Controversies in the Evaluation and Management of Chronic Cough

Surinder S. Birring

Chronic cough that cannot be explained after basic evaluation is a common reason for patients to be referred to respiratory outpatient clinics. Asthma, gastroesophageal reflux, and upper airway disorders frequently coexist with chronic cough. There is some controversy as to whether these conditions are causes or aggravants of cough. Heightened cough reflex sensitivity is an important feature in most patients. There is good evidence that it is reversible when associated with upper respiratory tract infection, angiotensin-converting enzyme inhibitor medications, and chronic cough associated with eosinophilic airway inflammation. In many patients, heightened cough reflex sensitivity is persistent and their cough is unexplained. There are few therapeutic options for patients with unexplained chronic cough. There is a pressing need to understand the genetic, molecular, and physiological basis of unexplained chronic cough and to develop novel antitussive drugs that down-regulate cough reflex sensitivity.

Keywords: chronic cough; cough hypersensitivity; asthma; postnasal drip; gastroesophageal reflux

Over the past 40 years much has been learned about how to evaluate and treat chronic cough, but it is clear that there is much further to go. In 1977, a systematic diagnostic approach was proposed that encouraged evaluation of the sites of the sensory limb of the cough reflex (1). Subsequent studies reported that extrapulmonary conditions such as upper airway diseases and gastroesophageal reflux disease (GERD) can cause cough. This led to the introduction of the anatomic diagnostic paradigm, which focuses on identifying the causes of cough (2) (Table 1). Although many investigators have used the paradigm with a high success rate, there are a significant number who have not. Success rates as low as 58% have been reported and the reasons for this are unclear (3). There is, however, agreement among clinicians that some patients with chronic cough do not respond to therapy despite extensive evaluation. This has led some investigators to suggest that a new approach to chronic cough is necessary (4). This article reviews the controversies in the evaluation of chronic cough in adults, highlights concerns about the current approach to cough, and suggests that therapy and future research need more focus on important mechanisms such as cough reflex hypersensitivity.

GASTROESOPHAGEAL REFLUX–ASSOCIATED CHRONIC COUGH

The evaluation of GER is one of the key components of the diagnostic pathway. Cough guidelines recommend an initial trial of therapy rather than invasive investigations to identify GER cough (5). Proton pump inhibitors (PPIs) are the most widely used therapy; if medical therapy fails, further investigation may result in antireflux surgery being recommended. A Cochrane review meta-analysis, however, concluded that the effect of antireflux therapy such as PPIs for chronic cough was inconsistent and of uncertain magnitude (6). A number of other observations have also led clinicians to question the importance of GER in chronic cough.

Are Tests for GER Necessary?

The diagnosis of GER cough on the basis of the presence of symptoms of GER is problematic because symptoms can vary and are not always present. Furthermore, GER can coexist in patients with cough due to other conditions. Ideally, objective demonstration of a temporal association between GER and cough should be sought. Endoscopy and barium esophagography are limited by their inability to detect the temporal relationship between episodes of GER and cough. Furthermore, endoscopy is often not helpful because the presence of esophagitis is uncommon in patients with chronic cough (7). Esophageal pH monitoring has been the most studied of all tests. A significant limitation of esophageal pH monitoring is its poor predictive value in determining the response to therapy for GER. In a study from Patterson and colleagues, only 28% of patients with a chronic cough and positive esophageal pH monitoring test had a long-term response to proton pump inhibitor therapy (8). Esophageal manometry is often combined with pH monitoring to detect episodes of cough objectively. Studies have led to caution in the interpretation of cough frequency data from esophageal manometry because it is significantly lower than that measured with sound-based cough monitors (9). This is thought to be due to an inhibitory effect of the esophageal probe on cough and the insensitivity of manometry for detecting cough, particularly low-intensity coughs. Nonacid (or weakly acid) GER has been recognized as a potential cause of GERD. It can constitute gas, liquid, solids, or a combination of these. The symptoms of acid and nonacid GER overlap, and therefore objective tests are necessary for detection. The advent of esophageal impedance monitoring has allowed assessment of nonacid GER, although it is in its infancy and not widely used at present. The limitations of this technique are that it is considerably more expensive than standard esophageal pH monitoring and that its usefulness in establishing a diagnosis of GER cough and ability to predict response to therapy have not been established; this deserves further study. At present, the routine use of objective investigations of GER cannot be recommended.
Are Proton Pump Inhibitors Effective in Chronic Cough?

Several randomized controlled trials of PPIs in chronic cough have not confirmed the success of earlier uncontrolled studies (6). In the largest study, Fathi and colleagues randomized 56 patients with chronic cough to receive esomeprazole 20 mg twice daily or placebo for 2 months (10). The change in cough-related quality of life, the primary outcome measure, was not significantly different between groups but PPIs were effective in relieving gastrointestinal symptoms of GER, as expected. The lack of clinical benefit with PPIs is not limited to patients with chronic cough; it is also seen in other airway conditions such as asthma, in which symptoms of GER are also common (11). There are limitations to these studies. First, objective outcome parameters such as cough frequency monitoring were not used and it is possible that a treatment effect was not detected. Second, it is possible that many patients with GER cough are treated in primary care and not referred to specialist clinics, leading to recruitment bias in clinical trials. Third, these studies were underpowered. Further trials are needed. These should be large, multicenter, randomized, placebo controlled, inclusive of patients in primary care, and utilize both objective and subjective cough severity outcome parameters. They should also assess the temporal relationship between GER and cough with esophageal pH/impedance monitoring to determine the selection criteria of patients suitable for therapy and not be limited to PPIs. Therefore, until further data are available, a trial of PPI should still be recommended (5).

Is Nonacid GER Important in Cough?

The fact that not all GER is acidic and that some patients have a poor response to acid suppression has focused attention on esophageal dysmotility and nonacid GER. Esophageal dysmotility is a common finding in patients with chronic cough, although its relevance to the pathogenesis is not known (12). It has been suggested that cough and esophageal dysmotility may represent a generalized abnormality of neural aerodigestive reflexes because of their coexistence. Decalmer and colleagues investigated the importance of nonacid GER with esophageal impedance studies in a large group of patients with chronic cough and compared them with healthy subjects (13). They found no difference in the number of acid or nonacid GER episodes between the groups. The temporal association between episodes of nonacid GER and cough has also been studied. Blondeau and colleagues have developed a statistical index of temporal association called the symptom association probability (SAP), obtained from esophageal impedance recordings (14). In their study, a positive SAP was found in only a small proportion (5%) of patients with chronic cough and cough itself caused episodes of GER. Smith and colleagues also provide important insights into the association between GER and cough (15). In contrast to Blondeau and colleagues, they found a positive symptom association for GER preceding cough within a 2-minute time interval in a much higher proportion of patients (48%), and the reasons for this are unclear (15). Only 44% of all coughs in patients with a positive symptom association followed episodes of GER. Furthermore, a significant number of patients (56%) had episodes of GER after cough. This suggests that factors other than GER are also important in patients with cough associated with GER and that anti-GER therapy alone may not lead to resolution of cough. The most appropriate time interval between episodes of GER and cough used to establish a causal association is not known. Episodes of GER and cough are more likely to be causally linked if this time interval is shorter, and hence there is a need for standardization (15). It is not known whether the SAP is predictive of response to therapy; this clearly needs further investigation in controlled studies before esophageal impedance monitoring can be recommended in the diagnostic algorithm for patients with cough. The therapeutic options for nonacid GER are largely dietary modifications, prokinetic drug therapy, and antireflux surgery in selected patients. No study has evaluated the relative roles of these therapies.

Is There a Role for Antireflux Surgery in the Management of Chronic Cough?

Current guidelines recommend surgery such as Nissen’s fundoplication for selected patients with cough and persistent GER despite optimal medical therapy (16). In practice, the use of surgical treatment for GER cough is highly variable. A number of case series of small numbers of patients report good success rates with surgery but controlled trials, objective cough outcome data, and long-term follow-up are lacking (5). Nissen’s fundoplication is not without risks; severe dysphagia, flatulence, inability to belch, and increased bowel symptoms are the most frequently reported complications. Furthermore, the number of fundoplications performed in the United States for GER is steadily declining because of lower than anticipated successful outcomes and patient dissatisfaction (17). Controlled studies of surgical therapy for GER cough are urgently needed. A placebo intervention is ethically and technically difficult to achieve but may be possible with endoscopic therapies in future. The clinical trials of bronchial thermoplasty for severe asthma highlight the importance of including a sham group when assessing an interventional procedure (18). The author’s view is that there are insufficient data to support the recommendation for antireflux surgery for patients with chronic cough.

Does Laryngopharyngeal Reflux Cause Cough?

Laryngopharyngeal reflux (LPR), the reflux of gastric contents into the laryngopharynx, is widely considered by otolaryngologists as a common cause of chronic cough. It can be associated with frequent throat clearing, hoarse voice, and globus (19). LPR cough has yet to gain widespread recognition among pulmonologists because there is significant overlap in the phenotype of patients diagnosed with GER cough and LPR cough. There are no pathognomonic symptoms, signs, or endoscopic findings of LPR. The diagnosis is usually based on laryngoscopic findings of erythema, edema, and thickening of the posterior pharynx that can potentially be indistinguishable from the trauma from coughing itself (20). PPIs are recommended for LPR cough, based on limited evidence (21). Further studies are needed to establish the importance of LPR in patients referred with chronic cough. This needs to include the demonstration of a temporal relationship between LPR and cough with pharyngeal impedance monitoring and randomized controlled trials of PPIs and other therapies.
UPPER AIRWAYS COUGH SYNDROME

Upper airways cough syndrome (UACS), also referred to as postnasal drip syndrome or rhinosinusitis cough, is associated with a wide range of upper airway symptoms. Allergic, infectious, and vasomotor etiologies are most common. More recently, chronic tonsillar enlargement and obstructive sleep apnea have been described in association with chronic cough (22–24). The assessment of UACS is limited by the lack of a diagnostic test; a trial of therapy is usually the first line of investigation. Nasendoscopy may confirm the presence of upper airway inflammation, but there is no evidence to suggest its routine use in cough without suggestive symptoms. Computed tomographic imaging of the sinuses has a poor positive predictive value in establishing a diagnosis of UACS and hence is not routinely recommended (16). The therapy for UACS is determined by the nature of the upper airway pathology. Nasal corticosteroids and first-generation sedating antihistamines are widely used.

UACS: Cause or Aggravant of Cough?

A number of observations have led some pulmonologists and otolaryngologists to question the importance of postnasal drip in the causation of chronic cough. Postnasal drip is a common symptom in the general population and is not always associated with cough. However, this observation alone is not sufficient to dismiss UACS as a cause of chronic cough because it may affect only susceptible patients, as seen with angiotensin-converting enzyme (ACE) inhibitor drugs. There are no unique features in history, examination, or investigations that identify UACS as a cause of cough. The paucity of randomized controlled trials of therapy for UACS is perhaps the most striking omission; addressing this will go a long way to establishing whether there is a causal link. Until then, patients with cough and upper airway symptoms should undergo a trial of nasal corticosteroids and/or antihistamines.

Silent Postnasal Drip or Unexplained Chronic Cough?

Silent postnasal drip is a term reserved for patients with chronic cough who do not complain of symptoms of rhinosinusitis but respond to upper airway–specific therapy (16). The prevalence of silent postnasal drip varies from no reported cases to significant numbers between cough clinics. This may be due to differences in diagnostic labeling or failure to use the correct medications. The diagnosis of silent postnasal drip is often based on the improvement in cough with a first-generation antihistamine such as dexbrompheniramine (16). Dexbrompheniramine is available in the United States but is not easily available in the United Kingdom and parts of Europe. The improvement in cough with antihistamines may, however, be due to its action on the central and peripheral cough reflex rather than an effect on rhinosinusitis and some investigators therefore prefer to call this condition “unexplained chronic cough” (25, 26). Although a randomized controlled trial in patients with acute cough and postnasal drip caused by upper respiratory tract infection reported a reduction in cough severity with dexbrompheniramine when used in combination with pseudoephedrine, there have been no controlled trials conducted in patients with chronic cough (27). A randomized controlled trial of dexbrompheniramine in chronic cough patients with and without upper airway symptoms is needed to determine its effectiveness. Until these data are available, a short-term trial of antihistamine is still recommended.

COUGH VARIANT ASTHMA

There is general consensus that asthma is an important cause of cough. The controversies relate largely to its evaluation. There are numerous diagnostic tests and effective therapeutic options available, in contrast to GER and UACS.

Which Diagnostic Test?

A diagnostic test for cough variant asthma should have high sensitivity and specificity, predict response to therapy, and be safe and affordable. Peak flow rate monitoring and bronchodilator responsiveness testing are widely used but are limited by their poor diagnostic sensitivity and specificity (28). Although bronchoprovocation challenge tests have high negative predictive value, positive predictive value is poor (29). The assessment of airway inflammation by induced sputum eosinophil cell count analysis and exhaled nitric oxide measurement offers high sensitivity and specificity and is predictive of response to corticosteroid therapy (28, 30). They also have the potential to guide titration of corticosteroid therapy (31). Exhaled nitric oxide measurement has the greatest promise; it is easy to measure and portable, and the cost has fallen considerably. Induced sputum assessment is limited by the labor costs of sputum induction, processing, and analysis but some institutions have demonstrated that a favorable cost–benefit profile is possible (31). Larger studies investigating the diagnostic accuracy and clinical usefulness of exhaled nitric oxide tests compared with induced sputum and bronchoprovocation tests are needed to determine which test is optimal for the investigation of cough variant asthma. Indirect airway challenge tests, such as mannitol, can potentially assess cough reflex sensitivity in addition to airway reactivity in a single study; this deserves further investigation (32).

Limitations of Diagnostic Trials of Inhaled Corticosteroids?

Trials of inhaled corticosteroids are widely used to establish a diagnosis of cough variant asthma. The limitation of trials of therapy is that, when patients fail to respond, it is not clear whether this is due to inadequate therapy for asthma or whether the cough is due to another cause. A significant number of patients with cough variant asthma fail to respond to an initial trial of inhaled corticosteroids, and this may be due to inadequate dose and duration of therapy, poor inhaler technique and compliance, the presence of small airway inflammation, neutrophilic airway inflammation, the need for systemic therapy, and inhaler-induced cough (33). The assessment of airway inflammation can be used to identify patients who are likely to respond to corticosteroids. The presence of eosinophilic airway inflammation should prompt the physician to explore reasons for treatment failure and initiate a further trial or intensify treatment. A short-term diagnostic trial of oral corticosteroids may be an alternative option.

Should Bronchodilator Therapy Be Used?

Inhaled bronchodilator therapy is recommended in combination with inhaled corticosteroids for the treatment of cough variant asthma (16). The evidence for the use of bronchodilators is limited. In one study, inhaled metaproterenol was compared with placebo in a randomized trial of nine patients with cough variant asthma (29). There was a greater reduction in cough severity scores with metaproterenol compared with placebo, but this was not confirmed by objective cough frequency measurement. The reduction in cough scores was not due to an amelioration of airflow hyperresponsiveness. Importantly, this study demonstrated that the mere presence of airway hyperresponsiveness by itself in chronic cough was a poor predictor of a diagnosis of asthma and cough was independent of bronchoconstriction. Further studies have found that bronchodilators are ineffective in acute cough and unexplained chronic cough in children (34, 35). A large randomized controlled trial of bronchodilator
therapy is needed to assess their role in chronic cough; this may be better achieved with long-acting bronchodilators.

**Eosinophilic Bronchitis/Atopic Cough**

Eosinophilic bronchitis (EB) is a relatively common cause of chronic cough and accounts for up to 15% of cases (36). EB can coexist with other airway diseases such as chronic obstructive pulmonary disease, occupational lung disease, and bronchiectasis (37). It is characterized by eosinophilic airway inflammation and in contrast to asthma, there is an absence of airway hyperresponsiveness. The latter is due to the absence of airway smooth muscle mast cell inflammation (38). Inhaled corticosteroids are the first-line therapy and effective. EB is seldom recognized outside specialist clinics and this may relate to the unavailability of diagnostic tests. EB is diagnosed by demonstrating eosinophilic airway inflammation with induced sputum cell analysis or exhaled nitric oxide measurement and the exclusion of airway hyperresponsiveness. If measures of airway inflammation are not available, a corticosteroid-responsive cough in a patient with a negative bronchoprovocation test is likely to be caused by EB. When both air inflammation and reactivity testing are not available, the distinction between asthma and EB is not always possible in a patient with a corticosteroid-responsive cough. It is unclear whether this distinction has clinical implications, but this needs investigation in longitudinal studies. It is perhaps more important to emphasize that a trial of corticosteroids is essential in patients with chronic cough to rule out asthma and EB. Long-term therapy for EB may be necessary because of persistent symptoms, risk of progression to asthma, and the development of fixed airflow obstruction (39).

Atopic cough (AC) is a cause of chronic cough reported almost exclusively in Japan (40). The reason for this is unclear but is thought to relate to environmental factors. AC is characterized by the presence of an atopic phenotype and/or sputum eosinophilia in the absence of airway hyperresponsiveness. The diagnosis is based on the presence of atopy (skin test/IgE) or induced sputum eosinophilia, cough reflex hypersensitivity, exclusion of airway hyperresponsiveness, and a negative trial of bronchodilator therapy (41). A simplified diagnostic criterion has been proposed that recommends a trial of therapy with an antihistamine or corticosteroid for atopic patients with a chronic cough without wheezing (41). There is considerable overlap in the diagnostic criteria for AC with EB. One of the differences is that bronchoalveolar eosinophilic inflammation is less common in AC and progression to asthma is rare (41).

**UNEXPLAINED CHRONIC COUGH: DISTINCT CONDITION OR INADEQUATE THERAPY FOR EXPLAINED COUGH?**

The cause of cough may not be identified because of a number of reasons including inadequate assessment, poor compliance with therapy, and ineffective therapy (42). However, many clinics report a high prevalence of unexplained chronic cough (UCC) after detailed investigations and treatment trials (3, 20, 43). Moreover, patients with UCC have some unique clinical characteristics that suggest their cough differs from explained cough (43).

**Clinical Characteristics**

There is no consensus concerning the best term by which to identify patients whose cough is unexplained after comprehensive investigations and treatment trials. The term idiopathic chronic cough is often used, but it may inhibit physicians from assessing patients thoroughly. Cough hypersensitivity syndrome has also been proposed to identify this group of patients and emphasizes that unexplained chronic cough is a condition involving an abnormality of the cough reflex (44, 45). The terms sensory neuropathic cough, laryngeal sensory neuropathy, sensory hyperreactivity, and vagal neuropathy-associated cough are used by otolaryngologists and it is likely that there is considerable overlap among patients with UCC. It is preferable that there be a consensus in terminology when describing these patients. Most of the current terms suggested hypersensitivity of the cough reflex, and this deserves further consideration.

The prevalence of UCC varies between clinics and has been reported to be as high as 42% of cases (3). Patients with UCC tend to be female, middle-aged, and have an onset of cough around menopause, but this also true of patients with explained chronic cough, although to a lesser extent (43, 46). Viral illness at onset of cough and association with airway infections with Bordetella pertussis and basidiomycetous fungi have been reported in patients with UCC (3, 47, 48). Patients with UCC have high levels of anxiety and symptoms of depression (49). This is thought to be a consequence of long-standing cough and its impact on health status; an improvement in psychological health status with therapy for cough supports this. Psychogenic cough is an extremely rare diagnosis in adults.

**Pathogenesis**

Patients with UCC have a strikingly increased sensitivity to cough challenge with capsaicin, which suggests an abnormality of the airway sensory nerves because capsaicin is a potent activator of unmyelinated C fibers (50). The importance of enhanced airway sensory nerve sensitivity in the pathogenesis of UCC is also supported by an increased density of sensory nerve fibers in the airways. An increase in neuromodulator content in the airways of patients with UCC has been reported (51). There is also increased expression of airway receptors that potentially mediate cough, such as the transient receptor potential vanilloid-1 (TRPV-1) ion channel present on C fibers (52). Furthermore, both CGBP nerve density and TRPV-1 receptor expression are related to the degree of capsaicin cough reflex sensitivity. The hypersensitivity of airway nerves may not be limited to just those involved in cough; enhanced sensitivity of the laryngeal glottic closure reflex and the high prevalence of vocal cord dysfunction and voice disorders in UCC raise the possibility of a generalized disorder of airways nerves (50, 53).

Airway inflammation may also be important in the pathogenesis of UCC. A number of inflammatory mediators such as histamine, prostaglandin E2, and cysteinyl-leukotrienes are elevated in the airways of patients with UCC and many are known to activate the cough reflex (54, 55). There is also an increased number of inflammatory cells in the airways; neutrophilia and lymphocytosis have been reported (43, 56, 57). Airway lymphocytosis has been associated with the presence of organ-specific autoimmune disease in UCC (43, 56). One study reported that the prevalence of autoimmune disease, particularly thyroid disease, was eight times higher in patients with UCC compared with control subjects (46). The prevalence of autoantibodies was also higher in UCC. Airway lymphocytosis is thought to result from the homing of inflammatory cells from primary sites of autoimmune inflammation to the airways (58, 59). The onset of cough around menopause is thought to be due to altered lung CD4+ T-lymphocyte immunity occurring after menopause (57). It is not known whether inflammation leads to airway remodeling in UCC. Airway structural changes such as goblet cell hyperplasia have been reported, but it is not clear whether they are related to the pathogenesis or are a consequence of cough (51, 60). Most research to date has focused on the activation of sensory nerves that leads to a reflex cough; future studies also need to identify the stimuli that sensitize the cough reflex.
Treatment

The therapeutic options for patients with UCC are limited. Opiates such as morphine sulfate can suppress cough but are associated with significant side effects such as sedation, and there is the risk of dependence (61). Their mechanism of action is likely to be central (61). Novel antitussive drugs with a peripheral site of action that down-regulate cough hypersensitivity are needed. Open label studies of drugs acting on peripheral nerves used to treat neuropathic pain, such as amitryptiline and gabapentin, have been reported to reduce cough severity but this needs further investigation in controlled trials (62). Antagonists to the TRPV-1 ion channel have been developed and need evaluation in clinical trials. A number of other molecular targets have been identified for antitussive drug development that can potentially down-regulate cough hypersensitivity; these include selective cannabinoid agonists (CB2 agonists), maxi-K channel openers, P2X3 antagonists, and p38 mitogen-activated protein (MAP) kinase inhibitors (63). There are nonpharmacological therapeutic options available for patients with UCC. A speech and language therapy program that included cough suppression, vocal hygiene maneuvers, and strategies that reduce vocal cord dysfunction was effective at reducing cough severity in a randomized controlled trial (53). Up to two-thirds of patients with UCC have identifiable triggers of cough (64). Cough physiotherapy that focuses on trigger avoidance and voluntary cough suppression is another promising therapy and deserves further evaluation (65). A long-term follow-up study of patients with UCC found that cough persisted in most patients but was reduced in severity in more than 50% of subjects (66). Patients with UCC had an increased decline in FEV₁ (63 ml/yr) and 13% developed airflow obstruction. The only independent predictor of FEV₁ decline was cough reflex sensitivity.

Limitations of the current approach to chronic cough

The emphasis of current guidelines is on the evaluation of conditions that coexist with chronic cough, such as GER, UACS, and asthma (16). However, the exact role of coexisting conditions in the pathogenesis of cough is unclear. There are several possibilities: (I) they cause cough reflex hypersensitivity; (2) they are triggers or aggravants of cough in patients with preexisting cough reflex hypersensitivity; (3) they, along with cough, are a manifestation of a generalized disorder of the upper aerodigestive tract; and (4) they are unrelated to the pathogenesis of cough. The evidence for treating coexisting conditions to reduce cough severity is not robust, as it consists largely of uncontrolled studies (16). The lack of control groups in clinical trials is a concern because significant placebo responses are common (4). The poor success rates in treating cough by some investigators have led them to propose that coexisting conditions are aggravants rather than the cause and that a new approach is needed to encourage further research and development in this field (4). The cause and pathogenesis of cough need to be investigated to move forward.

Cough reflex hypersensitivity is an important feature of chronic cough (50, 63). Future research should focus on understanding the sensitization of the cough reflex and the mechanisms involved in cough. A better understanding of the airway sensory nerves and their signaling pathways will potentially lead to the identification of novel therapies.

The new cough paradigm: cough reflex hypersensitivity

The cough reflex has an important role in airway protection and clearance of secretions. Most patients with unexplained chronic cough have an abnormally sensitive cough reflex. The sensitivity of the cough reflex can be assessed by measuring the cough response to a variety of airway irritants such as capsaicin, citric acid, and fog (67). The sensory receptors that mediate cough in humans are not fully understood, but members of the transient receptor potential (TRP) ion channel family are strong candidates (68). They are expressed on sensory neurons and are activated by temperature, osmolarity, stretch, and many nociceptive stimuli. Commonly reported triggers of cough such as scents, odors, cold air, food, speech, and laughter are likely to activate this pathway. Cough receptors are thought to be most concentrated in the laryngopharynx but are also expressed in the lower airways. There is evidence of increased expression of TRPV-1 on the airway nerves of patients with unexplained chronic cough (52).

A heightened cough reflex is an important feature of chronic cough irrespective of the diagnosis (50). Cough reflex sensitivity is more heightened in females than males and this may be why chronic cough is more prevalent in females (50). Cough reflex sensitivity is reported to be stable in most patients, and therefore variations in the number and intensity of coughs may be due to environmental triggers such as air pollution (69). Cough reflex hypersensitivity is also seen in healthy subjects; this is analogous to other airway reflexes such as bronchial hyperreactivity (50). For this reason, the positive predictive value of cough reflex testing for a diagnosis of cough hypersensitivity is likely to be low. The negative predictive value is not known but is likely to be good and may be of clinical value.

Heightened cough reflex sensitivity can be considered reversible or persistent in patients with chronic cough, in whom the cough is typically dry or minimally productive (Figure 1). It is absent in pulmonary conditions associated with a productive cough such as chronic obstructive pulmonary disease and bronchiectasis (70). The role of heightened cough reflex sensitivity in the pathogenesis of cough has been most studied in patients with angiotensin-converting enzyme inhibitor (ACE-I)–associated chronic cough. Approximately 10% of patients taking ACE-Is develop a chronic cough (71). The reason why only some patients develop cough is unclear. ACE-Is heighten cough reflex sensitivity by increasing substance P, bradykinin, and prostaglandin concentrations in airway secretions (71). The withdrawal of ACE-I usually leads to a reduction in cough severity and cough reflex sensitivity. ACE-I cough can also be managed with antiinflammatory drugs such as sodium cromoglycate and salindac (71). The reintroduction of ACE-I usually leads to recurrence of cough. A reversible cough reflex sensitivity is not unique to ACE-I–associated cough; it is also seen in patients with upper respiratory tract infection, cough variant asthma, and eosinophilic bronchitis (72) (Figure 1). It is not clear whether these conditions cause cough by increasing cough reflex sensitivity or trigger cough in a sensitized individual. In patients with GER or UACS, the evidence for a reduction in cough reflex hypersensitivity with specific therapy is not robust because this has not been evaluated in controlled trials. Cough and heightened cough reflex sensitivity can persist despite optimal management of coexisting conditions such as that in patients with UCC. Research into persistent cough hypersensitivity needs to be an area of priority.

Assessment of cough severity

One of the important challenges in chronic cough is to conduct large randomized controlled trials to address areas of controversy in clinical practice. The key to conducting a high-quality trial is to use validated cough severity outcome tools. Subjective tools such as cough visual analog scales, scores, and diaries are widely used (73) (Figure 2). The appreciation of the profound physical,
psychological, and social impact of cough has led to increasing use of health-related quality of life measures. Three validated, self-completed, cough-specific quality of life questionnaires are available: the Cough-specific Quality of Life Questionnaire (CQLQ), the Leicester Cough Questionnaire (LCQ), and the Chronic Cough Impact Questionnaire (CCIQ) (74–76). The LCQ and CQLQ have been used successfully in clinical trials evaluating antitussive therapy (61, 74, 75, 77).

The importance of developing objective measures of cough severity has been highlighted in the European Respiratory Society guidelines on the assessment of cough (67). Cough reflex sensitivity measurement is the most widely used objective test. Its limitations are that it is relatively time-consuming and it may not detect the effect of therapy if antitussive therapy is acting on a different cough reflex pathway (50). Advances in digital sound recording devices and improved battery life have led to the development of several cough frequency monitors that can record for 24 hours (78–80). Most represent work in progress. The goal is to automate cough counting by developing customized software, but this has been challenging because of difficulty in discriminating cough sounds from speech and other noise. Studies, however, report promising results; it has been possible to achieve a sensitivity and specificity for cough detection greater than 90% with some automated monitors (78). More than 80% of cough occurs during awake hours, and therefore a considerably shorter duration of cough monitoring may be sufficient to assess the efficacy of therapy. It is likely that cough intensity is also an important determinant of cough severity in some patients. Further studies are needed to investigate whether automated measures of cough intensity can be derived from sound-based cough monitors. Although the optimal assessment of cough severity is not known, it is likely that a combination of subjective and objective assessments will be necessary. It is essential that future clinical trials of antitussive drugs use well-validated cough severity assessment tools.

**CONCLUSIONS**

Unexplained chronic cough should be considered a disorder rather than just a symptom. Cough reflex hypersensitivity is a feature of most patients with unexplained chronic cough. The cause or aggravant of cough should be treated in patients with reversible cough hypersensitivity. Cough hypersensitivity is persistent in some patients, for whom there are few therapeutic options. There is a pressing need to develop antitussive drugs that down-regulate cough reflex sensitivity. This will be achieved by investment in research and development that leads to a better understanding of the genetic, molecular, and physiological basis of cough. Future trials of therapy for cough should be designed as randomized controlled trials and incorporate validated subjective and objective outcome parameters. There are clearly many challenges ahead for clinicians, researchers, and the pharmaceutical industry involved in the care of patients with cough as attempts are made to explain what is so far unexplained. However, there have been substantial improvements, giving us new tools and understanding. This should be a focus to go forward.
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