE, Gibson PG. The Role of Speech Pathology in the Management of Patients with Chronic Refractory Cough. Lung. 2011;PMID: 21989493.

Vijaya Bhargava K. Medicinal uses and pharmacological properties of Crocus sativus linn (saffron). International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(SUPPL. 3):22-26.

Wacogne I. Chronic cough in children had various aetiologies and common causes of adult cough were found in < 10% of children. Evidence-Based Medicine. 2006;11(6):187.

Warren MD, Cooper WO. Honey improves cough in children compared to no treatment. Journal of Pediatrics. 2008;152(5):739-740.

Weinberger M. The habit cough syndrome. Pediatric, Allergy, Immunology, and Pulmonology. 2010;23(2):125-129.

Yamasaki A, Hanaki K, Tomita K, et al. Cough and asthma diagnosis: Physicians' diagnosis and treatment of patients complaining of acute, subacute and chronic cough in rural areas of Japan. 2010;3:101-107.

Young EC, Smith JA. Quality of life in patients with chronic cough. Ther Adv Respir Dis. 2010;4(1):49-55. PMID: 20051447.

Zhao T, Qiu ZH, Wang L, et al. Validation of the reliability and clinical value on cough score. Respirology. 2011;16:195.

Ziment I. Controlled-release codeine in the treatment

of allergic cough. Advances in Therapy. 1987;4(2):63-72.

Study population does not have cough (KQ 1) or chronic cough (KQ 2)

Ainapure SS, Desai A, Korde K. Efficacy and safety of Ascoril in the management of cough--National Study Group report. J Indian Med Assoc. 2001;99(2):111, 114. PMID: 11482804.

Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. Thorax. 1998;53(11):963-8. PMID: 10193396.

Auffarth B, Postma DS, de Monchy JG, et al. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. Thorax. 1991;46(5):372-7. PMID: 2068695.

Azzopardi JF, Vanscolina AB. Clinical trial of a new anti-tussive ('Dimyril'). Br J Clin Pract. 1964;18:213-4. PMID: 14140732.

Banderali G, Riva E, Fiocchi A, et al. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. J Int Med Res. 1995;23(3):175-83. PMID: 7649341.

Barber CM, Curran AD, Bradshaw LM, et al. Reproducibility and validity of a Yan-style portable citric acid cough challenge. Pulm Pharmacol Ther. 2005;18(3):177-80. PMID: 15707851.

Barnes N, Pavord I, Chuchalin A, et al. A randomized, souble-blind, placebo-controlled study of CRTH2 antagonist OC000459 in moderate persistent asthma. Clinical and Experimental Allergy 2012;42(1):38-48.

Benini L, Ferrari M, Sembenini C, et al. Cough threshold in reflux oesophagitis: influence of acid and of laryngeal and oesophageal damage. Gut. 2000;46(6):762-7. PMID: 10807885.

Berthelot J, Weibel MA. Comparative clinical evaluation of the antitussive activity of butamirate citrate linctus (Sinecod(registered trademark)) v. a codeine-containing linctus (Netux(registered trademark)). Clinical Trials Journal. 1990;27(1):50-57.

Beumer HM, Hardonk HJ, Boter J, et al. Objective evaluation of antitussive agents under clinical conditions. Respiration. 1976;33(1):9-13. PMID: 1105726.

Bhalla P, Singh NP, Ravi K. Attenuation of angiotensin converting enzyme inhibitor induced cough by iron supplementation: role of nitric oxide. J Renin Angiotensin Aldosterone Syst. 2011;PMID: 21421658.

Blanc FX, Macedo P, Hew M, et al. Capsaicin cough sensitivity in smokers with and without airflow obstruction. Respir Med. 2009;103(5):786-90. PMID: 19136241.

Bossi R, Braga PC, Centanni S, et al. Antitussive activity and respiratory system effects of levodropropizine in man. Arzneimittelforschung. 1988;38(8):1159-62. PMID: 3196411.

Calesnick B, Christensen JA. Latency of cough response as a measure of antitussive agents. Clin Pharmacol Ther. 1967;8(3):374-80. PMID: 5338381.

Calesnick B, Vernick H. Antitussive activity of ethanol. Q J Stud Alcohol. 1971;32(2):434-41. PMID: 4932255.

Cao H, Han M, Li X, et al. Clinical research evidence of cupping therapy in China: A systematic literature review. BMC Complementary and Alternative Medicine. 2010;10

Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough. Comparison with dextromethorphan. Pulm Pharmacol Ther. 1997;10(2):89-96. PMID: 9425640.

Cavigioli G, Pelucchi A, Mastropasqua B, et al. Prevalence and repeatability of the cough response induced by inhalation of low chloride ion solutions in normal subjects. Monaldi Arch Chest Dis. 1995;50(5):352-5. PMID: 8541816.

Chakrabarti A, Pandhi P, Jindal SK, et al. A comparative randomized double-blind clinical trial of hexapneumine and clistine as antitussive agents. Int J Clin Pharmacol Ther Toxicol. 1987;25(6):310-2. PMID: 3305379.

Cho HB, Kwak HJ, Park SY, et al. Comparison of the incidence and severity of cough after alfentanil and remifentanil injection. Acta Anaesthesiol Scand. 2010;54(6):717-20. PMID: 20085544.

Cohen BM. Respiratory and cough mechanics in antitussive trials. Responsivity of objective indices to the treatment of acute upper respiratory tract infections. Respiration. 1975;32(1):32-45. PMID: 1090987.

Cox ID, Wallis PJ, Apps MC, et al. An electromyographic method of objectively assessing cough intensity and use of the method to assess effects of codeine on the dose-response curve to citric acid. Br J Clin Pharmacol. 1984;18(3):377-82. PMID: 6487476.

D'Urzo A, Ferguson GT, van Noord, JA, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPDL the GLOW1 trial. Respiratory Research 2011;12.

Damonte C, De Nadon J, Scarpazza G. Study of the spontaneous cough under a pharmacological treatment and of the cough induced by a non-specific bronchial stimulation. A simple method of cough recording. Giornale Italiano della Malattie del Torace. 1985;39(4):223-229.

Davenport PW, Bolser DC, Vickroy T, et al. The effect of codeine on the Urge-to-Cough response to inhaled capsaicin. Pulm Pharmacol Ther. 2007;20(4):338-46. PMID: 17292647.

Davenport PW, Vovk A, Duke RK, et al. The urge-to-cough and cough motor response modulation by the central effects of nicotine. Pulm Pharmacol Ther. 2009;22(2):82-9. PMID: 19100331.

De Castro G, Remondini R, dos Santos AZ, et al. Analysis of symptoms, clinical signs and oxygen support in patients with bronchiolitis before and after chest physiotherapy during hospitalization. Revist Paulist de Pediatria 2011;29(4):599-605.

Dicpinigaitis PV. Short- and long-term reproducibility of capsaicin cough challenge testing. Pulm Pharmacol Ther. 2003;16(1):61-5. PMID: 12657501.

Elliott WJ. Double-blind comparison of eprosartan and enalapril on cough and blood pressure in unselected hypertensive patients. Eprosartan Study Group. J Hum Hypertens. 1999;13(6):413-7. PMID: 10408592.

Fontana GA, Pantaleo T, Lavorini F, et al. Repeatability of cough-related variables during fog challenges at threshold and suprathreshold stimulus intensity in humans. Eur Respir J. 1999;13(6):1447-50. PMID: 10445625.

Fujimori K, Suzuki E, Arakawa M. [Effects of oxatomide, H1-antagonist, on postinfectious chronic cough; a comparison of oxatomide combined with dextromethorphan versus dextromethorphan alone]. Arerugi. 1998;47(1):48-53. PMID: 9528165.

Fukuhara A, Saito J, Sato S, et al. Validation study of asthma screening criteria based on subjective symptoms and fractional exhaled nitric oxide. Annals of Allergy, Asthma and Immunology. 2011;

Gillissen A, Richter A, Oster H. Clinical efficacy of short-term treatment with extra-fine HFA beclomethasone dipropionate in patients with post-infectious persistent cough. J Physiol Pharmacol. 2007;58 Suppl 5(Pt 1):223-32. PMID: 18204132.

Gupta VK. Metoclopramide aborts cough-induced headache and ameliorates cough--a pilot study. Int J Clin Pract. 2007;61(2):345-8. PMID: 16787437.

Irifune K, Hamada H, Ito R, et al. Antitussive effect of bakumondoto a fixed kampo medicine (six herbal components) for treatment of post-infectious prolonged cough: controlled clinical pilot study with 19 patients. Phytomedicine. 2011;18(8-9):630-3. PMID: 21514123.

Johansson A, Lowhagen O, Millqvist E, et al. Capsaicin inhalation test for identification of sensory hyperreactivity. Respir Med. 2002;96(9):731-5. PMID: 12243320.

Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ. 1995;310(6989):1225-9. PMID: 7767192.

Joo MJ, Au DH, Fitzgibbon ML, et al. Determinants of spirometry use and accuracy of COPD diagnosis in primary care. J Gen Intern Med. 2011;26(11):1272-7. PMID: 21713542.

Kamin W, Kieser M. Pinimenthol(registered trademark) ointment in patients suffering from upper respiratory tract infections - A post-marketing observational study. Phytomedicine. 2007;14(12):787-791.

Katsardis C, Coulie PJ. Pentoxyverine effectively controls irritating cough in preschool children. Acta Therapeutica. 1992;18(1):93-101.

Katsumata U, Sekizawa K, Inoue H, et al. Inhibitory actions of procaterol, a beta-2 stimulant, on substance P-induced cough in normal subjects during upper respiratory tract infection. Tohoku J Exp Med. 1989;158(1):105-6. PMID: 2476867.

Kelemen SA, Cseri T, Marozsan I. Graphometric analysis of cough tachogram. Acta Physiol Hung. 1987;70(2-3):323-8. PMID: 3434311.

Kiss J, Pongor F, Nagy M. Comparative investigation of Libexin and Hydrocodin. Ther Hung. 1968;16(2):79-82. PMID: 5666419.

Korpas J, Kelemen S. Tussiphonographic analysis of cough sound recordings performed by Schmidt-Voigt and Hirschberg and Szende. Acta Physiol Hung. 1987;70(2-3):167-70. PMID: 3434295.

Korpas J, Salat D, Sadlonova J, et al. The sensitivity of tussiphonography for assessing the effectiveness of treatment. Bratisl Lek Listy. 2000;101(2):71-7. PMID: 11039211.

Koskela HO, Purokivi MK, Tukiainen RM. Simultaneous versus video counting of coughs in hypertonic cough challenges. Cough. 2008;4:8. PMID: 18782429.

Kotlar W, Casini A. Comparative trial of a new antitussive agent: Double-blind, crossover study versus dropropyzine and placebo. Today's Therapeutic Trends. 1986;4(2):1-8.

Kotlar W, Casini A. A double-blind, cross-over study of a new antitussive agent versus dropropizine and placebo. Acta Toxicologica et Therapeutica. 1987;8(2):121-129.

Kotlar W, Kotlar A, Casini A, et al. Clinical trial of efficacy and tolerance on a new substance provided with antitussive activity. Clinical Trials Journal. 1986;23(5):281-292.

Kudi K, Takasaki J, Manabe T, et al. Systemic corticosteroids and early administration of antiviral agents for pneumonia with acute wheezing due to influenza a(h1n1)pdm09 in Japan. PLoS One 2012; 7(2).

Kuhn JJ, Hendley JO, Adams KF, et al. Antitussive effect of guaifenesin in young adults with natural colds. Objective and subjective assessment. Chest. 1982;82(6):713-8. PMID: 6754274.

Leidy NK, Rennard SI, Schmier J, et al. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. Chest. 2003;124(6):2182-91. PMID: 14665499.

Leidy NK, Schmier JK, Jones MK, et al. Evaluating symptoms in chronic obstructive pulmonary disease: validation of the Breathlessness, Cough and Sputum Scale. Respir Med. 2003;97 Suppl A:S59-70. PMID: 12564612.

Levesque M, Ghezzo H, L'Archeveque J, et al. Does the methacholine test reproduce symptoms? Can Respir J. 2010;17(5):224-8. PMID: 21037997.

Lowry R, Wood A, Higenbottam T. The effect of anticholinergic bronchodilator therapy on cough during upper respiratory tract infections. Br J Clin Pharmacol. 1994;37(2):187-91. PMID: 8186064.

Marguet C, Dean TP, Warner JO. Soluble intercellular adhesion molecule-1 (sICAM-1) and interferon-gamma in bronchoalveolar lavage fluid from children with airway diseases. Am J Respir Crit Care Med. 2000;162(3 Pt 1):1016-22. PMID: 10988123.

Mason NP, Barry PW, Despiau G, et al. Cough frequency and cough receptor sensitivity to citric acid challenge during a simulated ascent to extreme altitude. Eur Respir J. 1999;13(3):508-13. PMID: 10232417.

McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):250S-259S. PMID: 16428718.

Medici TC, Shang H, Grosgurin P, et al. No demonstrable effect of sobrerol as an expectorant in patients with stable chronic bronchial diseases. Bull Eur Physiopathol Respir. 1985;21(6):477-83. PMID: 3907738.

Millqvist E, Lowhagen O, Bende M. Quality of life and capsaicin sensitivity in patients with sensory airway hyperreactivity. Allergy. 2000;55(6):540-5. PMID: 10858984.

Moeller A, Diefenbacher C, Lehmann A, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. J

Allergy Clin Immunol. 2008;121(3):705-9. PMID: 18177695.

Mohar D, Berger WE, LaForce C, et al. Efficacy and tolerability study of ciclesonide nasal aerosol in patients with perennial allergic rhinitis. Allergy and Asthma Proceedings 2012;33(1):19-26.

Mossberg B, Philipson K, Strandberg K, et al. Clearance by voluntary coughing and its relationship to subjective assessment and effect of intravenous bromhexine. Eur J Respir Dis. 1981;62(3):173-9. PMID: 7308332.

Munyard P, Bush A. How much coughing is normal? Arch Dis Child. 1996;74(6):531-4. PMID: 8758131.

Munyard P, Busst C, Logan-Sinclair R, et al. A new device for ambulatory cough recording. Pediatr Pulmonol. 1994;18(3):178-86. PMID: 7800435.

Murty GE, Kelly PJ, Bradley PJ. Tussometry: an objective assessment of vocal cord function. Ann Otol Rhinol Laryngol. 1993;102(10):743-7. PMID: 8215091.

Murty GE, Kelly PJ, Veale D. Tussometry and lung function. Clin Otolaryngol Allied Sci. 1994;19(2):117-9. PMID: 8026087.

Nagata K, Tomii K, Otsuka K, et al. Evaluation of the chronic obstructive pulmonary disease assessment test for measurement of health-related quality of life in patients with interstitial lung disease. Respirology 2012;17(3):506-12. PMID: 22257381.

Nejla S, Fujimura M, Kamio Y. Comparison between tidal breathing and dosimeter methods in assessing cough receptor sensitivity to capsaicin. Respirology. 2000;5(4):337-42. PMID: 11192544.

Nesari T, Bhagwat BK, Johnson J, et al. Clinical validation of efficacy and safety of herbal cough formula: study of herbal cough syrup. J Herb Pharmacother. 2004;4(4):1-12. PMID: 15927921.

Ntournenopoulos G and Glickman Y. Computerised lung sound monitoring to assess effictiveness of chest physiotherapy and secretion removal: a feasibility study. Physiotherapy 2012;98(3):250-255.

Oduwole O, Meremikwu MM, Oyo-Ita A, et al. Honey for acute cough in children. Cochrane Database Syst Rev. 2010;(1):CD007094. PMID: 20091616.

Paknejad O, Hojjati SA, Pazoki M. The association between methacholine challenge test and respiratory symptoms: A study on 146 patients. Tehran University Medical Journal. 2011;68(11):662-667.

Pontiroli AE, Daffonchio L. Efficacy and tolerability of levodropropizine and clobutinol in elderly patients with nonproductive cough. Clinical Drug Investigation. 1997;14(3):175-182.

Prabhu Shankar S, Chandrashekharan S, Bolmall CS, et al. Efficacy, safety and tolerability of salbutamol + guaiphenesin + bromhexine (Ascoril) expectorant versus expectorants containing salbutamol and either guaiphenesin or bromhexine in productive cough: a randomised controlled comparative study. J Indian Med Assoc. 2010;108(5):313-4, 316-8, 320. PMID: 21121410.

Rece CA, Cherry AC, Jr., Reece AT, et al. Tape recorder for evaluation of coughs in children. Am J Dis Child. 1966;112(2):124-8. PMID: 5943997.

Rees PJ, Clark TJ. Assessment of antitussive effects by citric acid threshold. Br J Dis Chest. 1983;77(1):94-7. PMID: 6344901.

Roa CC, Jr., Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection. A randomized controlled trial. Arzneimittelforschung. 1995;45(3):267-72. PMID: 7741782.

Roberts JR, Aravapalli A, Pohl D, et al. Extraesophageal gastroesophageal reflux disease (GERD) symptoms are not more frequently associated with proximal esophageal reflux than typical GERD symptoms. Dis Esophagus 2012;pepubahead of print]. PMID: 22243631.

Rose JR. Pholcodine plus pseudoephedrine in the treatment of cough. A controlled trial. Practitioner. 1967;198(187):704-7. PMID: 4860038.

Rostami-Hodjegan A, Abdul-Manap R, Wright CE, et al. The placebo response to citric acid-induced cough: pharmacodynamics and gender differences. Pulm Pharmacol Ther. 2001;14(4):315-9. PMID: 11440560.

Rouhi H, Ganji F, Nasri H. Effects of ginger on the improvement of asthma [The evaluation of its' treatmental effects]. Pakistan Journal of Nutrition. 2006;5(4):373-376.

Ruel MT, Rivera JA, Santizo MC, et al. Impact of zinc supplementation on morbidity from diarrhea and

respiratory infections among rural Guatemalan children. Pediatrics. 1997;99(6):808-13. PMID: 9164774.

Saab BR, Pashayan N, El-Chemaly S, et al. Sesame oil use in ameliorating cough in children: a randomised controlled trial. Complement Ther Med. 2006;14(2):92-9. PMID: 16765847.

Schmidt M, Thomsen M, and Schmidt U. Suitability of Ive Extract for the treatment of Paudiatric Cough. Phytotherapy Research 2012; [epub ahead of print]. PMID: 22532491

Schultz A, Sly PD, Zhang G. et al. Incentive device improves spacer technique but not clinical outcome in preschool children with asthma. Journal of Paediatrics and Child Health 2012;48(1):52-56.

Singh P, Murty GE, Mahajan RP, et al. The tussometer: accuracy and reproducibility. Br J Anaesth. 1994;73(2):145-8. PMID: 7917725.

Speiser BL, Spratling L. Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys. 1993;25(4):579-87. PMID: 8454476.

Stauss-Grabo M, Atiye S, Warnke A, et al. Observational study on the tolerability and safety of film-coated tablets containing ivy extract (Prospan(R) Cough Tablets) in the treatment of colds accompanied by coughing. Phytomedicine. 2011;18(6):433-6. PMID: 21211950.

Stone RA, Barnes PJ, Chung KF. Effect of frusemide on cough responses to chloride-deficient solution in normal and mild asthmatic subjects. Eur Respir J. 1993;6(6):862-7. PMID: 8339807.

Stott NCH, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. Current Therapeutics. 1977;18(6):89-90.

Suguikawa TR, Garcia CA, Martinez EZ, et al. Cough and dyspnea during bronchoconstriction: comparison of different stimuli. Cough. 2009;5:6. PMID: 19555484.

Szeinberg A, Tabachnik E, Rashed N, et al. Cough capacity in patients with muscular dystrophy. Chest. 1988;94(6):1232-5. PMID: 3191765.

Thorpe CW, Toop LJ, Dawson KP. Towards a quantitative description of asthmatic cough sounds. Eur Respir J. 1992;5(6):685-92. PMID: 1628726.

van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health. 1992;28(6):442-6. PMID: 1466940.

Varechova S, Plevkova J, Hanacek J, et al. Role of gender and pubertal stage on cough sensitivity in childhood and adolescence. J Physiol Pharmacol. 2008;59 Suppl 6:719-26. PMID: 19218699.

Vizel E, Yigla M, Goryachev Y, et al. Validation of an ambulatory cough detection and counting application using voluntary cough under different conditions. Cough. 2010;6:3. PMID: 20504377.

Vohra S, Saab BR. Does sesame oil reduce cough in children?: Commentary. Focus on Alternative and Complementary Therapies. 2007;12(1):17-19.

Wong CH, Matai R, Morice AH. Cough induced by low pH. Respir Med. 1999;93(1):58-61. PMID: 10464850.

Woodcock A, McLeod RL, Sadeh J, et al. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung. 2010;188 Suppl 1:S47-52. PMID: 19937046.

Yang P, Cheville AL, Wampfler JA, et al. Quality of life and symptom burden among long-term lung cancer survivors. J Thorac Oncol 2012;7(1):64-70. PMID: 22134070.

Yiallouros PK, Savva SC, Kolokotroni O, et al. Low serum high-density lipoprotein cholesterol in childhood is associated with adolescent asthma. Clinical and Experimental Allergy 2012;42(3):423-432.

Yoder KE, Shaffer ML, La Tournous SJ, et al. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. Clin Pediatr (Phila). 2006;45(7):633-40. PMID: 16928841.

Study population does not have chronic cough of unknown etiology or refractory chronic cough of known etiology, or has patients with invasive respiratory tract instrumentation (KQ 2 only)

Altunaiji S, Kukuruzovic R, Curtis N, et al. Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev. 2007;(3):CD004404. PMID: 17636756.

Altunaiji S, Kukuruzovic R, Curtis N, et al. Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev. 2005;(1):CD004404. PMID: 15674946.

Ambrogi V, Baldi A, Schillaci O, et al. Clinical impact of extraplural pneumonectomy for malignant pleural mesothelioma. Annals of Surgical Oncology 2012;19(5):1692-9. PMID: 22193885.

Aubier M, Levy J, Clerici C, et al. Protective effect of theophylline on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis. 1991;143(2):346-50. PMID: 1990951.

Aylward M, Bater PA, Davies DE, et al. Clinical therapeutic evaluation of methylcysteine hydrochloride in patients with chronic obstructive bronchitis: a balanced double-blind trial with placebo control. Curr Med Res Opin. 1978;5(6):461-71. PMID: 350498.

Birkebaek NH, Kristiansen M, Seefeldt T, et al. Bordetella pertussis and chronic cough in adults. Clin Infect Dis. 1999;29(5):1239-42. PMID: 10524969.

Buonpensiero P, De Gregorio F, Sepe A, et al. Hyaluronic acid improves "pleasantness" and tolerability of nebulized hypertonic saline in a cohort of patients with cystic fibrosis. Adv Ther. 2010;27(11):870-8. PMID: 20953746.

Caramia G, Gagliardini R, Ruffini E, et al. The management of cystic fibrosis with carbocysteine lysine salt: single-blind comparative study with ambroxol hydrochloride. J Int Med Res. 1995;23(4):284-93. PMID: 7589772.

Chang AB, Lasserson TJ, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev. 2006;(4):CD004823. PMID: 17054216.

Chang AB, Lasserson TJ, Kiljander TO, et al. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. BMJ. 2006;332(7532):11-7. PMID: 16330475.

Dettmar PW, Strugala V, Fathi H, et al. The online Cough Clinic: developing guideline-based diagnosis and advice. Eur Respir J. 2009;34(4):819-24. PMID: 19324957.

Edwards GF, Steel AE, Scott JK, et al. S-carboxymethylcysteine in the fluidification of sputum and treatment of chronic airway obstruction. Chest. 1976;70(4):506-13. PMID: 789027.

Fisman EZ, Grossman E, Motro M, et al. Clinical evidence of dose-dependent interaction between aspirin and angiotensin-converting enzyme inhibitors. J Hum Hypertens. 2002;16(6):379-83. PMID: 12037691.

Freeman LW, Welton D. Effects of imagery, critical thinking, and asthma education on symptoms and mood state in adult asthma patients: a pilot study. J Altern Complement Med. 2005;11(1):57-68. PMID: 15750364.

Gallon A. Evaluation of chest percussion in the treatment of patients with copious sputum production. Respir Med. 1991;85(1):45-51. PMID: 2014357.

Gawchik S, Goldstein S, Prenner B, et al. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. Ann Allergy Asthma Immunol. 2003;90(4):416-21. PMID: 12722964.

Gebbie T, Harris EA, O'Donnell TV, et al. Multicentre, short-term therapeutic trial of disodium cromoglycate, with and without prednisone, in adults with asthma. Br Med J. 1972;4(5840):576-80. PMID: 4629980.

Glass J, Archer LN, Adams W, et al. Nebulised cromoglycate, theophylline, and placebo in preschool asthmatic children. Arch Dis Child. 1981;56(8):648-

51. PMID: 6791596.

Gottfarb P, Brauner A. Children with persistent cough--outcome with treatment and role of Moraxella catarrhalis? Scand J Infect Dis. 1994;26(5):545-51. PMID: 7710536.

Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. Lancet. 1995;345(8941):13-6. PMID: 7799699.

Irwin RS, Pratter MR, Holland PS, et al. Postnasal drip causes cough and is associated with reversible upper airway obstruction. Chest. 1984;85(3):346-52. PMID: 6697790.

Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest. 2002;121(4):1132-40. PMID: 11948043.

Ishiura Y, Fujimura M, Yamamoto H, et al. Effect of an orally active Th2 cytokine inhibitor, suplatast on "atopic cough" tosilate. Arzneimittelforschung. 2008;58(6):297-302. PMID: 18677972.

Kim CK, Callaway Z, Kim DW, et al. Eosinophil Degranulation Is More Important than Eosinophilia in Identifying Asthma in Chronic Cough. J Asthma. 2011;PMID: 22022864.

Kim SH, Jeong JH, Kwak HJ, et al. Measurement of nasal nitric oxide is useful for the diagnosis of sinusitis-induced prolonged cough. Tohoku J Exp Med. 2011;223(2):145-51. PMID: 21307634.

Kinoshita M, Lee SH, Hang LW, et al. Efficacy and safety of indacaterol 150 and 300 (mu)g in chronic obstructive pulmonary disease patients from six Asian areas including Japan: a 12-week, placebo-controlled study.

Respirology 2012;17(2):379-389.

Kivastik J, Gibson AM, Primhak RA. Methacholine challenge in pre-school children--which outcome measure? Respir Med. 2007;101(12):2555-60. PMID: 17720470.

Kivastik J, Gibson AM, Primhak RA. Feasibility of shortened methacholine challenge in preschool children. Pediatr Pulmonol. 2006;41(2):146-50. PMID: 16353178.

Kooi EM, Schokker S, Marike Boezen H, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial. Pulm Pharmacol Ther. 2008;21(5):798-804. PMID: 18647656.

Korpas J, Vrabec M, Sadlonova J, et al. Analysis of the cough sound frequency in adults and children with bronchial asthma. Acta Physiol Hung. 2003;90(1):27-34. PMID: 12666872.

Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. J Asthma. 2009;46(7):692-8. PMID: 19728207.

Lalloo UG, Lim S, DuBois R, et al. Increased sensitivity of the cough reflex in progressive systemic sclerosis patients with interstitial lung disease. Eur Respir J. 1998;11(3):702-5. PMID: 9596124.

Laube BL, Auci RM, Shields DE, et al. Effect of rhDNase on airflow obstruction and mucociliary clearance in cystic fibrosis. Am J Respir Crit Care Med. 1996;153(2):752-60. PMID: 8564129.

Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. Value Health. 2010;13(8):965-75. PMID: 20659270.

Li AM, Lex C, Zacharasiewicz A, et al. Cough frequency in children with stable asthma: correlation with lung function, exhaled nitric oxide, and sputum eosinophil count. Thorax. 2003;58(11):974-8. PMID: 14586052.

Li AM, Tsang TW, Chan DF, et al. Cough frequency in children with mild asthma correlates with sputum neutrophil count. Thorax. 2006;61(9):747-50. PMID: 16670174.

Lorin MI, Denning CR. Evaluation of postural drainage by measurement of sputum volume and consistency. Am J Phys Med. 1971;50(5):215-9. PMID: 5113410.

Luque CA, Vazquez Ortiz M. Treatment of ACE inhibitor-induced cough. Pharmacotherapy. 1999;19(7):804-10. PMID: 10417028.

Mackay TW, Fitzpatrick MF, Douglas NJ. Non-adrenergic, non-cholinergic nervous system and overnight airway calibre in asthmatic and normal subjects. Lancet. 1991;338(8778):1289-92. PMID: 1682685.

Macklem PT, Fraser RG, Brown WG. Bronchial pressure measurement in emphysema and bronchitis. J Clin Invest. 1965;44:897-905. PMID: 14322023.

Malmberg LP, Pelkonen A, Hakulinen A, et al. Intraindividual variability of infant whole-body plethysmographic measurements: effects of age and disease. Pediatr Pulmonol. 1999;28(5):356-62. PMID: 10536067.

Marchal F, Schweitzer C, Moreau-Colson C. Respiratory impedance response to a deep inhalation in children with history of cough or asthma. Pediatr Pulmonol. 2002;33(6):411-8. PMID: 12001273.

Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, et al. Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. Respir Med. 2006;100(9):1623-32. PMID: 16434174.

Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, et al. Quality-of-life determinants in patients with clinically stable bronchiectasis. Chest. 2005;128(2):739-45. PMID: 16100162.

Matos S, Birring SS, Pavord ID, et al. Detection of cough signals in continuous audio recordings using hidden Markov models. IEEE Trans Biomed Eng. 2006;53(6):1078-83. PMID: 16761835.

McEwan JR, Choudry NB, Fuller RW. The effect of sulindac on the abnormal cough reflex associated with dry cough. J Pharmacol Exp Ther. 1990;255(1):161-4. PMID: 2213552.

McGarvey LP, Savage DA, Feeney SA, et al. Is there an association between angiotensin-converting enzyme gene variants and chronic nonproductive cough? Chest. 2000;118(4):1091-4. PMID: 11035682.

Mitchell C, Miles J. Lower respiratory tract symptoms in Queensland schoolchildren. The questionnaire: its reliability and validity. Aust N Z J Med. 1983;13(3):264-9. PMID: 6579940.

Miyashita N, Fukano H, Yoshida K, et al. Chlamydia pneumoniae infection in adult patients with persistent cough. J Med Microbiol. 2003;52(Pt 3):265-9. PMID: 12621093.

Mochizuki H, Arakawa H, Tokuyama K, et al. Bronchial sensitivity and bronchial reactivity in children with cough variant asthma. Chest. 2005;128(4):2427-34. PMID: 16236905.

Moroni M, Porta C, Gualtieri G, et al. Inhaled sodium cromoglycate to treat cough in advanced lung cancer patients. Br J Cancer. 1996;74(2):309-11. PMID: 8688342.

Nobata K, Fujimura M, Tsuji H, et al. Longitudinal changes of pulmonary function and bronchial responsiveness in cough-variant asthma treated with bronchodilators alone. Allergy Asthma Proc. 2006;27(6):479-85. PMID: 17176782.

Oldini C, Vecchi E. Double-blind investigation of the antitussive effectiveness of cloperastine. Current Therapeutic Research - Clinical and Experimental. 1987;42(1):99-105.

Pacheco A, Faro V, Cobeta I, et al. Gastro-oesophageal reflux, eosinophilic airway inflammation and chronic cough. Respirology. 2011;16(6):994-9. PMID: 21651646.

Park SW, Lee YM, Jang AS, et al. Development of chronic airway obstruction in patients with eosinophilic bronchitis: a prospective follow-up study. Chest. 2004;125(6):1998-2004. PMID: 15189914.

Paul IM, Beiler J, McMonagle A, et al. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161(12):1140-6. PMID: 18056558.

Paul IM, Beiler JS, King TS, et al. Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms. Pediatrics. 2010;126(6):1092-9. PMID: 21059712.

Paul IM, Shaffer ML, Yoder KE, et al. Dose-response relationship with increasing doses of dextromethorphan for children with cough. Clin Ther. 2004;26(9):1508-14. PMID: 15531013.

Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114(1):e85-90. PMID: 15231978.

Petty TL. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest. 1990;97(1):75-83. PMID: 2403903.

Redey T, Skoda E. Clinical use of Libexin, a new peripheral antitussive. Ther Hung. 1967;15(3):117-9. PMID: 4866485.

Robinson M, Hemming AL, Moriarty C, et al. Effect of a short course of rhDNase on cough and mucociliary clearance in patients with cystic fibrosis. Pediatr Pulmonol. 2000;30(1):16-24. PMID: 10862158.

Robinson M, Regnis JA, Bailey DL, et al. Effect of hypertonic saline, amiloride, and cough on mucociliary clearance in patients with cystic fibrosis. Am J Respir Crit Care Med. 1996;153(5):1503-9. PMID: 8630593.

Rusconi F, Panisi C, Dellepiane RM, et al. Pulmonary and sinus diseases in primary humoral immunodeficiencies with chronic productive cough. Arch Dis Child. 2003;88(12):1101-5. PMID: 14670780.

Schaefer MK, Shehab N, Cohen AL, et al. Adverse events from cough and cold medications in children. Pediatrics. 2008;121(4):783-7. PMID: 18227192.

Schulz M, Hammerlein A, Hinkel U, et al. Safety and usage pattern of an over-the-counter ambroxol cough syrup: a community pharmacy-based cohort study. Int J Clin Pharmacol Ther. 2006;44(9):409-21. PMID: 16995329.

Serrao N, Magnani R, Libardi S, et al. The effect of low-intensity laser in a patient with chronic obstructive pulmonary disease during respiratory therapy. Lasers in Surgery and Medicine 2012;44:54.

Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. J Altern Complement Med. 2010;16(7):787-93. PMID: 20618098.

Sundar KM, Daly SE, Pearce MJ, et al. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. Cough. 2010;6(1):2. PMID: 20398333.

Suwanjutha S, Chantarojanasiri T. The role of ketotifen in children with recurrent bronchitis. J Int Med Res. 1985;13(1):24-30. PMID: 3979657.

Tamaoki J, Yokohori N, Tagaya E, et al. Comparable effect of a leukotriene receptor antagonist and long-acting beta-adrenergic agonist in cough variant asthma. Allergy Asthma Proc. 2010;31(5):78-84. PMID: 20929598.

Townley RG, Bronstein SB. A double blind clinical evaluation of glyceryl guaiacolate. Ann Allergy. 1963;21:683-91. PMID: 14085798.

Watson RR, Zibadi S, Rafatpanah H, et al. Oral administration of the purple passion fruit peel extract reduces wheeze and cough and improves shortness of breath in adults with asthma. Nutr Res. 2008;28(3):166-71. PMID: 19083404.

Wojcicki J, Szwed G, Drozdowska-Ksiazek D. The antitussive and expectorant drug Duopect evaluated by the preferential test. Arch Immunol Ther Exp (Warsz). 1976;24(4):549-52. PMID: 793565.

No intervention of interest OR the intervention is intended to treat the underlying etiology

Allen CJ, Anvari M. Does laparoscopic fundoplication provide long-term control of gastroesophageal reflux related cough? Surg Endosc. 2004;18(4):633-7. PMID: 15026893.

Allen CJ, Anvari M. Preoperative symptom evaluation and esophageal acid infusion predict response to laparoscopic Nissen fundoplication in gastroesophageal reflux patients who present with cough. Surg Endosc. 2002;16(7):1037-41. PMID: 12165818.

Anbar RD. Hypnosis in pediatrics: applications at a pediatric pulmonary center. BMC Pediatr. 2002;2:11. PMID: 12460456.

Anbar RD, Hall HR. Childhood habit cough treated with self-hypnosis. J Pediatr. 2004;144(2):213-7. PMID: 14760264.

Baldi F, Cappiello R, Cavoli C, et al. Proton pump inhibitor treatment of patients with gastroesophageal reflux-related chronic cough: a comparison between two different daily doses of lansoprazole. World J Gastroenterol. 2006;12(1):82-8. PMID: 16440422.

Bede O, Szenasi Z, Danka J, et al. Toxocariasis associated with chronic cough in childhood: a

longitudinal study in Hungary. J Helminthol. 2008;82(4):357-63. PMID: 18752712.

Blager FB, Gay ML, Wood RP. Voice therapy techniques adapted to treatment of habit cough: a pilot study. J Commun Disord. 1988;21(5):393-400. PMID: 3183084.

Bucca CB, Culla B, Guida G, et al. Unexplained chronic cough and vitamin B-12 deficiency. Am J Clin Nutr. 2011;93(3):542-8. PMID: 21248188.

Chan PW, Debruyne JA. Inhaled nedocromil sodium for persistent cough in children. Med J Malaysia. 2001;56(4):408-13. PMID: 12014758.

Chang A, Marchant JM, McKean M, et al. Inhaled cromones for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2004;(2):CD004436. PMID: 15106252.

Chang AB, Gaffney JT, Eastburn MM, et al. Cough quality in children: a comparison of subjective vs. bronchoscopic findings. Respir Res. 2005;6:3. PMID: 15638942.

Chang AB, Halstead RA, Petsky HL. Methylxanthines for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2005;(3):CD005310. PMID: 16034969.

Chang AB, McKean M, Morris P. Inhaled anti-cholinergics for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2004;(1):CD004358. PMID: 14974067.

Chang AB, Peake J, McElrea MS. Anti-histamines for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2008;(2):CD005604. PMID: 18425925.

Chang AB, Phelan PD, Carlin JB, et al. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child. 1998;79(1):6-11. PMID: 9771244.

Chang AB, Winter D, Acworth JP. Leukotriene receptor antagonist for prolonged non-specific cough in children. Cochrane Database Syst Rev. 2006;(2):CD005602. PMID: 16625643.

Charpin J and Weibel MA. Comparative evaluation of the antitussive activity of butamirate citrate linctus versus clobutinol syrup. Respiration. 1990;57(4):275-9. PMID: 2095610.

Cheriyan S, Greenberger PA, Patterson R. Outcome of cough variant asthma treated with inhaled steroids. Ann Allergy. 1994;73(6):478-80. PMID: 7998659.

Chernish SM, Lewis G, Kraft B, et al. Clinical evaluation of a new antitussive preparation. Ann Allergy. 1963;21:677-82. PMID: 14085797.

Clough JB, Williams JD, Holgate ST. Profile of bronchial responsiveness in children with respiratory symptoms. Arch Dis Child. 1992;67(5):574-9. PMID: 1599291.

Clough JB, Williams JD, Holgate ST. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough and wheeze. A 12-month longitudinal study [published errarum appears in Am Rev Respir Dis 1992 Aug;146(2):540]. Am Rev Respir Dis. 1991;143(4 Pt 1):755-60. PMID: 2008988.

Cockcroft DW, Killian DN, Mellon JJ, et al. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy. 1977;7(3):235-43. PMID: 908121.

Cohen BM. Maximum voluntary cough ratios reflect antitussive activity of inhaled albuterol. N J Med. 1992;89(8):587-91. PMID: 1513504.

Davies MJ, Fuller P, Picciotto A, et al. Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. Arch Dis Child. 1999;81(1):38-44. PMID: 10373132.

Desjardins A, de Luca S, Cartier A, et al. Nonspecific bronchial hyperresponsiveness to inhaled histamine and hyperventilation of cold dry air in subjects with respiratory symptoms of uncertain etiology. Am Rev Respir Dis. 1988;137(5):1020-5. PMID: 3195801.

Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. J Asthma. 2002;39(4):291-7. PMID: 12095178.

Doan T, Patterson R, Greenberger PA. Cough variant asthma: usefulness of a diagnostic-therapeutic trial with prednisone. Ann Allergy. 1992;69(6):505-9. PMID: 1471782.

Ellul-Micallef R. Effect of terbutaline sulphate in chronic "allergic" cough. Br Med J (Clin Res Ed). 1983;287(6397):940-3. PMID: 6412896.

Evald T, Munch EP, Kok-Jensen A. Chronic non-asthmatic cough is not affected by inhaled beclomethasone dipropionate. A controlled double blind clinical trial. Allergy. 1989;44(7):510-4. PMID: 2683836.

Eysink PE, Bottema BJ, ter Riet G, et al. Coughing in pre-school children in general practice: when are RAST's for inhalation allergy indicated? Pediatr Allergy Immunol. 2004;15(5):394-400. PMID: 15482513.

Faruqi S, Wilmot R, Wright C, et al. Serum LDH in chronic cough: a potential marker of airway inflammation. Clin Respir J 2012;6(2):81-7. PMID: 21651741.

Fathi H, Moon T, Donaldson J, et al. Cough in adult cystic fibrosis: diagnosis and response to fundoplication. Cough. 2009;5:1. PMID: 19149907.

Field SK, Conley DP, Thawer AM, et al. Assessment and management of patients with chronic cough by Certified Respiratory Educators: a randomized controlled trial. Can Respir J. 2009;16(2):49-54. PMID: 19399308.

Fogari R, Zoppi A, Mugellini A, et al. Difference in incidence of cough induced by imidapril and ramipril: Role of prostaglandin synthesis inhibition. Biomedicine and Aging Pathology. 2011;1(2):73-77.

Fogari R, Zoppi A, Mugellini A, et al. Effects of amlodipine, nifedipine GITS, and indomethacin on angiotensin- converting enzyme inhibitor-induced cough: A randomized, placebo-controlled, double-masked, crossover study. Current Therapeutic Research - Clinical and Experimental. 1999;60(3):121-128.

Fogari R, Zoppi A, Tettamanti F, et al. Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. J Cardiovasc Pharmacol. 1992;19(5):670-3. PMID: 1381763.

Fogleman CD. GERD treatment for chronic nonspecific cough in children and adults. Am Fam Physician. 2011;84(5):502-4. PMID: 21888300.

Galvez RA, McLaughlin FJ, Levison H. The role of the methacholine challenge in children with chronic cough. J Allergy Clin Immunol. 1987;79(2):331-5. PMID: 3546464.

Ghafouri MA, Patil KD, Kass I. Sputum changes associated with the use of ipratropium bromide. Chest. 1984;86(3):387-93. PMID: 6236043.

Gibson PG, Hargreave FE, Girgis-Gabardo A, et al. Chronic cough with eosinophilic bronchitis: examination for variable airflow obstruction and response to corticosteroid. Clin Exp Allergy. 1995;25(2):127-32. PMID: 7750004.

Hannaway PJ, Hopper GD. Cough variant asthma in children. JAMA. 1982;247(2):206-8. PMID: 7053462.

Hedman J, Poussa T, Nieminen MM. A rapid dosimetric methacholine challenge in asthma diagnostics: a clinical study of 230 patients with dyspnoea, wheezing or a cough of unknown cause. Respir Med. 1998;92(1):32-9. PMID: 9519222.

Hersh MJ, Sayuk GS, Gyawali CP. Long-term therapeutic outcome of patients undergoing ambulatory pH monitoring for chronic unexplained cough. J Clin Gastroenterol. 2010;44(4):254-60. PMID: 19826278.

Hirsch SR, Viernes PF, Kory RC. Clinical and physiological evaluation of mucolytic agents nebulized with soproterenol: 10 per cent N-acetylcysteine verus 10 per cent 2-mercaptoethane sulphonate. Thorax. 1970;25(6):737-43. PMID: 4925508.

Hsiue TR, Hsieh AL, Chang HY, et al. Bronchoprovocation test by forced oscillation technique: airway hyperresponsiveness in chronic cough and psychogenic dyspnea subjects. J Formos Med Assoc. 1993;92(3):231-6. PMID: 8102275.

Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med. 1994;149(1):160-7. PMID: 8111576.

Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis. 1981;123(4 Pt 1):413-7. PMID: 7224353.

Ishiura Y, Fujimura M, Yamamori C, et al. Thromboxane antagonism and cough in chronic bronchitis. Ann Med. 2003;35(2):135-9. PMID: 12795341.

Joo JH, Park SJ, Park SW, et al. Clinical features of eosinophilic bronchitis. Korean J Intern Med.

2002;17(1):31-7. PMID: 12014210.

Kamano H, Mori T, Maeta H, et al. Analysis of Bordetella pertussis agglutinin titers during an outbreak of pertussis at a university in Japan. Jpn J Infect Dis. 2010;63(2):108-12. PMID: 20332572.

Kastelik JA, Aziz I, Ojoo JC, et al. Investigation and management of chronic cough using a probability-based algorithm. Eur Respir J. 2005;25(2):235-43. PMID: 15684286.

Kawai S, Baba K, Matsubara A, et al. The efficacy of montelukast and airway mast cell profiles in patients with cough variant asthma. J Asthma. 2008;45(3):243-50. PMID: 18415834.

Kiljander TO, Salomaa ER, Hietanen EK, et al. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. Eur Respir J. 2000;16(4):633-8. PMID: 11106204.

Kita T, Fujimura M, Ogawa H, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. Allergol Int. 2010;59(2):185-92. PMID: 20299826.

Konig P. Hidden asthma in childhood. Am J Dis Child. 1981;135(11):1053-5. PMID: 7294009.

Lee J, Kim M, Kim JH, et al. A cheaper, faster way to resolve chronic cough. J Fam Pract. 2007;56(8):641-6. PMID: 17669289.

Lieder A, and Issing W. Treatment for resilient cough owing to laryngopharyngeal reflux with a combination of proton pump inhibitor and Gaviscon® Advance: how we do it. Clinical Otolaryngology 2011;36(6):583-7. PMID: 22212545.

Liu SF, Lin MC, Chang HW. Relationship of allergic degree and PC20 level in adults with positive methacholine challenge test. Respiration. 2005;72(6):612-6. PMID: 16355001.

Malmberg LP, Pelkonen AS, Haahtela T, et al. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax. 2003;58(6):494-9. PMID: 12775859.

Marguet C, Jouen-Boedes F, Dean TP, et al. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1533-40. PMID: 10228122.

Mulrennan S, Wright C, Thompson R, et al. Effect of salbutamol on smoking related cough. Pulm Pharmacol Ther. 2004;17(3):127-31. PMID: 15123221.

Mund E, Christensson B, Gronneberg R, et al. Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough. Chest. 2005;127(5):1714-21. PMID: 15888851.

Nennig ME, Shinefield HR, Edwards KM, et al. Prevalence and incidence of adult pertussis in an urban population. JAMA. 1996;275(21):1672-4. PMID: 8637142.

Niimi A, Nguyen LT, Usmani O, et al. Reduced pH and chloride levels in exhaled breath condensate of patients with chronic cough. Thorax. 2004;59(7):608-12. PMID: 15223872.

Nishikawa M, Suzuki S, Miyazawa N, et al. Serum level of eosinophil cationic protein in patients with chronic cough: relationship to blood eosinophils and airway hyperresponsiveness. J Asthma. 1998;35(2):219-24. PMID: 9576148.

Nishimura H, Mochizuki H, Tokuyama K, et al. Relationship between bronchial hyperresponsiveness and development of asthma in children with chronic cough. Pediatr Pulmonol. 2001;31(6):412-8. PMID: 11389572.

Nogami H, Shoji S, Nishima S. Exhaled nitric oxide as a simple assessment of airway hyperresponsiveness in bronchial asthma and chronic cough patients. J Asthma. 2003;40(6):653-9. PMID: 14579996.

O'Connell F, Springall DR, Moradoghli-Haftvani A, et al. Abnormal intraepithelial airway nerves in persistent unexplained cough? Am J Respir Crit Care Med. 1995;152(6 Pt 1):2068-75. PMID: 8520777.

Ogawa H, Fujimura M, Takeuchi Y, et al. Sensitization to Bjerkandera adusta enhances severity of cough symptom in patients with fungus-associated chronic cough (FACC). Med Mycol J. 2011;52(3):205-12. PMID: 21891982.

Ogawa H, Fujimura M, Takeuchi Y, et al. Is Bjerkandera adusta Important to fungus-associated chronic cough as an allergen? Eight cases' reports. J Asthma. 2009;46(8):849-55. PMID: 19863292.

Ogawa H, Fujimura M, Takeuchi Y, et al. The importance of basidiomycetous fungi cultured from the sputum of chronic idiopathic cough: a study to determine the existence of recognizable clinical patterns to distinguish CIC from non-CIC. Respir Med. 2009;103(10):1492-7. PMID: 19473825.

Oh MJ, Lee JY, Lee BJ, et al. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. Chest. 2008;134(5):990-5. PMID: 18583518.

Otsuka K, Niimi A, Matsumoto H, et al. Plasma substance p levels in patients with persistent cough. Respiration. 2011;82(5):431-8. PMID: 21846969.

Pawar S, Lim HJ, Gill M, et al. Treatment of postnasal drip with proton pump inhibitors: a prospective, randomized, placebo-controlled study. Am J Rhinol. 2007;21(6):695-701. PMID: 18201449.

Pizzichini MM, Pizzichini E, Parameswaran K, et al. Nonasthmatic chronic cough: No effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. Can Respir J. 1999;6(4):323-30. PMID: 10463960.

Poe RH, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. Chest. 2003;123(3):679-84. PMID: 12628862.

Ponsioen BP, Hop WC, Vermue NA, et al. Efficacy of fluticasone on cough: a randomised controlled trial. Eur Respir J. 2005;25(1):147-52. PMID: 15640336.

Pornsuriyasak P, Charoenpan P, Vongvivat K, et al. Inhaled corticosteroid for persistent cough following upper respiratory tract infection. Respirology. 2005;10(4):520-4. PMID: 16135178.

Pounsford JC, Birch MJ, Saunders KB. Effect of bronchodilators on the cough response to inhaled citric acid in normal and asthmatic subjects. Thorax. 1985;40(9):662-7. PMID: 2932814.

Qiu Z, Wei W, Yu L, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology. 2010;15(5):830-836.

Rafferty P, Jackson L, Smith R, et al. Terfenadine, a potent histamine H1-receptor antagonist in the treatment of grass pollen sensitive asthma. Br J Clin Pharmacol. 1990;30(2):229-35. PMID: 1976343.

Ratner PH, Findlay SR, Hampel F, Jr., et al. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol. 1994;94(5):818-25. PMID: 7963150.

Robson RA, Taylor BJ, Taylor B. Sodium cromoglycate: spincaps or metered dose aerosol. Br J Clin Pharmacol. 1981;11(4):383-4. PMID: 6789851.

Rubin BK. An in vitro comparison of the mucoactive properties of guaifenesin, iodinated glycerol, surfactant, and albuterol. Chest. 1999;116(1):195-200. PMID: 10424525.

Rubin BK, Ramirez O, Ohar JA. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. Chest. 1996;109(2):348-52. PMID: 8620704.

Ryan NM, Vertigan AE, Gibson PG. Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement. Cough. 2009;5:4. PMID: 19292930.

Sagara H, Yukawa T, Kashima R, et al. Effects of pranlukast hydrate on airway hyperresponsiveness in non-asthmatic patients with Japanese cedar pollinosis. Allergol Int. 2009;58(2):277-87. PMID: 19390239.

Saito Y, Azuma A, Morimoto T, et al. Tiotropium ameliorates symptoms in patients with chronic airway mucus hypersecretion which is resistant to macrolide therapy. Intern Med. 2008;47(7):585-91. PMID: 18379141.

Sheikh A, Nolan D, Greenstone M. Long-acting beta-2-agonists for bronchiectasis. Cochrane Database Syst Rev. 2001;(4):CD002155. PMID: 11687145.

Shioya T, Ito N, Sasaki M, et al. Cough threshold for capsaicin increases by azelastine in patients with cough-variant asthma. Pulm Pharmacol. 1996;9(1):59-62. PMID: 8843511.

Shioya T, Ito N, Watanabe A, et al. Antitussive effect of azelastine hydrochloride in patients with bronchial asthma. Arzneimittelforschung. 1998;48(2):149-53. PMID: 9541725.

Shioya T, Satake M, Kagaya M, et al. Antitussive effects of the H1-receptor antagonist epinastine in

patients with atopic cough (eosinophilic bronchitis). Arzneimittelforschung. 2004;54(4):207-12. PMID: 15146933.

Shioya T, Satake M, Sano M, et al. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on cough variant asthma. Eur J Clin Pharmacol. 2002;58(3):171-6. PMID: 12107601.

Sipp JA, Haver KE, Masek BJ, et al. Botulinum toxin A: a novel adjunct treatment for debilitating habit cough in children. Ear Nose Throat J. 2007;86(9):570-2. PMID: 17970150.

Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. Ann Allergy Asthma Immunol. 2004;93(3):232-6. PMID: 15478381.

Takemura M, Niimi A, Matsumoto H, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. Respiration 2012;83(4):308-15. PMID: 22094623.

Theodore AC, Tseng CH, Li N, et al. Correlation of cough with disease activity and treatment with cyclosphosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study. Chest 2011; [epub ahead of print]. PMID: 22156609

Vardar R, Sweis R, Anggiansah A, et al. Upper esophageal sphincter and esophageal motility in patients with chronic cough and reflux: assessment by high-resolution manometry. Dis Esophagus 2012; [epub ahead of print]. PMID: 22591118.

Waring JP, Lacayo L, Hunter J, et al. Chronic cough and hoarseness in patients with severe gastroesophageal reflux disease. Diagnosis and response to therapy. Dig Dis Sci. 1995;40(5):1093-7. PMID: 7729270.

Yu L, Qiu Z, Lu H, et al. Clinical benefit of sequential three-step empirical therapy in the management of chronic cough. Respirology. 2008;13(3):353-8. PMID: 18399856.

No outcomes of interest

Abborr J, Holt A, Morton AM, et al. Patient indicators of a pulmonary exacerbation: preliminary reports from school aged children map onto those of adults. K Cyst Fibros 2012;11(3):180-6. PMID: 22172941.

Al-Mobeireek AF, Al-Sarhani A, Al-Amri S, et al. Chronic cough at a non-teaching hospital: Are extrapulmonary causes overlooked? Respirology. 2002;7(2):141-6. PMID: 11985737.

Ambrosino N, Callegari G, Galloni C, et al. Clinical evaluation of oscillating positive expiratory pressure for enhancing expectoration in diseases other than cystic fibrosis. Monaldi Arch Chest Dis. 1995;50(4):269-75. PMID: 7550205.

Anderson-james S, Mewcombe PA, Marchant JM, et al. Development of a children's acute cough specific quality of life quationnaire (PAC-QOL). Respirology 2012;17:76

Aquilina R, Bergero F, Noceti P, et al. Double blind study with neltenexine vs placebo in patients affected by acute and chronic lung diseases. Minerva Pneumologica. 2001;40(2):77-82.

Asilsoy S, Bayram E, Agin H, et al. Evaluation of chronic cough in children. Chest. 2008;134(6):1122-8. PMID: 18689594.

Avidan B, Sonnenberg A, Schnell TG, et al. Temporal associations between coughing or wheezing and acid reflux in asthmatics. Gut. 2001;49(6):767-72. PMID: 11709509.

Avital A, Uwyyed K, Berkman N, et al. Exhaled nitric oxide and asthma in young children. Pediatr Pulmonol. 2001;32(4):308-13. PMID: 11568992.

Ayik SO, Basoglu OK, Erdinc M, et al. Eosinophilic bronchitis as a cause of chronic cough. Respir Med. 2003;97(6):695-701. PMID: 12814157.

Aylward M, Maddock J, Davies DE, et al. Dextromethorphan and codeine: comparison of plasma kinetics and antitussive effects. Eur J Respir Dis. 1984;65(4):283-91. PMID: 6539224.

Badier M, Guillot C, Dubus JC. Bronchial challenge with carbachol in 3-6-year-old children: body plethysmography assessments. Pediatr Pulmonol. 1999;27(2):117-23. PMID: 10088935.

Bai J, Peat JK, Berry G, et al. Questionnaire items that predict asthma and other respiratory conditions in adults. Chest. 1998;114(5):1343-8. PMID: 9824012.

Bailly C, Crenesse D, Albertini M. Evaluation of impulse oscillometry during bronchial challenge testing in children. Pediatr Pulmonol. 2011;PMID: 21634033.

Bakirtas A, Turktas I. Methacholine and adenosine 5'-monophosphate challenges in preschool children with cough-variant and classic asthma. Pediatr Pulmonol. 2007;42(10):973-9. PMID: 17722054.

Bakker EM, van der Meijden JC, Nieuwhof EM, et al. Determining presence of lung disease in young children with cystic fibrosis: lung clearance index, oxygen saturation and cough frequency. J Cyst Fibros 2012;11(3):223-30. PMID: 22265603.

Barbara AM, Loeb M, Dolovich L, et al. Agreement between self-report and medical records on signs and symptoms of respiratory illness. Prim Care Respir J 2012; 21(2):145-52. PMID: 22273629.

Barnes TW, Afessa B, Swanson KL, et al. The clinical utility of flexible bronchoscopy in the evaluation of chronic cough. Chest. 2004;126(1):268-72. PMID: 15249470.

Bateman JR, Newman SP, Daunt KM, et al. Regional lung clearance of excessive bronchial secretions during chest physiotherapy in patients with stable chronic airways obstruction. Lancet. 1979;1(8111):294-7. PMID: 84947.

Bentur L, Beck R, Berkowitz D, et al. Adenosine bronchial provocation with computerized wheeze detection in young infants with prolonged cough: correlation with long-term follow-up. Chest. 2004;126(4):1060-5. PMID: 15486364.

Berninger A, Webber MP, Weakley J, et al. Quality of life in relation to upper and lower respiratory conditions among retired 9/11-exposed firefighters with pulmonary disability. Qual Life Res. 2010;19(10):1467-76. PMID: 20680691.

Beydon N, M'Buila C, Bados A, et al. Interrupter resistance short-term repeatability and bronchodilator response in preschool children. Respir Med. 2007;101(12):2482-7. PMID: 17720469.

Beydon N, Trang-Pham H, Bernard A, et al. Measurements of resistance by the interrupter technique and of transcutaneous partial pressure of oxygen in young children during methacholine challenge. Pediatr Pulmonol. 2001;31(3):238-46. PMID: 11276137.

Binder RE, Mitchell CA. Use of the productive cough test to confirm presence of respiratory symptoms in school-age children. Am Rev Respir Dis. 1975;112(3):461-3. PMID: 1163898.

Bingol Boz A, Aydn F, Celmeli F, et al. Does gastroesophageal reflux scintigraphy correlate with clinical findings in children with chronic cough? Nucl Med Commun. 2009;30(10):802-6. PMID: 19654561.

Blondeau K, Mertens V, Dupont L, et al. The relationship between gastroesophageal reflux and cough in children with chronic unexplained cough using combined impedance-pH-manometry recordings. Pediatr Pulmonol. 2010;PMID: 20967945.

Bogte A, Bredenoord AJ, Smout AJ. Diagnostic yield of oesophageal pH monitoring in patients with chronic unexplained cough. Scand J Gastroenterol. 2008;43(1):13-9. PMID: 18938747.

Borrelli O, Marabotto C, Mancini V, et al. Role of gastroesophageal reflux in children with unexplained chronic cough. Journal of Pediatric Gastroenterology and Nutrition. 2011;53(3):287-292.

Boulet LP, Laviolette M, Turcotte H, et al. Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. Chest. 1997;112(1):45-52. PMID: 9228356.

Boulet LP, Milot J, Boutet M, et al. Airway inflammation in nonasthmatic subjects with chronic cough. Am J Respir Crit Care Med. 1994;149(2 Pt 1):482-9. PMID: 8306050.

Braido F, Baiardini I, Balestracci S, et al. The relationship between asthma control and quality-of-life impairment due to chronic cough: a real-life study. Ann Allergy Asthma Immunol. 2008;101(4):370-4. PMID: 18939724.

Brightling CE, Ward R, Goh KL, et al. Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med. 1999;160(2):406-10. PMID: 10430705.

Brightling CE, Ward R, Wardlaw AJ, et al. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. Eur Respir J. 2000;15(4):682-6. PMID: 10780759.

Brunekreef B, Groot B, Rijcken B, et al. Reproducibility of childhood respiratory symptom questions. Eur Respir J. 1992;5(8):930-5. PMID: 1426200.

Bucca CB, Bugiani M, Culla B, et al. Chronic cough

and irritable larynx. J Allergy Clin Immunol. 2011;127(2):412-9. PMID: 21167571.

Bucknall CE, Neilly JB, Carter R, et al. Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. Br Med J (Clin Res Ed). 1988;296(6615):86-8. PMID: 2827838.

Caporalini R, Giosue GL. Neltenexine in lung diseases: An open, randomised, controlled study versus N-acetylcysteine comparison. Minerva Pneumologica. 2001;40(2):57-62.

Carney IK, Gibson PG, Murree-Allen K, et al. A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med. 1997;156(1):211-6. PMID: 9230750.

Ceyhan BB, Karakurt S. Effect of oxolamine on cough sensitivity in COPD patients. Respir Med. 2002;96(1):61-3. PMID: 11863211.

Chan KK, Ing AJ, Laks L, et al. Chronic cough in patients with sleep-disordered breathing. Eur Respir J. 2010;35(2):368-72. PMID: 20123846.

Chang AB, Gibson PG, Willis C, et al. Do sex and atopy influence cough outcome measurements in children? Chest. 2011;140(2):324-30. PMID: 21393395.

Chang AB, Phelan PD, Robertson CF, et al. Frequency and perception of cough severity. J Paediatr Child Health. 2001;37(2):142-5. PMID: 11328468.

Chang AB, Phelan PD, Sawyer SM, et al. Cough sensitivity in children with asthma, recurrent cough, and cystic fibrosis. Arch Dis Child. 1997;77(4):331-4. PMID: 9389238.

Chang AB, Phelan PD, Sawyer SM, et al. Airway hyperresponsiveness and cough-receptor sensitivity in children with recurrent cough. Am J Respir Crit Care Med. 1997;155(6):1935-9. PMID: 9196099.

Chatkin JM, Ansarin K, Silkoff PE, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. Am J Respir Crit Care Med. 1999;159(6):1810-3. PMID: 10351923.

Chausow AM, Banner AS. Comparison of the tussive effects of histamine and methacholine in humans. J Appl Physiol. 1983;55(2):541-6. PMID: 6352579.

Cho YS, Park SY, Lee CK, et al. Enhanced cough response to hyperpnea with cold air challenge in chronic cough patients showing increased cough sensitivity to inhaled capsaicin. Allergy. 2003;58(6):486-91. PMID: 12757448.

Choi WA, Park JH, Kim DH, et al. Cough assistance device for patients with glottis dysfunction and/or tracheostomy. J Rehabil Med 2012;44(4):351-5. PMID: 22453774.

Choudry NB, Fuller RW. Sensitivity of the cough reflex in patients with chronic cough. Eur Respir J. 1992;5(3):296-300. PMID: 1572441.

Christensen EF, Nedergaard T, Dahl R. Long-term treatment of chronic bronchitis with positive expiratory pressure mask and chest physiotherapy. Chest. 1990;97(3):645-50. PMID: 2106412.

Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. Pediatrics. 1981;67(1):6-12. PMID: 7243436.

Corsico AG, Villani S, Zoia MC, et al. Chronic productive cough in young adults is very often due to chronic rhino-sinusitis. Monaldi Arch Chest Dis. 2007;67(2):90-4. PMID: 17695692.

Cuijpers CE, Wesseling GJ, Swaen GM, et al. Asthma-related symptoms and lung function in primary school children. J Asthma. 1994;31(4):301-12. PMID: 8040154.

Dani VS, Mogre SS, Saoji R. Evaluation of chronic cough in children: clinical and diagnostic spectrum and outcome of specific therapy. Indian Pediatr. 2002;39(1):63-9. PMID: 11805355.

David D, Jallad N, Germino FW, et al. A Comparison of the Cough Profile of Fosinopril and Enalapril in Hypertensive Patients with a History of ACE Inhibitor-Associated Cough. Am J Ther. 1995;2(10):806-813. PMID: 11854791.

de Benedictis FM, Canny GJ, Levison H. Methacholine inhalational challenge in the evaluation of chronic cough in children. J Asthma. 1986;23(6):303-8. PMID: 3546254.

De Diego A, Martinez E, Perpina M, et al. Airway inflammation and cough sensitivity in cough-variant asthma. Allergy. 2005;60(11):1407-11. PMID: 16197473.

Deilami GD, Khandashpour M, Paknejad O, et al.

Evaluation of methacholine challenge test results in chronic cough patients referring to clinic of pulmonary disease. Acta Medica Iranica. 2009;47(3):175-179.

Demers RY, Fischetti LR, Neale AV. Incongruence between self-reported symptoms and objective evidence of respiratory disease among construction workers. Soc Sci Med. 1990;30(7):805-10. PMID: 2315748.

DeVault K, Achem S, Lee A, et al. Cough and GRRD: Prevalence, association and effect of gender in uninvestigated and untreated patients over age 65. American Journal of Gastroenterology. 2011;106:S29-S30.

Dohna-Schwake C, Ragette R, Teschler H, et al. IPPB-assisted coughing in neuromuscular disorders. Pediatr Pulmonol. 2006;41(6):551-7. PMID: 16617451.

Edwards GF, Lewis HE, Stafford D. The effect of pholcodine with and without an antihistamine on cough and expectoration. Br J Dis Chest. 1977;71(4):245-52. PMID: 22340.

Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med. 2006;354(3):229-40. PMID: 16421364.

Field GB. The application of a quantitative estimate of cough frequency to epidemiological surveys. Int J Epidemiol. 1974;3(2):135-43. PMID: 4854653.

Fifoot S, Wilson C, MacDonald J, et al. Respiratory exacerbations in children with cystic fibrosis: physiotherapy treatment outcomes. Physiother Theory Pract. 2005;21(2):103-11. PMID: 16392463.

Formanek W, Inci D, Lauener RP, et al. Elevated nitrite in breath condensates of children with respiratory disease. Eur Respir J. 2002;19(3):487-91. PMID: 11936527.

French CT, Fletcher KE, Irwin RS. A comparison of gender differences in health-related quality of life in acute and chronic coughers. Chest. 2005;127(6):1991-8. PMID: 15947311.

French CT, Fletcher KE, Irwin RS. Gender differences in health-related quality of life in patients complaining of chronic cough. Chest. 2004;125(2):482-8. PMID: 14769728.

Frigerio G, Lodola E, Sperotti L. The antitussive activity of diviminol (Z.424). Curr Ther Res Clin Exp. 1970;12(8):516-9. PMID: 4988838.

Fujimoto K, Yamaguchi S, Urushibata K, et al. Sputum eosinophilia and bronchial responsiveness in patients with chronic non-productive cough responsive to anti-asthma therapy. Respirology. 2003;8(2):168-74. PMID: 12753531.

Fujimura M, Abo M, Ogawa H, et al. Importance of atopic cough, cough variant asthma and sinobronchial syndrome as causes of chronic cough in the Hokuriku area of Japan. Respirology. 2005;10(2):201-7. PMID: 15823186.

Fujimura M, Kamio Y, Hashimoto T, et al. Cough receptor sensitivity and bronchial responsiveness in patients with only chronic nonproductive cough: in view of effect of bronchodilator therapy. J Asthma. 1994;31(6):463-72. PMID: 7961323.

Fujimura M, Ohkura N, Abo M, et al. Exhaled nitric oxide levels in patients with atopic cough and cough variant asthma. Respirology. 2008;13(3):359-64. PMID: 18399857.

Fujimura M, Sakamoto S, Matsuda T. Bronchodilator-resistive cough in atopic patients: bronchial reversibility and hyperresponsiveness. Intern Med. 1992;31(4):447-52. PMID: 1352997.

Fujimura M, Songur N, Kamio Y, et al. Detection of eosinophils in hypertonic saline-induced sputum in patients with chronic nonproductive cough. J Asthma. 1997;34(2):119-26. PMID: 9088298.

Gharagozlou M, Kompani F, Movahedi M. Comparison between peak expiratory flow rate and forced expiratory volume in one second in the evaluation of children suspected to have asthma. Iran J Allergy Asthma Immunol. 2004;3(1):21-4. PMID: 17301387.

Ghezzi M, Guida E, Ullmann N, et al. Weakly acidic gastroesophageal refulxes are frequently triggers in young children with chronic cough. Pediatric Pulmonology 2012; [epub ahead of print] PMID: 22553136.

Gibson PG, Simpson JL, Chalmers AC, et al. Airway eosinophilia is associated with wheeze but is uncommon in children with persistent cough and frequent chest colds. Am J Respir Crit Care Med. 2001;164(6):977-81. PMID: 11587982.

Gibson PG, Zlatic K, Scott J, et al. Chronic cough resembles asthma with IL-5 and granulocyte-macrophage colony-stimulating factor gene expression in bronchoalveolar cells. J Allergy Clin Immunol. 1998;101(3):320-6. PMID: 9525446.

Goss CH, Edwards TC, Ramsey BW, et al. Patient-reported respiratory symptoms in cystic fibrosis. J Cyst Fibros. 2009;8(4):245-52. PMID: 19481983.

Gross V, Reinke C, Dette F, et al. Mobile nocturnal long-term monitoring of wheezing and cough. Biomed Tech (Berl). 2007;52(1):73-6. PMID: 17313338.

Gulsvik A, Refvem OK. A scoring system on respiratory symptoms. Eur Respir J. 1988;1(5):428-32. PMID: 3169213.

Hadjikoutis S, Eccles R, Wiles CM. Coughing and choking in motor neuron disease. J Neurol Neurosurg Psychiatry. 2000;68(5):601-4. PMID: 10766890.

Hahn PY, Morgenthaler TY, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clin Proc. 2007;82(11):1350-5. PMID: 17976354.

Hammond CS. Evaluating cough: The role of dysphagia and aspiration. Journal of Respiratory Diseases. 2008;29(7):263-265.

Harnden A, Grant C, Harrison T, et al. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. BMJ. 2006;333(7560):174-7. PMID: 16829538.

Hensley MJ, Chalmers A, Clover K, et al. Symptoms of asthma: comparison of a parent-completed retrospective questionnaire with a prospective daily symptom diary. Pediatr Pulmonol. 2003;36(6):509-13. PMID: 14618643.

Higuchi O, Adachi Y, Itazawa T, et al. Relationship between rhinitis and nocturnal cough in school children. Pediatric Allergy and Immunology 2012; 23(6):562-6. PMID: 22554384.

Hunt J, Yu Y, Burns J, et al. Identification of acid reflux cough using serial assays of exhaled breath condensate pH. Cough. 2006;2:3. PMID: 16608520.

Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and clearance of esophageal acid. Chest. 1992;102(6):1668-71. PMID: 1446469.

Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and gastro-oesophageal reflux. Thorax. 1991;46(7):479-83. PMID: 1877035.

Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7. PMID: 2178528.

Irwin RS, French CT, Smyrnios NA, et al. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. Arch Intern Med. 1997;157(17):1981-7. PMID: 9308510.

Jain NB, Sullivan M, Kazis LE, et al. Factors associated with health-related quality of life in chronic spinal cord injury. Am J Phys Med Rehabil. 2007;86(5):387-96. PMID: 17449983.

Jakeways N, McKeever T, Lewis SA, et al. Relationship between FEV1 reduction and respiratory symptoms in the general population. Eur Respir J. 2003;21(4):658-63. PMID: 12762353.

Jarad NA and Sequeiros IM. A novel respiratory symptom scoring system for CF pulmonary exacerbations. QJM 2012;105(2):137-43. PMID: 21908385.

Jayaram S, Desai A. Efficacy and safety of Ascoril expectorant and other cough formula in the treatment of cough management in paediatric and adult patients--a randomised double-blind comparative trial. J Indian Med Assoc. 2000;98(2):68-70. PMID: 11016157.

Jesenak M, Babusikova E, Petrikova M, et al. Cough reflex sensitivity in various phenotypes of childhood asthma. J Physiol Pharmacol. 2009;60 Suppl 5:61-5. PMID: 20134041.

Jones PD, Hankin R, Simpson J, et al. The tolerability, safety, and success of sputum induction and combined hypertonic saline challenge in children. Am J Respir Crit Care Med. 2001;164(7):1146-9. PMID: 11673200.

Jones PW, Chen WH, Wilcox TK, et al. Characterizing and quantifying the symptomatic features of COPD exacerbations. Chest. 2011;139(6):1388-94. PMID: 21071529.

Kang H, Koh YY, Yoo Y, et al. Maximal airway

response to methacholine in cough-variant asthma: comparison with classic asthma and its relationship to peak expiratory flow variability. Chest. 2005;128(6):3881-7. PMID: 16354858.

Kapaskelis AM, Vouloumanou EK, Rafailidis PI, et al. High prevalence of antibody titers against Bordetella pertussis in an adult population with prolonged cough. Respir Med. 2008;102(11):1586-91. PMID: 18684605.

Kapur N, Masters IB, Morris PS, et al. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2011;PMID: 21830316.

Kapur N, Masters IB, Newcombe P, et al. The burden of disease in pediatric non-cystic fibrosis bronchiectasis. Chest. 2011;PMID: 21885727.

Kastelik JA, Thompson RH, Aziz I, et al. Sex-related differences in cough reflex sensitivity in patients with chronic cough. Am J Respir Crit Care Med. 2002;166(7):961-4. PMID: 12359654.

Kerem E, Wilschanski M, Miller NL, et al. Ambulatory quantitative waking and sleeping cough assessment in patients with cystic fibrosis. J Cyst Fibros. 2011;10(3):193-200. PMID: 21459051.

Knocikova J, Korpas J, Vrabec M, et al. Wavelet analysis of voluntary cough sound in patients with respiratory diseases. J Physiol Pharmacol. 2008;59 Suppl 6:331-40. PMID: 19218657.

Korpas J, Vrabec M, Sadlonova J, et al. Single, double and multi cough sound differentiation. Acta Physiologica Hungarica. 2005;92(3-4):203-209.

Koskela HD, Purokivi MK, Nieminen RM, et al. Asthmatic cough and airway oxidative stress. Respir Physiol Neurobiol 2012;181(3):346-50. PMID: 22546340.

Lim KG, Rank MA, Kita H, et al. Neuropeptide levels in nasal secretions from patients with and without chronic cough. Annals of Allergy, Asthma and Immunology. 2011;107(4):360-363.

Liu B, Yu L, Qiu ZH, et al. The diagnostic value of multichannel intraluminal esophageal impedance andph monitoring for gastroesophageal reflux-related chronic cough. Respirology. 2011;16:1.

Marchant JM, Masters IB, Taylor SM, et al. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax. 2006;61(8):694-8. PMID: 16670171.

Marchant JM, Masters IB, Taylor SM, et al. Evaluation and outcome of young children with chronic cough. Chest. 2006;129(5):1132-41. PMID: 16685002.

Matsumoto H, Tabuena RP, Niimi A, et al. Cough triggers and their pathophysiology in patients with prolonged or chronic cough. Allergol Int 2012;61(1):123-32. PMID: 22377525.

Moretti M, Lopez-Vidriero MT, Pavia D, et al. Relationship between bronchial reversibility and tracheobronchial clearance in patients with chronic bronchitis. Thorax. 1997;52(2):176-80. PMID: 9059481.

Morice AH, Faruqi S, Wright CE, et al. Cough hypersensitivity syndrome: a distinct clinical entity. Lung. 2011;189(1):73-9. PMID: 21240613.

Morrison RJ, Schindler JS. Evaluation and treatment of the patient with chronic cough referred to the otolaryngologist. Laryngoscope. 2011;121(Suppl 5):S256.

Murata A, Taniguchi Y, Hashimoto Y, et al. Discrimination of productive and non-productive cough by sound analysis. Intern Med. 1998;37(9):732-5. PMID: 9804079.

Mutalithas K, Watkin G, Willig B, et al. Improvement in health status following bronchopulmonary hygiene physical therapy in patients with bronchiectasis. Respir Med. 2008;102(8):1140-4. PMID: 18585027.

Nicolis FB, Pasquariello G. Controlled clinical trials of antitussive agents: an experimental evaluation of different methods. J Pharmacol Exp Ther. 1962;136:183-9. PMID: 14479574.

Nogami H, Odajima H, Shoji S, et al. Capsaicin provocation test as a diagnostic method for determining multiple chemical sensitivity. Allergology International. 2004;53(2):153-157.

O'Connell F, Thomas VE, Studham JM, et al. Capsaicin cough sensitivity increases during upper respiratory infection. Respir Med. 1996;90(5):279-86. PMID: 9499812.

Olivieri D, Ciaccia A, Marangio E, et al. Role of bromhexine in exacerbations of bronchiectasis.

Double-blind randomized multicenter study versus placebo. Respiration. 1991;58(3-4):117-21. PMID: 1745841.

Olivieri D, Del Donno M, Casalini A, et al. Activity of erdosteine on mucociliary transport in patients affected by chronic bronchitis. Respiration. 1991;58(2):91-4. PMID: 1862257.

Olseni L, Stentoft J, Hornblad Y. Mucus clearance in patients with chronic non-productive cough. Applied Cardiopulmonary Pathophysiology. 1996;6(2):139-144.

Paneroni M, Clini E, Simonelli C, et al. Safety and efficacy of short-term intrapulmonary percussive ventilation in patients with bronchiectasis. Respir Care. 2011;56(7):984-8. PMID: 21352670.

Parameswaran K, Allen CJ, Kamada D, et al. Sputum cell counts and exhaled nitric oxide in patients with gastroesophageal reflux, and cough or asthma. Can Respir J. 2001;8(4):239-44. PMID: 11521139.

Park HW, Kim SH, Chang YS, et al. Complementary roles of capsaicin cough sensitivity test and induced sputum test to methacholine bronchial provocation test in predicting response to inhaled corticosteroids in patients with chronic nonproductive cough. Ann Allergy Asthma Immunol. 2007;98(6):533-9. PMID: 17601265.

Paterson WG, Murat BW. Combined ambulatory esophageal manometry and dual-probe pH-metry in evaluation of patients with chronic unexplained cough. Dig Dis Sci. 1994;39(5):1117-25. PMID: 8174426.

Patria MF, Fusi M, Pietrogrande MC, et al. Serial high-resolution computed tomography (HRCT) in children with chronic productive cough and bronchiectasis unrelated to cystic fibrosis: Correlations with clinical evaluation. Italian Journal of Pediatrics. 2006;32(2):112-117.

Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest. 2001;120(4):1121-8. PMID: 11591548.

Pavia D, Agnew JE, Glassman JM, et al. Effects of iodopropylidene glycerol on tracheobronchial clearance in stable, chronic bronchitic patients. Eur J Respir Dis. 1985;67(3):177-84. PMID: 3908131.

Penman RW, O'Neill RP, Begley L. The progress of chronic airway obstruction in relation to measurements of airway resistance and lung elastic recoil. Am Rev Respir Dis. 1970;101(4):536-44. PMID: 5439875.

Petsios KT, Priftis KN, Tsoumakas C, et al. Cough affects quality of life in asthmatic children aged 8-14 more than other asthma symptoms. Allergol Immunopathol (Madr). 2009;37(2):80-8. PMID: 19445864.

Petsky HL, Acworth JP, Clark R, et al. Asthma and protracted bronchitis: who fares better during an acute respiratory infection? J Paediatr Child Health. 2009;45(1-2):42-7. PMID: 19208065.

Petsonk EL, Wang ML. Interpreting screening questionnaires: specific respiratory symptoms and their relationship to objective test results. J Occup Environ Med. 2010;52(12):1225-9. PMID: 21124238.

Pettit RS, Johnson CE. Airway-Rehydrating agents for the treatment of cystic fibrosis: Past, present, and future. Annals of Pharmacotherapy. 2011;45(1):49-59.

Piirila P, Sovijarvi AR. Differences in acoustic and dynamic characteristics of spontaneous cough in pulmonary diseases. Chest. 1989;96(1):46-53. PMID: 2736992.

Piquette CA, Clarkson L, Okamoto K, et al. Respiratory-related quality of life: relation to pulmonary function, functional exercise capacity, and sputum biophysical properties. J Aerosol Med. 2000;13(3):263-72. PMID: 11066029.

Plante C, Jacques L, Chevalier S, et al. Comparability of internet and telephone data in a survey on the respiratory health of children. Canadian Respiratory Journal 2012;19(1):13-8. PMID: 22332126.

Poe RH, Harder RV, Israel RH, et al. Chronic persistent cough. Experience in diagnosis and outcome using an anatomic diagnostic protocol. Chest. 1989;95(4):723-8. PMID: 2924600.

Power JT, Stewart IC, Connaughton JJ, et al. Nocturnal cough in patients with chronic bronchitis and emphysema. Am Rev Respir Dis. 1984;130(6):999-1001. PMID: 6508020.

Prieto L, Ferrer A, Ponce S, et al. Exhaled nitric

oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest. 2009;136(3):816-22. PMID: 19411296.

Prudon B, Birring SS, Vara DD, et al. Cough and glottic-stop reflex sensitivity in health and disease. Chest. 2005;127(2):550-7. PMID: 15705995.

Puolijoki H, Nieminen MM, Moilanen E, et al. Bradykinin: A putative mediator of enalapril-induced cough. Current Therapeutic Research - Clinical and Experimental. 1992;51(6):844-847.

Purokivi M, Koskela H, Koistinen T, et al. Assessment of inhaled corticosteroid treatment response in asthma using hypertonic histamine challenge-induced cough. Clin Respir J. 2010;4(2):67-73. PMID: 20565479.

Qiu Z, Yu L, Xu S, et al. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. Respirology. 2011;16(4):645-52. PMID: 21342332.

Ravez P, Richez M, Godart G, et al. Effect of intermittent high-frequency intrapulmonary percussive breathing on mucus transport. Eur J Respir Dis Suppl. 1986;146:285-9. PMID: 3536553.

Redding GJ, Kishioka C, Martinez P, et al. Physical and transport properties of sputum from children with idiopathic bronchiectasis. Chest. 2008;134(6):1129-34. PMID: 18753467.

Rehman A, Waraich MM, Irfanullah. Algorithm for the diagnosis of chronic cough in children 6 to 59-months. Pakistan Paediatric Journal. 2009;33(1):30-38.

Ren CL, Rosenfeld M, Mayer OH, et al. Analysis of the associations between lung function and clinical features in preschool children with Cystic Fibrosis. Pediatric Pulmonology 2012;47(6):574-81. PMID: 22081584.

Repsher LH. Treatment of stable chronic bronchitis with iodinated glycerol: a double-blind, placebo-controlled trial. J Clin Pharmacol. 1993;33(9):856-60. PMID: 8227484.

Ribeiro M, De Castro Pereira CA, Nery LE, et al. A prospective longitudinal study of clinical characteristics, laboratory findings, diagnostic spectrum and outcomes of specific therapy in adult patients with chronic cough in a general respiratory clinic. Int J Clin Pract. 2006;60(7):799-805. PMID: 16858753.

Ribeiro M, Pereira CA, Nery LE, et al. Methacholine vs adenosine on intra and extrathoracic airway hyperresponsiveness in patients with cough variant asthma. Allergy. 2008;63(5):527-32. PMID: 18394126.

Rietveld S, Rijssenbeek-Nouwens LH. Diagnostics of spontaneous cough in childhood asthma: results of continuous tracheal sound recording in the homes of children. Chest. 1998;113(1):50-4. PMID: 9440567.

Rietveld S, Rijssenbeek-Nouwens LH, Prins PJ. Cough as the ambiguous indicator of airway obstruction in asthma. J Asthma. 1999;36(2):177-86. PMID: 10227269.

Rietveld S, Van Beest I, Everaerd W. Psychological confounds in medical research: the example of excessive cough in asthma. Behav Res Ther. 2000;38(8):791-800. PMID: 10937427.

Rimoldi R, Bonollo L, Martini A, et al. Controlled clinical study of a cough-relief treatment (cardiazol-paracodina) in pneumopathic patients. Current Therapeutic Research - Clinical and Experimental. 1990;48(6):1053-65.

Rimsza ME, Newberry S. Unexpected infant deaths associated with use of cough and cold medications. Pediatrics. 2008;122(2):e318-22. PMID: 18676517.

Riordan MF, Beardsmore CS, Brooke AM, et al. Relationship between respiratory symptoms and cough receptor sensitivity. Arch Dis Child. 1994;70(4):299-304. PMID: 8185363.

Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with Cyctic Fibrosis: the ISIS Randomized Controlled Trial Inhaled Hypertonic Saline in Children With CF. JAMA 2012;307(21):2269-77. PMID: 22610452.

Rubin BK. Therapeutic aerosols and airway secretions. J Aerosol Med. 1996;9(1):123-30. PMID: 10160202.

Ryan NM, Vertigan AE, Ferguson J, et al. Clinical and physiological features of postinfectious chronic cough associated with H1N1 infection. Respiratory Medicine 2012;106(1):138-44. PMID: 22056406.

Ryan NM, Gibson PG. Characterization of laryngeal dysfunction in chronic persistent cough.

Laryngoscope. 2009;119(4):640-5. PMID: 19205007.

Sadlonova J, Salat D, Salatova V. Tussiphonogram in probands with chronic obstructive bronchitis. Acta Physiol Hung. 1987;70(2-3):171-5. PMID: 3434296.

Saito J, Harris WT, Gelfond J, et al. Physiologic, bronchoscopic, and bronchoalveolar lavage fluid findings in young children with recurrent wheeze and cough. Pediatr Pulmonol. 2006;41(8):709-19. PMID: 16779841.

Salat D, Korpas J, Salatova V, et al. The tussiphonogram during asthmatic attack. Acta Physiol Hung. 1987;70(2-3):223-5. PMID: 3434301.

Salmi T, Sovijarvi AR, Brander P, et al. Long-term recording and automatic analysis of cough using filtered acoustic signals and movements on static charge sensitive bed. Chest. 1988;94(5):970-5. PMID: 3180900.

Sano T, Ueda H, Bando H. A preliminary study of PEFR monitoring in patients with chronic cough. Lung. 2004;182(5):285-95. PMID: 15742241.

Sato S, Saito J, Sato Y, et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. Respir Med. 2008;102(10):1452-9. PMID: 18614345.

Schokker S, Kooi EM, de Vries TW, et al. Inhaled corticosteroids for recurrent respiratory symptoms in preschool children in general practice: randomized controlled trial. Pulm Pharmacol Ther. 2008;21(1):88-97. PMID: 17350868.

Sen RP, Walsh TE. Fiberoptic bronchoscopy for refractory cough. Chest. 1991;99(1):33-5. PMID: 1984981.

Serembe M, Barbetti M. Clinical trials on a new antitussive agent. 2-morpholinoethylic ester of a-phenoxyisobutyric acid (morphethylbutyne). Farmaco Prat. 1969;24(11):700-6. PMID: 4902988.

Sergysels R, Art G. A double-masked, placebo-controlled polysomnographic study of the antitussive effects of helicidine. Current Therapeutic Research - Clinical and Experimental. 2001;62(1):35-47.

Sevelius H, Colmore JP. Antitussive effect of ethyl dibunate in patients with chronic cough. Clin Pharmacol Ther. 1967;8(3):381-4. PMID: 5338382.

Sevelius H, Colmore JP. Objective assessment of antitussive agents in patients with chronic cough. J New Drugs. 1966;6(4):216-23. PMID: 5338653.

Shin SH, Hashimoto T, Hatano S. Automatic detection system for cough sounds as a symptom of abnormal health condition. IEEE Trans Inf Technol Biomed. 2009;13(4):486-93. PMID: 19273017.

Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54(4):449-54. PMID: 15753524.

Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest. 1995;108(4):991-7. PMID: 7555175.

Smyrnios NA, Irwin RS, Curley FJ, et al. From a prospective study of chronic cough: diagnostic and therapeutic aspects in older adults. Arch Intern Med. 1998;158(11):1222-8. PMID: 9625401.

Snijders D, Cattarozzi A, Panizzolo C, et al. Investigation of children with chronic nonspecific cough: any clinical benefit of bronchoscopy and bronchoalveolar lavage? Allergy Asthma Proc. 2007;28(4):462-7. PMID: 17883915.

Solopov VN, Lunichkina IV. Expectoration disturbances and bronchial obstruction. Respiration. 1991;58(5-6):287-93. PMID: 1792419.

Spiropoulos K, Stevens J, Eigen H, et al. Specificity and sensitivity of methacholine challenge test in children with normal and hyperreactive airways. Acta Paediatr Scand. 1986;75(5):737-43. PMID: 3564942.

Springer C, Godfrey S, Vilozni D, et al. Comparison of respiratory inductance plethysmography with thoracoabdominal compression in bronchial challenges in infants and young children. Am J Respir Crit Care Med. 1996;154(3 Pt 1):665-9. PMID: 8810603.

Stec SM, Grabczak EM, Bielicki P, et al. Diagnosis and management of premature ventricular complexes-associated chronic cough. Chest. 2009;135(6):1535-41. PMID: 19318662.

Strippoli MP, Silverman M, Michel G, et al. A parent-completed respiratory questionnaire for 1-year-old children: repeatability. Arch Dis Child. 2007;92(10):861-5. PMID: 17502330.

Su CL, Chang CC, Lin YK, et al. Randomized Crossover Study for Lung Expansion Therapy Using Negative Pressure and Positive Pressure in Bronchiectasis. Journal of Experimental and Clinical Medicine 2012.

Sugimura T, Ozaki Y, Tananari Y, et al. Auscultation using a pinwheel in young children presenting with cough. Pediatric Asthma, Allergy and Immunology. 2009;22(3):111-113.

Ternesten-Hasseus E, Johansson K, Lowhagen O, et al. Inhalation method determines outcome of capsaicin inhalation in patients with chronic cough due to sensory hyperreactivity. Pulm Pharmacol Ther. 2006;19(3):172-8. PMID: 15990345.

Ternesten-Hasseus E, Larsson C, Bende M, et al. Capsaicin provocation using two different inhalation devices. Respir Med. 2008;102(12):1784-90. PMID: 18703328.

Thiadens HA, de Bock GH, Dekker FW, et al. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. BMJ. 1998;316(7140):1286-90. PMID: 9554899.

Thiadens HA, De Bock GH, Van Houwelingen JC, et al. Can peak expiratory flow measurements reliably identify the presence of airway obstruction and bronchodilator response as assessed by FEV(1) in primary care patients presenting with a persistent cough? Thorax. 1999;54(12):1055-60. PMID: 10567623.

Thomas J, Heurich AE, Shepherd DA, et al. A system for the clinical assessment of the antitussive activity of caramiphen. Curr Ther Res Clin Exp. 1974;16(10):1082-90. PMID: 4215619.

Thompson KJ, Reeve J. A clinical trial of bromhexine. N Z Med J. 1972;76(483):73-6. PMID: 4264310.

Thomson ML, Pavia D, Gregg I, et al. The effect of bromhexine on mucociliary clearance from the human lung in chronic bronchitis. Scand J Respir Dis Suppl. 1974;90:75-9. PMID: 4533555.

Thomson ML, Pavia D, Jones CJ, et al. No demonstrable effect of S-carboxymethylcysteine on clearance of secretions from the human lung. Thorax. 1975;30(6):669-73. PMID: 769242.

Todokoro M, Mochizuki H, Tokuyama K, et al. Childhood cough variant asthma and its relationship to classic asthma. Ann Allergy Asthma Immunol. 2003;90(6):652-9. PMID: 12839325.

Turktas I, Dalgic N, Bostanci I, et al. Extrathoracic airway responsiveness in children with asthma-like symptoms, including chronic persistent cough. Pediatr Pulmonol. 2002;34(3):172-80. PMID: 12203845.

Urkin J, Ishay Y, Bilenko N, et al. Night-time cough in children with acute wheezing and with upper respiratory tract infection. Prim Care Respir J. 2008;17(4):217-21. PMID: 18633556.

Vaezi MF, Richter JE. Twenty-four-hour ambulatory esophageal pH monitoring in the diagnosis of acid reflux-related chronic cough. South Med J. 1997;90(3):305-11. PMID: 9076302.

Valenti S, Marenco G. Italian multicenter study on the treatment of chronic obstructive lung disease with bromhexine. A double-blind placebo-controlled trial. Respiration. 1989;56(1-2):11-5. PMID: 2690235.

Van Hirtum A, Berckmans D. Automated recognition of spontaneous versus voluntary cough. Med Eng Phys. 2002;24(7-8):541-5. PMID: 12237051.

Vardar R, Sweis R, Anggiansah A, et al. Pharyngeal and oesophageal dysmotility and dysfunction in patients with chronic cough: Assessment by high-resolution manometry. Gut. 2011;60:A165.

Vas M, Kun A. A new antitussive (libexin) for geriatric use. Ther Hung. 1967;15(1):32-4. PMID: 5343252.

Vertigan AE, Theodoros DG, Winkworth AL, et al. A comparison of two approaches to the treatment of chronic cough: perceptual, acoustic, and electroglottographic outcomes. J Voice. 2008;22(5):581-9. PMID: 17485195.

Wang J, Sicherer SH. Coughing in pre-school children in general practice: When are RAST's for inhalation allergy indicated? Pediatrics. 2005;116(2):559.

Wark PA, Gibson PG, Fakes K. Induced sputum eosinophils in the assessment of asthma and chronic cough. Respirology. 2000;5(1):51-7. PMID: 10728732.

Wongtim S, Chareonlap P, Mogmued S. Methacholine inhalation challenge in patients with

chronic cough induced by angiotensin-converting enzyme inhibitors. J Med Assoc Thai. 1996;79(3):166-70. PMID: 8708498.

Wongtim S, Mogmeud S, Limthongkul S, et al. The role of the methacholine inhalation challenge in adult patients presenting with chronic cough. Asian Pac J Allergy Immunol. 1997;15(1):9-14. PMID: 9251842.

Wongtim S, Mogmud S, Chareonlap P, et al. Standardization of methacholine inhalation challenge by a reservoir method. Asian Pac J Allergy Immunol. 1994;12(2):131-6. PMID: 7612106.

Worrall GJ. One hundred coughs: family practice case series. Can Fam Physician. 2008;54(2):236-7. PMID: 18272642.

Young EC, Brammer C, Owen E, et al. The effect of mindfulness meditation on cough reflex sensitivity. Thorax. 2009;64(11):993-8. PMID: 19679578.

Yu L, Qiu ZH, Wei WL, et al. Discrepancy between presumptive and definite causes of chronic cough. Chinese Medical Journal 2011;124(24):4138-43. PMID: 22340375.

Zanasi A, De Bernardi M, Messina P, et al. Cough sedation: Effectiveness and safety of the association dextromethorphan-guaiafenesin. Acta Toxicologica et Therapeutica. 1993;14(3):153-162.

Zgherea D, Pagala S, Mendiratta M, et al. Bronchoscopic findings in children with chronic wet cough. Pediatrics 2012;129(2):e364-9. PMID:22232311.

No comparator

Bastian RW, Vaidya AM, Delsupehe KG. Sensory neuropathic cough: a common and treatable cause of chronic cough. Otolaryngol Head Neck Surg. 2006;135(1):17-21. PMID: 16815176.

Bector NP, Puri AS. Solanum xanthocarpum (Kantakari) in chronic bronchitis, bronchial asthma and non-specific unproductive cough. (An experimental and clinical co-relation). J Assoc Physicians India. 1971;19(10):741-4. PMID: 5132261.

Chong CF, Chen CC, Ma HP, et al. Comparison of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease. Emerg Med J. 2005;22(6):429-32. PMID: 15911951.

Freestone C, Eccles R, Morris S, et al. Assessment of the antitussive efficacy of codeine using cough sound pressure levels as a means of measuring cough. Pulm Pharmacol. 1996;9(5-6):365. PMID: 9232676.

Homsi J, Walsh D, Nelson KA, et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care. 2002;19(1):49-56. PMID: 12171425.

Howard P, Cayton RM, Brennan SR, et al. Lignocaine aerosol and persistent cough. Br J Dis Chest. 1977;71(1):19-24. PMID: 831764.

Johansson EL, Ternesten-Hasseus E, Millqvist E. Down-regulation of cough sensitivity after eucapnic dry air provocation in chronic idiopathic cough. Pulm Pharmacol Ther. 2009;22(6):543-7. PMID: 19646543.

Kamimura M, Mouri A, Takayama K, et al. Cough challenge tests involving mechanical stimulation of the cervical trachea in patients with cough as a leading symptom. Respirology. 2010;15(8):1244-51. PMID: 20920133.

Kopriva F, Sobolova L, Szotkowska J, et al. Treatment of chronic cough in children with montelukast,a leukotriene receptor antagonist. J Asthma. 2004;41(7):715-20. PMID: 15584630.

Kuzniar TJ, Morgenthaler TI, Afessa B, et al. Chronic cough from the patient's perspective. Mayo Clin Proc. 2007;82(1):56-60. PMID: 17285786.

Leconte S, Ferrant D, Dory V, et al. Validated methods of cough assessment: a systematic review of the literature. Respiration. 2011;81(2):161-74. PMID: 21079381.

Levine BM. Systematic evaluation and treatment of chronic cough in a community setting. Allergy Asthma Proc. 2008;29(3):336-42. PMID: 18534091.

Lokshin B, Lindgren S, Weinberger M, et al. Outcome of habit cough in children treated with a brief session of suggestion therapy. Ann Allergy. 1991;67(6):579-82. PMID: 1750719.

Macedo P, Saleh H, Torrego A, et al. Postnasal drip

and chronic cough: An open interventional study. Respir Med. 2009;103(11):1700-5. PMID: 19481918.

Murry T, Branski RC, Yu K, et al. Laryngeal sensory deficits in patients with chronic cough and paradoxical vocal fold movement disorder. Laryngoscope. 2010;120(8):1576-81. PMID: 20564660.

Murry T, Tabaee A, Owczarzak V, et al. Respiratory retraining therapy and management of laryngopharyngeal reflux in the treatment of patients with cough and paradoxical vocal fold movement disorder. Ann Otol Rhinol Laryngol. 2006;115(10):754-8. PMID: 17076097.

Nunes CP, De Oliveira PC, De Oliveira JM, et al. Quality-of-life assessment and clinical-laboratory response to use of the combination of menthol, guaiacol, terpineol, eucalyptol, gomenol, and camphor in patients presenting persistent cough. Revista Brasileira de Medicina. 2010;67(4):104-109.

Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol. 1999;94(11):3131-8. PMID: 10566703.

Patel AS, Watkin G, Willig B, et al. Improvement in health status following cough-suppression physiotherapy for patients with chronic cough. Chron Respir Dis. 2011;PMID: 21990570.

Pratter MR, Bartter T, Lotano R. The role of sinus imaging in the treatment of chronic cough in adults. Chest. 1999;116(5):1287-91. PMID: 10559089.

Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. Ann Intern Med. 1993;119(10):977-83. PMID: 8214994.

Primbs K. Therapeutic activity of ambroxol theophyllinacetate in chronic obstructive pulmonary diseases. Clin Ther. 1985;7(6):733-6. PMID: 4075364.

Ryan NM, Vertigan AE, Bone S, et al. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough. Cough. 2010;6:5. PMID: 20663225.

Saunders DC. Trial of an anti-tussive preparation in droplet form. Practitioner. 1961;186:367-9. PMID: 13746793.

Sawada S, Suehisa H and Yamashita M. Inhalation of corticosteroid and beta-agonist for persistent cough following pulmonary resection. Gen Thorac Cardiovasc Surg 2012;60(5):285-8. PMID:23453538.

Singh VK. Clinical trial with 'ZeeTuss' - A herbal cough syrup in varieties of cough. JK Practitioner. 2000;7(3):214-217.

Tan NC, Ngoh SHA, Teo SSH, et al. Impact of cigarette smoking on symptoms and quality of life of adults with asthma managed in public primary care clinics in Singapore: a questionnaire study. Primary Care Respiratory Journal 2012; 21(1):90-93.

Tattersall AB, Bridgman KM, Huitson A. Irish general practice study of acetylcysteine (Fabrol) in chronic bronchitis. J Int Med Res. 1984;12(2):96-101. PMID: 6373444.

Tattersall AB, Bridgman KM, Huitson A. Acetylcysteine (Fabrol) in chronic bronchitis—a study in general practice. J Int Med Res. 1983;11(5):279-84. PMID: 6642068.

Toop LJ, Howie JG, Paxton FM. Night cough and general practice research. J R Coll Gen Pract. 1986;36(283):74-7. PMID: 3712337.

Vernon M, Leidy NK, Nacson A, et al. Measuring cough severity: Perspectives from the literature and from patients with chronic cough. Cough. 2009;5:5. PMID: 19298650.

Appendix E. QUADAS-2 Scoring of KQ 1 Studies

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded patients described	Random sample	Index test results independent	Reference standard correct	Appropriate interval between tests	Case-control design avoided	Threshold pre-specified	Reference standard results independent	Reference standard for all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Included patients do not match review question	Index test does not match review question	Target condition does not match review question	Study Rating
Archer, 1985[1]	Y	Y	Y	N	U	U	Y	Y	Y	U	U	Y	Y	Y	N	N	N	N	N	N	N	N	High risk of bias
Au, 2005[2]	Y	Y	N	N	N	U	Y	Y	Y	U	U	N	Y	N	N	N	N	N	Y	N	N	N	High risk of bias
Baiardini, 2005[3]	N	Y	Y	Y	U	U	U	U	Y	U	U	U	U	U	Y	Y	N	Y	Y	Y	N	Y	High risk of bias
Barnabe, 1995[4]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	N	N	Y	N	N	N	Low risk of bias
Barry, 2006[5]	U	Y	U	U	U	Y	Y	U	Y	U	Y	N	U	Y	Y	Y	Y	Y	Y	N	N	N	Low risk of bias
Berkhof, 2012[6]	N	Y	Y	Y	U	U	U	Y	Y	U	U	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	Low risk of bias
Birring, 2008[7]	Y	Y	Y	U	Y	Y	Y	Y	N	U	Y	N	Y	N	Y	U	U	N	Y	N	N	N	Low risk of bias
Birring, 2006[8]	Y	Y	Y	U	Y	U	Y	U	N	U	U	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Low risk of bias
Birring, 2003[9]	Y	Y	Y	Y	N	U	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	U	N	N	N	N	Low risk of bias
Braido, 2006[10]	Y	Y	Y	U	Y	U	Y	U	N	U	U	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Chang, 2012[11]	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Chang, 2003[12]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	U	N	N	N	N	N	N	Low risk of bias
Chang, 1998[13]	Y	Y	Y	U	U	U	U	Y	Y	U	Y	U	Y	Y	N	U	U	N	U	N	N	N	Low risk of bias
Chang, 1997[14]	N	Y	Y	Y	U	U	Y	Y	N	U	U	Y	Y	Y	N	Y	N	N	N	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded patients described	Random sample	Index test results independent	Reference standard correct	Appropriate interval between tests	Case-control design avoided	Threshold pre-specified	Reference standard results independent	Reference standard for all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Included patients do not match review question	Index test does not match review question	Target condition does not match review question	Study Rating
Chernecky, 2004[15]	Y	Y	U	Y	N	U	U	Y	Y	U	U	N	Y	Y	Y	Y	N	Y	Y	N	N	N	High risk of bias
Corrigan, 2003[16]	Y	Y	Y	Y	U	Y	Y	Y	N	U	Y	N	Y	Y	N	U	N	N	Y	N	N	N	Low risk of bias
Coyle, 2005[17]	U	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Crawford, 2008[18]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	N	Y	N	N	N	N	N	N	Low risk of bias
Dales, 1997[19]	N	Y	Y	N	N	Y	Y	Y	Y	U	Y	Y	U	Y	Y	N	N	N	N	Y	N	N	Low risk of bias
De Vito Dabbs, 2002[20]	Y	Y	Y	N	Y	Y	Y	Y	Y	U	Y	U	Y	U	U	N	N	N	U	Y	Y	N	Low risk of bias
Decalmer, 2007[21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Dicpinigaitis, 2006[22]	N	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	Y	U	N	N	N	High risk of bias
Doherty, 2000[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Low risk of bias
Doherty, 2000[24]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	Y	N	N	N	High risk of bias
Falconer, 1993[25]	N	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	U	Y	N	Y	N	N	Y	N	N	N	High risk of bias
Faniran, 1999[26]	Y	Y	U	U	N	Y	U	U	Y	U	U	U	N	U	N	Y	N	U	U	Y	N	U	High risk of bias
Faruqi, 2011[27]	Y	Y	U	U	U	Y	U	U	Y	U	U	U	Y	U	Y	N	N	U	N	N	N	U	Low risk of bias
Field, 2009[28]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
Fisman, 2001[29]	Y	Y	N	Y	Y	Y	N	N	Y	U	N	N	Y	N	Y	Y	N	N	N	N	N	N	High risk of bias
Fletcher, 2010[30]	Y	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Freestone, 1997[31]	Y	Y	N	N	U	Y	N	N	Y	U	N	N	Y	N	N	Y	N	N	Y	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded patients described	Random sample	Index test results independent	Reference standard correct	Appropriate interval between tests	Case-control design avoided	Threshold pre-specified	Reference standard results independent	Reference standard for all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Included patients do not match review question	Index test does not match review question	Target condition does not match review question	Study Rating
French, 1998[32]	Y	Y	Y	N	N	Y	Y	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
French, 2002[33]	Y	Y	N	N	N	Y	N	N	Y	U	N	N	Y	N	Y	N	N	N	N	N	N	N	Low risk of bias
Fuller, 1998[34]	Y	Y	N	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Y	N	Y	N	Y	Y	N	N	Y	High risk of bias
Hamutcu, 2002[35]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	U	Y	U	Y	N	Y	Y	N	N	N	N	Low risk of bias
Hartnick, 2009[36]	Y	Y	U	Y	N	Y	U	Y	Y	U	N	Y	Y	Y	Y	U	U	Y	N	N	N	N	Low risk of bias
Hoskyns, 1991[37]	Y	Y	N	Y	N	Y	U	Y	Y	U	U	Y	Y	Y	Y	U	N	U	N	N	N	N	Low risk of bias
Hsu, 1994[38]	N	Y	N	N	N	Y	U	Y	Y	U	U	U	Y	Y	U	N	N	Y	N	N	N	N	Low risk of bias
Huisman, 2007[39]	U	Y	Y	U	Y	Y	U	Y	Y	U	Y	Y	Y	Y	U	N	N	N	N	N	N	N	Low risk of bias
Irwin, 2002[40]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Low risk of bias
Jones, 2011[41]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	U	Y	Y	U	N	N	N	N	N	N	N	Low risk of bias
Kalpaklioglu, 2005[42]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Kelsall, 2011[43]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	Y	N	N	Y	N	N	N	Low risk of bias
Kelsall, 2009[44]	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Y	N	N	N	N	Y	N	N	Y	Low risk of bias
Kelsall, 2008[45]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	Y	U	U	U	N	N	N	Low risk of bias
Key, 2010[46]	N	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	N	N	N	N	Low risk of bias
Krahnke, 2004[47]	U	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	N	N	N	N	N	N	Low risk of bias
Krajnik, 2010[48]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	N	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded patients described	Random sample	Index test results independent	Reference standard correct	Appropriate interval between tests	Case-control design avoided	Threshold pre-specified	Reference standard results independent	Reference standard for all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Included patients do not match review question	Index test does not match review question	Target condition does not match review question	Study Rating
Leconte, 2011[49]	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Low risk of bias
Ma, 2009[50]	U	Y	Y	N	Y	U	Y	Y	Y	U	U	Y	Y	Y	U	N	N	Y	U	N	N	N	Low risk of bias
Marsden, 2008[51]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	U	Y	Y	U	U	N	U	N	N	N	N	Low risk of bias
Matos, 2007[52]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
Monz, 2010[53]	Y	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	N	N	N	N	N	N	Low risk of bias
Morice, 2007[54]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	U	Y	U	U	N	N	U	N	N	N	Low risk of bias
Murray, 2009[55]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	N	Y	N	Y	Low risk of bias
Mwachari, 2007[56]	Y	Y	U	U	U	Y	U	U	Y	U	U	U	Y	U	Y	Y	N	U	N	N	Y	U	Low risk of bias
Nandha, 2000[57]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Low risk of bias
Newcombe, 2011[58]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	U	N	N	N	Low risk of bias
Newcombe, 2010[59]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	U	N	N	N	Low risk of bias
Newcombe, 2008[60]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	U	U	N	N	N	Low risk of bias
Nieto, 2003[61]	Y	Y	U	U	U	Y	U	U	Y	Y	U	U	Y	U	U	Y	N	U	U	N	N	U	Low risk of bias
Novitsky, 2002[62]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
O'Connell 1994[63]	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Low risk of bias
Paul, 2006[64]	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	U	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Polley, 2008[65]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded patients described	Random sample	Index test results independent	Reference standard correct	Appropriate interval between tests	Case-control design avoided	Threshold pre-specified	Reference standard results independent	Reference standard for all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Included patients do not match review question	Index test does not match review question	Target condition does not match review question	Study Rating
Raj, 2009[66]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Ribeiro, 2007[67]	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Shaheen, 2011[68]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U	N	N	N	Y	N	N	Low risk of bias
Singapuri, 2008[69]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Smith, 2006[70]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Smith, 2006[71]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	N	N	N	U	N	N	Y	Low risk of bias
Smith, 2006[72]	Y	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
Smith, 2006[73]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	Y	N	N	N	Low risk of bias
Thomas, 1978[74]	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	U	Y	U	Y	N	N	N	N	N	N	Low risk of bias
Vernon, 2010[75]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Woodcock, 2010[76]	Y	Y	Y	N	U	Y	Y	Y	Y	U	U	U	Y	U	Y	Y	N	Y	N	N	N	N	Low risk of bias
Woolf, 1964[77]	N	N	Y	U	U	U	Y	Y	Y	U	Y	Y	U	Y	U	Y	N	N	N	Y	Y	N	High risk of bias
Zihlif, 2005[78]	Y	U	Y	N	U	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	N	N	U	Y	N	N	Low risk of bias

Abbreviations: N = No; Y = Yes; U = Unclear

References to Appendix E

1. Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.
2. Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.
3. Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.
4. Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.
5. Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.
6. Berkhof FF, Boom LN, ten Hertog NE, et al. The validity and precision of the leicester cough questionnaire in COPD patients with chronic cough. Health and Quality of Life Outcomes. 2012;10.
7. Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.
8. Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.
9. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.
10. Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.
11. Chang AB, Robertson CF, Van Asperen PP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest. 2012. PMID: 22459773.
12. Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.
13. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.
14. Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.
15. Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.
16. Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.
17. Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.
18. Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.
19. Dales RE, White J, Bhumgara C, et al. Parental reporting of childrens' coughing is biased. Eur J Epidemiol. 1997;13(5):541-5. PMID: 9258566.
20. De Vito Dabbs A, Hoffman LA, Dauber JH, et al. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. Prog Transplant. 2002;12(3):191-8; quiz 9-200. PMID: 12371045.
21. Decalmer SC, Webster D, Kelsall AA, et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.

22. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43. PMID: 17167006.

23. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax. 2000;55(12):1028-32. PMID: 11083888.

24. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.

25. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.

26. Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.

27. Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.

28. Field SK, Conley DP, Thawer AM, et al. Effect of the management of patients with chronic cough by pulmonologists and certified respiratory educators on quality of life: a randomized trial. Chest. 2009;136(4):1021-8. PMID: 19349387.

29. Fisman EZ, Shapira I, Motro M, et al. The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings. J Med. 2001;32(3-4):181-7. PMID: 11563816.

30. Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.

31. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.

32. French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61. PMID: 9701100.

33. French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.

34. Fuller P, Picciotto A, Davies M, et al. Cough and sleep in inner-city children. Eur Respir J. 1998;12(2):426-31. PMID: 9727796.

35. Hamutcu R, Francis J, Karakoc F, et al. Objective monitoring of cough in children with cystic fibrosis. Pediatr Pulmonol. 2002;34(5):331-5. PMID: 12357476.

36. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. Ear Nose Throat J. 2009;88(11):1213-7. PMID: 19924664.

37. Hoskyns EW, Thomson A, Decker E, et al. Effect of controlled release salbutamol on nocturnal cough in asthma. Arch Dis Child. 1991;66(10):1209-12. PMID: 1953004.

38. Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7(7):1246-53. PMID: 7925902.

39. Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.

40. Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest. 2002;121(4):1132-40. PMID: 11948043.

41. Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.

42. Kalpaklioglu AF, Kara T, Kurtipek E, et al. Evaluation and impact of chronic cough: comparison of specific vs generic quality-of-life questionnaires. Ann Allergy Asthma Immunol. 2005;94(5):581-5. PMID: 15945562.

43. Kelsall A, Houghton LA, Jones H, et al. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569-75. PMID: 20864619.

44. Kelsall A, Decalmer S, McGuinness K, et al. Sex differences and predictors of objective

cough frequency in chronic cough. Thorax. 2009;64(5):393-8. PMID: 19131447.

45. Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.

46. Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4. PMID: 20565979.

47. Krahnke J, Gentile D, Angelini B, et al. Comparison of objective and subjective measurements of cough frequency in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2004;93(3):259-64. PMID: 15478386.

48. Krajnik M, Damps-Konstanska I, Gorska L, et al. A portable automatic cough analyser in the ambulatory assessment of cough. Biomed Eng Online. 2010;9:17. PMID: 20226089.

49. Leconte S, Liistro G, Lebecque P, et al. The objective assessment of cough frequency: accuracy of the LR102 device. Cough. 2011;7(1):11. PMID: 22132691.

50. Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.

51. Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol. 2008;122(5):903-7. PMID: 18842290.

52. Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.

53. Monz BU, Sachs P, McDonald J, et al. Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. Respir Med. 2010;104(4):534-41. PMID: 19917525.

54. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.

55. Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31. PMID: 19196812.

56. Mwachari C, Nduba V, Nguti R, et al. Validation of a new clinical scoring system for acute bronchitis. Int J Tuberc Lung Dis. 2007;11(11):1253-9. PMID: 17958990.

57. Nandha D, Goodyer L, Woodruffe-Peacock C. Diary cards and the assessment of cough symptoms in community pharmacies. Pharm World Sci. 2000;22(1):17-20. PMID: 10815295.

58. Newcombe PA, Sheffield JK, Chang AB. Minimally important change in a Parent-Proxy Quality-of-Life questionnaire for pediatric chronic cough. Chest. 2011;139(3):576-80. PMID: 20947650.

59. Newcombe PA, Sheffield JK, Juniper EF, et al. Validation of a parent-proxy quality of life questionnaire for paediatric chronic cough (PC-QOL). Thorax. 2010;65(9):819-23. PMID: 20805179.

60. Newcombe PA, Sheffield JK, Juniper EF, et al. Development of a parent-proxy quality-of-life chronic cough-specific questionnaire: clinical impact vs psychometric evaluations. Chest. 2008;133(2):386-95. PMID: 18252913.

61. Nieto L, de Diego A, Perpina M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97(4):393-400. PMID: 12693800.

62. Novitsky YW, Zawacki JK, Irwin RS, et al. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc. 2002;16(4):567-71. PMID: 11972189.

63. O'Connell F, Thomas VE, Pride NB, et al. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994;150(2):374-80. PMID: 8049818.

64. Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.

65. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.

66. Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important

difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.

67. Ribeiro M, Pereira CA, Nery LE, et al. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. Ann Allergy Asthma Immunol. 2007;99(1):61-8. PMID: 17650832.

68. Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):225-34. PMID: 21083673.

69. Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.

70. Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.

71. Smith JA, Owen EC, Jones AM, et al. Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis. Thorax. 2006;61(5):425-9. PMID: 16449266.

72. Smith J, Owen E, Earis J, et al. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006;117(4):831-5. PMID: 16630941.

73. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.

74. Thomas JS, Lyons HA, Shepherd DA. D.A.T.A.—an advanced automated electronic cough counting system for the evaluation of antitussive agents. Curr Ther Res Clin Exp. 1978;23(1):66-77. PMID:

75. Vernon M, Kline Leidy N, Nacson A, et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4(4):199-208. PMID: 20519373.

76. Woodcock A, McLeod RL, Sadeh J, et al. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung. 2010;188 Suppl 1:S47-52. PMID: 19937046.

77. Woolf CR, Rosenberg A. Objective assessment of cough suppressants under clinical conditions using a tape recorder system. Thorax. 1964;19:125-30. PMID: 14128569.

78. Zihlif N, Paraskakis E, Lex C, et al. Correlation between cough frequency and airway inflammation in children with primary ciliary dyskinesia. Pediatr Pulmonol. 2005;39(6):551-7. PMID: 15806596.

Appendix F. Supplemental Tables

Table F-1. KQ 1—Study characteristics

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Studies in Adults and Adolescents						
Au, 2005[1]	64	Chronic bronchitis	- CBSAS - Pulmonary function tests - SGRQ - San Diego Shortness of Breath Questionnaire	Develop the CBSAS	Severity/QOL	High
Baiardini, 2005[2]	95	Chronic cough	- CCIQ	Develop the CCIQ	Severity/QOL	High
Barnabe, 1995[3]	119	Dry or slightly productive cough due to respiratory disorders	- Cough count (by a human) - Electronic sound recorder - VAS	Evaluate the efficacy and safety of moguisteine vs. codeine	Frequency Severity/QOL	Low
Barry, 2006[4]	33	Chronic cough	- Hull Automatic Cough Counter - Cough count by observer	Evaluate the Hull Automatic Cough Counter	Frequency	Low
Berkhof, 2012[5]	54	COPD	- LCQ - SGRQ - SF-36	Examine the psychometric performance of the LCQ in patients with COPD and chronic productive cough	Severity/QOL	Low
Birring, 2008[6]	65	Chronic cough	- Leicester Cough Monitor - Video recording - Cough count by 2 observers	Evaluate the Leicester Cough Monitor	Frequency	Low
Birring, 2006[7]	20	Chronic cough	- LCQ - Leicester Cough Monitor - Capsaicin cough challenge	Evaluate the Leicester Cough Monitor	Frequency Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Birring, 2003[8]	104	Chronic cough	- LCQ - Self-reported cough severity - Self-reported clinical change - SGRQ - SF-36 - Capsaicin cough challenge	Develop the LCQ	Severity/QOL	Low
Braido, 2006[9]	95	Chronic cough	- CCIQ - SF-36	Evaluate the CCIQ	Severity/QOL	Low
Chernecky, 2004[10]	31	Lung cancer	- LCCQ - Lung Cancer Wheezing Questionnaire	Evaluate the LCCQ and the Lung Cancer Wheezing Questionnaire	Severity/QOL	High
Coyle, 2005[11]	8	COPD	- LifeShirt cardio-respiratory monitoring system - Video recorder	Evaluate the LifeShirt system in COPD patients	Frequency	Low
Crawford, 2008[12]	671	Chronic bronchitis	- CASA-Q - SGRQ - SF-36 - Medical Research Council Dyspnea Scale - Self-reported symptom change scale - 24-hour ambulatory cardiorespiratory monitoring - 24-hour sputum specimen collection	Develop and validate the CASA-Q	Frequency Severity/QOL	Low
De Vito Dabbs, 2002[13]	37	Lung transplant	- Questionnaire for Lung Transplant Patients - Modified Symptom Frequency/Symptom Distress Scale - Functional Performance Inventory - Self-reported cough severity (VAS) - Pulmonary function tests - Qualitative interview	Reliability and validity of the Questionnaire for Lung Transplant Patients	Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Decalmer, 2007[14]	62	Chronic cough	- LCQ - Self-reported cough severity - Self-reported cough frequency - Citric acid cough challenge - Ambulatory cough recording	Compare cough reflex sensitivity and subjective assessments with objective cough counts	Frequency Severity/QOL	Low
Dicpini-gaitis, 2006[15]	100	Chronic cough	- CES-D - Subjective cough score	Estimate prevalence of depressive symptoms among patients with chronic cough	Severity/QOL	High
Doherty, 2000[16]	205	Asthma or COPD	- Questionnaire administered in hospital - Self-reported cough score - Self-reported cough severity (VAS) - Capsaicin cough challenge	Evaluate capsaicin cough challenge	Severity/QOL	High
Doherty, 2000[17]	15	Cryptogenic fibrosing alveolitis	- Self-reported cough severity (VAS) - Cough diary - Tussigenic challenge	Evaluate the relationship between capsaicin responsiveness and the severity of cryptogenic fibrosing alveolitis	Severity/QOL	Low
Faruqi, 2011[18]	25	Chronic cough	- LCQ - Symptom Assessment Score - Self-reported cough severity (VAS) - Self-reported composite cough score - 24-hour Hull Automatic Cough Counter - Capsaicin cough challenge	Compare objective and subjective measures of cough	Frequency Severity/QOL	Low
Field, 2009[19]	151	Chronic cough	- CQLQ - Cough-specific QoL - Subjective cough assessment	Evaluate whether certified respiratory educators could assist pulmonologists in managing patients with chronic cough	Severity/QOL	Low
Fisman, 2001[20]	21	Cough from ACE inhibitor	- Self-reported cough severity score - Self-reported cough frequency score - Combined severity and frequency score	Compare cough severity and frequency scores	Frequency Severity/QOL	High
Fletcher, 2010[21]	127	Cough	- Punum Ladder - Global Rating of Change Scale - CQLQ	Evaluate the GRC, Punum Ladder, and CQLQ	Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Freestone, 1997[22]	67	Cough from common cold	- Self-reported cough severity score - Audio recording device - Cough counts by observer	Assess the antitussive efficacy of codeine for cough	Frequency Severity/QOL	Low
French, 2002[23]	215	Chronic bronchitis or COPD	- CQLQ	Evaluation of CQLQ	Severity/QOL	Low
French, 1998[24]	28	Chronic cough	- Adverse Cough Outcome Survey - SIP	Assess the relationship between chronic cough and adverse psychosocial or physical effects	Severity/QOL	Low
Hsu, 1994[25]	47	Asthma or chronic cough	- Self-reported cough score - Self-reported asthma score - 24-hour ambulatory recorder	Evaluate an ambulatory cough recorder	Frequency	Low
Huisman, 2007[26]	152	Chronic cough	- LCQ - Modified Borg score for cough - HADS - Self-reported change in disease control	Validate a Dutch-language version of the LCQ	Severity/QOL	Low
Irwin, 2002[27]	8	Chronic cough due to gastroesophageal reflux disease	- ACOS - Self-reported cough severity (VAS)	Evaluate the relationship between esophageal acid suppression and chronic cough	Severity/QOL	Low
Jones, 2011[28]	27	Idiopathic pulmonary fibrosis	- LCQ - Self-reported cough severity score - Self-reported cough severity (VAS) - Cough challenge test	Mechanical induction of cough in idiopathic pulmonary fibrosis	Severity/QOL	Low
Kelsall, 2011[29]	57	Chronic cough	- Self-reported cough score - Self-reported cough severity (VAS) - 24-hour ambulatory cough recording	Compare objective and subjective measures of cough	Frequency Severity/QOL	Low
Kelsall, 2009[30]	86	Chronic cough	- LCQ - Electronic cough recorder - Tussigenic challenge - Cough history	Determine the predictors of objective cough frequency in patients with chronic cough	Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Kelsall, 2008[31]	70	Chronic cough	- LCQ - Self-reported cough severity (VAS) - Audio recording device - Cough count by observer	Compare methods of quantifying coughing	Frequency Severity/QOL	Low
Key, 2010[32]	19	Idiopathic pulmonary fibrosis	- LCQ - Cough severity VAS - 24-hour ambulatory cough recording - Manual cough count	Measure objective cough frequency	Frequency Severity/QOL	Low
Krahnke, 2004[33]	28	Cough	- Home telemetry device - Score	Validate novel measurement tools with video recording as gold standard	Frequency	Low
Krajnik, 2010[34]	16	Chronic cough	- Self-reported cough score (NRS) - Automatic portable cough analyzer	Evaluate an automatic portable cough analyzer	Frequency	Low
Leconte, 2011[35]	10	Cough	- LR102 Electronic cough recorder - Video cough recorder - LR102 device	Assess the accuracy of an automatic identification of cough episodes by the LR102	Severity/QOL	Low
Ma, 2009[36]	110	Chronic cough	- LCQ - SF-36 - Capsaicin cough challenge	Validate a Chinese-language version of the LCQ	Severity/QOL	Low
Marsden, 2008[37]	56	Asthma	- LCQ - Cough severity VAS - Numeric cough frequency score - Ambulatory cough sound recording - Citric acid cough challenge	Compare objective and subjective measures of cough in asthma	Frequency Severity/QOL	Low
Matos, 2007[38]	18	Cough	- Leicester Cough Monitor - Cough count by observer	Evaluation of the Leicester Cough Monitor	Frequency	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Monz, 2010[39]	59	Chronic bronchitis or COPD	- CASA-Q - Self-reported cough frequency - Self-reported shortness of breath - Self-reported phlegm production - Self-reported symptom change	Evaluate the CASA-Q	Severity/QOL	Low
Morice, 2007[40]	27	Chronic cough	- LCQ - Cough diary - Tussigenic challenge	Evaluate the efficacy of morphine sulfate for chronic cough	Severity/QOL	Low
Murray, 2009[41]	120	Cough	- LCQ	Compare the LCQ with the SGRQ	Severity/QOL	Low
Mwachari, 2007[42]	649	Acute bronchitis	- ABSS	Evaluate new scoring system	Severity/QOL	Low
Nandha, 2000[43]	48	Cough	- Cough diary	Compare cough diary with a structured recall interview	Severity/QOL	Low
Nieto, 2003[44]	101	Chronic cough	- Tussigenic challenge	Repeat tussigenic challenge to evaluate responsiveness to treatment	Severity/QOL	Low
Novitsky, 2002[45]	21	Chronic cough due to GERD	- ACOS - SIP	Prospective evaluation of consecutive patients with chronic cough due to GERD	Severity/QOL	Low
O'Connell, 1994[46]	87	Chronic cough	- Tussigenic challenge	Comparison of cough severity with cough sensitivity	Severity/QOL	Low
Polley, 2008[47]	147	Chronic cough	- EuroQol - LCQ - CQLQ	Compared with each other	Severity/QOL	Low
Raj, 2009[48]	52	Cough	- LCQ	Determination of minimal important difference for the LCQ	Severity/QOL	Low
Ribeiro, 2007[49]	64	Chronic cough	- Cough diary - Self-reported cough severity (VAS)	Compare the effects of beclomethasone and placebo in patients with chronic cough	Frequency Severity/QOL	Low
Shaheen, 2011[50]	40	Chronic cough	- CQLQ - Fisman cough severity/frequency scores	Assess the impact of high-dose acid suppression with proton pump inhibitors on chronic cough in subjects with rare or no heartburn	Frequency Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Singapuri, 2008[51]	13	Chronic cough	- Mannitol challenge test - LCQ - VAS	To investigate the utility of the mannitol challenge as a cough-provocation test in non-asthmatic chronic cough	Severity/QOL	Low
Smith, 2006[52]	8	Chronic cough	- Human cough count - Video recording device	Comparisons of digital audio recordings with video recordings	Frequency	Low
Smith, 2006[53]	19	Cystic fibrosis	- Electronic cough recorder - Score - Self-reported cough severity (VAS)	Evaluate objective measurements of cough during pulmonary exacerbations of cystic fibrosis	Frequency Severity/QOL	Low
Smith, 2006[54]	21	COPD	- Electronic cough recorder - Tussigenic challenge - Self-reported cough severity (VAS)	Quantify the effect of codeine on chronic cough	Frequency Severity/QOL	Low
Smith, 2006[55]	26	COPD	- Electronic recording device - Tussigenic challenge - Score - CQLQ	Determine relationships between objective cough rates, cough reflex sensitivity, subjective estimates of cough frequency, and cough-related quality of life in patients with COPD	Frequency Severity/QOL	Low
Thomas, 1978[56]	42	Chronic cough	- Automated electronic cough-counting device - Cough count	Evaluate a cough recording device	Frequency	Low
Vernon, 2010[57]	39	Chronic cough	- Cough severity diary	Evaluation of new cough severity diary	Severity/QOL	Low
Woodcock, 2010[58]	91	Subacute cough	- Electronic cough recorder - Cough diary	Evaluate the efficacy of a NOP1 agonist (SCH486757) in subacute cough	Frequency Severity/QOL	Low
Woolf, 1964[59]	1	Chronic cough	- Electronic cough recorder - Self-reported cough severity (VAS)	Assess the effects of cough suppressants	Frequency	High

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Studies in Adults, Adolescents, and Children						
Hamutcu, 2002[60]	14	Inpatients with cystic fibrosis	- Self-reported VAS score - Self-reported clinical cough score - LR100 cough monitoring device - Audio recording device - Pulmonary function tests	Objective monitoring of cough in children	Frequency	Low
Hartnick, 2009[61]	120	Parents of children with chronic cough	- Pediatric Cough Questionnaire - Parent-reported clinical change	Evaluate the Pediatric Cough Questionnaire	Severity/QOL	Low
Kalpakli-oglu, 2005[62]	40	Asthma	- LCQ - CQLQ - SF-36 - HADS	Compare specific vs. generic quality-of-life questionnaires for chronic cough	Severity/QOL	Low
Paul, 2006[63]	15	Cough	- Electronic recording device using an accelerometer	Validate new recording device using video recording as gold standard	Frequency Severity/QOL	Low
Studies in Children Only						
Archer, 1985[64]	8	Asthma	- Self-reported cough severity (VAS) - Self-reported cough severity (VCD) - Parent-reported cough severity (VAS) - Parent-reported cough severity (VCD) - 24-hour ambulatory cough meter	Compare recorded night cough counts with diary card scores	Frequency	High
Chang, 2012[65]	346	Chronic cough	- PC-QOL - PedsQL - Cough diary	Evaluate the burden and etiologies of children with chronic cough	Severity/QOL	Low
Chang, 2003[66]	37	Recurrent cough	- Ambulatory cough meter - Self-reported VAS (unspecified) - Parent-reported VAS (unspecified) - Capsaicin cough challenge	Compare measurements of cough severity	Frequency Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Chang, 1998[67]	39	Recurrent cough	- Self-reported cough severity (VAS) - Self-reported cough severity (VCD) - Parent-reported cough severity (VAS) - Parent-reported cough severity (VCD) - 24-hour ambulatory cough meter	Compare child and parent-reports with objective measurement of cough frequency, and comparison of VAS with VCD scoring of cough severity	Frequency Severity/QOL	Low
Chang, 1997[68]	21	Recurrent cough	- Ambulatory cough meter - Audio recording device	Describe and evaluate a modified Holter monitor for use as an ambulatory cough meter	Frequency	Low
Corrigan, 2003[69]	9	Infants with coughing illnesses	- LR100 cough monitoring device - Video recorder	Objective cough monitoring in infants	Frequency	Low
Dales, 1997[70]	41	Community sample	- Interviewer-administered questionnaire - Recording device - Cough counts	Assess possible bias in parental reporting of children's coughing	Frequency	Low
Falconer, 1993[71]	15	Asthma	- Self-reported presence of nocturnal cough - Self-reported respiratory symptoms - Recording device	Compare reported and recorded nocturnal cough	Frequency	High
Faniran, 1999[72]	109	Children with or without cough	- A questionnaire to assess cough prevalence	Develop a questionnaire to measure prevalence of persistent cough in children	Severity/QOL	High
Fuller, 1998[73]	39	Inner-city children with night cough	- Video cough recorder - Cough diary	Determine whether cough at night keeps children awake	Frequency Severity/QOL	High
Hoskyns, 1991[74]	16	Cough	- Audio recording device - Parental cough diaries	Compare diaries with electronic recording and assess response to salbutamol	Frequency	Low
Newcombe, 2011[75]	34	Chronic cough	- PC-QOL	Create and validate new questionnaire	Severity/QOL	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Dimensions	Risk of Bias
Newcombe, 2010[76]	43	Chronic cough	- PC-QOL	Validate PC-QOL by comparison with: - Audio recording - VAS - Pediatric Quality of Life Questionnaire - SF-12 - Verbal category descriptive score	Frequency Severity/QOL	Low
Newcombe, 2008[77]	170	Chronic cough	- PC-QOL	Validate PC-QOL by comparison with: - Pediatric Quality of Life Questionnaire - SF-12	Severity/QOL	Low
Zihlif, 2005[78]	20	Primary ciliary dyskinesia	- Electronic cough recorder - Self-reported cough severity (VAS)	Explore the relationship between cough frequency and airway inflammation	Frequency	Low

Abbreviations: ABSS=Acute Bronchitis Severity Score; ACE=angiotensin-converting enzyme; BPC=bronchoprovocation challenge; CASA-Q=Cough and Sputum Assessment Questionnaire; CBSAS=Chronic Bronchitis Symptoms Assessment Scale; CCIQ=Chronic Cough Impact Questionnaire; CES-D=Center for Epidemiologic Studies Depression Scale; COPD=chronic obstructive pulmonary disease; CQLQ=Cough-specific Quality of Life Questionnaire; EuroQol=European Quality of Life questionnaire; GERD=gastroesophageal reflux disease; GRC=Global Rating of Change; HADS=Hospital Anxiety and Depression Scale; LCQ=Leicester Cough Questionnaire; LCCQ=Lung Cancer Cough Questionnaire; PC-QOL=Parent Cough-Specific Quality-of-Life Questionnaire; QOL = quality-of-life; SF-36/SF-12=Medical Outcomes Study 36-Item/12-Item Short Form Health Survey; SGRQ=St. George's Respiratory Questionnaire; SIP=Sickness Impact Profile; VAS=visual analog scale; VCD=verbal category descriptive scale

Table F-2. Description of cough frequency assessment instruments

Instrument name	Description	Studies
Discriminator and Accumulator of Tussive Activity	Automatic electronic cough counter consisting of a microphone, transmitter, receiver, stereo tape recorder, discriminating circuit and electronic counter	Thomas, 1978[56]
Holter monitor cough meter	Consists of a Holter monitor and a cough processor, designed on a computer to select the most appropriate filters. Input signals to the cough meter consist of electromyogram and audio signals.	Chang, 1997[68]
Home Telemetry Device	Telemetry unit consisting of microphone fixed to the patient's neck and attached to a narrow frequency transmitter worn around the waist	Krahnke, 2004[33]
Hull Automatic Cough Counter	A program developed for the analysis of digital audio recordings. Uses digital signal processing to calculate characteristic spectral coefficients of sound events, which are then classified into cough and non-cough events by the use of a probabilistic neural network. Parameters such as the total number of coughs and cough frequency as a function of time can be calculated from the results of the audio processing.	Barry, 2006[4] Faruqi, 2011[18]
Leicester Cough Monitor	An automated ambulatory digital cough monitor that records sounds only. The initial recording system consisted of a portable digital audio recorder and a miniature condenser microphone. Sounds are analyzed using a cough detection algorithm based on a Hidden Markov Model design.	Birring, 2006[7] Birring, 2008[6] Matos, 2007[38]
Fisman Cough Severity Frequency Score	A VAS scored from 1-10, where 1="I never cough" and 10="I cough all day long'.	Shaheen, 2011[50] Fisman, 2001[20]
LifeShirt system	Ambulatory cardio-respiratory monitoring system which incorporates respiratory inductance plethysmography for the noninvasive measurement of volume and timing ventilatory variables, a unidirectional contact microphone, a single channel ECG, and a centrally located, 3-axis accelerometer	Coyle, 2005[11] Woodcock, 2010[58]
LifeShirt system Portable automatic cough analyzer	Device worn in a special pouch around the thorax and able to measure acoustic vibrations continuously and the signals being transferred to a recording of sound amplitude	Krajnik, 2010[34]
Logan Research (LR 100) cough monitor	LR 100 is a multiparametric recording device, worn in a waist bag, and connected to the chest by three EMG leads and a microphone. Two signals are recorded (a surface EMG and an audio signal), and cough is defined by a combination of rapid phasic bursts in both signals.	Corrigan, 2003[69] Hamutcu, 2002[60] Zihlif, 2005[78]
LR 201 cough frequency meter	Combined analysis of EMG signals from intercostal muscles and auditory signals.	Leconte, 2011[35]
Audio recorder	Consists of 486 notebook computer attached to a directional microphone. Data were collected at 4000 Hz, directly recorded in digital format, and saved as two channels.	Dales, 1997[70]

Instrument name	Description	Studies
Audio recorder	Condenser microphone attached to the subject's throat and connected to a digital sound meter.	Freestone, 1997[22]
Audio recorder	24-hour ambulatory cough sound recording.	Key, 2010[32]
Audio recorder	A digital recording device capable of making a 10-hour continuous recording and worn in a pouch around the waist was used. A lapel microphone was attached to the clothing approximately 30 cm from the mouth.	Marsden, 2008[37]
Cough Monitor Audio recorder	An accelerometer attached to the skin at the suprasternal notch measures vibration and transmits output data to an electronic package worn on the belt. Directional microphone placed near child's bedside and attached to voice activated tape recorder.	Hoskyns, 1991[74]
Audio recorders	A digital recording device capable of making a 10-hour continuous recording worn in a pouch around the waist and connected to a lapel placed ~30 cm from the mouth. Overnight cough recording device at the bedside (not further described).	Smith, 2006[55]
Audio recorder Video recorder	Digital audio player/recorder with a lapel microphone attached to the patient's night clothes. The amplified audio signal was channeled through an oscilloscope to allow real time monitoring of the signal. Video recordings were made using an infrared light source and a monochrome security camera	Smith, 2006[52]
24-hour ambulatory recorder and EMG	Unidirectional microphone attached to the chest wall. EMG signals recorded from surface electrodes.	Hsu, 1994[25]
24-hour ambulatory recorder	Consisting of a lapel microphone with either a modified MP3 player or a validated custom-built recording device.	Kelsall, 2008[31]
Cough Monitor	An accelerometer attached to the skin at the suprasternal notch measures vibration and transmits output data to an electronic package worn on the belt.	Paul, 2006[63]
Panasonic Ag-6040 time-lapse recorder and JVC TK-S240E video camera	A time-lapse recorder, a camera with infra-red light and a microphone.	Fuller, 1998[73]
Recording device	A custom-built recording device with an air microphone and chest wall sensor (Vitalojak, Vitalograph, UK)	Kelsall, 2009[30]
Nomad Jukebox 3 (Creative Technology Ltd, Singapore) and a lapel microphone (AOI, ECM-1025)	Digitial recording devices positioned 30 cm from the mouth	Smith, 2006[53]
Recording device	Hospital room recording system comprised of a microphone connected to a device which produced a time signal once every hour.	Woolf, 1964[59]

Abbreviations: ECG=electrocardiographic; EMG=electromyographic; VAS=visual analog scale

Table F-3. KQ 2—Study characteristics

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Diseases	Number of Patients	Study Quality
Cass, 1953[79]	Antitussive (opiates) vs. Antitussive (other) vs. Placebo	U.S.	Persistent cough	NR	69	Fair
Cass, 1954[80]	Antitussive (opiates) vs. Antitussive (other) vs. Placebo	U.S.	Persistent cough	NR	65	Poor
Cass, 1956[81]	Antitussive (opiates) vs. Antitussive (other) vs, Antitussive (other) Placebo	U.S.	Persistent cough	NR	63	Fair
Simon, 1957[82]	Antitussive (anesthetics) vs. Antitussive (anesthetics)	U.S.	Chronic asthmatic bronchitis/pulmonary emphysema	COPD	59	Poor
Simon, 1960[83]	Antitussive (anesthetics) vs. Antitussive (opiates) vs. Placebo	U.S.	Chronic asthmatic bronchitis/pulmonary emphysema	Chronic bronchitis, pulmonary emphysema	45	Poor
Woolf, 1964[59]	Antitussive (opiates) vs. Placebo	Canada	Chronic cough	Chronic bronchitis, emphysema	10	Poor
Vakil, 1966[84]	Antitussive (other) vs. Placebo	Asia	Chronic cough	Chronic bronchitis, TB	70	Fair
Sevelius, 1971[85]	Antitussive (opiates) vs. Antitussive (opiates) vs. Placebo	U.S.	Chronic cough secondary to obstructive emphysema and chronic bronchitis	COPD	12	Fair
Wojcicki, 1975[86]	Antitussive (other) vs. Protussive (expectorants) vs. Placebo	Europe	Cough and nocturnal paroxysms of coughing	Chronic bronchitis, cystic fibrosis, TB	32	Good
Lilienfield, 1976[87]	Antihistamine vs. Antihistamine	U.S.	NR	Chronic bronchitis, cystic fibrosis, sarcoidosis, histoplasmosis	13	Fair

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Diseases	Number of Patients	Study Quality
Matts, 1977[88]	Antitussive (other) vs. Protussive (expectorants)	UK	Chronic cough.	Post viral infection	50	Fair
Sabot, 1977[89]	Antitussive (opiates) vs. Antitussive (opiates) vs. Placebo	Europe	Chronic cough	NR	24	Fair
Clarke, 1979[90]	Protussive (mucolytic) vs. Protussive (mucolytic)	UK	Chronic bronchitis	Chronic bronchitis	11	Good
Dierckx, 1981[91]	Antitussive (opiates) vs. Antitussive (other) vs. Placebo	Europe	Chronic cough	Asthma, chronic bronchitis, cystic fibrosis, TB	38	Fair
Diwan, 1982[92]	Antitussive (anesthetics) vs. Antitussive (opiates)	Asia	Chronic cough	COPD, chronic bronchitis, TB	60	Fair
Matthys, 1983[93]	Antitussive (opiates) vs. Antitussive (other) vs. Placebo	Europe	Chronic cough secondary to pulmonary TB, bronchial cancer, or obstructive lung disease	TB, bronchial cancer, obstructive lung disease	16	Fair
Gastpar, 1984[94]	Antitussive (opiates) vs. Antitussive (other)	Europe	Cough secondary to upper respiratory tract disease	NR	90	Poor
Jackson, 1984[95]	Protussive (mucolytic) vs. Placebo	UK	Chronic bronchitis	Chronic bronchitis	121	Poor
Ruhle, 1984[96]	Antitussive (other) vs. Antitussive (other) vs. Placebo	Europe	Chronic cough	COPD, asthma, chronic bronchitis, TB	24	Fair
Guyatt, 1987[97]	Protussive (mucolytic) vs. Placebo	Canada	Chronic productive cough	Chronic bronchitis	78	Fair
van Hengstum, 1988[98]	Protussive (nonpharmacological) vs. Protussive (nonpharmacological)	Europe	Chronic bronchitis	Chronic bronchitis	8	Fair

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Diseases	Number of Patients	Study Quality
Reid, 1989[99]	Antihistamine vs. Placebo	Australia/ New Zealand	Children, chronic recurrent cough and/or wheeze with evidence of airway hyperreactivity	Asthma	189	Fair
Dueholm, 1992[100]	Protussive (mucolytic) vs. Placebo	UK	Chronic bronchitis	Chronic bronchitis	51	Fair
Holmes, 1992[101]	Anticholinergic vs. Placebo	Australia/ New Zealand	Persistent cough secondary to prior upper respiratory tract infection	Post-viral URTI	13	Good
van Asperen, 1992[102]	Antihistamine vs. Placebo	Australia/ New Zealand	Children, chronic cough and/or wheeze	Unexplained cough	112	Good
Aversa, 1993[103]	Antitussive (other) vs. Placebo	Europe	Chronic lung disease	COPD, unexplained cough, neoplasm, pulmonary fibrosis	73	Fair
Del Donno, 1994[104]	Antitussive (other) vs. Antitussive (other)	Europe	Dry or slightly productive cough	COPD, unexplained cough, acute or unspecified bronchitis, other respiratory disease	99	Good
Barnabe, 1995[3]	Antitussive (opiates) vs. Antitussive (other)	Europe	Dry or slightly productive cough	COPD, unexplained cough, neoplasm, pulmonary fibrosis	113	Fair
Parvez, 1996[105] Study 1	Protussive (expectorants) vs. Placebo	Asia	Chronic productive cough secondary to bronchopulmonary disease	COPD, cystic fibrosis	60	Good
Parvez, 1996[105] Study 2	Protussive (mucolytic) vs. Placebo	Asia	Chronic productive cough secondary to bronchopulmonary disease	COPD, cystic fibrosis	24	Good
Tanaka, 1996[106]	Antihistamine vs. Placebo	Asia	Chronic cough	UACS	17	Fair
Luporini, 1998[107]	Antitussive (opiates) vs. Antitussive (other)	Europe	Persistent, nonproductive cough	Lung cancer	124	Fair

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Diseases	Number of Patients	Study Quality
Aliprandi, 2004[108] Study 1	Antitussive (other) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	COPD, asthma, chronic bronchitis	50	Poor
Aliprandi, 2004[108] Study 2	Antitussive (other) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	COPD, asthma, chronic bronchitis	60	Fair
Aliprandi, 2004[108] Study 3	Antitussive (other) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	COPD asthma, chronic bronchitis	40	Fair
Aliprandi, 2004[108] Study 4	Antitussive (opiates) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	COPD, asthma, chronic bronchitis	120	Fair
Aliprandi, 2004[108] Study 5	Antitussive (opiates) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	COPD, chronic bronchitis	60	Fair
Aliprandi, 2004[108] Study 6	Antitussive (other) vs. Antitussive (other)	Europe	Chronic nonproductive cough secondary to chronic bronchitis, bronchial asthma, COPD or medication.	Cough “of varying origin,” ACE inhibitor cough	120	Fair
Chaudhuri, 2004[109]	Corticosteroid vs. Placebo	UK	Chronic cough	GERD, asthma, UACS, bronchiectasis, eosinophilic bronchitis, bronchitis	88	Fair
Smith, 2006[54]	Antitussive (opiate) vs. Placebo	UK	COPD with cough	COPD	19	Fair
Vertigan, 2006[110]	Antitussive (nonpharmacological) vs. Placebo	Australia/ New Zealand	Chronic cough	GERD, asthma, UACS, ACE inhibitor	87	Fair
Morice, 2007[40]	Antitussive (opiates) vs. Placebo	UK	Chronic cough	Unexplained cough	27	Poor
Ribeiro, 2007[49]	Corticosteroid vs. Placebo	S. America	Chronic cough	Unexplained cough	64	Good
Ramsay, 2008[111]	Antitussive (other) vs. Placebo	UK	Chronic cough	None	42	Good

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Diseases	Number of Patients	Study Quality
Wei, 2010[112]	Bronchodilator vs. Bronchodilator	Asia	Non- or mildly productive cough	Cough variant asthma; GERD, nonasthmatic eosinophilic bronchitis; UACS	214	Fair
Yousaf, 2010[113]	Antibiotic vs. Placebo	UK	Chronic cough	Unexplained cough	30	Good
Mukaida, 2011[114]	Antitussive (other) vs. Placebo	Asia	Chronic cough secondary to COPD	COPD	19	Fair
Marchant, 2012[115]	Antibiotic vs. Placebo	Australia/ New Zealand	Children, chronic cough	NR	50	Good

Abbreviations: ACE=angiotensin-converting enzyme; COPD=chronic obstructive pulmonary disease; GERD=gastroesophageal reflux disease; NR=not reported; TB=tuberculosis; UACS=upper airway cough syndrome; URTI=upper respiratory tract infection

References to Appendix F

1. Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.
2. Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.
3. Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.
4. Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.
5. Berkhof FF, Boom LN, ten Hertog NE, et al. The validity and precision of the leicester cough questionnaire in COPD patients with chronic cough. Health and Quality of Life Outcomes. 2012;10. PMID:
6. Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.
7. Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.
8. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.
9. Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.
10. Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.
11. Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.
12. Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.
13. De Vito Dabbs A, Hoffman LA, Dauber JH, et al. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. Prog Transplant. 2002;12(3):191-8; quiz 9-200. PMID: 12371045.
14. Decalmer SC, Webster D, Kelsall AA, et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.
15. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43. PMID: 17167006.
16. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.
17. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax. 2000;55(12):1028-32. PMID: 11083888.
18. Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.
19. Field SK, Conley DP, Thawer AM, et al. Effect of the management of patients with chronic cough by pulmonologists and certified respiratory educators on quality of life: a randomized trial. Chest. 2009;136(4):1021-8. PMID: 19349387.
20. Fisman EZ, Shapira I, Motro M, et al. The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings. J Med. 2001;32(3-4):181-7. PMID: 11563816.
21. Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum

Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.

22. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.

23. French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.

24. French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61. PMID: 9701100.

25. Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7(7):1246-53. PMID: 7925902.

26. Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.

27. Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest. 2002;121(4):1132-40. PMID: 11948043.

28. Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.

29. Kelsall A, Houghton LA, Jones H, et al. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569-75. PMID: 20864619.

30. Kelsall A, Decalmer S, McGuinness K, et al. Sex differences and predictors of objective cough frequency in chronic cough. Thorax. 2009;64(5):393-8. PMID: 19131447.

31. Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.

32. Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4. PMID: 20565979.

33. Krahnke J, Gentile D, Angelini B, et al. Comparison of objective and subjective measurements of cough frequency in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2004;93(3):259-64. PMID: 15478386.

34. Krajnik M, Damps-Konstanska I, Gorska L, et al. A portable automatic cough analyser in the ambulatory assessment of cough. Biomed Eng Online. 2010;9:17. PMID: 20226089.

35. Leconte S, Liistro G, Lebecque P, et al. The objective assessment of cough frequency: accuracy of the LR102 device. Cough. 2011;7(1):11. PMID: 22132691.

36. Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.

37. Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol. 2008;122(5):903-7. PMID: 18842290.

38. Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.

39. Monz BU, Sachs P, McDonald J, et al. Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. Respir Med. 2010;104(4):534-41. PMID: 19917525.

40. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.

41. Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31. PMID: 19196812.

42. Mwachari C, Nduba V, Nguti R, et al. Validation of a new clinical scoring system for acute bronchitis. Int J Tuberc Lung Dis. 2007;11(11):1253-9. PMID: 17958990.

43. Nandha D, Goodyer L, Woodruffe-Peacock C. Diary cards and the assessment of cough symptoms in community pharmacies. Pharm World Sci. 2000;22(1):17-20. PMID: 10815295.

44. Nieto L, de Diego A, Perpina M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97(4):393-400. PMID: 12693800.

45. Novitsky YW, Zawacki JK, Irwin RS, et al. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc. 2002;16(4):567-71. PMID: 11972189.

46. O'Connell F, Thomas VE, Pride NB, et al. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994;150(2):374-80. PMID: 8049818.

47. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.

48. Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.

49. Ribeiro M, Pereira CA, Nery LE, et al. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. Ann Allergy Asthma Immunol. 2007;99(1):61-8. PMID: 17650832.

50. Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):225-34. PMID: 21083673.

51. Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.

52. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.

53. Smith JA, Owen EC, Jones AM, et al. Objective measurement of cough during pulmonary exacerbations in adults with cystic fibrosis. Thorax. 2006;61(5):425-9. PMID: 16449266.

54. Smith J, Owen E, Earis J, et al. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006;117(4):831-5. PMID: 16630941.

55. Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.

56. Thomas JS, Lyons HA, Shepherd DA. D.A.T.A.—an advanced automated electronic cough counting system for the evaluation of antitussive agents. Curr Ther Res Clin Exp. 1978;23(1):66-77.

57. Vernon M, Kline Leidy N, Nacson A, et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4(4):199-208. PMID: 20519373.

58. Woodcock A, McLeod RL, Sadeh J, et al. The efficacy of a NOP1 agonist (SCH486757) in subacute cough. Lung. 2010;188 Suppl 1:S47-52. PMID: 19937046.

59. Woolf CR, Rosenberg A. Objective assessment of cough suppressants under clinical conditions using a tape recorder system. Thorax. 1964;19:125-30. PMID: 14128569.

60. Hamutcu R, Francis J, Karakoc F, et al. Objective monitoring of cough in children with cystic fibrosis. Pediatr Pulmonol. 2002;34(5):331-5. PMID: 12357476.

61. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. Ear Nose Throat J. 2009;88(11):1213-7. PMID: 19924664.

62. Kalpaklioglu AF, Kara T, Kurtipek E, et al. Evaluation and impact of chronic cough: comparison of specific vs generic quality-of-life questionnaires. Ann Allergy Asthma Immunol. 2005;94(5):581-5. PMID: 15945562.

63. Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.

64. Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.

65. Chang AB, Robertson CF, Van Asperen PP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a

standardized management pathway. Chest. 2012. PMID: 22459773.

66. Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.

67. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.

68. Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.

69. Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.

70. Dales RE, White J, Bhumgara C, et al. Parental reporting of childrens' coughing is biased. Eur J Epidemiol. 1997;13(5):541-5. PMID: 9258566.

71. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.

72. Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.

73. Fuller P, Picciotto A, Davies M, et al. Cough and sleep in inner-city children. Eur Respir J. 1998;12(2):426-31. PMID: 9727796.

74. Hoskyns EW, Thomson A, Decker E, et al. Effect of controlled release salbutamol on nocturnal cough in asthma. Arch Dis Child. 1991;66(10):1209-12. PMID: 1953004.

75. Newcombe PA, Sheffield JK, Chang AB. Minimally important change in a Parent-Proxy Quality-of-Life questionnaire for pediatric chronic cough. Chest. 2011;139(3):576-80. PMID: 20947650.

76. Newcombe PA, Sheffield JK, Juniper EF, et al. Validation of a parent-proxy quality of life questionnaire for paediatric chronic cough (PC-QOL). Thorax. 2010;65(9):819-23. PMID: 20805179.

77. Newcombe PA, Sheffield JK, Juniper EF, et al. Development of a parent-proxy quality-of-life chronic cough-specific questionnaire: clinical impact vs psychometric evaluations. Chest. 2008;133(2):386-95. PMID: 18252913.

78. Zihlif N, Paraskakis E, Lex C, et al. Correlation between cough frequency and airway inflammation in children with primary ciliary dyskinesia. Pediatr Pulmonol. 2005;39(6):551-7. PMID: 15806596.

79. Cass LJ, Frederik WS. Evaluation of a new antitussive agent. N Engl J Med. 1953;249(4):132-6. PMID: 13063699.

80. Cass LJ, Frederik WS, Andosca JB. Quantitative comparison of dextromethorphan hydrobromide and codeine. Am J Med Sci. 1954;227(3):291-6. PMID: 13138597.

81. Cass LJ, Frederik WS. Quantitative comparison of cough-suppressing effects of romilar and other antitussives. J Lab Clin Med. 1956;48(6):879-85. PMID: 13376983.

82. Simon SW. A comparative study of two new non-narcotic antitussive drugs. Ohio Med. 1957;53(12):1426-7. PMID: 13493953.

83. Simon SW. Symptomatic treatment of asthmatic bronchitis. J Am Geriatr Soc. 1960;8:107-11. PMID: 14446944.

84. Vakil BJ, Mehta AJ, Prajapat KD. Trial of pipazethate as an antitussive. Clin Pharmacol Ther. 1966;7(4):515-9. PMID: 5328471.

85. Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. Clin Pharmacol Ther. 1971;12(3):449-55. PMID: 4936034.

86. Wojcicki J, Samochowiec L, Szwed G, et al. The use of Duopect as expectorant–antitussive agent. Arch Immunol Ther Exp (Warsz). 1975;23(1):135-42. PMID: 1090275.

87. Lilienfield LS, Rose JC, Princiotto JV. Antitussive activity of diphenhydramine in chronic cough. Clin Pharmacol Ther. 1976;19(4):421-5. PMID: 773581.

88. Matts SG. A trial of Lotussin and linctus diphenhydramine in patients wth an irritant cough. J Int Med Res. 1977;5(6):470-2. PMID: 338397.

89. Sabot G, Bagnato A, Frigerio G. Controlled evaluation of the antitussive activity of viminol p-hydroxybenzoate. Int J Clin

Pharmacol Biopharm. 1977;15(4):181-3. PMID: 323163.

90. Clarke SW, Lopez-Vidriero MT, Pavia D, et al. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol. 1979;7(1):39-44. PMID: 104724.

91. Dierckx P, Leblanc G, Decoster A, et al. Double-blind study of glaucine in chronic cough. Int J Clin Pharmacol Ther Toxicol. 1981;19(9):396-9. PMID: 7028646.

92. Diwan J, Dhand R, Jindal SK, et al. A comparative randomized double-blind clinical trial of isoaminile citrate and chlophedianol hydrochloride as antitussive agents. Int J Clin Pharmacol Ther Toxicol. 1982;20(8):373-5. PMID: 6749701.

93. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. J Int Med Res. 1983;11(2):92-100. PMID: 6852361.

94. Gastpar H, Criscuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. Curr Med Res Opin. 1984;9(1):21-7. PMID: 6373156.

95. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. J Int Med Res. 1984;12(3):198-206. PMID: 6376210.

96. Ruhle KH, Criscuolo D, Dieterich HA, et al. Objective evaluation of dextromethorphan and glaucine as antitussive agents. Br J Clin Pharmacol. 1984;17(5):521-4. PMID: 6375709.

97. Guyatt GH, Townsend M, Kazim F, et al. A controlled trial of ambroxol in chronic bronchitis. Chest. 1987;92(4):618-20. PMID: 3308343.

98. van Hengstum M, Festen J, Beurskens C, et al. The effect of positive expiratory pressure versus forced expiration technique on tracheobronchial clearance in chronic bronchitics. Scand J Gastroenterol Suppl. 1988;143:114-8. PMID: 3291088.

99. Reid JJ. Double-blind trial of ketotifen in childhood chronic cough and wheeze. Immunol Allergy Pract. 1989;11(4):143-50. PMID:

100. Dueholm M, Nielsen C, Thorshauge H, et al. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. Respir Med. 1992;86(2):89-92. PMID: 1615189.

101. Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respir Med. 1992;86(5):425-9. PMID: 1462022.

102. van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health. 1992;28(6):442-6. PMID: 1466940.

103. Aversa C, Cazzola M, Clini V, et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. Drugs Exp Clin Res. 1993;19(6):273-9. PMID: 8013271.

104. Del Donno M, Aversa C, Corsico R, et al. Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough. Drug Investigation. 1994;7(2):93-100. PMID:

105. Parvez L, Vaidya M, Sakhardande A, et al. Evaluation of antitussive agents in man. Pulm Pharmacol. 1996;9(5-6):299-308. PMID: 9232667.

106. Tanaka S, Hirata K, Kurihara N, et al. Effect of loratadine, an H1 antihistamine, on induced cough in non-asthmatic patients with chronic cough. Thorax. 1996;51(8):810-4. PMID: 8795669.

107. Luporini G, Barni S, Marchi E, et al. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. Eur Respir J. 1998;12(1):97-101. PMID: 9701421.

108. Aliprandi P, Castelli C, Bernorio S, et al. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41. PMID: 15553659.

109. Chaudhuri R, McMahon AD, Thomson LJ, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. J Allergy Clin Immunol. 2004;113(6):1063-70. PMID: 15208586.

110. Vertigan AE, Theodoros DG, Gibson PG, et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065-9. PMID: 16844725.

111. Ramsay J, Wright C, Thompson R, et al. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br J Clin Pharmacol. 2008;65(5):737-41. PMID: 18279476.

112. Wei W, Yu L, Wang Y, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology. 2010;15(5):830-6. PMID: 20546197.

113. Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010;65(12):1107-10. PMID: 20965928.

114. Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. Phytomedicine. 2011;18(8-9):625-9. PMID: 21177084.

115. Marchant J, Masters IB, Champion A, et al. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax. 2012. PMID: 22628120.