Effective Health Care Program

Comparative Effectiveness Review
Number 100

Assessment and Management of Chronic Cough

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Comparative Effectiveness Review

Number 100

Assessment and Management of Chronic Cough

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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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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?

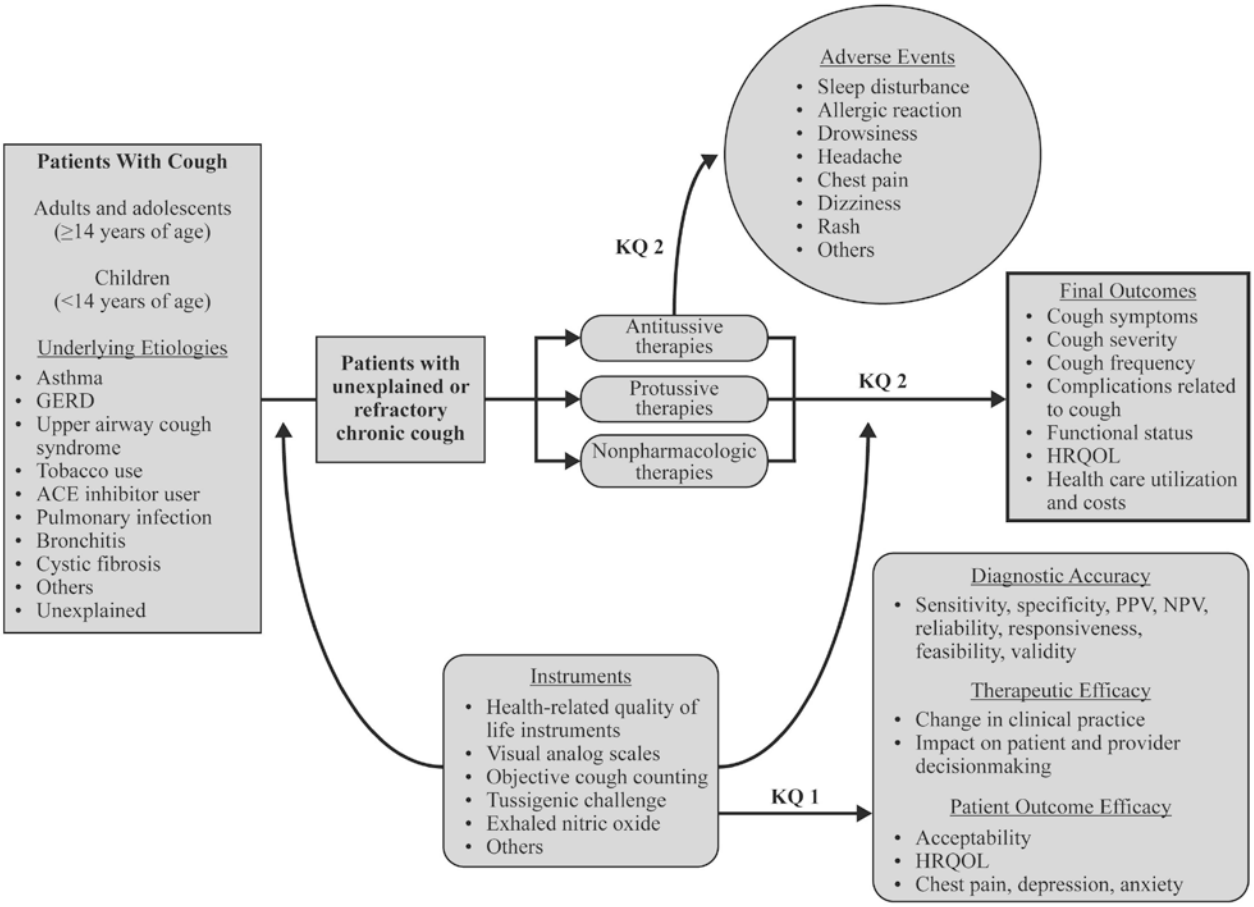
KQ 2: In adults and adolescents (≥14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?

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 ≤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.

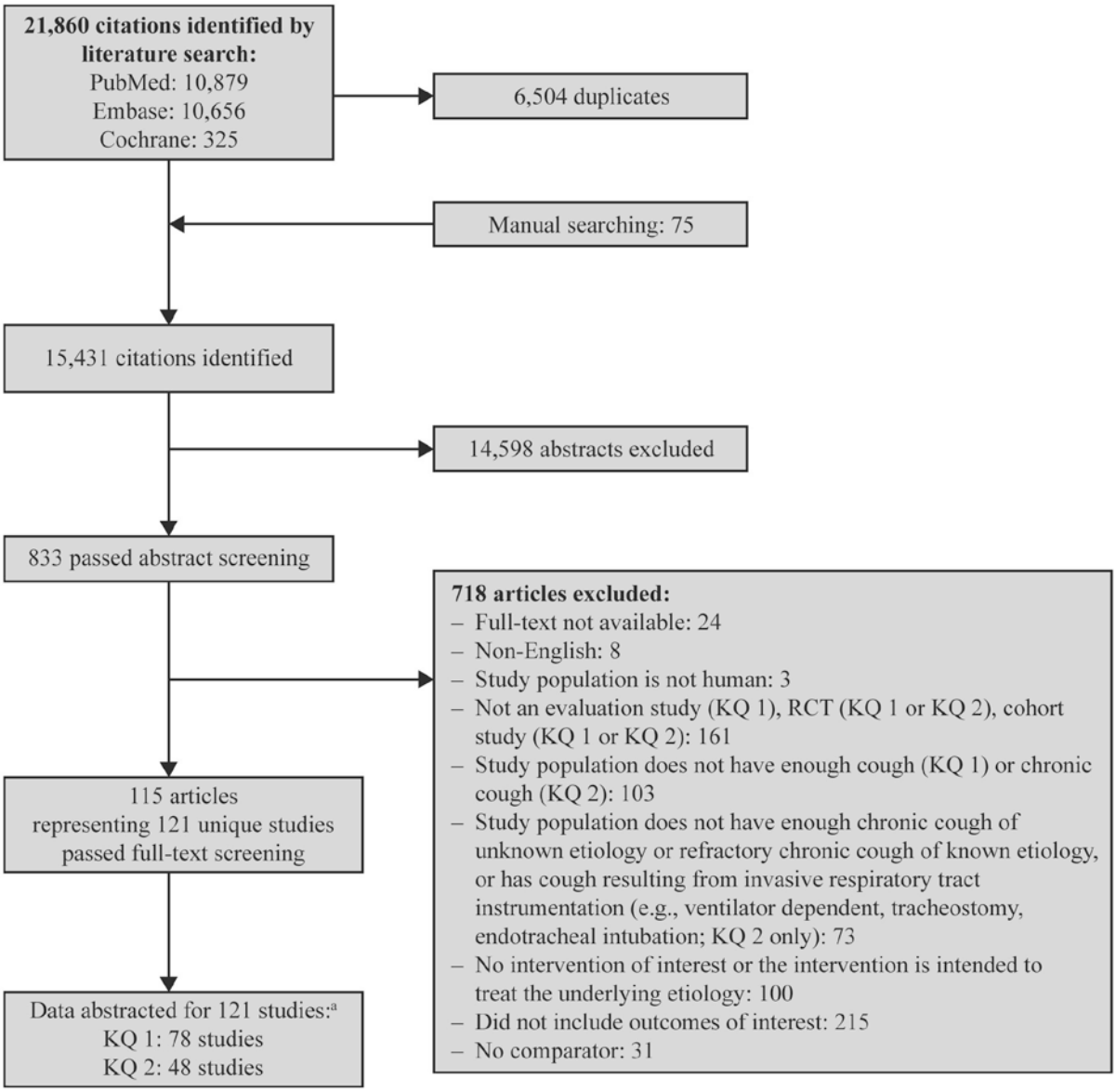
Applicability

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; 215 subjects Range of r = 0.75–0.93	**Insufficient SOE** 0 studies/subjects	**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** 0 studies/subjects	**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.

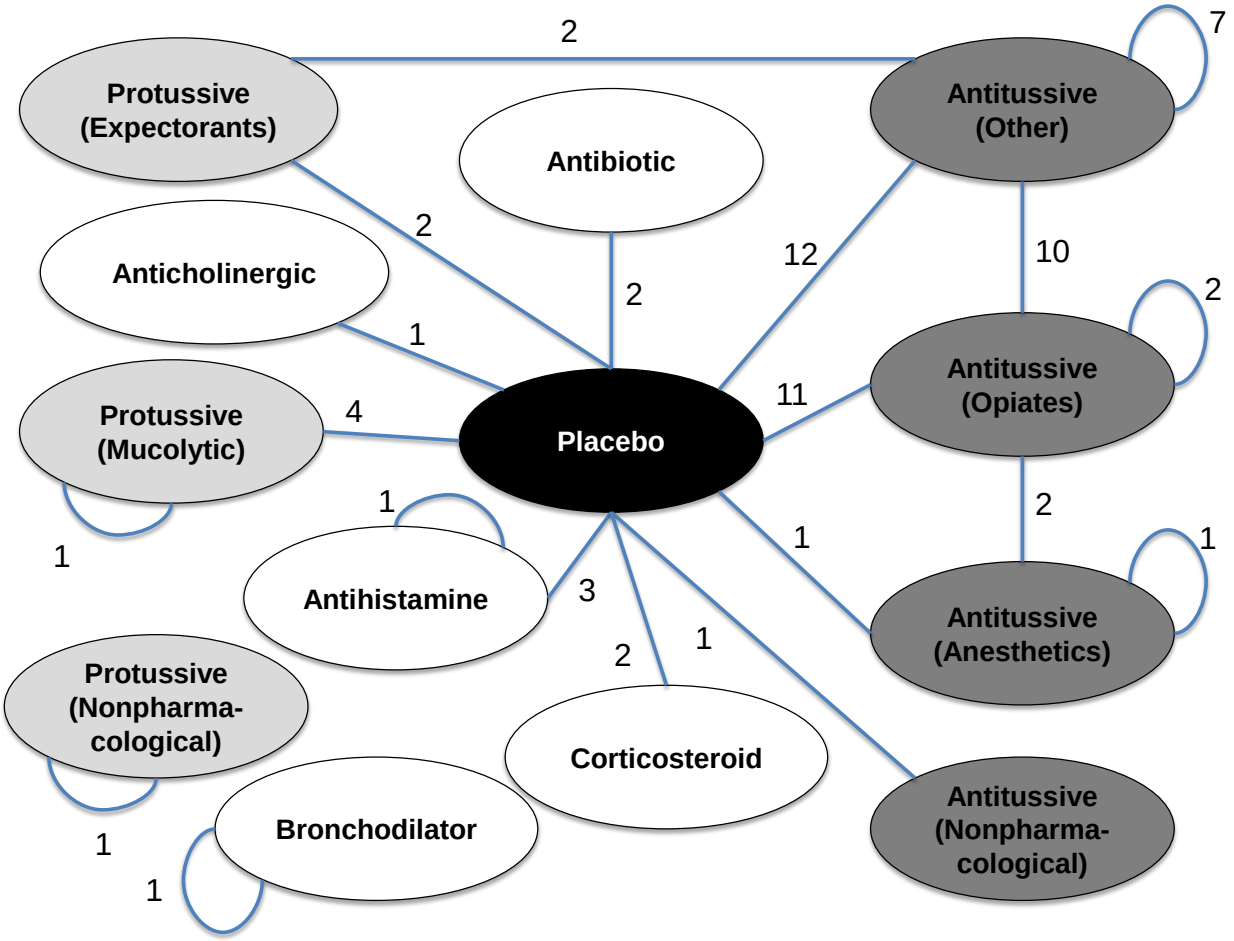
- There were several important quality limitations in the literature, including (1) too few good-quality studies focusing on chronic cough; (2) relatively short durations of followup (3) a diversity of outcomes measured across studies, which limited between-study comparisons; and (4) when similar outcomes 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, dextromethor-phan, 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.

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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

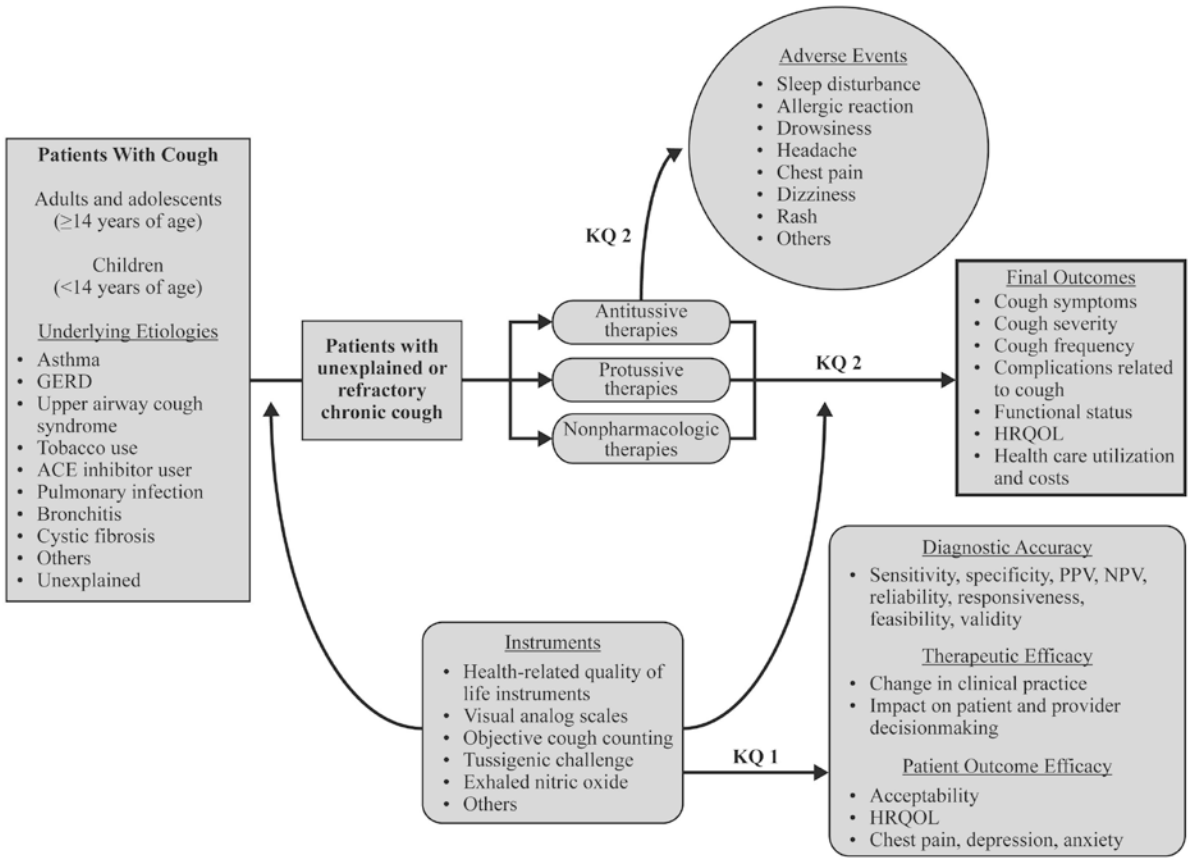
With input from our Key Informants, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods chapter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

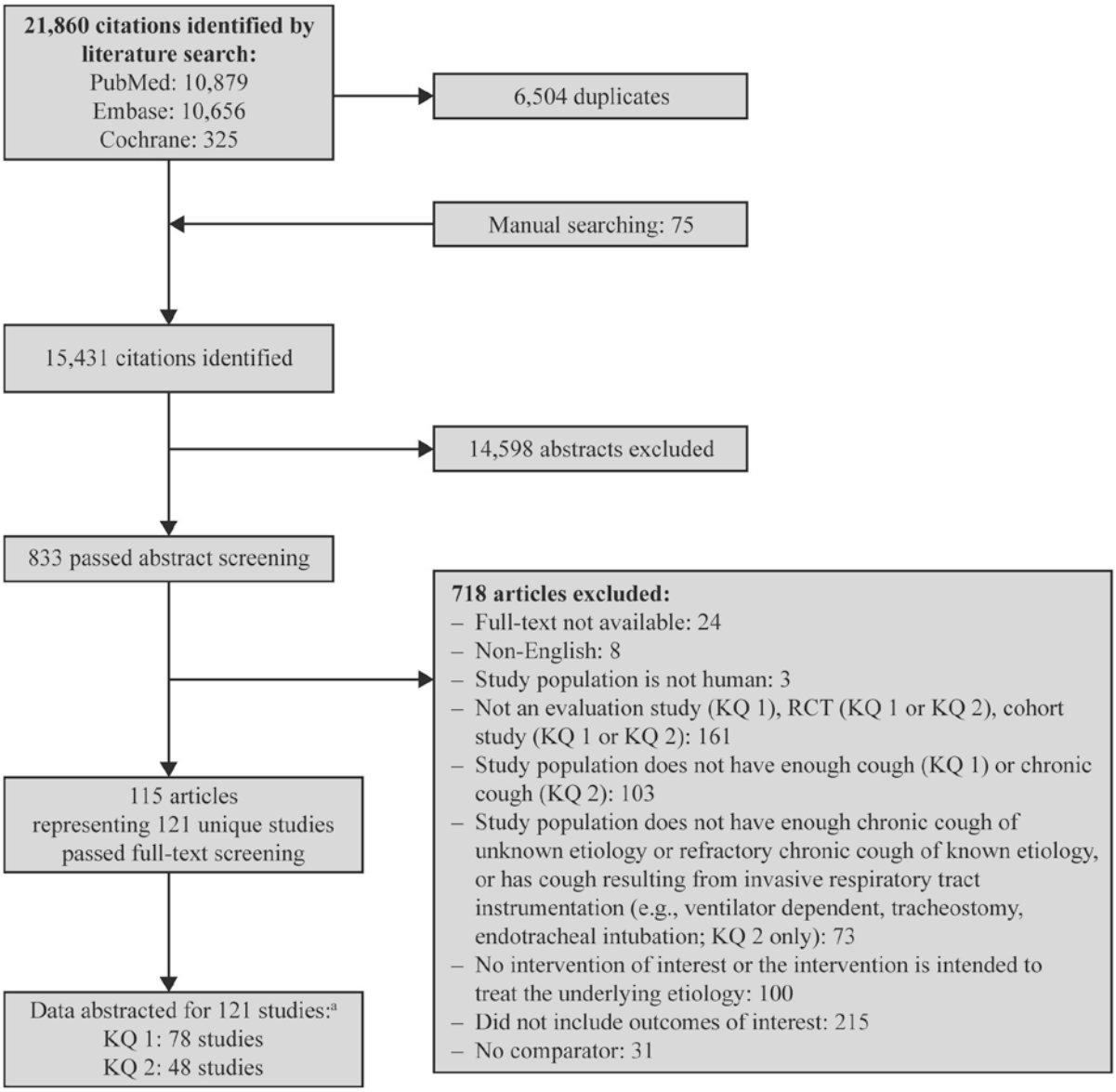
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

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 ($p \leq 0.001$)
	LCQ Physical	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.55 ($p \leq 0.001$)
	LCQ Psycholo-gical	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.59 ($p \leq 0.001$)
	LCQ Social	Log total time spent coughing	Yes	No	No	Spearman coefficient: -0.55 ($p \leq 0.001$)

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: 0.89 (p<0.001) Test-retest paired t-value: -1.39
	Physical complaints	NA	No	Yes	No	Cronbach's α: 0.88 (p<0.001) Test-retest paired t-value: -0.92
	Psycho-social issues	NA	No	Yes	No	Cronbach's α: 0.91 (p<0.001) Test-retest paired t-value: -0.19
	Functional abilities	NA	No	Yes	No	Cronbach's α: 0.85 (p<0.001) Test-retest paired t-value: -1.21
	Emotional well-being	NA	No	Yes	No	Cronbach's α: 0.77 (p<0.001) Test-retest paired t-value: -1.44
	Extreme physical complaints	NA	No	Yes	No	Cronbach's α: 0.93 (p<0.001) Test-retest paired t-value: -0.24
	Personal safety fears	NA	No	Yes	No	Cronbach's α: 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.

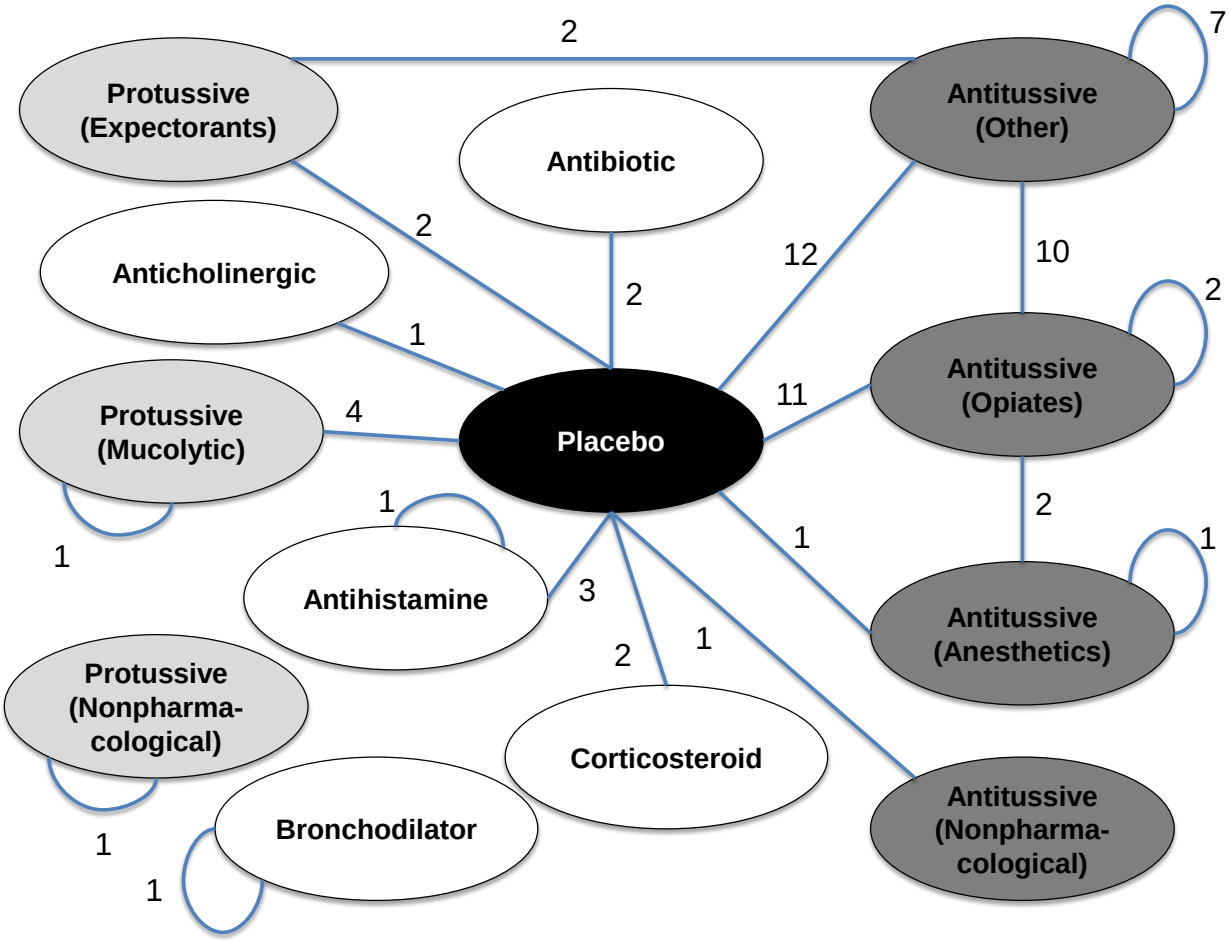
Description of Included Studies

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

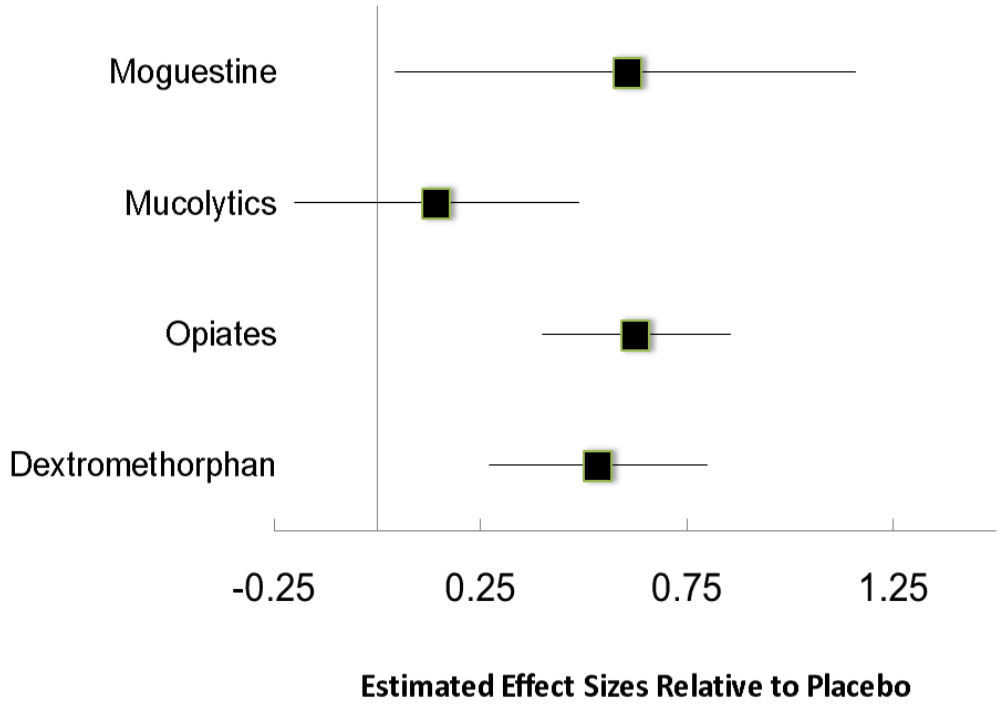
although it had a small sample size and the description of diagnostic evaluation of cough was minimal, it otherwise had good applicability.

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

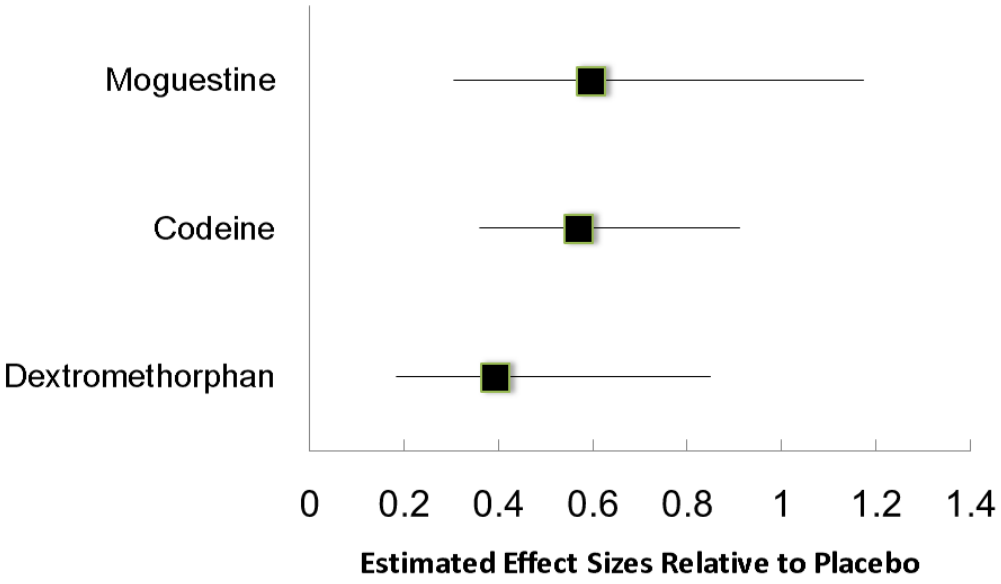


Table 9. Patient-centered outcomes data

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 (215)	Low	Inconsistent	Direct	Imprecise	Range of r=0.75–0.93
Reliability (repeatability)					**Insufficient SOE**
0	NA	NA	NA	NA	NA
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**
0	NA	NA	NA	NA	NA
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.

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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

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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.

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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

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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

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