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REVIEW

Cough: an unmet clinical need

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Cough is among the most common complaints for which patients worldwide seek medical attention. Thus, the evaluation and treatment of cough result in tremendous financial expenditure and consumption of health care resources. Yet, despite the clinical significance of cough, research efforts aimed at improving diagnostic capabilities and developing more effective therapeutic agents have been, to date, disappointing in their limited scope and outcomes. Acute cough due to the common cold represents the most common type of cough. Currently, available medications for the symptomatic management of acute cough are inadequate due to lack of proven efficacy and/or their association with undesirable or intolerable side effects at anti-tussive doses. Subacute cough, often representing a prolonged post-viral response, is typically refractory to standard anti-tussive therapy. Few clinical trials have evaluated therapeutic options for subacute cough. Diagnostic challenges facing the clinician in the management of chronic cough include the determination of whether symptoms of upper airway cough syndrome (formerly, postnasal drip syndrome) or gastro-oesophageal reflux disease are indeed the underlying cause of cough. Chronic, refractory unexplained (formerly, idiopathic) cough must be distinguished from cough that has not been fully evaluated and treated according to current guideline recommendations. Eagerly awaited are new safe and effective anti-tussive agents for use when cough suppression is desired, regardless of underlying aetiology of cough, as well as practical, validated ambulatory cough counters to aid clinical assessment and future research in the field of cough.

LINKED ARTICLES

This article is part of a themed issue on Respiratory Pharmacology. To view the other articles in this issue visit <http://dx.doi.org/10.1111/bph.2011.163.issue-1>

Abbreviations

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVA, cough-variant asthma; FeNO, exhaled nitric oxide; GERD, gastro-oesophageal reflux disease; LPR, laryngopharyngeal reflux; LTRA, leukotriene receptor antagonist; OTC, over the counter; PNDS, postnasal drip syndrome; QOL, quality of life; SAP, symptom association probability; TLESR, transient lower oesophageal sphincter relaxation; TRPV1, transient receptor potential vanilloid-1; UACS, upper airway cough syndrome; URI, acute viral upper respiratory tract infection

Introduction

Cough is among the most common symptoms for which patients seek medical attention (Cherry *et al.*, 2008). Hence, the assessment and treatment of cough necessitates enormous financial expenditure. For example, annual amounts spent solely on non-prescription, over-the-counter (OTC) remedies for the self-treatment of cough and cold symptoms are estimated at \$3.6 billion in the United States (The Nielsen

Company, 2007) and over £100 million in the United Kingdom (Proprietary Association of Great Britain, 2005). The perceived importance of cough as a clinical problem worldwide is evidenced by the fact that recently, no less than five major pulmonary societies have published guidelines on the diagnosis and management of cough: the European Respiratory Society (Morice *et al.*, 2004), the American College of Chest Physicians (Irwin *et al.*, 2006), the British Thoracic Society (Morice *et al.*, 2006), the Japanese Respiratory Society

(Kohno *et al.*, 2006) and the German Respiratory Society (Kardos *et al.*, 2010). Yet, despite the availability of numerous published guideline documents, physicians, especially subspecialists, remain challenged with a significant percentage of patients whose cough remains unimproved, or only partially treated, despite adherence to recommended protocols (Pavord and Chung, 2008). Among the shortcomings of all published cough management guidelines is the dearth of evidence from adequately performed, randomized, controlled trials to support that proposed therapeutic interventions will indeed address the underlying aetiology of a patient's cough and thus ameliorate or eliminate the symptom. Thus, in the setting of cough refractory to standard therapy, a physician is left uncertain as to whether: the correct aetiology of cough has not yet been discerned; a correct diagnosis has been established and recommended treatment has been administered, yet the patient's cough persists; or, the patient has unexplained cough, a term proposed in the American College of Chest Physicians cough guidelines (Irwin *et al.*, 2006) to describe a cough that persists despite a thorough diagnostic evaluation, specific and appropriate therapeutic trials aimed at potential causes of cough, and exclusion of uncommon causes.

The goal of the present review is to identify and discuss current diagnostic and therapeutic challenges facing the clinician treating patients with cough. The discussion will consider cough in terms of its duration (acute cough <3 weeks; subacute cough 3–8 weeks; chronic cough >8 weeks) as is generally accepted and proposed in current cough management guidelines (Morice *et al.*, 2004; Irwin *et al.*, 2006). Focus on the duration of cough is appropriate, as it aids in generating a differential diagnosis (Table 1).

Table 1

Major causes of cough*

Acute
Acute viral upper respiratory tract infection (common cold)
Subacute
Post-viral
Bordetella pertussis (whooping cough)
Chronic cough not yet of 8-weeks duration
Chronic
Upper airway cough syndrome (postnasal drip syndrome)
Eosinophilic airway inflammation
Asthma
Non-asthmatic eosinophilic bronchitis
Gastro-oesophageal reflux diseases
Laryngopharyngeal reflux
Angiotensin converting-enzyme inhibitors
Occupational/Environmental
Unexplained

*In adult non-smokers without history of chronic lung disease.

Acute cough

Acute cough is an extremely common condition, most often due to acute viral upper respiratory tract infection (URI; common cold). Cough due to URI is usually transient and self-limited. However, if cough is bothersome and disruptive to the patient, symptomatic treatment is appropriate. Unfortunately, therapeutic options for cough suppression are extremely limited. In the United States, only three non-prescription (over-the-counter; OTC) agents are approved as anti-tussives: (i) chlorpheniramine, a medication available for purchase only through the Internet from a limited number of suppliers, and about which no research has been published since the early 1960s; (ii) diphenhydramine, a first-generation sedating antihistamine; and (iii) dextromethorphan (FDA, 1987, 1994). Animal studies in various species (Eddy *et al.*, 1969; Bolser *et al.*, 1993; Kotzer *et al.*, 2000; McLeod *et al.*, 2010) and studies of induced cough in humans (Bickerman *et al.*, 1957; Karttunen *et al.*, 1987; Grattan *et al.*, 1995; Ramsay *et al.*, 2008) have clearly demonstrated the anti-tussive effect of dextromethorphan. Recently, controversy has arisen because of the dearth of adequately performed clinical trials demonstrating the efficacy of dextromethorphan in acute cough due to URI (Bolser, 2006; Dicpinigaitis *et al.*, 2009). Similarly, a paucity of data exists for the efficacy of prescription cough products. The widely used narcotic anti-tussive, codeine, has not been shown to be efficacious against acute cough due to the common cold in prospective, blinded, controlled trials (Eccles *et al.*, 1992; Freestone and Eccles, 1997). When narcotics do provide symptomatic relief at recommended doses, they often do so at the expense of undesirable side effects such as sedation and gastrointestinal discomfort. Recently, the anti-cholinergic agent tiotropium has been shown to inhibit induced cough in subjects with acute URI (Dicpinigaitis *et al.*, 2008), but the clinical significance of this observation awaits elucidation in prospective clinical trials.

Thus, a significant need exists for safe, effective anti-tussives that can suppress acute cough without undesirable or intolerable side effects. Unfortunately, it will be difficult to demonstrate the efficacy of a potential new agent for acute cough due to URI, for the same reasons that data on currently available medications are scant: (i) because cough associated with the common cold is typically transient and self-limited, very large and hence, expensive trials would be necessary to provide adequate power to detect a clinically relevant effect; (ii) the large placebo effect observed in most trials of anti-tussives (Eccles, 2010); and (iii) the lack of well-validated, commercially available technology for objective cough counting (Smith and Woodcock, 2008).

Subacute cough

Subacute cough refers to a cough of 3–8-week duration (Morice *et al.*, 2004; Irwin *et al.*, 2006). Most cases of subacute cough likely represent a post-viral cough that has extended beyond 3 weeks. Post-viral cough may be particularly refractory to treatment. Based on limited trial data and anecdotal experience/expert opinion, recommended therapies include

inhaled ipratropium, inhaled corticosteroids, short courses of oral corticosteroids (for severe paroxysms), codeine and dextromethorphan (Braman, 2006). Prospective, randomized controlled trials of therapeutic agents aimed at post-viral cough are lacking.

Cough due to *Bordetella pertussis* (whooping cough) typically lasts for 4–6 weeks but can persist for months. Usually, by the time severe cough occurs, the effective treatment window for the underlying pathogen has passed. Symptomatic therapy with inhaled long-acting β -agonists, antihistamines, corticosteroids and pertussis Ig have not been shown to be helpful for the paroxysmal cough (Braman, 2006). Symptoms classically associated with pertussis, i.e. post-tussive emesis and an inspiratory whooping sound, are not strong predictors of the presence of *B. pertussis* infection (Cornia *et al.*, 2010). Recent evidence from animal experiments suggests that the severe, paroxysmal cough of pertussis may be mediated by the inflammatory peptide bradykinin (Hewitt and Canning, 2010).

Some patients presenting with subacute cough will progress to a diagnosis of chronic cough once the duration of cough reaches 8 weeks. The differential diagnosis of chronic cough is discussed below.

Chronic cough

Upper airway cough syndrome (UACS; post-nasal drip syndrome)

The American College of Chest Physicians 2006 guidelines adopted the term upper airway cough syndrome or UACS to replace the term post-nasal drip syndrome, as it was felt that the new terminology more effectively addressed the possibility that cough could be due, not only to the post-nasal drip itself, but to irritation or inflammation of upper airway structures that directly stimulate cough receptors independent of, or in addition to, post-nasal drip (Irwin *et al.*, 2006). More recently, the concept of a ‘unified airway’ has been proposed based on epidemiological and physiological data suggesting that the upper and lower airways may be linked through local inflammatory processes. The model suggests that systemic propagation of inflammation occurs through trafficking of inflammatory mediators, thus promoting a system-wide response in the respiratory mucosa through which pathology in one portion of this system can stimulate and influence pathophysiological changes at a site distal to the initial site of inflammation (Krouse and Altman, 2010). Consistent with this hypothesis, recent studies incorporating induced cough in humans have demonstrated enhancement of cough reflex sensitivity in the presence of rhinosinusitis (Tatar *et al.*, 2009).

UACS can result from a multiplicity of rhinosinus conditions (Table 2), and has been considered the most common cause of chronic cough in adults in the United States (Pratter, 2006a). Treatment for UACS-induced cough should be targeted at the underlying aetiology, and is often effective. However, when UACS is due to acute viral upper respiratory tract infection, or, is being treated empirically as the first step in a diagnostic-therapeutic algorithm for chronic cough of unclear aetiology, the combination of a first-generation anti-

Table 2

Potential causes of upper airway cough syndrome*

Allergic rhinitis
Perennial non-allergic rhinitis
Vasomotor rhinitis
Nonallergic rhinitis with eosinophilia (NARES)
Post-infectious rhinitis
Following upper respiratory tract infection
Bacterial sinusitis
Allergic fungal sinusitis
Rhinitis due to anatomic abnormalities
Rhinitis due to physical or chemical irritants
Occupational rhinitis
Rhinitis medicamentosa
Rhinitis of pregnancy

*Adapted from Pratter (2006a).

histamine and decongestant is recommended (Irwin *et al.*, 2006). A complicating factor in interpreting a response to this form of therapy, and thus assigning a diagnosis to the patient, is the possibility that symptomatic relief is achieved not through amelioration of post-nasal drip, but by a primary anti-tussive effect of the antihistamine. Indeed, diphenhydramine has been demonstrated to inhibit citric acid-induced cough in healthy volunteers (Packman *et al.*, 1991), while more recently, dexbrompheniramine has been shown to inhibit activation of the transient receptor potential vanilloid-1 (TRPV1) ion channel in human TRPV1-expressing human embryonic kidney (HEK) cells and rat dorsal root ganglia neuron preparations (Sadofsky *et al.*, 2008). TRPV1 has received significant attention recently as a particularly relevant receptor in human cough, and thus represents a compelling target for the development of potential new anti-tussive agents (Adcock, 2009).

Eosinophilic airway inflammation (asthma and non-asthmatic eosinophilic bronchitis)

Multiple prospective studies have shown that asthma is among the most common aetiologies of chronic cough (24–29%) in adult non-smokers (Irwin *et al.*, 1990; Pratter *et al.*, 1993; McGarvey *et al.*, 1998). Usually, cough is accompanied by the typical features of dyspnoea and wheezing, but may represent the sole or predominant symptom in the setting of an unremarkable physical examination and normal pulmonary function studies. Such a presentation describes a subgroup of asthmatics termed to have cough-variant asthma, or CVA (Dicipinigaitis, 2006a).

Asthmatic cough typically responds to standard asthma therapy of inhaled bronchodilators and inhaled corticosteroids. The leukotriene receptor antagonists (LTRA) zafirlukast (Dicipinigaitis *et al.*, 2002) and montelukast (Spector and Tan, 2004; Kita *et al.*, 2010) have been shown to be particularly effective in CVA, and should be added to a regimen of inhaled corticosteroids before escalation to therapy with systemic

corticosteroids (Dicpinigaitis, 2006a). Given a paucity of data on the natural history of CVA, it remains unclear whether monotherapy with LTRAs is sufficient to prevent the sequelae of chronic airway inflammation as are seen in the typical form of asthma.

Non-asthmatic eosinophilic bronchitis distinguishes itself from asthma by the absence of reversible airway obstruction and bronchial hyperresponsiveness, but the associated cough, as in asthma, is usually quite responsive to inhaled corticosteroid therapy (Brightling, 2010). Clinical response has been correlated with decreases in sputum eosinophil count and cough reflex sensitivity, thus supporting a causal relationship between cough and eosinophilic airway inflammation (Brightling, 2010). Only rarely is systemic treatment with oral corticosteroids required. The efficacy of LTRAs in chronic cough due to non-asthmatic eosinophilic bronchitis has not been investigated. Furthermore, the natural history of non-asthmatic eosinophilic bronchitis is yet to be elucidated fully. Preliminary long-term (>1 year) follow-up data from 32 patients suggest that although a minority (16%) of patients develop fixed airflow obstruction, the condition is rarely self-limiting; 66% of patients had persistent symptoms and/or ongoing airway inflammation (Berry *et al.*, 2005).

Recently, exhaled nitric oxide has been proposed as a useful biomarker to confirm the presence of eosinophilic airway inflammation and thus, predict a favourable response to inhaled corticosteroid therapy in both asthmatic cough as well as cough due to non-asthmatic eosinophilic bronchitis (Lim, 2010). Absence of a response to systemic corticosteroids should prompt evaluation for other aetiologies of chronic cough.

Gastro-oesophageal reflux disease (GERD)

Perhaps the greatest challenges to the clinician evaluating a patient with chronic cough are the confirmation of the presence of gastro-oesophageal reflux and, more importantly, the determination that reflux, if present, is responsible for the cough (Table 3). Indeed, the diagnosis of GERD, including the use of empiric therapeutic trials with proton pump inhibitor medications (PPIs), remains problematic, even in the setting of typical reflux symptoms (Lacy *et al.*, 2010). The response rate to PPI therapy in patients in whom cough is the sole or predominant symptom is even less (Chang *et al.*, 2006; Pauwels *et al.*, 2009).

Potential mechanisms proposed to explain GERD-induced cough include: (i) refluxate within the oesophagus triggering a distal oesophageal-tracheobronchial reflex; (ii) refluxate extending beyond the oesophagus into the larynx (laryngopharyngeal reflux; LPR) where sensory afferent cough receptors reside; and (iii) microaspiration (Figure 1). Furthermore, it has recently been appreciated that cough may be induced by non-acidic or weakly acidic refluxate, thus explaining why some patients whose cough was refractory to aggressive acid suppression experienced resolution of cough subsequent to anti-reflux surgery (laparoscopic Nissen fundoplication) (Irwin *et al.*, 2002).

Recently, the diagnostic evaluation of the patient with unexplained cough has been improved by the increased availability of combined oesophageal pH-impedance monitoring that allows detection of both acid (pH > 4) and non-acid reflux events (Tokayer, 2008). Initial studies dem-

Table 3

Challenges in the management of cough due to gastro-oesophageal reflux disease (GERD)

Diagnosis

Poor sensitivity and specificity of empiric therapeutic trials with proton pump inhibitor medications (PPIs)

Standard diagnostic studies for acid reflux, such as 24-hour oesophageal pH measurement, may fall within normal range of number of reflux events, even when reflux is the cause of chronic cough.

Treatment

Aggressive acid suppression therapy may be inadequate due to the presence of non-acid or weakly-acid refluxate as the cause of cough.

When aggressive acid suppression therapy fails, and reflux remains the suspected aetiology of chronic cough, addition of a prokinetic agent is appropriate. However, the available therapeutic options are severely limited.

In the setting of failure of maximal medical therapy, surgical intervention (laparoscopic Nissen fundoplication) may be considered. However, data on the outcome of surgical intervention for chronic cough due to GERD are limited, and do not demonstrate a uniformly positive outcome.

onstrate that this modality significantly enhances the diagnostic yield for detecting gastro-oesophageal reflux in patients with atypical GERD symptoms, and has been proposed as the new diagnostic gold standard (Bajbouj *et al.*, 2007; Kahrilas, 2010; Lee *et al.*, 2010). Interestingly, multiple studies incorporating this technology to evaluate chronic cough sufferers have not demonstrated an increased number of reflux events compared with data from healthy volunteers, but proposed a causal relationship based on observed temporal associations between reflux events and cough (Smith *et al.*, 2010a). Though most recent studies incorporating these newest diagnostic methods have demonstrated intra-oesophageal reflux as being most relevant (Smith *et al.*, 2010a), other investigators have suggested a prominent role for laryngopharyngeal reflux in patients with chronic cough (Patterson *et al.*, 2009).

A recent study combining simultaneous acoustic cough recording with pH-impedance monitoring, in addition to cough reflex sensitivity measurement, in a group of unselected patients with chronic cough has shed further light on the association of reflux and cough (Smith *et al.*, 2010b). Subjects in this study demonstrated a symptom association probability (SAP) of cough preceded by reflux, as well as reflux preceded by cough. This observation supports the concept that not only may reflux induce cough, but cough may cause or exacerbate reflux, through mechanisms including increased intra-thoracic pressure, thus generating a self-perpetuating process of cough stimulation. Notably, SAP-positive subjects did not have a greater degree of oesophageal acid exposure or degree of erosive disease compared with SAP-negative subjects, but they did have enhanced cough reflex sensitivity, thus suggesting a

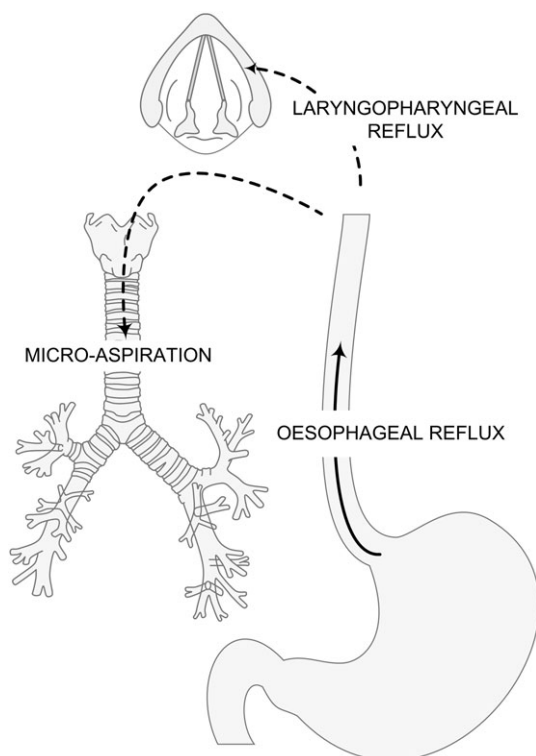


Figure 1

Potential mechanisms linking gastro-oesophageal reflux events and cough (reprinted with permission from Smith *et al.*, 2010a).

mechanism of sensitization at the level of sensory afferents in the oesophagus and/or central sensitization at the level of the brainstem.

For patients with chronic cough in whom GERD is confirmed or suspected, acid suppressive therapy is indicated, and can be escalated to an aggressive regimen of a twice-daily PPI, taken one-half hour before breakfast and dinner, with or without a histamine-2 antagonist (i.e. ranitidine 150 mg) at bedtime. Recently, liquid alginate suspensions have been evaluated as alternate or complementary therapy for symptoms of LPR. The alginate is believed to form a physical barrier floating above the gastric contents, thus inhibiting backflow of refluxate into the oesophagus (McGlashan *et al.*, 2009). In addition to pharmacological therapy, anti-reflux lifestyle measures should be stressed: sleep with head elevated, do not eat within 2 h of bedtime, and avoid reflux-promoting foods and beverages including alcohol, caffeine, chocolate, peppermint, and spicy or greasy foods (Irwin, 2006).

If cough persists despite strict adherence to the above-described regimen for 2–3 months, and reflux remains the presumed aetiology, then empiric addition of a prokinetic agent is appropriate. Unfortunately, the clinician's options in this regard are extremely limited (Merati, 2010). One prospective study demonstrated the ability of a prokinetic agent (cisapride or metoclopramide) to reduce or eliminate cough in subjects whose cough did not respond to PPI therapy alone (Poe and Kallay, 2003). Cisapride was removed from the United States market in 2000 due to its association with QT interval prolongation and ventricular arrhythmias (Layton

et al., 2003). Other available prokinetic agents include bethanechol, a muscarinic agonist that must be avoided in asthmatics, and erythromycin, the use of which raises concern of numerous drug interactions, cardiac arrhythmias and emergence of resistant bacteria (Berthet *et al.*, 2010). Furthermore, neither bethanechol nor erythromycin has ever been specifically evaluated in cough associated with GERD.

Hence, physicians in the United States and elsewhere are essentially left with metoclopramide to treat reflux-induced cough refractory to PPI therapy, but this agent is often associated with sedation and other undesirable effects and has been implicated as a cause of tardive dyskinesia after prolonged use (Rao and Camilleri, 2010). Domperidone, a dopaminergic antagonist like metoclopramide, has been used as a prokinetic outside the United States. Published data for the efficacy of this drug in reflux-induced cough are also lacking. Furthermore, domperidone has been associated with serious ventricular arrhythmias and sudden cardiac death (Johannes *et al.*, 2010). Thus, the lack of safe and effective prokinetic agents for physicians to use in the setting of presumed reflux-induced cough refractory to acid suppression therapy represents a significant unmet clinical need.

An area of current investigation that may yield therapeutic options beyond that of acid suppression involves the γ -aminobutyric acid type B (GABA-B) receptor agonists. Transient lower oesophageal sphincter relaxation (TLESR) promotes the occurrence of gastro-oesophageal reflux. The GABA-B agonist baclofen has been shown to inhibit TLESR, and reduces the number of reflux episodes in subjects with GERD, reduces GERD symptoms in one study of chronic administration and increases basal lower oesophageal sphincter pressure in healthy volunteers and subjects with GERD (Kuo and Holloway, 2010). In addition, baclofen has been shown to be an anti-tussive agent independent of its effect on reflux by inhibiting capsaicin-induced cough in healthy volunteers (Dicipinigaitis and Dobkin, 1997). Despite such compelling evidence, baclofen has not gained widespread use because of undesirable side effects including sedation, dizziness, headache and confusion. Hence, newer GABA-B agonists with more specific peripheral activity and less central effects are currently the subject of active research (Kuo and Holloway, 2010).

When maximal medical therapy has failed to alleviate reflux-induced cough, surgical intervention may be considered. Data on outcomes of surgical fundoplication are still limited, and results to date confirm that a satisfactory outcome is not guaranteed. In one retrospective study of long-term (median 53 months) outcomes of laparoscopic anti-reflux surgery, atypical GERD symptoms including cough were reported to have improved in 65–75% of 128 patients. Of note, 33% of these post-operative patients were receiving daily antacid therapy at the time of interview (Kaufman *et al.*, 2006). Another retrospective study evaluated 51 patients, out of a total of 240 who underwent surgical fundoplication, with predominantly extra-oesophageal symptoms of GERD. The 40 patients available for analysis (at a mean of 53.3 months post-surgery) were asked to grade their overall quality of life (QOL); 25% reported QOL as excellent, 32.5% as good, 32.5% as satisfactory and 10% reported overall QOL as bad (Iqbal *et al.*, 2009). One prospective study describing a community hospital experience with

laparoscopic Nissen fundoplication found, as in other studies, greater improvement in typical rather than atypical GERD symptoms after long-term follow up (mean 24.6 months) of 84 patients. Comparison of pre- and post-operative symptom scores demonstrated a 58% improvement in cough. In the study group as a whole, 74% reported significant atypical GERD symptoms preoperatively; only 7% reported exclusively atypical symptoms (Ranson *et al.*, 2007). Thus, further guidance is awaited from prospective trials of anti-reflux surgery in patients with refractory, GERD-induced chronic cough to assist the physician and patient in the difficult decision of whether to pursue a surgical option. Of particular significance from future studies would be the identification of specific characteristics predictive of a successful outcome after surgery.

Angiotensin-converting enzyme (ACE) inhibitors

Chronic cough is a well-described class effect of the ACE inhibitor medications. The incidence of ACE inhibitor-induced cough has been reported to be in the range of 5–35%, and occurs more often in women, non-smokers and persons of Chinese origin (Dicpinigaitis, 2006b). Cough occurs more commonly in patients receiving ACE inhibitor therapy for congestive heart failure than in those receiving these drugs for treatment of hypertension (Bangalore *et al.*, 2010). Cough may occur within hours of the first dose of medication, or its onset may be delayed for weeks to months after the initiation of therapy. Although numerous small studies have shown various drugs to be partially effective, the only uniformly successful intervention for ACE inhibitor-induced cough is cessation of the offending agent. Cough usually resolves within 1 week of discontinuation of the ACE inhibitor. However, in a subgroup of patients, a month or more may be required for resolution of cough. In a patient with chronic cough of unknown aetiology, ACE inhibitor therapy must be discontinued regardless of the temporal relation between the onset of cough and the initiation of the ACE inhibitor. If cough resolves after cessation of therapy with an ACE inhibitor, and a compelling reason remains for treatment with this drug class, a repeat trial of ACE inhibitor therapy may be attempted. Studies have shown that the occurrence of cough with angiotensin-receptor blockers is similar to that of the non-ACE-inhibitor drugs against which they were compared (Dicpinigaitis, 2006b).

Occupational/environmental

In the evaluation of a patient with chronic cough, most physicians will appropriately seek to eliminate potential exogenous causative agents such as primary inhaled cigarette smoke and ACE inhibitor medications. In addition, a thorough history must be performed to identify other potentially relevant factors in the environment or workplace that could be causing or enhancing chronic cough. Epidemiological studies have demonstrated that environmental exposure to particulate matter, irritant gases, second-hand tobacco smoke, mixed pollutants and moulds is associated with increased cough (Joad *et al.*, 2007). Furthermore, chronic cough is among the most prevalent work-related airway disorders, as documented in, for example, coal miners, hard-

rock miners, tunnel workers and concrete manufacturing workers (Groneberg *et al.*, 2006). In addition, some individuals appear to experience irritation and cough after exposure to non-toxic amounts of common substances such as perfumes, pesticides, paint and automobile exhaust, among many others (Brooks, 2010). This group presents a particular challenge in terms of discerning the underlying cause(s) of chronic cough.

Unexplained cough

In their 2006 cough management guidelines, the American College of Chest Physicians adopted the term *unexplained cough* to replace the previously used term *idiopathic cough*, as it was felt that the term *unexplained cough* better describes a condition that is likely due to multiple underlying aetiologies rather than a single entity (Pratter, 2006b). The challenge facing the clinician is to ascertain that a complete and thorough evaluation has been performed, including diagnostic-therapeutic trials with appropriate medications at adequate doses and for sufficient duration, before a diagnosis of unexplained cough is conferred. Nevertheless, there appears to exist a group of patients with genuine unexplained cough, and recent investigations have allowed the description of a particular phenotype of such individuals. Patients with apparent true unexplained chronic cough are often middle-aged (perimenopausal) women with prolonged dry cough and demonstrable cough reflex hypersensitivity (McGarvey, 2008). Additional studies have shown that such patients tend to have airway inflammation characterized by increased numbers of mast cells (McGarvey *et al.*, 1999) and lymphocytes (Birring *et al.*, 2003), and an increased incidence of organ-specific autoimmune disorders (Birring *et al.*, 2004). Interestingly, the recently proposed entity of post-viral vagal neuropathy, in which chronic cough associated with laryngeal symptoms such as throat clearing follow an URI, appears to affect predominantly women in their fifth decade of life (Rees *et al.*, 2009; Greene and Simpson, 2010).

Recently, the Cough Hypersensitivity Syndrome has been proposed to explain why a subgroup of individuals with common conditions such as rhinitis, asthma and GERD develop chronic, refractory cough, whereas the majority of the population with the same underlying conditions does not (Morice, 2010). At present, satisfactory therapeutic agents to manage chronic, unexplained cough are lacking. New safe and effective anti-tussive medications, as well as pharmacological agents aimed at the hypersensitized cough reflex likely underlying this condition, are eagerly awaited.

Non-pharmacological therapy of cough

The clinician must be cognizant of the fact that non-pharmacological therapeutic strategies may be vital to the successful treatment of cough. As discussed above, elimination of exogenous factors potentially causing or exacerbating cough is essential. These include cigarette smoking, ACE inhibitors, and potential environmental as well as occupational triggers. For cough due to GERD, anti-reflux lifestyle measures are an essential component of a multifaceted

treatment approach. Recent evidence supports an important role for speech language pathology management in the treatment of chronic cough refractory to medical therapy (Gibson and Vertigan, 2009; Ryan *et al.*, 2010).

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Conflict of interest

I have no conflicts of interest related to this manuscript.

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