Assessing Cough Severity and Efficacy of Therapy in Clinical Research

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To review the literature on identifying cough and to make evidence-based recommendations for assessing the efficacy of cough-modifying agents in clinical research.


Results/conclusions: To optimally evaluate the efficacy of cough-modifying agents, investigators should use both subjective and objective methods, because they have the potential to measure different things. A patient’s subjective response is likely the only one that measures the impact of the intensity of cough. With respect to subjective methods, it is recommended that a cough-specific health-related quality-of-life instrument be utilized because valid and reliable instruments exist. Even though visual analog scales have not been psychometrically tested, they are recommended because they are commonly used and valid, and they are likely to yield different but complementary results. Because there are cough-specific health-related quality-of-life instruments that have been fully psychometrically tested, and the same cannot be said for visual analog scales, this is a reason to use cough-specific health-related quality-of-life instruments as the primary, subjective outcome measure of choice. With respect to objective methods, tussigenic challenges can be used before and after the intervention to assess the effect of therapy on cough sensitivity. They are most likely to be helpful in disease states in which cough reflex sensitivity is known to be heightened. Because the act of coughing has the potential to traumatize the upper airway (e.g., vocal cords), assessing the presence of upper airway edema before and after therapy with flow-volume loops may be useful. Investigators must be cautious and not assume that observing changes suggestive of inflammation and edema of upper airway structures is specific for any particular disease. Cough counting is recommended with a computerized methodology that is reliable and accurate, noninvasive and portable, and easy to use in unattended, ambulatory real-life settings within a subject’s home environment when it can be done over a 24-h period of time.

Key words: assessing airway inflammation; assessing the efficacy of cough treatments; assessing the impact of cough; capsaicin challenge; citric acid challenge; character and timing of cough; cough counting; cough quality-of-life questionnaire; cough scoring systems; cough-specific health-related quality-of-life instruments; dentifying cough; exhaled nitric oxide; flow-volume loops; health-related quality-of-life instruments; Leicester cough questionnaire; lipid-laden macrophages in sputum; sickness impact profile; tussigenic challenges; visual analog scales

Abbreviations: BCSS = breathlessness, cough, and sputum scale; CQLQ = cough quality-of-life questionnaire; LCQ = Leicester cough questionnaire

From a historical perspective, a great deal has been learned about the diagnosis and treatment of cough over the past 30 years.¹ In order for further advances to take place, it will be important for patients to be evaluated with valid and reliable methods by which to objectively identify cough,

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Assessing the Characteristics of Cough

Cough can be easily recognized because of its distinctive sound. By listening to taped recordings of healthy subjects, it has been determined that cough is uncommon, but occurs more often during colder than warmer months, during wakefulness compared with sleep, and in men compared to women. While men have been heard to cough more during these monitoring sessions, these findings cannot be explained by the results of tussigenic challenges. Tussigenic challenges have revealed that healthy women and women with chronic cough have lower cough thresholds than healthy men and men with chronic cough. The tendency for cough to be provoked may be reduced by advancing age. Although gender differences are apparent in baseline cough reflex sensitivity, there do not appear to be ethnic differences among healthy white, Indian, or Chinese subjects. The absence of nocturnal coughing should not be used to suggest the presence of psychogenic cough or cough caused by gastroesophageal reflux disease, because cough caused by a variety of diseases such as chronic bronchitis and gastroesophageal reflux disease is unlikely to occur once patients fall asleep. Because the periodicity of cough can vary throughout the day, cough counting for fixed, short intervals is likely to be a poor reflection of a 24-h total.

While cough can be caused by a variety of different disorders originating from a multiplicity of anatomic locations, neither the character of the cough (eg, wet, dry, paroxysmal, barking, and honking) nor the timing of cough (eg, nocturnal, and with or without meals) is helpful in predicting its cause. Because an increased sensitivity of the afferent limb of the cough reflex during an inhaled tussigenic challenge with capsaicin has been observed with nonproductive coughs caused by asthma, gastroesophageal reflux disease, viral upper respiratory tract infections, and angiotensin-converting enzyme inhibitors, capsaicin cough challenges in these diseases may be helpful in assessing the response to drug treatments. However, these challenges are not likely to be helpful in other upper respiratory tract conditions with unproductive coughs or in productive coughs caused by bronchiectasis, because the cough reflex sensitivity to capsaicin does not appear to be increased in patients with these conditions. On the other hand, cough reflex sensitivity appears to be increased in patients with COPD when assessed by citric acid cough challenges, and inconsistently increased when assessed by inhaled capsaicin challenges. It is not clear why this dissociation exists in response to different tussigenic stimuli; perhaps, it is related to such methodological issues as the instability of the tussigenic solution that is used or the specific agent provoking cough by means of different pathways. Despite the fact that cough challenges have been carried out for > 50 years, standardized and uniformly accepted normal values for the cough response to specific tussive agents have yet to be established, and methodologies utilized by different investigators have often been difficult to compare. To allow for greater accuracy and comparability of tussigenic challenges and their role in the diagnosis and treatment of cough in the future, standardization guidelines for tussigenic challenges will need to be established.

Intermittent coughing can create bursts of elevations in manometrically obtained intrathoracic or intrabdominal pressures; however, observing these bursts does not prove that they are caused by coughing, because they also can be caused by any event that transiently increases these parameters. For instance, other involuntary reflexes or acts, such as sneezing, retching, and hiccupping, or passing flatus or throat clearing also can cause these bursts.

Assessing the Effects of Drug Treatment on Cough

The effects of drug treatments on cough can be assessed by subject or by objective methods. Subjective methods have included patient diaries, visual analog scales, a variety of investigator-conceived cough-scoring systems, symptom scales (eg,
the breathlessness, cough, and sputum scale (BCSS))\textsuperscript{24} for specific diseases such as COPD that are not focused solely on cough but on other symptoms as well, general health-related quality-of-life instruments (eg, sickness impact profile)\textsuperscript{25} and cough-specific health-related quality-of-life instruments (eg, cough quality-of-life questionnaire [CQLQ],\textsuperscript{26} and Leicester cough questionnaire [LCQ]).\textsuperscript{27}) Although all of these subjective instruments appear to have been useful in the studies cited, only the BCSS, CQLQ, and LCQ have undergone extensive psychometric testing. They have been found to be valid and reliable. While a disease-specific symptom questionnaire for gastroesophageal reflux disease has been found to be reproducible, valid, and responsive to change, and it assesses cough, it was developed primarily to evaluate GI symptoms.\textsuperscript{28}

The BCSS, which was designed as part of a daily diary, assesses the severity of the following three symptoms of COPD: breathlessness; cough; and sputum. Patients are asked to evaluate each symptom on a 5-point Likert-type scale ranging from 0 to 4, with higher scores indicating a more severe manifestation of the symptom. The CQLQ is a self-administered, 28-item questionnaire that is scored on a 4-point Likert-type scale, with higher scores indicating a more adverse effect of cough on health-related quality of life. It has been tested in patients with acute and chronic coughs. The LCQ is a self-administered, 19-item questionnaire that is scored on a 7-point Likert-type scale with a higher score indicating better health status. To date, the performances of the CQLQ and LCQ have not been compared. Only the CQLQ has compared the scores of patients complaining of acute and chronic cough with those of a control group not complaining of cough.

The major limitation of patient diaries is that their utility is more dependent on patient motivation than the other methods. Patient diaries require subjects to be highly motivated and constantly vigilant while awake, and a surrogate with the same attributes fill out the diary while the subject sleeps. While visual analog scales have been utilized in a variety of studies with a variety of anchoring descriptors, neither diaries nor visual analog scales have been rigorously tested for validity or reliability.

Objective methods for assessing cough include measuring cough frequency with or without the use of a variety of pharmacologic tussigenic agents\textsuperscript{20} by counting either the sound of cough or acoustical patterns consistent with cough in real time\textsuperscript{29–31} or from tape recordings,\textsuperscript{9,13,32,33} or counting events that are consistent with coughing using esophageal\textsuperscript{34,35} or rectal pressure monitoring,\textsuperscript{36} abdominal electromyographic recordings with surface electrodes,\textsuperscript{37} or simultaneous recordings of acoustic and bed movement measurements.\textsuperscript{38} Other objective methods that can be used before and after intervention include comparing flow-volume loops to assess the reversibility of extrathoracic variable upper airway obstruction caused from the trauma of coughing\textsuperscript{21,39} comparing the volume and consistency of spontaneously expectorated sputum,\textsuperscript{40} comparing indexes of airway inflammation in induced sputum samples,\textsuperscript{41,42} and comparing exhaled nitric oxide levels.\textsuperscript{43}

With respect to the utility of objective methods for assessing cough, capsaicin and citric acid appear to be the two best agents for provoking cough in humans. However, their tussigenic effects often do not correlate with each other. Therefore, the use of these agents in the study of pathologic cough should be tailored to the specific spectrum of diseases in which each agent has been shown to provoke cough. Studies performed to date show that capsaicin and citric acid are not universally useful in provoking cough across a wide spectrum of diseases. In healthy subjects, capsaicin is the better agent, because it has fewer side effects, more reliably provokes cough, and generates the most reproducible dose-response curves.\textsuperscript{44,45} In addition, stability studies on stored solutions exist for capsaicin alone.\textsuperscript{18} These data show that solutions of capsaicin at higher concentrations (2 to 128 \textmu mol/L) remain stable over 6 months when stored in the dark at 4°C, that lower concentrations stored under identical conditions break down, and that solutions stored at room temperature, regardless of light protection, degrade within 6 months.

For cough counting to be most useful, it should be performed continuously at least during waking hours and preferably for 24 hours. Counting by observer with or without compressing data is labor-intensive and/or constrains the experimental design (eg, having to place a rectal probe, using a special bed with strain gauges, or using a soundproof room). A computerized methodology that is reliable and accurate, non-invasive and portable, and easy to use in unattended, ambulatory real-life settings within a subject’s home environment would be ideal. While a study published in 2001\textsuperscript{46} has suggested that such a device is available, the study does not provide the testing characteristics of the cough detection method that relates to the sensitivity and specificity of the detection algorithm to distinguish cough from other sounds.

The results of two prospective studies\textsuperscript{21,39} show that flow-volume loops may be useful in assessing the effect of coughing on the extrathoracic airways in patients with acute and chronic coughs. The first study\textsuperscript{39} was a before-and-after intervention trial in patients with chronic cough caused by a variety of
upper airway cough syndromes, which were previously referred to as *postnasal drip syndromes*. The second study,21 was a randomized, double-blind, placebo-controlled trial in patients with acute cough caused by the common cold. Although coughs were caused by upper airway cough syndromes in both studies, the most likely explanation for the reversible, extrathoracic, variable upper airway obstructions was vocal cord edema caused by the act of coughing itself, rather than the postnasal discharge or throat clearing.21 It was postulated that vocal cord edema probably developed from the trauma of the violent undulations of the laryngeal structures during coughing when intrathoracic air, under pressures of as much as 300 mm Hg, passed the vocal cords at velocities approaching 500 miles per hour during the expiratory phase of coughing.21 It remains to be determined whether reversible upper airway obstruction will also be present in coughs caused by diseases other than upper airway cough syndromes.

Studies that assess volume and consistency of expectorated sputum are unlikely to be consistently reliable for a variety of reasons not related to the drug being studied, such as the patients swallowing more or less mucus, or producing more or less saliva during the study period.25 Studies that assess airway inflammation in induced sputum41,42 appear promising for assessing antiinflammatory therapy. If airway inflammation is to be assessed, only those methods that have been rigorously tested, validated, and shown to be reproducible should be used. While considering these methods, investigators should appreciate that performing and interpreting these standardized methods is time-consuming and require special expertise. Utilizing the method of Pizzichini et al,42 it has been possible to distinguish eosinophilic neutrophilic inflammation. While chronic cough in subjects with induced sputum eosinophilia improved with inhaled budesonide therapy, chronic cough did not improve with inhaled budesonide therapy in subjects with mild neutrophilia without an increase in sputum eosinophilia. Because indices of airway inflammation in induced sputum samples have not been systematically assessed in a wide spectrum of diseases causing chronic cough, the sensitivity, specificity, and positive and negative predictive values of cell and fluid phase markers in determining the causes of cough are not known. Efforts are underway47,48 to standardize the methods and interpretation of induced sputum sample analyses and to better define their clinical role. Likewise, the accurate interpretation of finding increased numbers of lipid-laden macrophages in induced sputum samples will require additional studies. Even though an increased number of lipid-laden macrophages in induced sputum samples predicted that oropharyngeal reflux had occurred by dual-channel 24-h esophageal pH monitoring, it was not determined that these same patients actually aspirated.

Relevant to this discussion regarding cough, the subjects of the study were not coughing; they either reported GI complaints that were consistent with gastroesophageal reflux disease or had mild asthma.28 Because exhaled nitric oxide can be a marker of airway inflammation in patients with asthma, its measurement may be of potential benefit in diagnosing the cause of chronic cough.47,49 Preliminary studies43,50 to date have not shown exhaled nitric oxide measurements to be particularly helpful. In a cross-sectional study50 of patients with nonasthmatic cough or mildly symptomatic asthma associated with symptomatic gastroesophageal reflux disease, there was no evidence of worsening airway inflammation as measured by levels of exhaled nitric oxide.

The Optimal Methods of Evaluating the Efficacy of Cough-Modifying Agents

To optimally evaluate the efficacy of cough-modifying agents, investigators should use both subjective and objective methods, because they have the potential to measure different things. A patient's subjective response is likely the only one that measures the impact of the intensity of cough. While it is likely to be very important, the concept of cough intensity and how to directly measure it have received very little attention in the literature to date. With respect to subjective methods, it is recommended that a cough-specific health-related quality-of-life instrument be utilized because valid and reliable instruments exist.26,27 Even though visual analog scales have not been psychometrically tested, they are recommended because they are commonly used and valid, and they are likely to yield different but complementary results to the cough-specific health-related quality-of-life instruments. For instance, while a visual analog scale assesses severity only, a health-related quality-of-life instrument can assess how cough severity impacts a patient’s health-related quality of life in multiple domains. Because there are cough-specific health-related quality-of-life instruments that have been fully psychometrically tested, and because the same cannot be said for visual analog scales, this is a reason to use cough-specific health-related quality-of-life instruments as the primary subjective outcome measure of choice.

With respect to objective methods, tussigenic challenges can be used before and after the intervention to assess the effect of therapy on cough sensitivity. They are most likely to be helpful in disease states in which cough reflex sensitivity is...
known to be heightened. Because the act of coughing has the potential to traumatize the upper airway (eg, vocal cords), assessing the presence of upper airway edema before and after therapy with flow-volume loops may be useful. Investigators must be cautious and not assume that observing changes suggestive of inflammation and edema of upper airway structures is specific for any particular disease. Cough counting is recommended with a computerized methodology that is reliable and accurate, noninvasive and portable, and easy to use in unattended, ambulatory real-life settings within a subject’s home environment when it can be done over a 24-h period of time.

**SUMMARY OF RECOMMENDATIONS**

1. In patients with chronic cough, to optimally evaluate the efficacy of cough-modifying agents, investigators should use both subjective and objective methods because they have the potential to measure different things. A patient’s subjective response is likely to be the only one that measures the impact of the intensity of cough. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough, with respect to subjective methods, it is recommended that a valid and reliable cough-specific, health-related, quality-of-life instrument be utilized. Level of evidence, fair; benefit, substantial; grade of recommendation, A

3. When assessing patients with chronic cough, even though visual analog scales have not been psychometrically tested, they are recommended because they are commonly used and valid, and they are likely to yield different but complementary results to cough-specific, health-related, quality-of-life instruments. Level of evidence, low; benefit, intermediate; grade of recommendation, C

4. When assessing patients with chronic cough, because health-related quality-of-life instruments have been psychometrically tested and visual analog scales have not, the cough-specific, health-related, quality-of-life instruments are recommended as the primary subjective outcome measure. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

5. In patients with chronic cough, with respect to objective methods, tussigenic challenges should be used before and after the intervention to assess the effect of therapy on cough sensitivity only in disease states in which cough reflex sensitivity is known to be heightened. Level of evidence, low; benefit, small/weak; grade of recommendation, C

6. In patients with chronic cough, because the act of coughing has the potential to traumatize the upper airway (eg, the vocal cords), assessing the presence of upper airway edema before and after therapy with flow-volume loops is useful. Level of evidence, low; benefit, intermediate; grade of recommendation, C

7. In patients undergoing treatment for chronic cough, cough counting over 24 h is recommended with a computerized methodology that is reliable and accurate, noninvasive and portable, and easy to use in unattended, ambulatory, real-life settings within a patient’s home environment. Level of evidence, low; benefit, intermediate; grade of recommendation, C

**REFERENCES**


34 Sharpey-Schafer E. Effects of coughing on intrathoracic pressure, arterial pressure and peripheral blood flow. J Physiol 1953; 122:351–357