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Number XX

Assessment and Management of Chronic Cough

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Preface

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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. 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 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: Sixty studies (5430 subjects) evaluated instruments for assessing cough. The Leicester Cough Questionnaire (LCQ) was the most widely studied instrument; based on our findings of fair to moderate correlation with other cough measurement tools, there is moderate strength of evidence (SOE) to support the LCQ's validity in assessing severity of cough (SOE = moderate [validity], high [internal consistency and reliability], insufficient [responsiveness]). Electronic recording devices are accurate for assessing cough frequency but show variable correlation with other tools (SOE = high [validity], moderate [reliability], insufficient [responsiveness]). Visual analog scales have little data to validate their accuracy in assessing cough, and inconsistent correlations with other tools (SOE = insufficient [validity, reliability and responsiveness]). We identified no studies exploring the impact of cough assessment instruments on therapeutic efficacy or patient outcome efficacy.

Forty-two studies (2622 patients) evaluated 57 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 demonstrated the most promise for managing chronic cough. In particular, codeine and dextromethorphan have been shown to reduce cough frequency and severity. 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 or the management of cough in children (2 studies each).

Conclusions: Several instruments for assessing cough severity, frequency, and impact on 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, especially in the absence of a commonly used gold standard. Although the evidence is sparse, the opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise for managing chronic cough. Our review highlights the need for further studies in patient populations with unexplained or refractory chronic cough and 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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Effective Health Care

Assessment and Management of Chronic Cough

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

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 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 non-respiratory 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. Such chronic cough is responsible for up to 38 percent of pulmonary outpatient visits.[2,3] 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 comparative effectiveness of instruments to evaluate cough and the comparative effectiveness of treatments for the symptom of cough for patients with either refractory or unexplained 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). Chronic cough becomes chronic as a result of its underlying etiology being 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.

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.[4] 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,[5,6] and one focused on children.[7] Guidelines from the American College of Chest Physicians (ACCP), last updated in 2006, are the most comprehensive resource and will be the subject of a future update.[6]

If treatment of the underlying etiology fails to resolve the cough, or if no cause can be identified, 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 stimulus and 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.[8]

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 pharmacologic 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

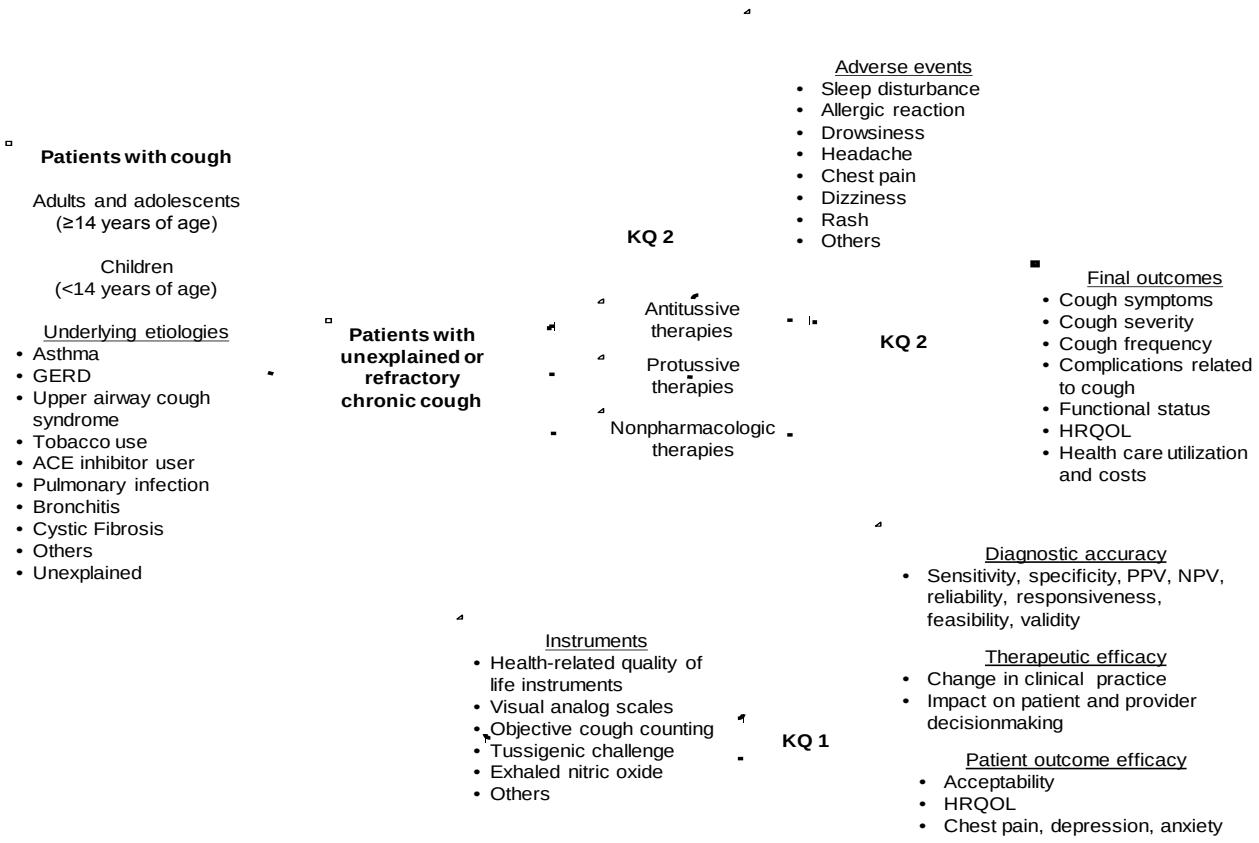
This comparative effectiveness review (CER) was funded by the Agency for Healthcare Research and Quality (AHRQ) and is designed to evaluate the comparative effectiveness of measurement tools for assessing cough and of symptomatic treatments for chronic cough.

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



Abbreviations: 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*)[9] and *Methods Guide for Medical Test Reviews* (hereafter referred to as the *Medical Test Guide*).[10]

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). 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; metaRegister of Controlled Trials; the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index.

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. Articles were excluded if the therapy was directed at an underlying etiology rather than the symptom of cough, if patients received 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 Distiller SR 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*.[9] 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[11] 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 a considered various measures of test performance. For cough recording devices, we reported sensitivity and specificity, with human cough counts serving as the reference standard. For questionnaires, we reported correlation coefficients, internal consistency measures, test-retest results, and minimal importance difference estimates, when available. In general, the published literature in this field relies on correlation with other cough instruments for validation of cough questionnaires.

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 grouped interventions by drug class, considering opiate antitussive drugs and mucolytic protussive drugs to be similar enough to combine with one another. We considered measures of cough frequency, regardless of the scale used, to be similar enough to combine using effect sizes; 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*.[9,12] and *Medical Test Guide*.[10] 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.

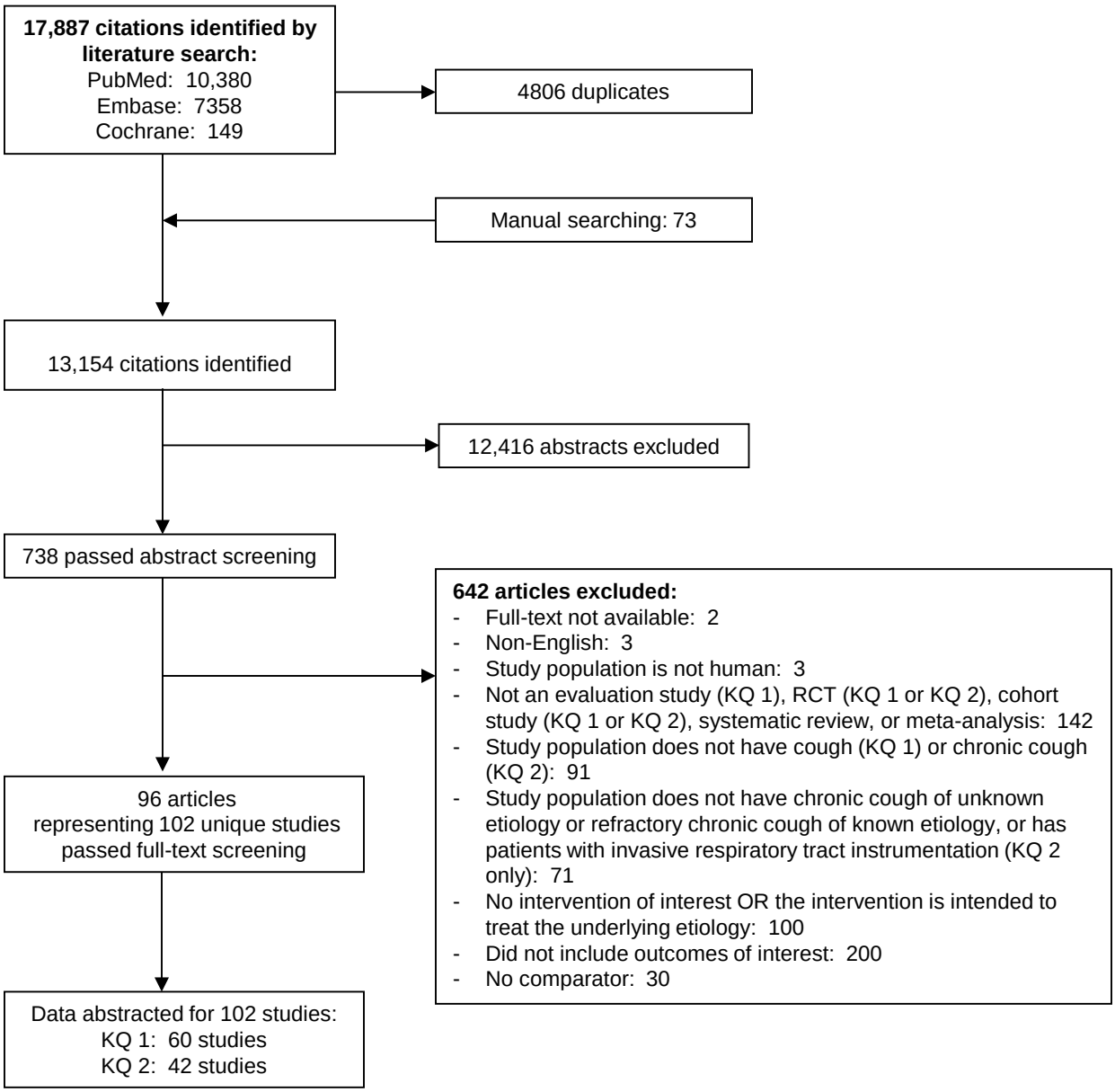
Applicability

We assessed applicability across our KQs using the method described in the *Methods Guide*.[9,13] 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 to 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 17,887 citations, 4806 of which were duplicate citations. Manual searching identified 73 additional citations, for a total of 13,154 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 738 full-text articles were retrieved and screened. Of these, 642 were excluded at the full-text screening stage, leaving 96 articles for data abstraction. Overall, we included 102 studies represented by 96 publications: 60 studies were relevant to KQ 1, 42 to KQ 2. Studies were conducted in Europe (53.9 percent); Asia (9.8 percent); the United States or Canada (20.6 percent); Australia or New Zealand (10.7 percent); and other locations (7.8 percent). Twelve studies in KQ 1 (20 percent) and two studies in KQ 2 (5 percent) included children. Forty-one (41) studies (40 percent) were published before 2000. No additional information was found through our grey literature search.

Figure B. Literature flow diagram



Abbreviations: KQ = key question; RCT = randomized controlled trial

Key Question 1. Instruments Used to Assess Cough

Key points from the Results chapter are:

- The Leicester Cough Questionnaire (LCQ) is the most widely studied cough-specific quality-of-life questionnaire. Validity of the LCQ was established primarily by fair to moderate correlation with other cough measurement tools. It demonstrates good internal consistency and reliability.
- The Parent Cough-specific Quality-of-Life questionnaire (PC-QOL) has been validated in the pediatric population and shows fair to moderate correlation with other subjective and

objective cough measurement tools, but there is insufficient evidence to assess internal consistency and reliability.

- Other cough-specific quality-of-life questionnaires, such as the Cough-specific Quality of Life Questionnaire (CQLQ), Chronic Cough Impact Questionnaire (CCIQ), and the Punum Ladder, 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 non-cough symptoms and so are less valuable tools for cough assessment.
- Electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with other cough measurement tools.
- Electronic recording devices may be most useful in the research setting but may be less practical in the clinical setting due to their cost, inconvenience to the patient, and technical and analytical requirements.
- Although they are widely used both in research and practice, visual analog scales use a variety of different measurement scales, often assess different cough outcomes, have little to no data to validate their accuracy in assessing cough, and have inconsistent correlations with other cough measurement tools. These tools are usually simple and easy to use, but more data are needed to determine how useful they are in assessing cough or monitoring responsiveness before they can be used as comparators when measuring the validity of other tools.
- Diaries and other subjective scores overall show variable to poor correlation with other cough measurement tools when used as reference tests.
- The majority of reference tests used in the included studies have not previously been validated.
- 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.

Sixty studies met the inclusion criteria for KQ 1. Of these, 51 (85 percent) were judged to have a low risk of bias and 9 (15 percent) were judged to have a high risk of bias. In most cases, the funding source was not reported or was unclear. None of the studies was an RCT. Sample sizes ranged from 8 to 671 subjects; overall, the 60 studies involved 5430 subjects.

All of the cough instruments evaluated in the included studies can be considered assessments of cough frequency, cough severity, impact of cough on quality of life, or a combination of the three. Most of the studies compared one instrument with one or more other assessments of cough frequency, severity, or impact on quality of life. Thirty-one studies (52 percent) included a quality-of-life questionnaire, and 22 (37 percent) included an electronic device designed to measure cough frequency. Only six studies (10 percent) included visual analog scales as an index test. Most studies which included 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. In most studies no information was given regarding previous validation of reference tests. Thirty-one studies (52 percent) enrolled patients with chronic cough of mixed, unknown, or unspecified etiology; 9 (15 percent) enrolled patients with acute cough or cough of unspecified duration, and 20 (33 percent) focused on specific clinical conditions such as chronic bronchitis, asthma, or lung cancer. Twelve studies (20

percent) included only children, while an additional four studies (6.7 percent) included both adults and children.

We focused our detailed synthesis on quality-of-life questionnaires (12 quality-of-life questionnaires used in 30 studies involving 1590 patients), electronic recording devices (22 studies involving 814 patients), and visual analog scales (6 studies involving 240 patients), as these were the most widely encountered tools in the studies we evaluated. 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.

Table A summarizes the findings of our review and the strength of evidence[12] for the available outcomes of validity, internal consistency, reliability, and responsiveness for the various 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. Among the quality-of-life questionnaires evaluated, only the LCQ and CQLQ were represented by four or more published studies; as such, they are they only two questionnaires for which we generated strength of evidence tables.

Table A. Summary of strength of evidence and effect estimate for KQ 1

Instrument	Validity (Correlation With Other Measures of Cough)	Internal Consistency (Cronbach's Alpha)	Reliability (Repeatability)	Responsiveness
Leicester Cough Questionnaire (LCQ)	Moderate SOE Range of r = 0.26–0.88	High SOE Range of r = 0.77–0.93	High SOE Range of r = 0.86–0.92	Insufficient SOE Range of ES = 0.84–19.5
Cough-specific Quality of Life Questionnaire (CQLQ)	Moderate SOE Range of r = 0.24–0.56	Insufficient SOE Range of r = 0.75–0.93	Insufficient SOE NA	Insufficient SOE Range of MID = 10.6–21.9
Electronic recording devices	High SOE Range of r = 0.89–0.99	NA	Moderate SOE Range of r = 0.8–1.0	Insufficient SOE Detected change with treatment
Visual analog scales	Insufficient SOE No summary measure	NA	Insufficient SOE NA	Insufficient SOE Sensitivity of 0.81–0.95 for detecting clinically important change

Abbreviations: CQLQ = Cough-specific Quality of Life Questionnaire; ES = effect size; KQ = key question; LCQ = Leicester Cough Questionnaire; MID = minimal important difference; NA = not applicable; r = correlation coefficient; SOE = strength of evidence

Key Question 2. Nonspecific Therapies for Chronic Cough

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.

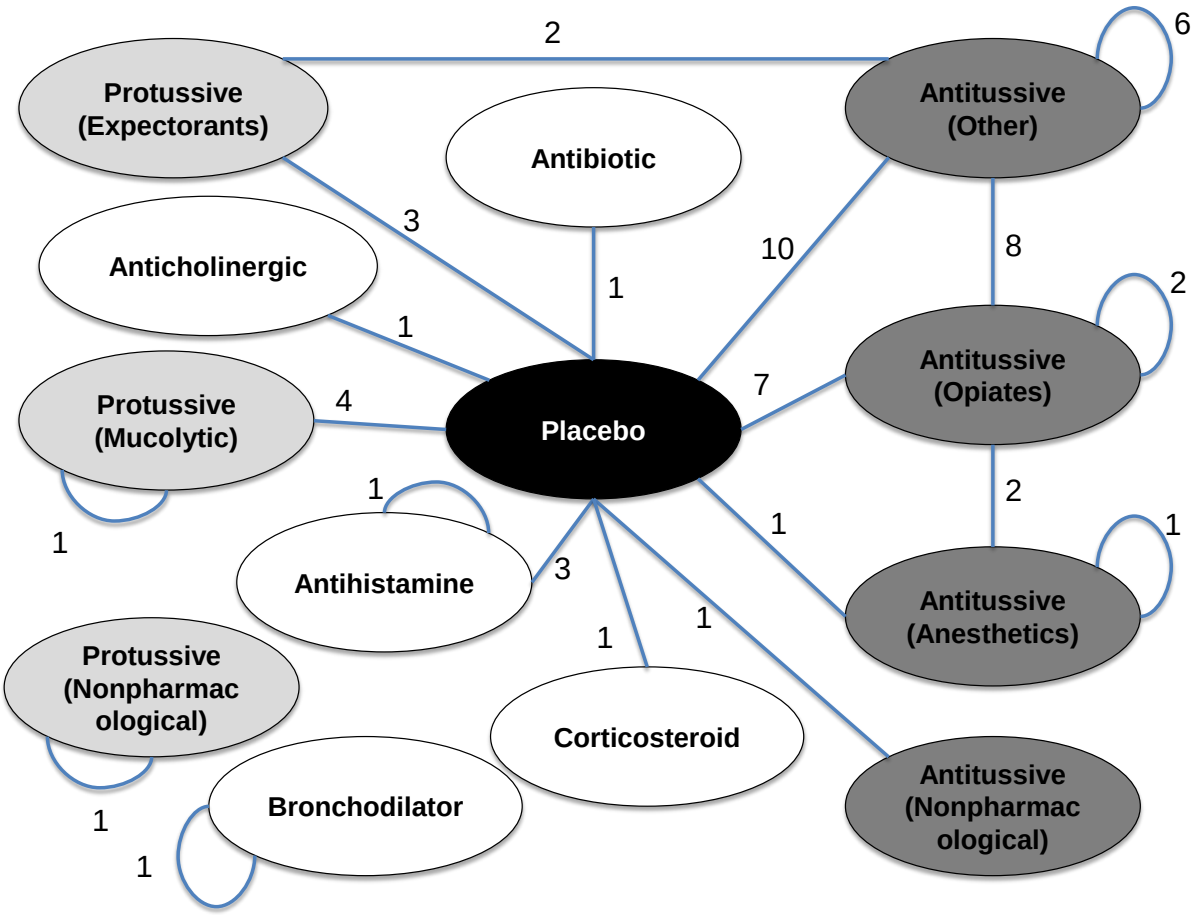
- The opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise for managing the symptom of chronic cough.
- All preparations appeared to be well-tolerated, but side effects and adverse events were uncommonly reported.
- There were few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough.
- Outcomes assessed and methods of measuring these outcomes varied widely across studies.
- Data on nonpharmacological therapies for chronic cough were sparse.
- Studies evaluating management of unidentified or refractory chronic cough in children are extremely limited.
- Patients with unexplained or refractory chronic cough are not well-defined as a population in the evidence base, restricting the applicability of many studies.
- When similar outcomes were assessed across studies, the tools used were diverse and inconsistent, making comparison and interpretation difficult.

Fifty-seven comparisons from 42 studies evaluated therapies in patients with chronic cough and met our inclusion criteria. The 42 studies were described in 36 publications. Thirty-two of the 42 studies were parallel-group RCTs, and 8 were randomized crossover studies. The range of years of publication was 1956 to 2011; 69 percent of the articles were published before 2000. Only two studies were performed in children.

A total of 2622 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. Twenty-eight (28) studies (67 percent) had a followup duration of 2 weeks or less. The majority of studies were rated fair in quality (26 studies, 62 percent); 10 studies were good in quality, and 6 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 42 studies represented 20 different types of comparisons within or between treatment classes and included studies of 57 individual agents. The majority of comparisons (33, or 58 percent) were placebo-controlled. The most common comparisons were between other antitussives and placebo (10 studies, 17 percent of comparisons), followed by other antitussives and antitussive opiates (8 studies, 14 percent) and antitussive opiates versus placebo (7 studies, 12 percent). Sixteen comparisons (28 percent) reflected comparisons 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 tools used were diverse and inconsistent, making comparison and interpretation difficult.

We were, however, able to evaluate the relative effects on cough severity for three classes of treatments for chronic cough: antitussive opiates, antitussive dextromethorphan, and protussive mucolytics. This analysis included 11 studies and 526 patients. Most of the 11 studies compared the treatment to placebo, but one compared opiates to dextromethorphan and placebo. Because each study used a different measure of severity, we converted all results to effect sizes. Relative to placebo, the effect of dextromethorphan on cough severity was 0.599 (95 percent confidence interval [CI], -0.009 to 1.206; p = 0.0527), the effect of opiates was 0.426 (95 percent CI, -0.001 to 0.852; p = 0.0502) and the effect of mucolytics was 0.144 (95 percent CI -0.225 to 0.513; p = 0.394). The studies showed marginal heterogeneity (p = 0.092). Although not quite reaching the conventional level of statistical significance, the effects of dextromethorphan and opiates compared to placebo on cough severity support a statistical trend and suggest that the findings between studies are reasonably similar.

We considered a similar meta-analysis for cough frequency, but the four studies comparing codeine and placebo had too many differences in outcome reporting so that meta-analysis was not considered to be appropriate.

Table B summarizes 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 and effect estimate for KQ 2

Treatment Comparison	Cough Severity	Cough Frequency	Adverse Effects
Antitussive (anesthetic) versus antitussive (opiate)	Insufficient SOE No significant differences	Insufficient SOE No significant differences	Insufficient SOE No significant differences
Antitussive (opiate) versus antitussive (other)	Insufficient SOE Opiates and dextromethorphan had similar effect sizes in MTM vs. placebo, p ~ 0.050—0.053	Insufficient SOE No summary measure	Insufficient SOE No summary measure
Protussive (mucolytic) versus antitussive (other)	Insufficient SOE Mucolytics had much smaller effect size vs. placebo, p = NS, in MTM compared with dextromethorphan	Insufficient SOE No summary measure	Insufficient SOE NA
Protussive (mucolytic) versus antitussive (opiate)	Insufficient SOE Mucolytics had much smaller effect size vs. placebo, p = NS, in MTM compared with codeine	Insufficient SOE No summary measure	Insufficient SOE NA

Abbreviations: KQ = key question; MTM = mixed treatment meta-analysis; NA = not applicable; NS = not statistically significant; SOE = strength of evidence

Discussion

Key Findings

We reviewed 60 studies involving 5430 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 is the most widely studied cough-specific quality-of-life questionnaire, 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 accurate for assessing cough frequency, but they show variable correlation with other cough measurement tools. 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 42 studies involving 2622 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. We did not identify any studies of currently available treatments for chronic cough in children. No data were identified in our search regarding the risk of harm from cough medicines in children.

Applicability

For our analysis of instruments for the assessment of cough (KQ 1), most of the studies were conducted in Europe (31 studies, or 52 percent); 26 of these were conducted exclusively in the UK. Fifteen (25 percent) of the studies were conducted in the United States or Canada. 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.

In terms of our evaluation of therapies for the treatment of unexplained or refractory chronic cough (KQ 2), our strict inclusion/exclusion criteria focusing on this population increased the applicability of the included studies, but decreased the availability of evidence for our review. 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. The majority of studies took place in Europe, with 7 in the UK and 17 in other countries in Europe (total of 57 percent), while only 7 (17 percent) took place within the United States or Canada. 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 (excluding cystic fibrosis and bronchiectasis), studies with mixed etiologies (including, for example, tuberculosis, lung cancer) and from different eras and geographic locations challenge the usefulness of data on treatment.

We were only able to identify two studies of children eligible for inclusion for KQ 2. Unfortunately, both studies have low applicability to today's management of children with chronic cough. 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 1956 to 2011, with 29 (69 percent) 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.

Research Gaps

We found sufficient evidence to suggest that the LCQ (for adults) and the CQLQ (for children) may be valid instruments for assessing severity of cough, and that electronic recording devices, in general, appear to be valid assessments of cough frequency compared to 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 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.[14] Results are as follows:

KQ 1—Instruments used to assess cough:

- Evidence establishing the responsiveness, validity, reliability, and consistency of available assessment instruments
- Validity of cough measurement tools in the pediatric population
    - Current evidence is insufficient; additional validation or measurement studies focusing on the pediatric population are needed. Suggest starting with additional studies of the CQLQ.
- 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 or provider reporting in use of cough assessment tools
    - Insufficient evidence curently exists; could be explored through observational studies
- 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.

Conclusions

There is no established gold standard for assessing either frequency or severity of cough, thereby making it difficult to quantitatively assess test accuracy for cough instruments. Validity of questionnaires was generally demonstrated in the published literature by correlation with other cough assessment instruments and by demonstrating internal consistency, 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. Several instruments, including the LCQ, the PC-QOL, and electronic recording devices, show good internal consistency but variable correlation with other cough measurement tools. This suggests that these tools demonstrate variable validity. There is a paucity of studies that evaluated the reliability of questionnaires. The lack of validated reference tests and large variability in the 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. There were few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough. Although the evidence is sparse, the opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise 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 or evaluating management of unidentified or refractory chronic cough in children are extremely limited.

Our systematic review highlights the clear need for further studies in patient populations with unexplained or refractory chronic cough and for more systematic design and reporting of these studies and assessment of their patient-centered outcomes.

Glossary

ACCP	American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
CCIQ	Chronic Cough Impact Questionnaire
CDSR	Cochrane Database of Systematic Reviews
CER	comparative effectiveness review
CI	confidence interval
CQLQ	Cough-specific Quality of Life Questionnaire
FDA	U.S. Food and Drug Administration
KQ(s)	key question(s)
LCQ	Leicester Cough Questionnaire
PC-QOL	Parent Cough-specific Quality-of-Life questionnaire
PICOTS	population, interventions, comparators, outcomes, timing of outcomes, and settings
QUADAS-2	QUality Assessment tool for Diagnostic Accuracy Studies-2
RCT	randomized controlled trial
TEP	Technical Expert Panel
WHO	World Health Organization

References

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. Available at: http://www.cdc.gov/nchs/ahcd.htm. Accessed March 16, 2012.
2. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis. 1981;123(4 Pt 1):413-7. PMID: 7224353.
3. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7. PMID: 2178528.
4. U.S. Food and Drug Administration. Special Features: An Important FDA Reminder for Parents: Do Not Give Infants Cough and Cold Products Designed for Older Children. Available at: http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm263948.htm. Accessed May 25, 2012.
5. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J. 2007;29(6):1256-76. PMID: 17540788.
6. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S. PMID: 16428686.
7. Finnish Medical Society Duodecim. Chronic cough in a child. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007. Available at: http://www.guideline.gov/content.aspx?id=12798. Accessed March 16, 2012.
8. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22(2):159-62. PMID: 19061964.
9. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed April 16, 2012.
10. Agency for Healthcare Research and Quality. Methods Guide for Medical Test Reviews. Rockville, MD: Agency for

Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct. Accessed May 30, 2012.

11. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.

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

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

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

Internet Citation

[To be provided in the final report.]

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 non-respiratory 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. Such chronic cough is responsible for up to 38 percent of pulmonary outpatient visits.[2,3]

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 percent), feeling self-conscious (55 percent), insomnia (45 percent), changes in lifestyle (45 percent), musculoskeletal pain (45 percent), hoarseness (43 percent), excessive perspiration (42 percent), and urinary incontinence (39 percent).[4] 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 refractory or unexplained chronic cough.

Measurement methods to formally evaluate cough severity 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.[5] 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 of a patient's chronic cough.

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.

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).[2,3,6-8] Several prospective studies[2,3,7-10] 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). Chronic cough becomes chronic as a result of its underlying etiology being 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, the American College of Chest Physicians (ACCP) 2006 guidelines recommend an empiric approach to diagnosis and treatment.[11] 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.[12-14] However, the lack of clinical studies specific to children also limits the available evidence and therefore possible evidence-based options for treating children.[12] 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.[15-18] 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.

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,[11,19] and one focused on children.[20] Guidelines from the ACCP, last updated in 2006, are the most comprehensive resource and will be the subject of a future update.[11] 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.

If treatment of the underlying etiology fails to resolve the cough, or if no cause can be identified, then the cough may be treated symptomatically (Table 1). 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.[21]

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 pharmacologic 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.

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

Broad Category	Medication/Therapy Class	Therapy Name
Nonspecific pharmacologic antitussives (cough suppressants)	Anesthetics	Benzonatate
	Opiates	Codeine, hydrocodone
	Other	Dextromethorphan

Broad Category	Medication/Therapy Class	Therapy Name
Nonpharmacologic 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
Nonpharmacologic 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 patients received 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?

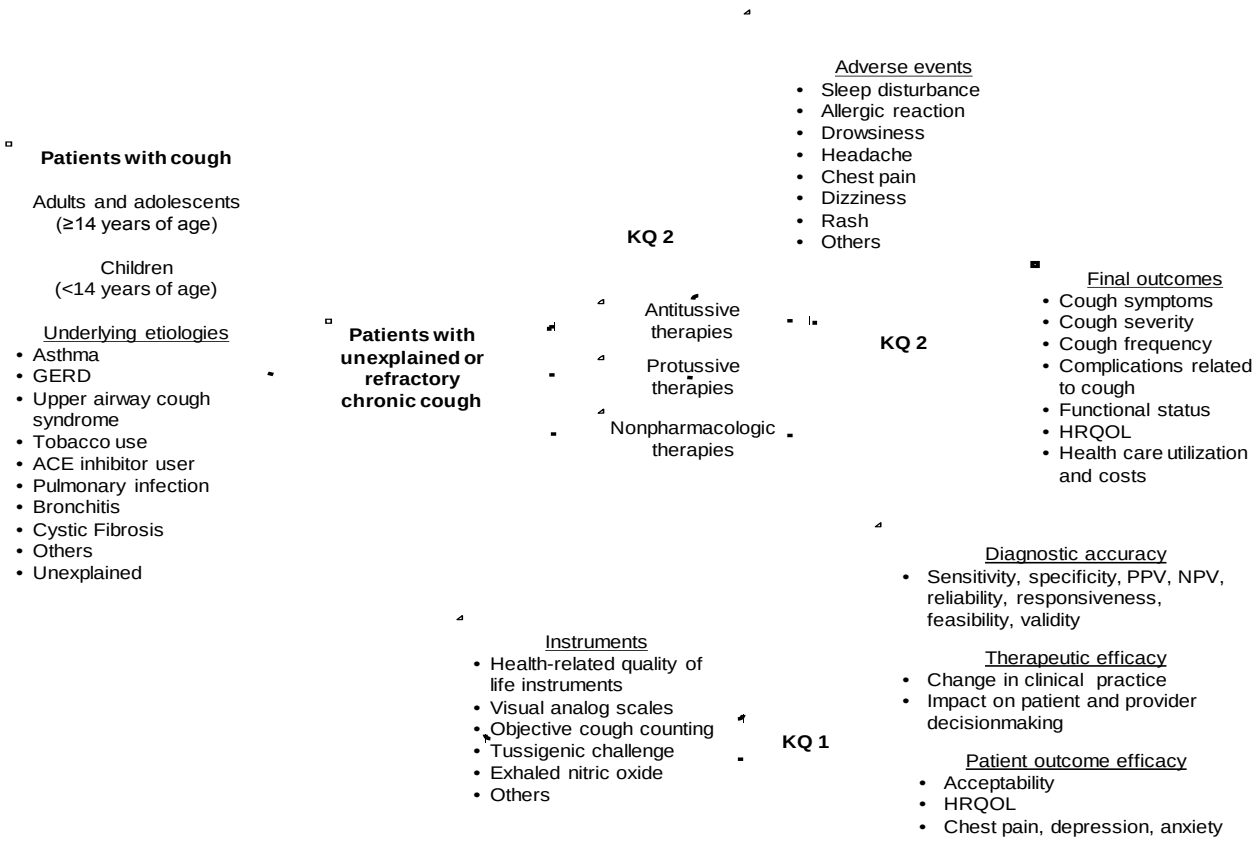
  (a) In patients with unexplained chronic cough

  (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



Abbreviations: 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*)[22] and *Methods Guide for Medical Test Reviews* (hereafter referred to as the *Medical Test Guide*).[23] 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.[24] 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). 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; metaRegister of Controlled Trials; the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. 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 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	KQ2: • 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	None

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 for background only)	• Non-English-language publications[b]

[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.

Abbreviations: 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

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*,[22] 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*.[22] 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[25] 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.

KQ1—Test Performance Measures

For KQ 1, we considered various measures of test performance. For cough recording devices, we reported sensitivity and specificity, with human cough counts serving as the reference standard. For questionnaires, we reported correlation coefficients, internal consistency measures, test-retest results, and minimal importance difference estimates, when available. In general, the published literature in this field relies on correlation with other cough instruments for validation of cough questionnaires.

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 grouped interventions by drug class, considering opiate antitussive drugs and mucolytic protussive drugs to be similar enough to combine with one another. We considered measures of cough frequency, regardless of the scale used, to be similar enough to combine using effect sizes; 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. 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 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. 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*[22,26] and *Medical Test Guide;*[23] 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 versus observational study), number of studies, and aggregate study quality; for KQ 1, assessed using the QUADAS-2 instrument[25]
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, 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

Abbreviations: 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*.[22,27] 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 to 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, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final 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 the main categories of cough measurement tools evaluated in the included studies. 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.

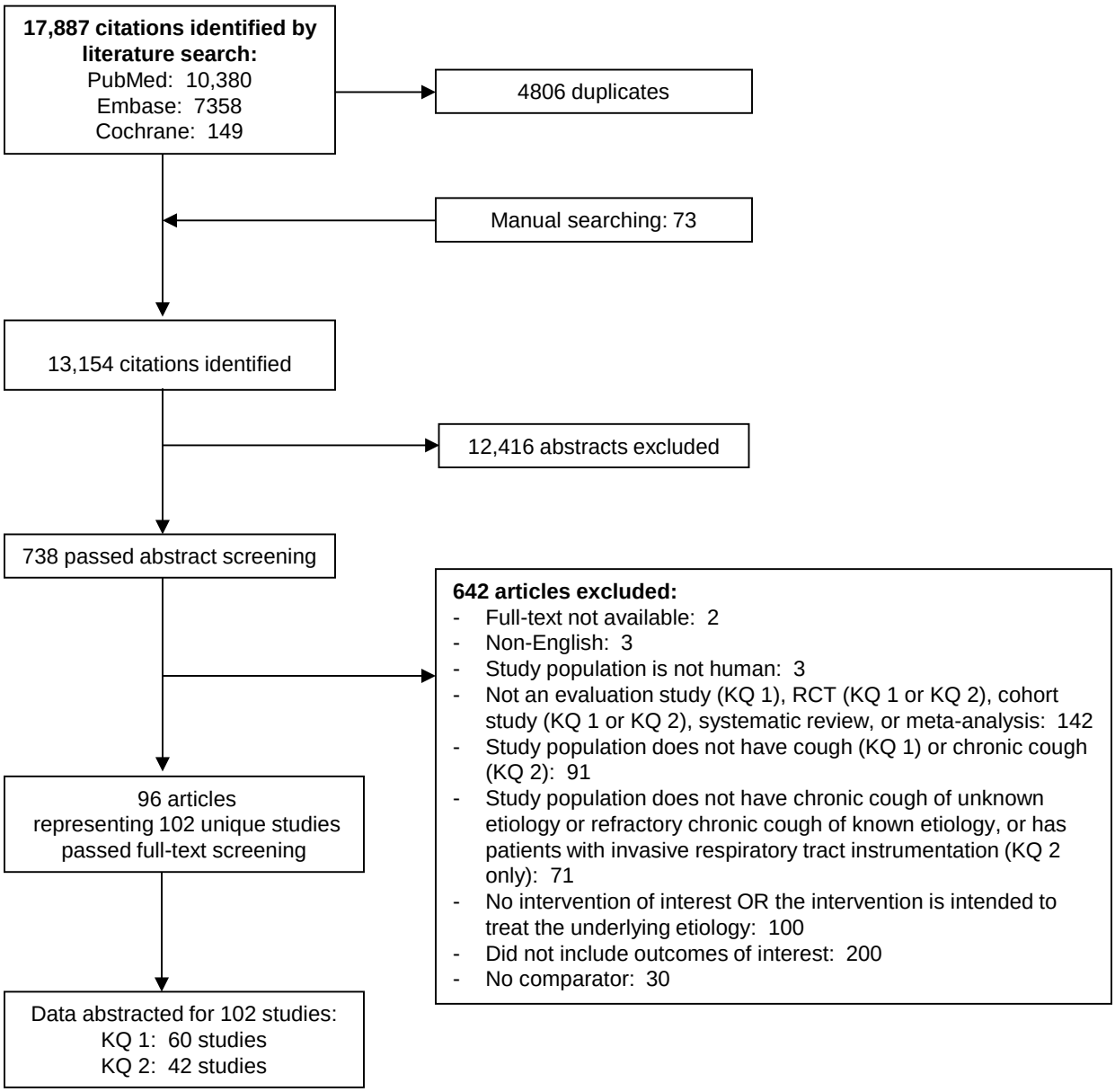
A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

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 17,887 citations, 4806 of which were duplicate citations. Manual searching identified 73 additional citations, for a total of 13,154 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 738 full-text articles were retrieved and screened. Of these, 642 were excluded at the full-text screening stage, leaving 96 articles for data abstraction. These 96 articles described 102 unique studies, 60 of which were relevant to KQ 1, and 42 of which were relevant to KQ 2. 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



Abbreviations: KQ = key question; RCT = randomized controlled trial

Description of Included Studies

Overall, we included 102 studies represented by 96 publications: 60 studies were relevant to KQ 1, 42 to KQ 2. Studies were conducted in Europe (53.9 percent); Asia (9.8 percent); the United States or Canada (20.6 percent); Australia or New Zealand (10.7 percent); and other locations (7.8 percent). Twelve studies in KQ 1 (20 percent) and two studies in KQ 2 (5 percent) included children. Forty-one (41) studies (40 percent) 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

- The Leicester Cough Questionnaire (LCQ) is the most widely studied cough-specific quality-of-life questionnaire. Validity of the LCQ was established primarily by fair to moderate correlation with other cough measurement tools. It demonstrates good internal consistency and reliability.
- The Parent Cough-specific Quality-of-Life questionnaire (PC-QOL) has been validated in the pediatric population and shows fair to moderate correlation with other subjective and objective cough measurement tools, but there is insufficient evidence to assess internal consistency and reliability.
- Other cough-specific quality-of-life questionnaires, such as the Cough-specific Quality of Life Questionnaire (CQLQ), Chronic Cough Impact Questionnaire (CCIQ), and the Punum Ladder, 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 non-cough symptoms and so are less valuable tools for cough assessment.
- Electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with other cough measurement tools.
- Electronic recording devices may be most useful in the research setting but may be less practical in the clinical setting due to their cost, inconvenience to the patient, and technical and analytical requirements.
- Although they are widely used both in research and practice, visual analog scales use a variety of different measurement scales, often assess different cough outcomes, have little to no data to validate their accuracy in assessing cough, and have inconsistent correlations with other cough measurement tools. These tools are usually simple and easy to use, but more data are needed to determine how useful they are in assessing cough or monitoring responsiveness before they can be used as comparators when measuring the validity of other tools.
- Diaries and other subjective scores overall show variable to poor correlation with other cough measurement tools when used as reference tests.
- The majority of reference tests used in the included studies have not previously been validated.
- 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

Sixty studies met the inclusion criteria for this key question (KQ).[28-87] Study characteristics are summarized in Table 5. Fifteen studies (25 percent) were conducted in the United States or Canada,[29,39,41-44,46,52,55,57,66,71,80,86,87] and 31 (52 percent) in Europe,[32-35,40,42,45,47,48,50,53,56,58-61,63-65,67,69,70,72,74,78,79,81-85] including 26 (43 percent) conducted exclusively in the UK[32-34,40,42,45,47,48,50,53,56,58,59,61,63-65,69,70,72,74,79,81-85] Of the 60 studies, 51 (85 percent) were judged to have a low risk of bias and 9 (15 percent) were judged to have a high risk of bias (see Appendix E for details). In most cases, the funding source was not reported or was unclear. None of the studies was a randomized controlled trial (RCT). Sample sizes ranged from 8 to 671 subjects; overall, the 60 studies involved 5430 subjects.

All of the cough instruments evaluated in the included studies can be considered assessments of cough frequency, cough severity, impact of cough on quality of life, or a combination of the three. Most of the studies compared one instrument with one or more other assessments of cough frequency, severity, or impact on quality of life. Thirty-one studies (52 percent) included a quality-of-life questionnaire, and 22 (37 percent) included an electronic device designed to measure cough frequency. Only six studies (10 percent) included visual analog scales as an index test. Most studies which included 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. In most studies no information was given regarding previous validation of reference tests. Thirty-one studies (52 percent) enrolled patients with chronic cough of mixed, unknown, or unspecified etiology; 9 (15 percent) enrolled patients with acute cough or cough of unspecified duration, and 20 (33 percent) focused on specific clinical conditions such as chronic bronchitis, asthma, or lung cancer. Twelve studies (20 percent) included only children,[28,36-38,40,43,48,49,58,75-77] while an additional four studies (6.7 percent) included both adults and children.[56,57,62,80]

We focused our synthesis on quality-of-life questionnaires, electronic recording devices, and visual analog scales, as these were the most widely encountered tools in the studies we evaluated. Below, we summarize the evidence for the validity, reliability, and responsiveness of these three types of tools. 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.

Table 5. KQ 1—Study characteristics

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Studies in Adults Only					
Au, 2005[29]	64	Chronic bronchitis	- CBSAS - Pulmonary function tests - SGRQ - San Diego Shortness of Breath Questionnaire	Develop the CBSAS	High
Baiardini, 2005[30]	95	Chronic cough	- CCIQ	Develop the CCIQ	High
Barry, 2006[31]	33	Chronic cough	- Hull Automatic Cough Counter - Cough count by observer	Evaluate the Hull Automatic Cough Counter	Low
Birring, 2008[32]	65	Chronic cough	- Leicester Cough Monitor - Video recording - Cough count by 2 observers	Evaluate the Leicester Cough Monitor	Low
Birring, 2006[33]	20	Chronic cough	- LCQ - Leicester Cough Monitor - Capsaicin cough challenge	Evaluate the Leicester Cough Monitor	Low
Birring, 2003[34]	104	Chronic cough	- LCQ - Self-reported cough severity - Self-reported clinical change - SGRQ - SF-36 - Capsaicin cough challenge	Develop the LCQ	Low
Braido, 2006[35]	95	Chronic cough	- CCIQ - SF-36	Evaluate the CCIQ	Low
Chernecky, 2004[39]	31	Lung cancer	- LCCQ - Lung Cancer Wheezing Questionnaire	Evaluate the LCCQ and the Lung Cancer Wheezing Questionnaire	High

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Coyle, 2005[41]	8	COPD	- LifeShirt cardio-respiratory monitoring system - Video recorder	Evaluate the LifeShirt system in COPD patients	Low
Crawford, 2008[42]	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	Low
De Vito Dabbs, 2002[44]	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	Low
Decalmer, 2007[45]	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	Low
Dicpinigaitis, 2006[46]	671	Chronic cough	- CES-D - Subjective cough score	Estimate prevalence of depressive symptoms among patients with chronic cough	High

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Doherty, 2000[47]	205	Asthma or COPD	- Questionnaire administered in hospital - Self-reported cough score - Self-reported cough severity (VAS) - Capsaicin cough challenge	Evaluate capsaicin cough challenge	High
Faruqi, 2011[50]	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	Low
Fisman, 2001[51]	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	High
Fletcher, 2010[52]	127	Cough	- Punum Ladder - Global Rating of Change Scale - CQLQ	Evaluate the GRC, Punum Ladder, and CQLQ	Low
Freestone, 1997[53]	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	Low
French, 2002[55]	215	Chronic bronchitis or COPD	- CQLQ	Evaluation of CQLQ	Low
French, 1998[54]	28	Chronic cough	- Adverse Cough Outcome Survey - SIP	Assess the relationship between chronic cough and adverse psychosocial or physical effects	Low
Hsu, 1994[59]	47	Asthma or chronic cough	- Self-reported cough score - Self-reported asthma score - 24-hour ambulatory recorder	Evaluate an ambulatory cough recorder	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Huisman, 2007[60]	152	Chronic cough	- LCQ - Modified Borg score for cough - HADS - Self-reported change in disease control	Validate a Dutch-language version of the LCQ	Low
Jones, 2011[61]	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	Low
Kelsall, 2011[64]	57	Chronic cough	- Self-reported cough score - Self-reported cough severity (VAS) - 24-hour ambulatory cough recording	Compare objective and subjective measures of cough	Low
Kelsall, 2008[63]	70	Chronic cough	- LCQ - Self-reported cough severity (VAS) - Audio recording device - Cough count by observer	Compare methods of quantifying coughing	Low
Key, 2010[65]	19	Idiopathic pulmonary fibrosis	- LCQ - Cough severity VAS - 24-hour ambulatory cough recording - Manual cough count	Measure objective cough frequency	Low
Krahnke, 2004[66]	28	Cough	- Home telemetry device - Score	Validate novel measurement tools with video recording as gold standard	Low
Krajnik, 2010[67]	16	Chronic cough	- Self-reported cough score (NRS) - Automatic portable cough analyzer	Evaluate an automatic portable cough analyzer	Low
Ma, 2009[68]	110	Chronic cough	- LCQ - SF-36 - Capsaicin cough challenge	Validate a Chinese-language version of the LCQ	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Marsden, 2008[69]	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	Low
Matos, 2007[70]	18	Cough	- Leicester Cough Monitor - Cough count by observer	Evaluation of the Leicester Cough Monitor	Low
Monz, 2010[71]	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	Low
Murray, 2009[72]	120	Cough	- LCQ	Compare the LCQ with the SGRQ	Low
Mwachari, 2007[73]	649	Acute bronchitis	- ABSS	Evaluate new scoring system	Low
Nandha, 2000[74]	48	Cough	- Cough diary	Compare cough diary with a structured recall interview	Low
Nieto, 2003[78]	101	Chronic cough	- Tussigenic challenge	Repeat tussigenic challenge to evaluate responsiveness to treatment	Low
O'Connell, 1994[79]	87	Chronic cough	- Tussigenic challenge	Comparison of cough severity with cough sensitivity	Low
Polley, 2008[81]	147	Chronic cough	- EuroQol - LCQ - CQLQ	Compared with each other	Low
Raj, 2009[82]	52	Cough	- LCQ	Determination of minimal important difference for the LCQ	Low
Singapuri, 2008[83]	29	Chronic cough	- Tussigenic challenge	Evaluating new tussigenic challenge test by comparing with: - VAS - Tussigenic challenge - LCQ	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Smith, 2006[84]	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	Low
Smith, 2006[85]	8	Chronic cough	- Human cough count - Video recording device	Comparisons of digital audio recordings with video recordings	Low
Thomas, 1978[86]	42	Chronic cough	- Automated electronic cough-counting device - Cough count	Evaluate a cough recording device	Low
Vernon, 2010[87]	39	Chronic cough	- Cough severity diary	Evaluation of new cough severity diary	Low
Studies in Adults and Children					
Hamutcu, 2002[56]	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	Low
Hartnick, 2009[57]	120	Parents of children with chronic cough	- Pediatric Cough Questionnaire - Parent-reported clinical change	Evaluate the Pediatric Cough Questionnaire	Low
Kalpaklioglu, 2005[62]	40	Asthma	- LCQ - CQLQ - SF-36 - HADS	Compare specific vs. generic quality-of-life questionnaires for chronic cough	Low
Paul, 2006[80]	15	Cough	- Electronic recording device using an accelerometer	Validate new recording device using video recording as gold standard	Low

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Studies in Children Only					
Archer, 1985[28]	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	High
Chang, 2003[38]	37	Recurrent cough	- Ambulatory cough meter - Self-reported VAS (unspecified) - Parent-reported VAS (unspecified) - Capsaicin cough challenge	Compare measurements of cough severity	Low
Chang, 1998[36]	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	Low
Chang, 1997[37]	21	Recurrent cough	- Ambulatory cough meter - Audio recording device	Describe and evaluate a modified Holter monitor for use as an ambulatory cough meter	Low
Corrigan, 2003[40]	9	Infants with coughing illnesses	- LR100 cough monitoring device - Video recorder	Objective cough monitoring in infants	Low
Dales, 1997[43]	41	Community sample	- Interviewer-administered questionnaire - Recording device - Cough counts	Assess possible bias in parental reporting of children's coughing	Low
Falconer, 1993[48]	15	Asthma	- Self-reported presence of nocturnal cough - Self-reported respiratory symptoms - Recording device	Compare reported and recorded nocturnal cough	High
Faniran, 1999[49]	109	Children with or without cough	- A questionnaire to assess cough prevalence	Develop a questionnaire to measure prevalence of persistent cough in children	High

Study	N	Patient Population	Cough Measures	Study Objectives	Risk of Bias
Hoskyns, 1991[58]	16	Cough	- Audio recording device - Parental cough diaries	Compare diaries with electronic recording and assess response to salbutamol	Low
Newcombe, 2011[75]	34	Chronic cough	- PC-QOL	Create and validate new questionnaire	Low
Newcombe, 2010[77]	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	Low
Newcombe, 2008[76]	170	Chronic cough	- PC-QOL	Validate PC-QOL by comparison with: - Pediatric Quality of Life Questionnaire - SF-12	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; 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; 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

Detailed Synthesis

Quality-of-Life Questionnaires

We identified 12 quality-of-life questionnaires used in 30 studies involving 1590 patients (ranging from 19 to 671) that have been employed to assess cough and response to treatment for cough (Tables 6 and 7).[29,30,33-35,39,42,44,45,50,52,54,55,57,60-63,65,68,69,71,72,75-77,81,82,84,87] Five of these studies included children.[57,62,75-77] Of the 30 studies, nine (30 percent) were conducted in the United States or Canada.[29,39,42,44,52,55,57,71,87] Three studies[29,30,39] (10 percent) were judged to have a high risk of bias, and the remaining 27 (90 percent) to have low risk of bias. Some of the questionnaires evaluated 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], Punum Ladder, and Cough Severity Diary [CSD]), 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], and the Questionnaire for Lung Transplant Patients [QLTP]); still others are general quality-of-life questionnaires such as the Global Rating of Change (GRC) scale.

Of the cough-specific questionnaires, the LCQ is the most widely studied, with 16 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,[34,61,65,72] while most of the remaining studies showed only fair to moderate correlation with a variety of other cough measurement tools, both objective and subjective.[33,34,45,54,60,62,68,69] 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.

The PC-QOL has been evaluated in the pediatric population, and the studies to date show good internal consistency and moderate to good correlation with other cough measures such as electronic recording devices, subjective symptom scores, and other questionnaires.[75-77]

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 have been variable or lacking.

Validity

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. For the studies included in this report, correlation of quality-of-life questionnaires with other cough instruments was poor to moderate, with absolute values of Spearman coefficients ≥ 0.80 reported in one or more studies assessing the LCQ,[34,50,60,61,88] PC-QOL,[75] CCIQ,[30] LCCQ,[39] Punum Ladder,[52] and QLTP.[44]

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.

Reliability

Reliability of questionnaires 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.

Responsiveness

Responsiveness is an especially important characteristic for instruments designed to assess cough severity, frequency, or impact. An instrument may not need to be responsive to change in a patient's clinical status in order to be useful at the time of a patient's initial evaluation, but it does need to be able to detect clinically meaningful change if it is to be used to assess the effectiveness of a given course of treatment. Unfortunately, few studies assessed and reported questionnaires' responsiveness. A single study estimated the minimal important difference (MID) of the LCQ and its three domains,[82] and three studies estimated effect size as measured by the LCQ.[34,60,68] Effect sizes were estimated in studies involving the PC-QOL,[77] CCIQ,[30] and Punum Ladder.[52]

Table 6. Description of cough questionnaires

Measure	Type of Scale	Population Derived	Domains	No. of Items	Scoring
Adult Populations					
Adverse Cough Outcome Survey (ACOS)	– 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)	– Self-completed – Condition-specific	Adults with acute or chronic smoking-related cough	– 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

Measure	Type of Scale	Population Derived	Domains	No. of Items	Scoring
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
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

Abbreviations: 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

Table 7. Results of studies of cough questionnaires

Study	Index Test	Comparator(s)	Results
Birring, 2003[34]	LCQ Total	Cough severity	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	Spearman coefficient: -0.54
		SF-36	Spearman coefficient: 0.46
	LCQ Physical	–	Cronbach's α : 0.79 Repeatability (intraclass correlation): 0.93 Responsiveness (effect size based on clinical change score): 1
	LCQ Psychological	–	Cronbach's α : 0.89 Repeatability (intraclass correlation): 0.9 Responsiveness (effect size based on clinical change score): 1.75
	LCQ Social	–	Cronbach's α : 0.85 Repeatability (intraclass correlation): 0.88 Responsiveness (effect size based on clinical change score): 0.84
Birring, 2006[33]	LCQ Total	Cough frequency	Spearman coefficient: 0.6 ($p<0.05$)
		C2 (concentration of capsaicin causing 2 coughs)	Spearman coefficient: -0.1 (NS)
Decalmer, 2007[45]	LCQ Total	Log total time spent coughing	Spearman coefficient: -0.62 ($p\leq0.001$)
	LCQ Physical	Log total time spent coughing	Spearman coefficient: -0.55 ($p\leq0.001$)
	LCQ Psychological	Log total time spent coughing	Spearman coefficient: -0.59 ($p\leq0.001$)
	LCQ Social	Log total time spent coughing	Spearman coefficient: -0.55 ($p\leq0.001$)
Faruqi, 2011[50]	LCQ Total	Repeat LCQ score	Spearman coefficient: 0.91 ($p<0.001$)
		Hull Cough Counter	Spearman coefficient: -0.6 ($p<0.001$)

Study	Index Test	Comparator(s)	Results
Huisman, 2007[60]	LCQ Total	–	Cronbach's α : 0.93 Repeatability (intraclass correlation): 0.93 Responsiveness (avg improvement score [95% CI]): 5.28 (4.41 to 6.15)
		Modified Borg score	Spearman coefficient: -0.41
		HADS	Spearman coefficient: -0.42
		SF-36 General Health	Spearman coefficient: 0.41
	LCQ Physical	–	Cronbach's α : 0.77 Repeatability (intraclass correlation): 0.86 Responsiveness (avg improvement score [95% CI]): 1.42 (1.14 to 1.71)
		Modified Borg score	Spearman coefficient: -0.37
		HADS	Spearman coefficient: -0.42
		SF-36 General Health	Spearman coefficient: 0.54
	LCQ Psychological	–	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	Spearman coefficient: -0.38
		HADS	Spearman coefficient: -0.39
		SF-36 General Health	Spearman coefficient: 0.28
	LCQ Social	–	Cronbach's α : 0.83 Repeatability (intraclass correlation): 0.93 Responsiveness (avg improvement score [95% CI]): 2.10 (1.70 to 2.49)
		Modified Borg score	Spearman coefficient: -0.36
		HADS	Spearman coefficient: -0.46
		SF-36 General Health	Spearman coefficient: 0.3
Jones, 2011[61]	LCQ Total	Cough symptom score	Spearman coefficient: -0.86 (p<0.0001)
		Cough challenge	Spearman coefficient: -0.72 (p<0.0001)
Kalpaklioglu, 2005[62]	LCQ Total	Audio recording device	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)
Kelsall, 2008[63]	LCQ Total	Time spent coughing	Spearman coefficient: r = 0.36 (p=0.11)

Study	Index Test	Comparator(s)	Results
Key, 2010[65]	LCQ Total	Total cough rates	Spearman coefficient: -0.76 (p<0.001)
	LCQ Physical	–	Spearman coefficient: -0.76 (p<0.001)
	LCQ Psychological	–	Spearman coefficient: -0.74 (p<0.001)
	LCQ Social	–	Spearman coefficient: -0.80 (p<0.001)
	LCQ Total	Day cough rates	Spearman coefficient: -0.72 (p<0.001)
	LCQ Physical	–	Spearman coefficient: -0.72 (p=0.001)
	LCQ Psychological	–	Spearman coefficient: -0.71 (p=0.001)
	LCQ Social	–	Spearman coefficient: -0.77 (p<0.001)
	LCQ Total	Night cough rates	Spearman coefficient: -0.46 (p=0.048)
	LCQ Physical	–	Spearman coefficient: -0.46 (p=0.048)
	LCQ Psychological	–	Spearman coefficient: -0.55 (p=0.016)
	LCQ Social	–	Spearman coefficient: -0.46 (p=0.048)
Ma, 2009[68]	LCQ Total (posttreatment)	–	Responsiveness: 14.2 to 19.5
	LCQ Physical (posttreatment)	–	Responsiveness: 6.3 to 13.5
	LCQ Psychological (posttreatment)	–	Responsiveness: 6.5 to 17.4
	LCQ Social (posttreatment)	–	Responsiveness: 6.7 to 10.7
	LCQ Total	SF-36-physical	Spearman coefficient: 0.39 (p<0.0001)
		SF-36-mental	Spearman coefficient: 0.30 (p<0.001)
		Challenge-log C5	Spearman coefficient: 0.134 (p=0.25)
Marsden, 2008[69]	LCQ Total	Daytime spent coughing	Spearman coefficient: 0.54 (p<0.001)
Murray, 2009[72]	LCQ Total	SGRQ	Spearman coefficient; -0.7 (p<0.0001) Cronbach's α : 0.96 (95% CI 0.93-0.97) p<0.0001 Repeatability: Median score (IQR) baseline 11.3 (9.3-13.7) and after 2-wk antibiotics 17.8 (15-18.8) p<0.0001
Polley, 2008[81]	LCQ Total	CQLQ	Spearman coefficient: R = -0.56 (p<0.001)
		EQ-5D	Spearman coefficient: r = 0.60 (p=0.008)
		EQ-VAS	Spearman coefficient: r = 0.43 (p=0.07)
Raj, 2009[82]	LCQ Total	GCRC Score	Responsiveness: MID = 1.3 (SD 3.2)
	LCQ Physical	–	Responsiveness: MID = 0.2 (SD 0.8)
	LCQ Psychological	–	Responsiveness: MID = 0.2 (SD 1.1)
	LCQ Social	–	Responsiveness: MID = 0.8 (SD 1.5)
Vernon, 2010[87]	LCQ Total	CSD	Spearman coefficient: r = -0.62 (p<0.0001)
	LCQ Physical	–	Spearman coefficient: r = -0.43 (p<0.01)
	LCQ Psychological	–	Spearman coefficient: r = -0.56 (p<0.001)
	LCQ Social	–	Spearman coefficient: r = -0.60 (p<0.0001)
Fletcher, 2010[52]	CQLQ	GRC	Responsiveness: MID = 10.58 (SD 10.63)
		Punum Ladder	Responsiveness: MID = 21.89 (SD 15.38)

Study	Index Test	Comparator(s)	Results
French, 2002[55]	CQLQ Total	Repeat testing	Cronbach's α : 0.89 (p<0.001) Test-retest paired t-value: -1.39
	Physical complaints	–	Cronbach's α : 0.88 (p<0.001) Test-retest paired t-value: -0.92
	Psychosocial issues	–	Cronbach's α : 0.91 (p<0.001) Test-retest paired t-value: -0.19
	Functional abilities	–	Cronbach's α : 0.85 (p<0.001) Test-retest paired t-value: -1.21
	Emotional well-being	–	Cronbach's α : 0.77 (p<0.001) Test-retest paired t-value: -1.44
	Extreme physical complaints	–	Cronbach's α : 0.93 (p<0.001) Test-retest paired t-value: -0.24
	Personal safety fears	–	Cronbach's α : 0.75 (p<0.001) Test-retest paired t-value: -1.28
Polley, 2008[81]	CQLQ Total	LCQ	Spearman coefficient: R = -0.56 (p<0.001)
		EQ-5D	Spearman coefficient: r = -0.30 (p=0.23)
		EQ-VAS	Spearman coefficient: r = -0.24 (p=0.33)
Smith, 2006[84]	CQLQ Total	Time spent coughing	Spearman coefficient: r = 0.36 (p=0.06)
Newcombe, 2008[76]	PC-QOL	Cough score	Spearman correlation coefficient: r = 0.15
		PedsQL-psychosocial	Cronbach's α : r = 0.81; Spearman coefficient: r = -0.33
		PedsQL-physical	Cronbach's α : r = 0.84; Spearman coefficient: r = -0.47 (p<0.01)
		PedsQL-emotional	Cronbach's α : r = 0.71; Spearman coefficient: r = -0.16 (p=NS)
		PedsQL-social	Cronbach's α : r = 0.70; Spearman coefficient: r = -0.18 (p<0.01)
		PedsQL-school	Cronbach's α : r = 0.70; Spearman coefficient: r = -0.51 (p<0.05)
		SF-12-physical	Cronbach's α : r = 0.83; Spearman coefficient: r = -0.14 (p=NS)
		SF-12-role physical	Cronbach's α : r = 0.87; Spearman coefficient: r = -0.33 (p=NS)
		SF-12-role emotional	Cronbach's α : r = 0.91; Spearman coefficient: r = -0.31 (p<0.05)
		SF-12-mental health	Cronbach's α : r = 0.56; Spearman coefficient: r = -0.06 (p=NS)
Newcombe, 2010[77]	PC-QOL Total	VCD	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	Spearman coefficient: r = -0.55 (p=0.001)
		Cough counts	Spearman coefficient: r = -0.32 (p=0.074)
		PedsQL (total score)	Spearman coefficient: r = 0.46 (p<=0.034)
	PC-QOL Physical		Effect size based on clinical change score: 0.41
	PC-QOL Psychological		Effect size based on clinical change score: 0.32
	PC-QOL Social		Effect size based on clinical change score: 0.32
Newcombe, 2011[75]	PC-QOL Total	VCD	Spearman coefficient: p = -0.70 (p<0.001) Cronbach's α : 0.84
	PC-QOL Physical	–	Spearman coefficient: p = -0.65 (p<0.001)
	PC-QOL Psychological	–	Spearman coefficient: p = -0.64 (p<0.001)
	PC-QOL Social	–	Spearman coefficient: p = -0.55 (p=0.001)

Study	Index Test	Comparator(s)	Results
Crawford, 2008[42]	CASA-Q Cough symptoms	–	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.77 Cronbach's α : 0.85
		SGRQ Symptoms	Spearman coefficient: -0.17 (p=0.0003)
		SGRQ Impact	Spearman coefficient: -0.32 (p<0.0001)
		SGRQ Activities	Spearman coefficient: -0.04 (p=0.38)
		SGRQ Total	Spearman coefficient: -0.25 (p<0.0001)
	CASA-Q Cough impact	–	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.88 Cronbach's α : 0.91
		SGRQ Symptoms	Spearman coefficient: -0.23 (p<0.0001)
		SGRQ Impact	Spearman coefficient: -0.54 (p<0.0001)
		SGRQ Activities	Spearman coefficient: -0.27 (p<0.0001)
		SGRQ Total	Spearman coefficient: -0.49 (p<0.0001)
	CASA-Q Sputum symptoms	–	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.80 Cronbach's α : 0.80
	CASA-Q Sputum impact	–	Among stable subjects (n=118); p-values NR: Repeatability (intraclass correlation): 0.82 Cronbach's α : 0.89
Monz, 2010[71]	CASA-Q Cough symptom	PGI-C response-"Very much better"	Mean change in CASA-Q domain score (SD) between day 1 and 43: 26.9 (21.30)
		PGI-C response-"Better"	Mean change in CASA-Q domain score (SD) between day 1 and 43: 19.4 (22.51)
		PGI-C response-"A little better"	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"	Mean change in CASA-Q domain score (SD) between day 1 and 43: 28.6 (21.28)
		PGI-C response-"Better"	Mean change in CASA-Q domain score (SD) between day 1 and 43: 22.9 (19.41)
		PGI-C response-"A little better"	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	"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)."

Study	Index Test	Comparator(s)	Results
Baiardini, 2005[30]	CCIQ	–	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/concentration	–	Cronbach's α : 79.98
	CCIQ Relationship	–	Cronbach's α : 86.98
	CCIQ Daily life impact	–	Cronbach's α : 69.04
	CCIQ Mood	–	Cronbach's α : 65.41
	CCIQ	SF-36	Low correlation, except for "daily life impact" item that correlated with 3 SF-36 domains
Braido, 2006[35]	CCIQ Daily life impact	SF-36 Physical functioning	Spearman coefficient: 0.281
		SF-36 Vitality	Spearman coefficient: 0.291
		SF-36 Physical summary	Spearman coefficient: 0.333
	CCIQ Relationship	–	None
French, 1998[54]	ACOS	SIP Total	With successful treatment, the average number of ACOS complaints decreased from 8.6 to 1.9 (p<0.001)
	ACOS Exhaustion	SIP Total	Spearman coefficient: 0.58 (p<0.001)
	ACOS Lifestyle change	SIP Total	Spearman coefficient: 0.54 (p<0.001)
	ACOS Cannot sing in church	SIP Total	Spearman coefficient: 0.31 (p=0.05)
	ACOS Hoarseness	SIP Total	Spearman coefficient: 0.43 (p=0.006)
	ACOS Aching all over	SIP Total	Spearman coefficient: 0.36 (p<0.03)
	Number of ACOS events	SIP-body care and movement	Spearman coefficient: 0.31 (p=0.03)
		SIP-home management	Spearman coefficient: 0.33 (p=0.02)
		SIP-social interaction	Spearman coefficient: 0.46 (p=0.001)
		SIP-alertness behavior	Spearman coefficient: 0.45 (p=0.002)
		SIP-communication	Spearman coefficient: 0.38 (p=0.009)
		SIP-recreation	Spearman coefficient: 0.31 (p=0.04)
Au, 2005[29]	CBSAS	FEV1 Prebronchodilator	Spearman coefficient: -0.38 (p<0.01)
		FEV1 Postbronchodilator	Spearman coefficient: -0.32 (p<0.01)
		FVC Prebronchodilator	Spearman coefficient: -0.44 (p<0.01)
		FVC Postbronchodilator	Spearman coefficient: -0.40 (p<0.01)
		SGRQ Total	Spearman coefficient: 0.67 (p<0.01)
		SGRQ Symptoms	Spearman coefficient: 0.67 (p<0.01)
		SGRQ Activity	Spearman coefficient: 0.49 (p<0.01)
		SGRQ Impact	Spearman coefficient: 0.58 (p<0.01)
		San Diego Shortness of Breath Questionnaire	Spearman coefficient: 0.49 (p<0.01)
Vernon, 2010[87]	CSD Total	Patient VAS severity rating	Spearman coefficient: r = 0.84 (p<0.0001)
		Clinician VAS severity rating	Spearman coefficient: r = 0.35 (p<0.05)
		LCQ Total	Spearman coefficient: r = -0.62 (p<0.0001)

Study	Index Test	Comparator(s)	Results
Fletcher, 2010[52]	GRC 6-month minus baseline score	CQLQ at 6 months	Spearman coefficient: 0.673
		CQLQ at 1 month	Spearman coefficient: 0.025
Chernecky, 2004[39]	LCCQ	–	Cronbach's α : 0.98 (p<0.001)
	LCCQ	LCCQ-"How much coughing do you have?"	Spearman coefficient: 0.80 (p=0.10)
Hartnick, 2009[57]2484	PCQ	Time point 1	Cronbach's α : 0.914 (p<0.001) Repeatability: Test-retest correlation (stable patients)
		Time point 2	Cronbach's α : 0.951 (p<0.001) Repeatability: Q1 = 0.5 (p<0.001)
		Time point 3	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)
Fletcher, 2010[52]	Punum Ladder	CQLQ	Inter-item correlations among the Punum Ladder scales associated with the 6 CQLQ subscales ranged from 0.31-0.69 (mean=0.53) Cronbach's α : 0.89 Repeatability: Test-retest reliability coefficient Responsiveness: Effect size from 0 to 1 month: 1.10
	Punum Ladder 6-month change score	6-month CQLQ change score	Spearman coefficient: 0.714 (p<0.0001) Repeatability: Total = 0.88
	Punum Ladder 6-month change score	6-month GRC change score	Spearman coefficient: 0.623 (p<0.0001) Repeatability: Individual items range 0.64 to 0.91
	Punum Ladder 6-month minus baseline score	CQLQ at 6 months	Spearman coefficient: 0.374
	Punum Ladder 6-month minus baseline score	CQLQ at 1 month	Spearman coefficient: -0.374

Study	Index Test	Comparator(s)	Results
De Vito Dabbs, 2002[44]	QLTP Total	–	Spearman coefficient: 0.7 Cronbach's α : 0.82 Repeatability (intraclass correlation): 0.9
	QLTP Respiratory symptoms	–	Cronbach's α : 0.76 Repeatability (intraclass correlation): 0.8
	QLTP General symptoms	–	Cronbach's α : 0.8 Repeatability (intraclass correlation): 0.9
	QLTP Activities of daily living	–	Cronbach's α : 0.896 Repeatability (intraclass correlation): 0.89
	QLTP Total	MSFSD	Spearman coefficient: 0.5
	QLTP Respiratory symptoms	MSFSD	Spearman coefficient: 0.5
	QLTP General symptoms	MSFSD	Spearman coefficient: 0.51
	QLTP Activities of daily living	Functional Performance Inventory	Spearman coefficient: 0.7
	QLTP Shortness of breath	VAS	Spearman coefficient: 0.93
	QLTP Severity of cough	VAS	Spearman coefficient: 0.87

Abbreviations: ACOS = Adverse Cough Outcome Survey; CASA-Q = Cough and Sputum Assessment Questionnaire; CBSAS = Chronic Bronchitis Symptoms Assessment Scale; CCIQ = Chronic Cough Impact Questionnaire; CI = confidence interval; CQLQ = Cough-specific Quality of Life Questionnaire; 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; 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 = minimal important difference; MSFSD = Modified Symptom Frequency/Symptom Distress scale; NS = not statistically significant; PC-QOL = Parent Cough-Specific Quality-of-Life questionnaire; PedsQL = Pediatric Quality of Life Inventory; PGC-I = Patient Global Impression of Change; QLTP = Questionnaire for Lung Transplant Patients; SD = standard deviation; SF-36/SF-12= Medical Outcomes Study 36-Item/12-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire; Spearman coefficient = Spearman correlation coefficient; VAS = visual analog scale; VCD = verbal category descriptive scale

Electronic Recording Devices

Twenty-two studies (37 percent) involving 814 patients (range 8 to 145) evaluated the ability of electronic recording devices to measure cough frequency (Tables 8 and 9).[31-33,37,40,41,43,50,53,56,58,59,63,65-67,69,70,80,84-86] Of the 22 studies, 4 (18 percent) were conducted in the United States or Canada.[41,43,66,80] All 22 studies had low risk of bias. A variety of reference standards were employed to validate these devices including human count (5 studies), other electronic recording devices (4 studies), video recording devices (5 studies), quality-of-life questionnaires (5 studies), subjective scoring (including visual analog scales, 8 studies), and laboratory tussigenic challenges (4 studies). Four studies comparing sound recording devices with human cough count/video recording,[32,59,80,85] and one study comparing sound recording devices with another electronic recording device[56] showed strong correlation between the measures. One study comparing sound recording devices with the LCQ showed moderately strong correlation.[65] Other studies comparing sound recording devices with other cough measurement tools demonstrated only fair to moderate correlation.[33,50,53,66,67,69,84] In a few studies, the authors reported variable sensitivity, good PPV, and excellent specificity and NPV when comparing the electronic recording devices with human cough counts.[31,32,40,41,43,70]

All of the studies included in this analysis evaluated devices in an adult population. Thus, while electronic recording devices are often employed as reference standards in studies involving children, we did not find any studies involving children aimed at validating these devices. While many of the studies commented on acceptability of the devices to patients, none provided any significant detail.

Validity

Five studies estimated the sensitivity and specificity of five different cough recording devices to assess cough frequency, with human cough counting as the reference standard.[31,32,40,43,70] A sixth study[86] calculated a correlation coefficient between cough counts as measured by an electronic recording device and human cough count. In all six 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 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 impact, which are the constructs that were usually being assessed by the instruments with which recording devices were compared.

Reliability

Five studies assessed the reliability of recording devices.[31-33,50,86] Intraclass correlation coefficients were consistently ≥ 0.80, with reproducibility reported to be 100 percent in one study.[31]

Responsiveness

A single study[53] evaluated the responsiveness of an electronic recording device to clinical change over time. In this randomized, placebo-controlled study, two cough recording devices, as

well as patient-reported scores of cough severity, demonstrated a decrease in patients' frequency of cough over the course of the trial.

In summary, it is difficult to determine practical use of electronic recording devices. As noted, a few studies included data regarding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the measurement tools. The findings from these studies support the validity of cough recording devices as an accurate measure of cough frequency. Some validations occurred under laboratory conditions, making it difficult to accurately judge the usefulness of the instruments tested in real-world situations. Furthermore, these devices are not readily or commercially available, thereby limiting widespread use. In addition, no studies investigated whether results from these testing devices actually influenced decisionmaking in regard to patient care.

Table 8. Description of electronic recording devices

Name of Recording Device	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[86]
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[37]
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[66]
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[31] Faruqi, 2011[50]
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[33] Birring, 2008[32] Matos, 2007[70]
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[41]
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[40] Hamutcu, 2002[56]

Name of Recording Device	Description	Studies
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[67]
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[43]
Audio recorder	Condenser microphone attached to the subject's throat and connected to a digital sound meter.	Freestone, 1997[53]
Audio recorder	24-hour ambulatory cough sound recording.	Key, 2010[65]
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[69]
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[58]
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[84]
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[85]
24-hour ambulatory recorder and EMG	Unidirectional microphone attached to the chest wall. EMG signals recorded from surface electrodes.	Hsu, 1994[59]
24-hour ambulatory recorder	Consisting of a lapel microphone with either a modified MP3 player or a validated custom-built recording device.	Kelsall, 2008[63]
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[80]

Abbreviations: ECG = electrocardiographic; EMG = electromyographic

Table 9. Results of studies of electronic recording devices

Study	Index Test	Comparator(s)	Results
Barry, 2006[31]	Hull Automatic Cough Counter	Cough count (by a human)	SN: 0.80 SP: 0.96 Reproducibility: 100%
Birring, 2006[33]	Leicester Cough Monitor	Electronic cough recorder (sound or pressure)	Reliability (intraclass correlation coefficient): 0.8
		Leicester Cough Questionnaire	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)	Correlation: 0.9 (p=0.008)
		Capsaicin tussigenic challenge (C2)	Correlation: 0.8 (p<=0.05)
Chang, 1997[37]	Holter monitor cough meter	Electronic cough recorder (sound or pressure)	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).
Corrigan, 2003[40]	Logan Research (LR 100) cough monitor	Video cough recorder	SN: 81.00% PPV: 0.8
Coyle, 2005[41]	LifeShirt system	Video cough recorder	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 vs. daytime: SN, SP, PPV, NPV = p<0.0001
Dales, 1997[43]	Electronic cough recorder	Cough count (by a human)	SN: 80 SP: 95 Accuracy: 90
		Cough diaries	Kappa: ≤0.10
Faruqi, 2011[50]	Hull Automated Cough Counter	Leicester Cough Questionnaire	Correlation: -0.62 (p<0.001)
		SAS	Correlation: 0.54 (p<0.001)
		VAS	Correlation: 0.38 (p=0.007)
		C2	Correlation: -0.45 (p=0.001)
		C5	Correlation: -0.55 (p<0.001)
		Reproducibility	r = 0.91, (p < 0.001)

Study	Index Test	Comparator(s)	Results
Freestone, 1997[53]	Electronic cough recorder	Index test (electronic cough recorder)	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)
Hamutcu, 2002[56]	Logan Research (LR 100) cough monitor	Electronic cough recorder (sound or pressure) – tape recorder	Correlation: 0.96, p<0.0001
		Score	Correlation: NS
		VAS	Correlation: NS
Hsu, 1994[59]	24-hour ambulatory recorder and EMG	Cough count (by a human)	Correlation: 0.99, p<0.005
		Score	Correlation: 0.96, p<0.005
Kelsall, 2008[63]	24-hour ambulatory recorder Parameters measured: cough epochs, explosive phases, cough seconds	Cough count (by a human)	Correlation: Cough epochs c/w cough seconds (r2=0.84) Correlation: Cough epochs c/w explosive phases (r2=0.80) Correlation: Cough seconds c/w explosive phases (r2=0.98)
		Daytime VAS	Correlation: with explosive phases: r=0.45 (p<=0.001)
			Correlation: with cough seconds: r=0.44 (p<=0.001)
			Correlation: with cough epochs: r=0.40 (p=0.001)
		Nighttime VAS	Correlation: with explosive phases: r=0.67 (p<=0.001)
			Correlation: with cough seconds: r=0.64 (p<=0.001)
			Correlation: with cough epochs: r=0.60 (p<=0.001)
		LCQ	Correlation: with explosive phases: r=-0.53 (p<=0.001)
			Correlation: with cough seconds: r=-0.53 (p<=0.001)
			Correlation: with cough epochs: r=-0.46 (p<=0.001)
Key, 2010[65]	Electronic cough recorder	Cough count (by a human)	Correlation: Mean difference 0.9 (±1.7)
		VAS	Correlation: Day r = 0.80 (p < 0.001) Night r = 0.71 (p = 0.001)
		Leicester Cough Questionnaire	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)

Study	Index Test	Comparator(s)	Results
Krajnik, 2010[67]	Portable automatic cough analyzer	Daytime total cough incidents, score	Correlation: 0.63 (p=0.22)
		Daytime cough incidents per hour, score	Correlation: 0.60 (p=0.29)
		Time spent coughing per hour during the day, score	Correlation: 0.48 (p=0.1)
		Nighttime cough incidents per hour, score	Correlation: 0.29 (p=0.34)
		Time spent coughing per hour during the night, score	Correlation: 0.26 (p=0.4)
		Total time spent coughing per hour	Correlation: 0.37 (p=0.21)
		Total cough incidents per hour	Correlation: 0.52 (p=0.066)
Marsden, 2008[69]	Electronic cough recorder	Tussigenic challenge (C5)	Correlation: 0.08 (p=0.65)
		Tussigenic challenge (C2)	Correlation: 0.39 (p=-0.03)
		Score	Correlation: 0.32 (p=0.45)
		Leicester Cough Questionnaire	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)
Matos, 2007[70]	Leicester Cough Monitor	Cough count (by a human)	SN: 97.8 (IQR 88.1 to 99.1)
Thomas, 1978[86]	DATA	Cough count (by a human)	Rel (intraclass correlation coefficient): 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
Birring, 2008[32]	Leicester Cough Algorithm	Cough count (by a human)	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: (intraclass correlation coefficient): 0.9
Krahnke, 2004[66]	Audio cough recorder	Daytime score	Correlation: 0.54 (p<0.0001)
		Nighttime score	Correlation: 0.39 (p=0.0006)
		Daytime plus nighttime score	Correlation: 0.51 (p<0.001)
Paul, 2006[80]	Accelerometer	Video recorder	Correlation: 0.997 (p<0.001)

Study	Index Test	Comparator(s)	Results
Smith, 2006[84]	Electronic cough recorder	Tussigenic challenge	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	
		Score	
		Cough-specific quality of life	
Smith, 2006[85]	Video recorder	Cough count (by a human)	Manual counting of cough sounds from digital audio recordings has excellent agreement with simultaneous video recordings in laboratory conditions
Hoskyns, 1991[58]	Audio cough recorder	Parental night cough diary	Correlation: ($r=0.588$, $p<0.02$) during medication week; no correlation during placebo week

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; LCQ = Leicester Cough Questionnaire; NPV = negative predictive value; PPV = positive predictive value; SN = sensitivity; SP = specificity; VAS = visual analog scale

Visual Analog Scales

We identified 6 studies involving 240 patients (ranging in age from 19 to 62 years) that compared a visual analog scale to another cough instrument (Table 10). Of the six studies, five (83 percent) were conducted in the UK,[45,50,64,65,69] and one in Israel.[51] One study (16 percent) was judged to have a high risk of bias,[51] and the remaining five (83 percent) to have low risk of bias.

We did not identify any validation studies of visual analog scales and found inconsistent correlations between these subjective scores and objective cough measurements or quality-of-life questionnaires. The results of these studies were variable, with one showing fairly strong correlation with an electronic recording device,[65] while most showed only poor to moderate correlation with other cough measures.[45,50,51,64,69] It is difficult to truly assess the accuracy of visual analog scales, as the scales themselves are not consistent. Even in our six included studies, some scales measured cough frequency, while others measured cough severity.

Validity

We did not identify any validation studies of visual analog scales and found inconsistent correlations between these subjective scores and objective cough measurements or quality-of-life questionnaires in the five studies that reported such correlations.[45,50,64,65,69]

Reliability

We did not identify any reliability studies of visual analog scales.

Responsiveness

A single study[51] commented on the responsiveness of a visual analog scale instrument. In this study, the visual analog cough frequency score identified 17 out of 22 patients (76 percent) who reported a beneficial modification of cough over the course of 1 week.

Table 10. Results of studies with VAS instruments

Study	Population	Description Given of VAS	Comparator(s)	Correlation	Responsive-ness
Decalmer, 2007[45]	Adults	100 mm linear scale marked with a horizontal line by the patient, with 0 mm representing ‘‘no cough’’ and 100 mm ‘‘worst cough’’	Electronic cough recorder	Daytime: 0.46 ($p < 0.001$) Nighttime: 0.61 ($p < 0.001$)	-
Faruqi, 2011[50]	Adults	100 mm linear VAS for both day and night. Patients were instructed to indicate where on the scale they perceived “how cough has affected me?”	LCQ SAS Cough count C2 C5	LCQ: -0.62 ($p < 0.001$) SAS: 0.60 ($p < 0.001$) Cough count: 0.38 ($p = 0.007$) C2: -0.09 ($p = 0.537$) C5: -0.16 ($p = 0.45$)	-

Study	Population	Description Given of VAS	Comparator(s)	Correlation	Responsive-ness
Fisman, 2001[51]	Adults	Cough frequency score (0–10) was obtained using a visual analog scale: 0 = I never cough; 10 = I cough all day	Severity score	-	76.00%
Kelsall, 2011[64]	Adults	0–100 mm scale (0 = no cough; 100 = worst cough)	Electronic cough recorder (night)	0.45 (p = 0.001)	-
Key, 2010[65]	Adults	Cough severity on a linear 100 mm VAS	Electronic cough recorder (day) Electronic cough recorder (night)	Day: 0.80 (p = 0.001) Night: 0.71 (p = 0.001)	-
Marsden, 2008[69]	Adults	100-mm linear VAS to indicate severity of their cough from ''no cough'' to ''worst cough''	Electronic cough recorder	Daytime: 0.45 (p = 0.002) Nighttime: 0.43 (p =0.003)	-

Abbreviations: LCQ = Leicester Cough Questionnaire; SAS = Symptom Assessment Scale; VAS = visual analog scale

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

- 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.
- All preparations appeared to be well-tolerated, but side effects and adverse events were uncommonly reported.
- There were few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough.
- Outcomes assessed and methods of measuring these outcomes varied widely across studies.
- Data on nonpharmacological therapies for chronic cough were sparse.
- Studies evaluating management of unidentified or refractory chronic cough in children are extremely limited.
- Patients with unexplained or refractory chronic cough are not well-defined as a population in the evidence base, restricting the applicability of many studies.

- When similar outcomes were assessed across studies, the tools used were diverse and inconsistent, making comparison and interpretation difficult.

Description of Included Studies

Fifty-seven (57) comparisons from 42 studies evaluated therapies in patients with chronic cough and met our inclusion criteria. The 42 studies were described in 36 publications.[89-124] Study characteristics are summarized in Table 11. Thirty-two (32) of the 42 studies were parallel-group RCTs,[89-92,94,96-99,101-104,106,108,110,111,113-116,118-124] and 8 were randomized crossover studies.[93,95,100,105,107,109,112,117] The range of years of publication was 1956 to 2011; 29 (69 percent) of the articles were published before 2000. Only two studies[110,119] were performed in children. The majority of studies took place in Europe, with 7 in the UK and 17 in other countries in Europe (total of 57 percent); 7 studies took place in Asia, 6 in the United States, 4 in Australia/New Zealand, and 1 in Canada. A total of 2622 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. Twenty-eight (28) studies (67 percent) had a followup duration of 2 weeks or less. The majority of studies were rated fair in quality (n = 26, or 62 percent); 10 studies were good in quality, and 6 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.

Table 11. KQ 2—Study characteristics

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Respiratory Disease	Number of Patients	Study Quality
Cass, 1956[92]	Antitussive (opiates) vs. Antitussive (other)	U.S.	Persistent cough	NR	63	Fair
Simon, 1957[115]	Antitussive (anesthetics) vs. Antitussive (anesthetics)	U.S.	Chronic asthmatic bronchitis/pulmonary emphysema	COPD	59	Poor
Simon, 1960[116]	Antitussive (anesthetics) vs. Antitussive (opiates) vs. Placebo	U.S.	Chronic asthmatic bronchitis/pulmonary emphysema	Chronic bronchitis, pulmonary emphysema	45	Poor
Vakil, 1966[118]	Antitussive (other) vs. Placebo	Asia	Chronic cough	Chronic bronchitis, TB	70	Fair
Sevelius, 1971[114]	Antitussive (opiates) vs. Placebo	U.S.	Chronic cough secondary to obstructive emphysema and chronic bronchitis	COPD	12	Fair
Wojcicki, 1975[123]	Antitussive (other) vs. Protussive (expectorants)	Europe	Cough and nocturnal paroxysms of coughing	Chronic bronchitis, cystic fibrosis, TB	32	Good
Lilienfield, 1976[102]	Antihistamine vs. Antihistamine	U.S.	NR	Chronic bronchitis, cystic fibrosis, sarcoidosis, histoplasmosis	13	Fair
Matts, 1977[105]	Antitussive (other) vs. Protussive (expectorants)	UK	Chronic cough.	Post viral infection	50	Fair
Sabot, 1977[113]	Antitussive (opiates) vs. Antitussive (opiates) vs. Placebo	Europe	Chronic cough	NR	24	Fair
Clarke, 1979[93]	Protussive (mucolytic) vs. Protussive (mucolytic)	UK	Chronic bronchitis	Chronic bronchitis	11	Good
Dierckx, 1981[95]	Antitussive (opiates) vs. Antitussive (other) vs. Placebo	Europe	Chronic cough	Asthma, chronic bronchitis, cystic fibrosis, TB	38	Fair
Diwan, 1982[96]	Antitussive (anesthetics) vs. Antitussive (opiates)	Asia	Chronic cough	COPD, chronic bronchitis, TB	60	Fair
Matthys, 1983[104]	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

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Respiratory Disease	Number of Patients	Study Quality
Gastpar, 1984[98]	Antitussive (opiates) vs. Antitussive (other)	Europe	Cough secondary to upper respiratory tract disease	NR	90	Poor
Jackson, 1984[101]	Protussive (mucolytic) vs. Placebo	UK	Chronic bronchitis	Chronic bronchitis	121	Poor
Ruhle, 1984[112]	Antitussive (other) vs. Antitussive (other) vs. Placebo	Europe	Chronic cough	COPD, asthma, chronic bronchitis, TB	24	Fair
Guyatt, 1987[99]	Protussive (mucolytic) vs. Placebo	Canada	Chronic productive cough	Chronic bronchitis	78	Fair
van Hengstum, 1988[120]	Protussive (nonpharmacological) vs. Protussive (nonpharmacological)	Europe	Chronic bronchitis	Chronic bronchitis	8	Fair
Reid, 1989[110]	Antihistamine vs. Placebo	Australia/ New Zealand	Children, chronic recurrent cough and/or wheeze with evidence of airway hyperreactivity	Asthma	189	Fair
Dueholm, 1992[97]	Protussive (mucolytic) vs. Placebo	UK	Chronic bronchitis	Chronic bronchitis	51	Fair
Holmes, 1992[100]	Anticholinergic vs. Placebo	Australia/ New Zealand	Persistent cough secondary to prior upper respiratory tract infection	Post-viral URTI	13	Good
van Asperen, 1992[119]	Antihistamine vs. Placebo	Australia/ New Zealand	Children, chronic cough and/or wheeze	Unexplained cough	112	Good
Aversa, 1993[90]	Antitussive (other) vs. Placebo	Europe	Chronic lung disease	COPD, unexplained cough, neoplasm, pulmonary fibrosis	73	Fair
Del Donno, 1994[94]	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[91]	Antitussive (opiates) vs. Antitussive (other)	Europe	Dry or slightly productive cough	COPD, unexplained cough, neoplasm, pulmonary fibrosis	113	Fair

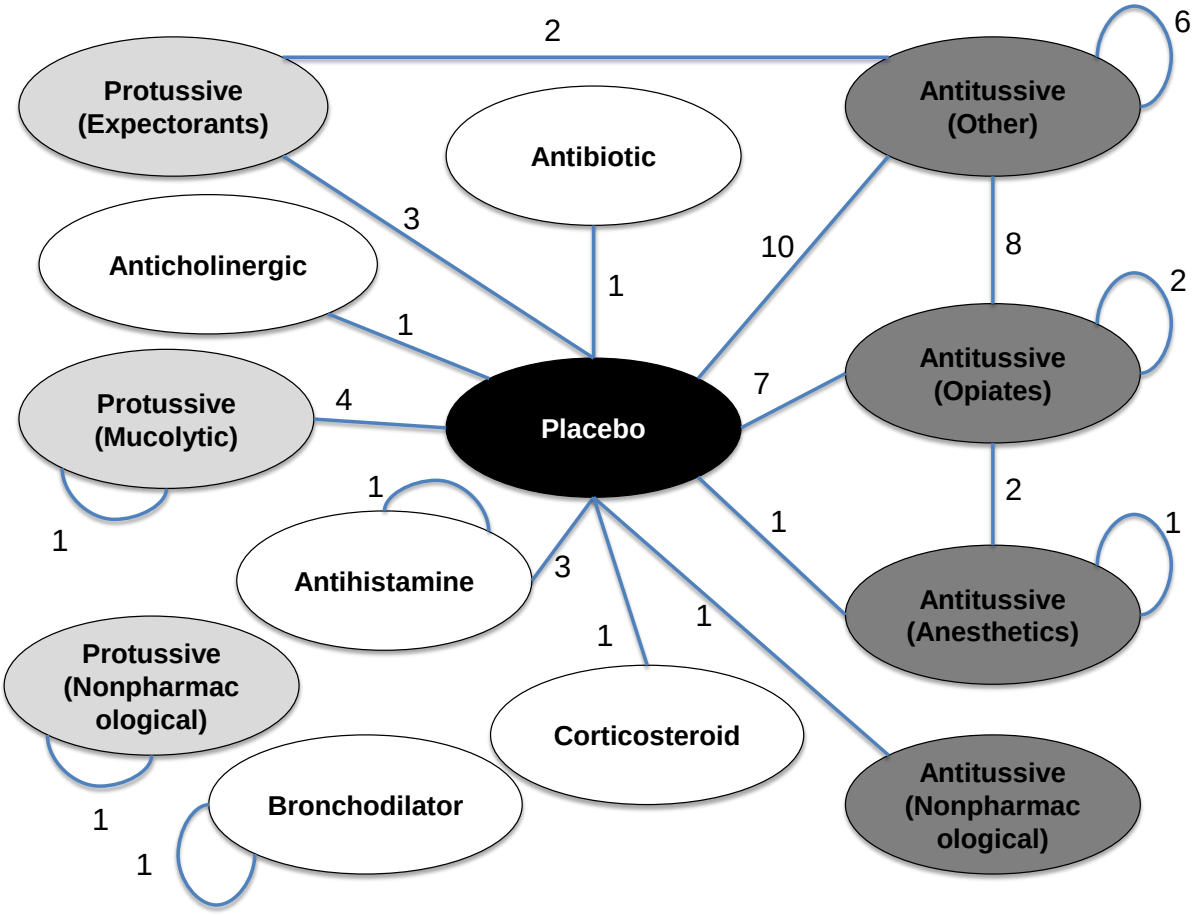
Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Respiratory Disease	Number of Patients	Study Quality
Parvez, 1996[108] Study 1	Protussive (expectorants) vs. Placebo	Asia	Chronic productive cough secondary to bronchopulmonary disease	COPD, cystic fibrosis	60	Good
Parvez, 1996[108] Study 2	Protussive (mucolytic) vs. Placebo	Asia	Chronic productive cough secondary to bronchopulmonary disease	COPD, cystic fibrosis	24	Good
Tanaka, 1996[117]	Antihistamine vs. Placebo	Asia	Chronic cough	UACS	17	Fair
Luporini, 1998[103]	Antitussive (opiates) vs. Antitussive (other)	Europe	Persistent, nonproductive cough	Lung cancer	124	Fair
Aliprandi, 2004[89] 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[89] 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[89] 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[89] 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[89] 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[89] 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
Vertigan, 2006[121]	Antitussive (nonpharmacological) vs. Placebo	Australia/ New Zealand	Chronic cough	GERD, asthma, UACS, ACE inhibitor	87	Fair
Morcie, 2007[106]	Antitussive (opiates) vs. Placebo	UK	Chronic cough	Unexplained cough	27	Poor
Ribeiro, 2007[111]	Antitussive (other) vs. Placebo	S. America	Chronic cough	Unexplained cough	64	Good
Ramsay, 2008[109]	Antitussive (other) vs. Placebo	UK	Chronic cough	None	42	Good

Study	Intervention comparison(s)	Geographic Location	Cough/Population Description	Included Respiratory Disease	Number of Patients	Study Quality
Wei, 2010[122]	Bronchodilator vs. Bronchodilator	Asia	Non- or mildly productive cough	Cough variant asthma; GERD, nonasthmatic eosinophilic bronchitis; UACS	214	Fair
Yousaf, 2010[124]	Antibiotic vs. Placebo	UK	Chronic cough	Unexplained cough	30	Good
Mukaida, 2011[107]	Antitussive (other) vs. Placebo	Asia	Chronic cough secondary to COPD	COPD	19	Fair

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

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 3 represents the various categories of agents and the comparisons among these agents represented in the included studies. The 42 studies represented 20 different types of comparisons within or between treatment classes and included studies of 57 individual agents. The majority of comparisons (33, or 58 percent) were placebo-controlled. The most common comparisons were between other antitussives and placebo (10 studies, 17 percent of comparisons), followed by other antitussives and antitussive opiates (8 studies, 14 percent) and antitussive opiates versus placebo (7 studies, 12 percent). Sixteen comparisons (28 percent) reflected comparisons 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 (Table 11).

Table 12 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 (48 studies, 84 percent) and cough frequency (35 studies, 61 percent). 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 12. 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	1	Yousaf, 2010[124]	Erythromycin	Placebo	X	X		X	X						
Anticholinergic vs. Placebo	1	Holmes, 1992[100]	Ipratropium bromide inhaler	Placebo	X										X
Antihistamine vs. Antihistamine	1	Lilienfield, 1976[102]	Diphenhydramine	Diphenhydramine		X								X	
Antihistamine vs. Placebo	3	Tanaka, 1996[117]	Loratadine	Placebo					X						
		Reid, 1989[110]*	Ketotifen	Placebo	X			X							
		van Asperen, 1992[119]*	Ketotifen	Placebo	X										
Antitussive (anesthetics) vs. Antitussive (anesthetics)	1	Simon, 1957[115]	Benzonatate	Linctussal (bencantyl)	X										
Antitussive (anesthetics) vs. Antitussive (opiates)	2	Simon, 1960[116]	Benzonatate	Dihydrocodeinone	X	X					X				
		Diwan, 1982[96]	Isoaminile citrate	Clophedianol HCl		X							X		
Antitussive (anesthetics) vs. Placebo	1	Simon, 1960[116]	Benzonatate	Placebo	X	X					X				
Antitussive (nonpharmacological) vs. Placebo	1	Vertigan, 2006[121]	SPEICH-C	Placebo	X							X			
Antitussive (opiates) vs. Antitussive (opiates)	2	Sabot, 1977[113]	Viminol p-OHB	Viminol p-OHB	X										
		Sevelius, 1971[114]	Codeine	Codeine		X									

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)	8	Dierckx, 1981[95]	Codeine	Glaucine	X	X									
		Barnabe, 1995[91]	Codeine	Moguisteine	X	X									
		Gastpar, 1984[98]	Codeine	Glaucine	X	X									
		Luporini, 1998[103]	Dihydrocodeine rhodanate	Levodropropizine	X		X					X		X	
		Matthys, 1983[104]	Codeine	Dextromethorphan	X	X					X				
		Aliprandi, 2004[89]	Codeine	Levocloperastine	X	X	X								
		Aliprandi, 2004[89]	Codeine	Levocloperastine	X	X	X								
		Cass, 1956[92]	Codeine	Dextromethorphan	X										
Antitussive (opiates) vs. Placebo	7	Simon, 1960[116]	Dihydrocodeinone	Placebo	X	X					X				
		Sabot, 1977[113]	Vviminol p-OHB	Placebo	X										
		Morice, 2007[106]	Morphine sulfate	Placebo	X			X	X				X		
		Sevelius, 1971[114]	Codeine	Placebo	X	X									
		Dierckx, 1981[95]	Codeine	Placebo	X	X									
		Matthys, 1983[104]	Codeine	Placebo	X	X					X				
		Cass, 1956[92]	Codeine	Placebo	X										

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. Antitussive (other)	6	Ruhle, 1984[112]	Glaucine	Dextromethorphan	X	X							X		
		Aliprandi, 2004[89]	Levocloperastine	Levodropropizine	X	X	X								
		Del Donno, 1994[94]	Moguisteine	Dextromethorphan	X	X							X		
		Aliprandi, 2004[89]	Levocloperastine	Levodropropizine	X	X	X								
		Aliprandi, 2004[89]	Levocloperastine	Levodropropizine	X	X	X								
		Aliprandi, 2004[89]	Levocloperastine	DL-cloperastine	X	X							X		
Antitussive (other) vs. Placebo	10	Dierckx, 1981[95]	Glaucine	Placebo	X	X									
		Matthys, 1983[104]	Dextromethorphan	Placebo	X	X					X				
		Ruhle, 1984[112]	Glaucine	Placebo	X	X							X		
		Ruhle, 1984[112]	Dextromethorphan	Placebo	X	X							X		
		Ramsay, 2008[109]	Dextromethorphan	Placebo	X			X	X				X		
		Aversa, 1993[90]	Moguisteine	Placebo		X									
		Vakil, 1966[118]	Pipazethate	Placebo		X									
		Wojcicki, 1975[123]	Duopect	Placebo	X										
		Mukaida, 2011[107]	Bakumondoto	Placebo	X	X									
		Cass, 1956[92]	Dextromethorphan	Placebo	X										

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[123]	Duopect	Glycerol	X										
		Matts, 1977[105]	Diphenhydramine	Guaifenesin							X				
Bronchodilator vs. Bronchodilator	1	Wei, 2010[122]	Diprophylline	Methoxyphenamine	X	X		X							
Corticosteroid vs. placebo	1	Ribeiro, 2007[111]	Beclomethasone	Placebo	X	X	X								
Protussive (expectorants) vs. Placebo	3	Parvez, 1996[108]	Guaifenesin	Placebo	X	X									
		Wojcicki, 1975[123]	Glycerol	Placebo	X										
		Parvez, 1996[108]	Guafenesin	Placebo	X	X									
Protussive (mucolytic) vs. Placebo	4	Dueholm, 1992[97]	N-acetylcysteine	Placebo	X			X							X
		Clarke, 1979[93]	Bromhexine	Placebo	X	X									
		Guyatt, 1987[99]	Ambroxol	Placebo	X										
		Jackson, 1984[101]	N-acetylcysteine	Placebo	X							X			
Protussive (mucolytic) vs. Protussive (mucolytic)	1	Clarke, 1979[93]	2-mercapto-ethane-sulphonate	Hypertonic saline		X				X					
Protussive (nonpharmacological) vs. Protussive (nonpharmacological)	1	van Hengstum, 1988[120]	Positive expiratory pressure mask	Forced expiration						X					

*Two studies included only children.

Detailed Synthesis

Table 13 summarizes the patient-centered outcomes data collected for each study.

Studies Involving Opiate Antitussives

Among the studies reviewed, we found 23 comparisons within 13 studies involving opiate antitussives: 7 comparisons were with placebo,[92,95,104,106,113,114,116] 2 comparisons were of different doses of the same opiates,[113,114] 2 comparisons were with anesthetic antitussives,[96,116] and 8 comparisons were with nonopioid/nonanesthetic antitussives.[89,91,92,95,98,103,104] In the seven comparisons of opiates to placebo,[92,95,104,106,113,114,116] opiates were more effective for improving cough frequency, cough severity, and/or quality of life (LCQ) in five of the studies.[92,95,104,106,114] 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.[106] 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.[114] 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.[113]

When compared with anesthetic antitussives, opiates were not more effective for cough in the two studies making this comparison.[96,116] Opiates (only codeine derivatives in these studies) were compared to 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.[104] In another study, the two agents were comparable for cough severity.[92] Two studies comparing codeine to glaucine reported conflicting results; one noted significantly better improvement in cough severity and frequency with glaucine,[98] 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.[95] Codeine or dihydrocodeine were similar in effectiveness for cough to moguisteine,[91] levodropropizine,[103] and levocloperastine[89] 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.[91] In another study, the percentage of patients experiencing somnolence while taking dihydrocodeine was significantly higher (22 percent) than in in the group receiving levodropropizine (8 percent).[103]

Studies Involving Anesthetic Antitussives

Anesthetic antitussives were examined in three studies resulting in four comparisons: one comparison was with placebo,[116] two were with opioids,[96,116] and one study compared two anesthetic antitussives.[115] Benzonatate was not superior to placebo in the one study making this comparison.[116] Clophedianol and benzonatate were not more effective for cough than opiates in the two studies making these comparisons.[96,116] 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.[115]

Studies Involving Other Antitussives

We found 25 comparisons in 19 studies involving other (i.e., nonopioid/nonanesthetic) antitussives: 9 were comparisons with placebo,[90,92,95,104,107,109,112,118] 7 were comparisons between 2 non-opioid/non-anesthetic antitussives,[89,92,94,112] 1 was a comparison of a combined antitussive/expectorant with the expectorant alone,[123] and 8 were comparisons with opioids[89,91,92,95,98,103,104] (see the section on "Studies Involving Opiate Antitussives" for a summary of these studies). Four studies compared dextromethorphan with placebo,[92,104,109,112] with 3 of these supporting the efficacy of dextromethorphan for treatment of cough.[92,104,109] In one study,[104] dextromethorphan 20 mg twice a day was more effective than placebo for reducing both cough frequency and severity. In another study,[109] 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 a third study, dextromethorphan 10 mg and 20 mg were better than placebo for improvement of cough severity.[92] In the one negative study,[112] 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.[112] Another study of glaucine 30 mg noted lower cough frequency than placebo after 4 hours.[95] 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.[107] Moguistene 200 mg 3 times a day was more effective than placebo for reducing cough frequency over 4 days.[90] Pipazethate 20 mg did not reduce cough frequency compared with placebo.[118]

In seven studies, none of the "other" antitussives was found to be superior to another in comparisons made among them,[89,94,112] nor were different doses of the same agent.[92]

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).[123] 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.[92]

Studies Involving Protussives

There were nine comparisons involving protussives: three were comparisons of an expectorant to placebo,[108,123] one was a comparison of an expectorant to an 'other' antitussive,[123] four were comparisons of a mucolytic to placebo,[97,99,101,108] and one study compared a mucolytic to another mucolytic.[93] Compared with placebo, the expectorant guaifenesin did not reduce cough frequency in one study.[108] 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.[108] 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).[123] 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 to placebo: N-acetylcysteine 200 mg 3 times a day,[101] N-acetylcysteine 4 mg inhaled via metered-dose inhaler 4 times a day,[97] bromhexine 16 mg 4 times a day.[108] or ambroxol 60 mg twice a day.[99] In a comparison of inhaled aerosols, 2-mercapto-ethane sulfonate was not more effective than hypertonic saline at improving tracheobronchial clearance.[93]

Studies Involving Nonantitussive and Nonprotussive Pharmacotherapies

We identified four studies examining the effect of antihistamine medication on cough[102,110,117,119] Two of these studies were in children[110,119] and are discussed separately below. In the adult studies, one compared diphenhydramine 50 mg to diphenhydramine 25 mg to placebo, all preparations scheduled 4 times a day.[102] 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 to placebo. In a placebo-controlled study,[117] 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.[124] A study compared ipratroprium bromide 20 mcg inhaler, 4 puffs 4 times a day, to placebo and found improvements in cough severity and dyspnea associated with cough.[100] 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.[122]

Studies Involving Nonpharmacological Therapies

We identified only two studies that evaluated the comparative safety and effectiveness of nonpharmacological interventions for chronic cough.[120,121] Van Hengstum et al.[120] compared 20 minutes of positive expiratory pressure (PEP) physiotherapy to 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 to placebo among 87 adult patients with refractory chronic cough of at least 2 months in duration.[121] 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

Two studies addressed the treatment of chronic cough in children.[110,119] Both evaluated ketotifen, an H1-antihistimine and mast-cell stabilizer. 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,[119] and the other 214 children between 2 and 6 years of age over 12 weeks.[110] 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 to 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.

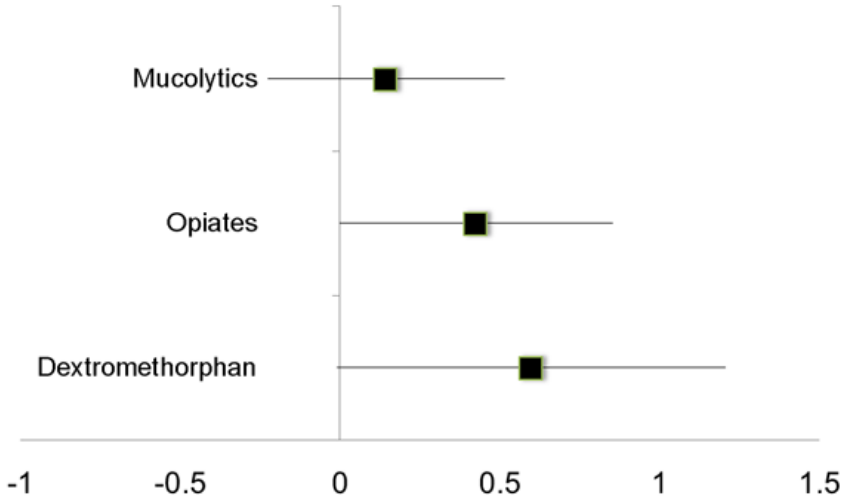
These studies have low applicability to the management of children with chronic cough. In both studies, all subjects likely had asthma as their source of chronic cough. These studies were published over 20 years ago (in 1989 and 1992). The management of asthma has significantly changed since these studies 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.

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 12), precluded us from performing meta-analyses on almost all outcomes.

We were, however, able to evaluate the relative effects on cough severity for three classes of treatments for chronic cough: antitussive opiates, antitussive dextromethorphan, and protussive mucolytics. This analysis included 11 studies and 526 patients. Most of the 11 studies compared the treatment to placebo,[95,97,99,101,104,106,108,109,112,113,116] but one compared opiates to dextromethorphan and placebo.[104] Because each study used a different measure of severity, we converted all results to effect sizes. Relative to placebo, the effect of dextromethorphan on cough severity was 0.599 (95 percent confidence interval [CI], -0.009 to 1.206; $p = 0.0527$), the effect of opiates was 0.426 (95 percent CI, -0.001 to 0.852; $p = 0.0502$) and the effect of mucolytics was 0.144 (95 percent CI -0.225 to 0.513; $p = 0.394$; Figure 4). The studies showed marginal heterogeneity ($p = 0.092$). Although not quite reaching the conventional level of statistical significance, the effects of dextromethorphan and opiates compared to placebo on cough severity support a statistical trend and suggest that the findings between studies are reasonably similar.

Figure 4. Meta-analysis of data on cough severity



We considered a similar meta-analysis for cough frequency, but the four studies[95,104,114,116] comparing codeine and placebo had too many differences in outcome reporting so that meta-analysis was not considered to be appropriate.

Table 13. 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[124]	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)		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)		
Anticholinergic vs. Placebo	Holmes, 1992[100]	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						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

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antihistamine vs. Antihistamine	Lilienfield, 1976[102]		16-hr cough count assessed at day 3: Diphenhydramine 50 mg: 163.8 (SEM 24.2) Diphenhydramine 25 mg: 175.8 (SEM 27.9)					There was little or no apparent correlation between antitussive effectiveness and incidence of drowsiness
Antihistamine vs. Placebo	Tanaka, 1996[117]					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) $p<0.05$		
	Reid, 1989[110]	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)			Reduction in the number of housebound days due to respiratory symptoms: Ketotifen: $p = 0.036$ Placebo: p = NS			

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	van Asperen, 1992[119]	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						
Antitussive (anesthetics) vs. Antitussive (anesthetics)	Simon, 1957[115]	No. of patients with excellent or good relief at least 2 wk from treatment: Benzonatate = 43/52 Linctussal (bencantyl) = 22/41 p<0.05						
Antitussive (anesthetics) vs. Antitussive (opiates)	Diwan, 1982[96]		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)				Side effects were not troublesome and did not require a reduction in dose or withdrawal of treatment	
	Simon, 1960[116]	No. of patients with severity lessened: Benzonatate = 28/45 Dihydrocodeinone = 29/45	No. of patients with frequency lessened: Benzonatate = 32/45 Dihydrocodeinone = 30/45					Patient preference: Benzonatate = 27% Dihydrocodeinone = 49% p<0.05

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (anesthetics) vs. Placebo	Simon, 1960[116]	No. of patients with severity lessened: Benzonatate = 28/45 Placebo = 26/45	No. of patients with frequency lessened: Benzonatate = 32/45 Placebo = 30/45					Patient preference: Benzonatate = 27% Placebo = 18% p<0.05
Antitussive (nonpharma-cological) vs. Placebo	Vertigan, 2006[121]	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						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

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (opiates) vs. Antitussive (other)	Barnabe, 1995[91]	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)					

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Gastpar, 1984[98]	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					

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Luporini, 1998[103]	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)		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)				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)

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Matthys, 1983[104]	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)					Patient preference (% patients rating) Codeine = 12.5% (Best), 12.5% (Worst) Dextromethor-phan = 87.5% (Best), 6.25% (Worst) p<0.001
	Dierckx, 1981[95]	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					
	Aliprandi, 2004[89]	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)				
	Aliprandi, 2004[89]	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)				

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Cass, 1956[92]	Mean daily cough score (0-4) over the 10 days: Codeine = 0.78 Dextromethorphan = 0.86						
Antitussive (opiates) vs. Placebo	Matthys, 1983[104]	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					Patient preference (% patients rating) Codeine = 12.5% (Best), 12.5% (Worst) Placebo = 0% (Best), 81.25% (Worst) p<0.001
	Morice, 2007[106]	Mean difference of daily score (0-9) after 28 days: Morphine = 3.45 (SD 1.76) Placebo = 4.98 (SD 1.68)			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%)	
	Dierckx, 1981[95]	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					

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Sabot, 1977[113]	Mean score (0-3) assessed over 3-hr period 1 hr after dose: Viminol p-OHB = 2.04 Placebo = 3.66 p<0.05						
	Sevelius, 1971[114]		Average reduction compared to placebo in diurnal cough counts: Codeine (7.5mg) = 29% Codeine (15mg) = 42% Codeine (30mg) = 56% Codeine (60mg) = 67% p<0.005					
	Simon, 1960[116]	No. of patients with severity lessened: Dihydrocodeinone = 29/45 Placebo = 26/45	No. of patients with frequency lessened: Dihydrocodeinone = 30/45 Placebo = 30/45					Patient preference: Dihydrocodeinone = 49% Placebo = 18% p<0.05
Antitussive (other) vs. Antitussive (other)	Aliprandi, 2004[89]	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				

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Ruhle, 1984[112]	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				Incidence of side effects after three treatments: Glaucine = 1 Dextromethor-phan = 8 $p<0.05$	
	Del Donno, 1994[94]	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 versus at baseline: Moguisteine = 29.4% Dextromethor-phan = 30%				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)	
	Aliprandi, 2004[89]	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) $p<0.05$				

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Aliprandi, 2004[89]	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)				
	Aliprandi, 2004[89]	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				
Antitussive (other) vs. Placebo	Aversa, 1993[90]		Reduction in number of coughs in the interval 8-10am on day four versus day one: Moguisteine: 42% Placebo: 14% p=0.028					

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Matthys, 1983[104]	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					Patient preference (% patients rating) Dextromethor-phan = 87.5% (Best), 6.25% (Worst) Placebo = 0% (Best), 81.25% (Worst) p<0.001
	Mukaida, 2011[107]	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					
	Ramsay, 2008[109]	Mean VAS score (1-5) at day 5: Dextromethorphan = 1.39 Placebo = 1.66 Difference = -0.26 (CI -0.99 to 0.46)			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	
	Ribeiro, 2007[111]	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				No. of patients with no sleep disturbance after 2 wk: Beclomethasone = 42/44 Placebo = 19/20	

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Dierckx, 1981[95]	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					
	Ruhle, 1984[112]	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				Incidence of side effects after three treatments: Dextromethor-phan = 8 Placebo = 2 p<0.05	
	Ruhle, 1984[112]	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				Incidence of side effects after three treatments: Glaucine = 1 Placebo = 2	
	Vakil, 1966[118]		Average of 3 hrly cough counts: Pipazethate = 53.2 Placebo = 52.6					
	Wojcicki, 1975[123]	No. of patients with marked or moderate relief: Duopect = 28/32 Placebo = 3/32 p<0.05						

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Antitussive (other) vs. Protussive (expectorants)	Matts, 1977[105]							Patient preference for treatment: Diphenhydramine = 36/49 patients Guaifenesin = 13/49 patients
	Wojcicki, 1975[123]	No. of patients with marked or moderate relief: Duopect = 28/32 Glycerol = 13/32 p<0.05						
Bronchodilator vs. Bronchodilator	Wei, 2010[122]	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%		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)			
Protussive (expectorants) vs. Placebo	Parvez, 1996[108]	Median change in average cough intensity on day 14: Gaifensesin = -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)					
	Wojcicki, 1975[123]	No. of patients with marked or moderate relief: Glycerol = 13/32 Placebo = 3/32 p<0.05						

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Protussive (mucolytic) vs. Placebo	Dueholdm, 1992[97]	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			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)			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)
	Jackson, 1984[101]	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						Physician-reported global assessment over 3 mo period: N-acetylcysteine = 85% patients/change Placebo = 68% patients/change p = 0.063

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
	Clarke, 1979[93]		Mean number of coughs, 6 hr after inhalation: 2-mercapto-ethane sulphonate = 99 (SD 154) Placebo = 92 (SD 112)					
	Clarke, 1979[93]		Mean number of coughs, 6 hr after inhalation: hypertonic saline = 91 (SD 116) Placebo = 92 (SD 112)					
	Parvez, 1996[108]	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)					
	Guyatt, 1987[99]	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)						
Protussive (mucolytic) vs. Protussive (mucolytic)	Clarke, 1979[93]		Mean number of coughs, 6 hr after inhalation: 2-mercapto-ethane sulphonate = 99 (SD 154) hypertonic saline = 91 (SD 116)					

Comparison	Study	Cough Severity	Cough Frequency	Nighttime Awakenings	Functional Status	Tussigenic Challenge	Adverse Events	Other Outcomes
Protussive (nonpharmacological) vs. Protussive (nonpharmacological)	van Hengstum, 1988[120]							Retention after therapy: Positive expiratory pressure = 70 (SD 14) Forced expiration technique = 46 (SD 15) p<0.02

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

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

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 60 studies involving 5430 patients that evaluated instruments used to assess cough (key question [KQ] 1) and 42 studies involving 2622 patients that evaluate nonspecific (or symptomatic) therapies to treat patients with chronic cough (KQ2). 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) is the most widely studied cough-specific quality-of-life questionnaire, 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 Cough-specific Quality of Life Questionnaire (CQLQ), Chronic Cough Impact Questionnaire (CCIQ), and the Punum Ladder, 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 non-cough symptoms, and their focus on multiple symptoms leads them to be less valuable tools specifically for assessing cough.

Electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with other cough measurement tools. 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. 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 14-17 summarize the strength of evidence[26] for the available outcomes of validity, internal consistency, reliability, and responsiveness for the various instruments. These outcomes all represent aspects of the diagnostic accuracy of the cough measurement tools we assessed. 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 and CQLQ were represented by four or more published studies; as such, they are they only two questionnaires for which we generated strength of evidence tables.

Table 14. Summary of the strength of evidence for KQ 1—Leicester Cough Questionnaire (LCQ)

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)					**Moderate SOE**
9 (534)	Low	Consistent	Indirect	Precise	Range of r = 0.26–0.88
Internal consistency (Cronbach's alpha)					**High SOE**
2 (256)	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					**Insufficient SOE**
3 (366)	Moderate	Inconsistent	Indirect	Imprecise	Range of ES = 0.84–19.5

Abbreviations: ES = effect size; KQ = key question; LCQ = Leicester Cough Questionnaire; r = correlation coefficient; SOE = strength of evidence

Table 15. Summary of the strength of evidence for KQ 1—Cough-specific Quality of Life Questionnaire (CQLQ)

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)					**Moderate SOE**
4 (427)	Low	Consistent	Indirect	Precise	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	Insufficient	Insufficient	Insufficient	Insufficient	NA
Responsiveness					**Insufficient SOE**
1 (127)	Insufficient	Inconsistent	Indirect	Imprecise	Range of MID = 10.6–21.9

Abbreviations: CQLQ = Cough-specific Quality of Life Questionnaire; KQ = key question; MID = minimal important difference; NA = not applicable; r = correlation coefficient; SOE = strength of evidence

Table 16. Summary of the strength of evidence for KQ 1—electronic recording devices

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)					**High SOE**
17 (546)	Low	Consistent	Direct	Precise	Range of r = 0.89–0.99
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 in both studies

Abbreviations: KQ = key question; r = correlation coefficient; SOE = strength of evidence

Table 17. Summary of the strength of evidence for KQ 1—visual analog scales

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**
7 (279)	Low	Inconsistent	Indirect	Imprecise	No summary measure
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

Abbreviations: 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 tools 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.[125] 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.[126] 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.[106,111,124] 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 only two studies of one therapy (oral ketotifen) which is not currently available in the United States.[110,119]

Tables 18-21 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 18. Summary of the strength of evidence for KQ 2—antitussive (anesthetic) versus antitussive (opiate)

Number of Studies (Subjects)	Domains Pertaining to 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	No significant differences
Cough frequency					**Insufficient SOE**
2 (105)	RCTs/Low	Insufficient	Direct	Imprecise	No significant differences
Adverse effects					**Insufficient SOE**
1 (60)	RCTs/Low	Insufficient	Direct	Imprecise	No significant differences

Abbreviations: CI = confidence interval; KQ = key question; RCTs = randomized controlled trials; SOE = strength of evidence

Table 19. Summary of the strength of evidence for KQ 2—antitussive (opiate) versus antitussive (other)

Number of Studies (Subjects)	Domains Pertaining to SOE				Strength of Evidence (SOE)
	Risk of Bias	Consistency	Directness	Precision	Effect Estimate (95% CI)
Cough severity					**Insufficient SOE**
14 (824)	RCTs/Low	Inconsistent	Indirect	Imprecise	Opiates and dextromethorphan had similar effect sizes in MTM vs. placebo, p ~ 0.050—0.053
Cough frequency					**Insufficient SOE**
6 (437)	RCTs/Low	Inconsistent	Direct	Imprecise	No summary measure
Adverse effects					**Insufficient SOE**
5 (273)	RCTs/Low	Insufficient	Direct	Imprecise	No summary measure

Abbreviations: CI = confidence interval; KQ = key question; MTM = mixed treatment meta-analysis; RCTs = randomized controlled trials; SOE = strength of evidence

Table 20. Summary of the strength of evidence for KQ 2—protussive (mucolytic) versus antitussive (other)

Number of Studies (Subjects)	Domains Pertaining to 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	

Abbreviations: 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 21. Summary of the strength of evidence for KQ 2—protussive (mucolytic) versus antitussive (opiate)

Number of Studies (Subjects)	Domains Pertaining to 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	

Abbreviations: CI = confidence interval; KQ = key question; NS = not statistically significant; 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.[127] 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,[31,32,36,43,59,63,65-67,70,85,86] and studies that evaluated disease-specific, health-related quality-of-life questionnaires.[29] Our review summarized 60 studies involving 5430 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;[126] our review identified a few more trials of codeine[95,104] and dextromethorphan,[104,109,112] as well as trials of other opiates,[106,113] glaucine ([95,112] and benzonatate.[115,116] 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.[128] The recommendations therefore focused exclusively on populations outside the scope of our review, namely on patients with respiratory muscle weakness and 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), most of the studies were conducted in Europe (31 studies, or 52 percent). Twenty-six of those 31 studies were conducted exclusively in the UK. Fifteen (25 percent) of the studies were conducted in the United States or Canada. Overall, the study instruments were generally adequately described. The main study reporting issue impacting applicability was the description of the study population. Sociodemographic and clinical characteristics of the study populations were often poorly 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.

In terms of our evaluation of therapies for the treatment of unexplained or refractory chronic cough (KQ 2), our strict inclusion/exclusion criteria focusing on this population increased the applicability of the included studies, but decreased the availability of evidence for our review. 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 42 studies involving 2622 patients (median number of patients per study = 55). The majority of studies took place in Europe, with 7 in the UK and 17 in other countries in Europe (total of 57 percent); while only 7 (17 percent) took place within the United States or Canada. 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 (excluding cystic fibrosis and bronchiectasis), studies with mixed etiologies (including, for example, tuberculosis, lung cancer) and from different eras and geographic locations challenge the usefulness of data on treatment.

We were only able to identify two studies of children eligible for inclusion in our review. Unfortunately, both studies have low applicability to today's management of children with chronic cough. Both 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.

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). While we excluded drugs that had been withdrawn from the U.S. market (e.g., for safety issues), we decided to retain studies of drugs that were still 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 to 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 1956 to 2011, with 29 (69 percent) 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[126]). 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,[129] 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.[130] 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 would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. With this exclusion our initial search still returned over 13,000 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.[131] 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, moguestine) or even separate drugs with certain similarities (e.g., codeine and dextromethorphan). A physiological classification such as that used by Bolser et al.[126] 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 (for adults) and the CQLQ (for children) may be valid instruments for assessing severity of cough, and that electronic recording devices, in general, appear to be valid assessments of cough frequency compared to 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.[132] 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
- Validity of cough measurement tools in the pediatric population
    - Current evidence is insufficient; additional validation or measurement studies focusing on the pediatric population are needed. Suggest starting with additional studies of the CQLQ.
- 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 or provider reporting in use of cough assessment tools
    - Insufficient evidence curently exists; could be explored through observational studies
- 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 are the lack of validation studies for the pediatric population across all cough instruments, lack of validation studies of subjective 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 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 recommend that future cough validation studies use a common reference standard such as objective human cough count. 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 suffers from 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. Future research recommendations 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 apparent minimal 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,(4349) included in our review involved such an approach.[107]

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

two 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

There is no established gold standard for assessing either frequency or severity of cough, thereby making it difficult to quantitatively assess test accuracy for cough instruments. Validity of questionnaires was generally demonstrated in the published literature by correlation with other cough assessment instruments and by demonstrating internal consistency, 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. Several instruments, including the LCQ, the PC-QOL, and electronic recording devices, show good internal consistency but variable correlation with other cough measurement tools. This suggests that these tools demonstrate variable validity. There is a paucity of studies that evaluated the reliability of questionnaires. The lack of validated reference tests and large variability in the 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 few good-quality studies focusing on chronic cough using reliable outcome measurements over durations of followup pertinent to chronic cough. Although the evidence is sparse, the opioid and certain nonopioid/nonanesthetic antitussives demonstrated the most promise 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 or evaluating management of unidentified or refractory chronic cough in children are extremely limited.

Our systematic review highlights the clear need for further studies in patient populations with unexplained or refractory chronic cough and for more systematic design and reporting of these studies and assessment of their patient-centered outcomes.

References

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. Available at: http://www.cdc.gov/nchs/ahcd.htm. Accessed March 16, 2012.
2. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis. 1981;123(4 Pt 1):413-7. PMID: 7224353.
3. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990;141(3):640-7. PMID: 2178528.
4. Irwin RS, Curley FJ. The treatment of cough. A comprehensive review. Chest. 1991;99(6):1477-84. PMID: 2036833.
5. Molassiotis A, Bryan G, Caress A, et al. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. Respir Med. 2010;104(7):934-44. PMID: 20385478.
6. Holinger LD, Sanders AD. Chronic cough in infants and children: an update. Laryngoscope. 1991;101(6 Pt 1):596-605. PMID: 2041439.
7. Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. Ann Intern Med. 1993;119(10):977-83. PMID: 8214994.
8. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest. 1995;108(4):991-7. PMID: 7555175.
9. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med. 1996;156(9):997-1003. PMID: 8624180.
10. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371(9621):1364-74. PMID: 18424325.
11. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S. PMID: 16428686.
12. Smyth RL. Research with children. Paediatric practice needs better evidence—gained in collaboration with parents and children. BMJ. 2001;322(7299):1377-8. PMID: 11397728.
13. Sinaiko AR, Daniels SR. The use of short-acting nifedipine in children with hypertension: another example of the need for comprehensive drug testing in children. J Pediatr. 2001;139(1):7-9. PMID: 11445783.
14. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-83S. PMID: 16428719.
15. Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. Arch Dis Child. 2002;86(3):170-5. PMID: 11861232.
16. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114(1):e85-90. PMID: 15231978.
17. Kelly LF. Pediatric cough and cold preparations. Pediatr Rev. 2004;25(4):115-23. PMID: 15060179.
18. Hestand HE, Teske DW. Diphenhydramine hydrochloride intoxication. J Pediatr. 1977;90(6):1017-8. PMID: 859051.
19. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J. 2007;29(6):1256-76. PMID: 17540788.
20. Finnish Medical Society Duodecim. Chronic cough in a child. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007. Available at: http://www.guideline.gov/content.aspx?id=12798. Accessed March 16, 2012.
21. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22(2):159-62. PMID: 19061964.

22. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed April 16, 2012.
23. Agency for Healthcare Research and Quality. Methods Guide for Medical Test Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct. Accessed May 30, 2012.
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. PMID: 19621072.
25. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.
26. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010;63(5):513-23. PMID: 19595577.
27. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.
28. Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.
29. Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.
30. Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.
31. Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.
32. Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.
33. Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.
34. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.
35. Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.
36. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.
37. Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.
38. Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.
39. Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.
40. Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.
41. Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.
42. Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.

43. Dales RE, White J, Bhumgara C, et al. Parental reporting of childrens' coughing is biased. Eur J Epidemiol. 1997;13(5):541-5. PMID: 9258566.
44. De Vito Dabbs A, Hoffman LA, Dauber JH, et al. Evaluating the reliability and validity of the Questionnaire for Lung Transplant Patients. Prog Transplant. 2002;12(3):191-8; quiz 9-200. PMID: 12371045.
45. Decalmer SC, Webster D, Kelsall AA, et al. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.
46. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest. 2006;130(6):1839-43. PMID: 17167006.
47. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.
48. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.
49. Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.
50. Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.
51. Fisman EZ, Shapira I, Motro M, et al. The combined cough frequency/severity scoring: a new approach to cough evaluation in clinical settings. J Med. 2001;32(3-4):181-7. PMID: 11563816.
52. Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.
53. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.
54. French CL, Irwin RS, Curley FJ, et al. Impact of chronic cough on quality of life. Arch Intern Med. 1998;158(15):1657-61. PMID: 9701100.
55. French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.
56. Hamutcu R, Francis J, Karakoc F, et al. Objective monitoring of cough in children with cystic fibrosis. Pediatr Pulmonol. 2002;34(5):331-5. PMID: 12357476.
57. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. Ear Nose Throat J. 2009;88(11):1213-7. PMID: 19924664.
58. Hoskyns EW, Thomson A, Decker E, et al. Effect of controlled release salbutamol on nocturnal cough in asthma. Arch Dis Child. 1991;66(10):1209-12. PMID: 1953004.
59. Hsu JY, Stone RA, Logan-Sinclair RB, et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7(7):1246-53. PMID: 7925902.
60. Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.
61. Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.
62. Kalpaklioglu AF, Kara T, Kurtipek E, et al. Evaluation and impact of chronic cough: comparison of specific vs generic quality-of-life questionnaires. Ann Allergy Asthma Immunol. 2005;94(5):581-5. PMID: 15945562.
63. Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.
64. Kelsall A, Houghton LA, Jones H, et al. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569-75. PMID: 20864619.
65. Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4. PMID: 20565979.
66. Krahnke J, Gentile D, Angelini B, et al. Comparison of objective and subjective measurements of cough frequency in patients with seasonal allergic rhinitis. Ann

Allergy Asthma Immunol. 2004;93(3):259-64. PMID: 15478386.
67. Krajnik M, Damps-Konstanska I, Gorska L, et al. A portable automatic cough analyser in the ambulatory assessment of cough. Biomed Eng Online. 2010;9:17. PMID: 20226089.
68. Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.
69. Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol. 2008;122(5):903-7. PMID: 18842290.
70. Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.
71. Monz BU, Sachs P, McDonald J, et al. Responsiveness of the cough and sputum assessment questionnaire in exacerbations of COPD and chronic bronchitis. Respir Med. 2010;104(4):534-41. PMID: 19917525.
72. Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(1):125-31. PMID: 19196812.
73. Mwachari C, Nduba V, Nguti R, et al. Validation of a new clinical scoring system for acute bronchitis. Int J Tuberc Lung Dis. 2007;11(11):1253-9. PMID: 17958990.
74. Nandha D, Goodyer L, Woodruffe-Peacock C. Diary cards and the assessment of cough symptoms in community pharmacies. Pharm World Sci. 2000;22(1):17-20. PMID: 10815295.
75. Newcombe PA, Sheffield JK, Chang AB. Minimally important change in a Parent-Proxy Quality-of-Life questionnaire for pediatric chronic cough. Chest. 2011;139(3):576-80. PMID: 20947650.
76. Newcombe PA, Sheffield JK, Juniper EF, et al. Development of a parent-proxy quality-of-life chronic cough-specific questionnaire: clinical impact vs psychometric evaluations. Chest. 2008;133(2):386-95. PMID: 18252913.
77. Newcombe PA, Sheffield JK, Juniper EF, et al. Validation of a parent-proxy quality of life questionnaire for paediatric chronic cough (PC-QOL). Thorax. 2010;65(9):819-23. PMID: 20805179.
78. Nieto L, de Diego A, Perpina M, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97(4):393-400. PMID: 12693800.
79. O'Connell F, Thomas VE, Pride NB, et al. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med. 1994;150(2):374-80. PMID: 8049818.
80. Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.
81. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.
82. Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.
83. Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.
84. Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.
85. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.
86. Thomas JS, Lyons HA, Shepherd DA. D.A.T.A.—an advanced automated electronic cough counting system for the evaluation of antitussive agents. Curr Ther Res Clin Exp. 1978;23(1):66-77.
87. Vernon M, Kline Leidy N, Nacson A, et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4(4):199-208. PMID: 20519373.
88. Murray CS, Pipis SD, McArdle EC, et al. Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population. Thorax. 2002;57(5):388-92. PMID: 11978912.

89. Aliprandi P, Castelli C, Bernorio S, et al. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41. PMID: 15553659.
90. Aversa C, Cazzola M, Clini V, et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. Drugs Exp Clin Res. 1993;19(6):273-9. PMID: 8013271.
91. Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.
92. Cass LJ, Frederik WS. Quantitative comparison of cough-suppressing effects of romilar and other antitussives. J Lab Clin Med. 1956;48(6):879-85. PMID: 13376983.
93. Clarke SW, Lopez-Vidriero MT, Pavia D, et al. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol. 1979;7(1):39-44. PMID: 104724.
94. Del Donno M, Aversa C, Corsico R, et al. Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough. Drug Investigation. 1994;7(2):93-100.
95. Dierckx P, Leblanc G, Decoster A, et al. Double-blind study of glaucine in chronic cough. Int J Clin Pharmacol Ther Toxicol. 1981;19(9):396-9. PMID: 7028646.
96. Diwan J, Dhand R, Jindal SK, et al. A comparative randomized double-blind clinical trial of isoaminile citrate and chlophedianol hydrochloride as antitussive agents. Int J Clin Pharmacol Ther Toxicol. 1982;20(8):373-5. PMID: 6749701.
97. Dueholm M, Nielsen C, Thorshauge H, et al. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. Respir Med. 1992;86(2):89-92. PMID: 1615189.
98. Gastpar H, Criscuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. Curr Med Res Opin. 1984;9(1):21-7. PMID: 6373156.
99. Guyatt GH, Townsend M, Kazim F, et al. A controlled trial of ambroxol in chronic bronchitis. Chest. 1987;92(4):618-20. PMID: 3308343.
100. Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respir Med. 1992;86(5):425-9. PMID: 1462022.
101. Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (Fabrol) in chronic bronchitis: a double-blind placebo controlled study. J Int Med Res. 1984;12(3):198-206. PMID: 6376210.
102. Lilienfield LS, Rose JC, Princiotto JV. Antitussive activity of diphenhydramine in chronic cough. Clin Pharmacol Ther. 1976;19(4):421-5. PMID: 773581.
103. Luporini G, Barni S, Marchi E, et al. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. Eur Respir J. 1998;12(1):97-101. PMID: 9701421.
104. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. J Int Med Res. 1983;11(2):92-100. PMID: 6852361.
105. Matts SG. A trial of Lotussin and linctus diphenhydramine in patients wth an irritant cough. J Int Med Res. 1977;5(6):470-2. PMID: 338397.
106. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.
107. Mukaida K, Hattori N, Kondo K, et al. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. Phytomedicine. 2011;18(8-9):625-9. PMID: 21177084.
108. Parvez L, Vaidya M, Sakhardande A, et al. Evaluation of antitussive agents in man. Pulm Pharmacol. 1996;9(5-6):299-308. PMID: 9232667.
109. Ramsay J, Wright C, Thompson R, et al. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br J Clin Pharmacol. 2008;65(5):737-41. PMID: 18279476.
110. Reid JJ. Double-blind trial of ketotifen in childhood chronic cough and wheeze. Immunol Allergy Pract. 1989;11(4):143-50.
111. Ribeiro M, Pereira CA, Nery LE, et al. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. Ann

Allergy Asthma Immunol. 2007;99(1):61-8. PMID: 17650832.
112. Ruhle KH, Criscuolo D, Dieterich HA, et al. Objective evaluation of dextromethorphan and glaucine as antitussive agents. Br J Clin Pharmacol. 1984;17(5):521-4. PMID: 6375709.
113. Sabot G, Bagnato A, Frigerio G. Controlled evaluation of the antitussive activity of viminol p-hydroxybenzoate. Int J Clin Pharmacol Biopharm. 1977;15(4):181-3. PMID: 323163.
114. Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. Clin Pharmacol Ther. 1971;12(3):449-55. PMID: 4936034.
115. Simon SW. A comparative study of two new non-narcotic antitussive drugs. Ohio Med. 1957;53(12):1426-7. PMID: 13493953.
116. Simon SW. Symptomatic treatment of asthmatic bronchitis. J Am Geriatr Soc. 1960;8:107-11. PMID: 14446944.
117. Tanaka S, Hirata K, Kurihara N, et al. Effect of loratadine, an H1 antihistamine, on induced cough in non-asthmatic patients with chronic cough. Thorax. 1996;51(8):810-4. PMID: 8795669.
118. Vakil BJ, Mehta AJ, Prajapat KD. Trial of pipazethate as an antitussive. Clin Pharmacol Ther. 1966;7(4):515-9. PMID: 5328471.
119. van Asperen PP, McKay KO, Mellis CM, et al. A multicentre randomized placebo-controlled double-blind study on the efficacy of Ketotifen in infants with chronic cough or wheeze. J Paediatr Child Health. 1992;28(6):442-6. PMID: 1466940.
120. van Hengstum M, Festen J, Beurskens C, et al. The effect of positive expiratory pressure versus forced expiration technique on tracheobronchial clearance in chronic bronchitics. Scand J Gastroenterol Suppl. 1988;143:114-8. PMID: 3291088.
121. Vertigan AE, Theodoros DG, Gibson PG, et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065-9. PMID: 16844725.
122. Wei W, Yu L, Wang Y, et al. Efficacy and safety of modified sequential three-step empirical therapy for chronic cough. Respirology. 2010;15(5):830-6. PMID: 20546197.
123. Wojcicki J, Samochowiec L, Szwed G, et al. The use of Duopect as expectorant–antitussive agent. Arch Immunol Ther Exp (Warsz). 1975;23(1):135-42. PMID: 1090275.
124. Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010;65(12):1107-10. PMID: 20965928.
125. Kuehn BM. Withdrawal of infant cold medicines decreases ED visits by half, CDC finds. JAMA. 2010;304(24):2686. PMID: 21177501.
126. Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):238S-49S. PMID: 16428717.
127. Leconte S, Ferrant D, Dory V, et al. Validated methods of cough assessment: a systematic review of the literature. Respiration. 2011;81(2):161-74. PMID: 21079381.
128. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):250S-9S. PMID: 16428718.
129. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics. 1997;99(6):918-20. PMID: 9190557.
130. U.S. Food and Drug Administration. Public Health Advisory: FDA Recommends that Over-the-Counter (OTC) Cough and Cold Products not be used for Infants and Children under 2 Years of Age. Date of release 1/2008. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051137.htm. Accessed April 23, 2012.
131. Chang AB. Therapy for cough: where does it fall short? Expert Review of Respiratory Medicine. 2011;5(4):503-13. PMID: 21859270.
132. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF.

Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. :

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