

## Chronic Cough 2

### Management of chronic cough

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Cough that remains unexplained after basic clinical assessment is a common reason for referral to secondary care. Much of the evidence about management of isolated chronic cough is derived from case series; this evidence suggests that isolated chronic cough is usually due to asthma, gastro-oesophageal reflux disease, and upper airway conditions, and that it can be cured in most people by treatment of these conditions. However, there is increasing recognition that satisfactory control of chronic cough is not achieved in a substantial number of patients seen in secondary care. Moreover, there is a concern that perpetuation of the belief that chronic cough is solely due to the effects of comorbid conditions is inhibiting research into the pathophysiology of an abnormally heightened cough reflex, and jeopardising development of improved treatments. We advocate a change in emphasis, which makes a clear distinction between cough due to corticosteroid-responsive eosinophilic airway diseases and corticosteroid-resistant non-eosinophilic cough. We recommend that some factors with weak evidence of an association with cough are best viewed as potential aggravating factors of an intrinsic abnormality of the cough reflex, rather than the cause. We call for more research into the basic mechanisms and pharmacological control of an abnormally heightened cough reflex, and recommend ways to assess the effects of potentially antitussive treatments.

#### Introduction

Chronic cough is defined as cough lasting for more than 8 weeks.<sup>1</sup> This definition is based on evidence that a cough lasting longer than this duration is unlikely to be due to a respiratory tract infection.<sup>2</sup> Chronic cough is a common symptom of almost all chronic respiratory, and some non-respiratory conditions. Several recognisable causes of chronic cough, such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, lung cancer, an inhaled foreign body, pulmonary tuberculosis, sarcoidosis, idiopathic pulmonary fibrosis, and heart failure will be obvious after clinical assessment, spirometry, and chest radiography. The diagnostic approach and management of these conditions is outside the scope of this Series. We will focus on the diagnosis and management of chronic cough in adults when no obvious cause can be identified by such an assessment. Cough is the primary focus of referral in 38% and the sole focus in 10% of patients seen in a typical adult respiratory clinic.<sup>3</sup>

Patients referred with isolated chronic cough<sup>1,4,5</sup> are assessed on the basis of the anatomic, diagnostic protocol originally described by Irwin and colleagues<sup>6</sup> more than 25 years ago. This protocol is so named because the emphasis is on the importance of conditions—especially, asthma, rhinosinusitis, and gastro-oesophageal reflux—that affect structures within the anatomical distribution of vagal afferent nerves.<sup>6–8</sup> Important modifications to the protocol are the recognition that eosinophilic bronchitis without asthma is an important cause of chronic cough, and acceptance that non-invasive assessment of airway inflammation is a desirable step in the assessment of patients with chronic cough.<sup>9,10</sup> Although this protocol has undoubtedly been an important advance in the management of chronic cough, it remains largely based on expert opinion, with an absence of evidence from randomised, double-blind, placebo-controlled trials

supporting central tenets of the protocol. Nevertheless, there are many reports of successful management of cohorts of patients with chronic cough, by use of variants of the anatomic, diagnostic approach to investigation.<sup>3,6,9–18</sup> The findings in these reports should be tempered by those from others, in which management has not been as successful.<sup>19–21</sup> There is increasing recognition that up to 46% of patients seen in secondary care with chronic cough have an unexplained cough, despite extensive investigation and treatment trials (see the preceding part of this Series), suggesting that aspects of the anatomic, diagnostic investigation protocol need to be modified. The most important difficulties with present management protocols apply especially to patients whose cough is not due to an obvious major factor such as smoking or treatment with an angiotensin-converting enzyme (ACE) inhibitor, and who do not have evidence of an eosinophilic airway disease (panel).

We propose that when treating patients in whom cough is not due to an obvious pulmonary disease or a major factor such as smoking or treatment with ACE inhibitors, a distinction should be drawn between cough due to eosinophilic airway diseases and non-eosinophilic chronic cough. This distinction is supported by the

#### Search strategy and selection criteria

We made a detailed appraisal of published peer-reviewed research over the past 10 years using PubMed for articles in English. The search terms included “Cough” in combination with “treatment”, “asthma”, “postnasal drip”, “eosinophilic bronchitis”, “gastrooesophageal reflux”, “cigarette smoking”, “guidelines”, “prevalence”, and “infections”. We also had publications accumulated because of our involvement in cough treatment and research over the past 15 years.

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This is the second in a Series of two papers about chronic cough

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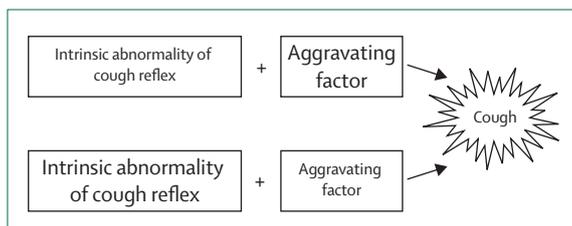
**Panel: Difficulties with management protocols**

- Scarce evidence from randomised controlled trials that interventions against potential causes actually help the cough<sup>4,22–25</sup>
- Frequent clinical observation that although interventions against potential causes of chronic cough might result in a subjective improvement in cough severity, they rarely eliminate the cough completely
- Absence of clarity as to the basis for assigning cough to a specific cause; the substantial variation in the frequency of reported causes in published series
- Difficulty in relating objective measures of the presence of potential causes to the success of therapeutic interventions<sup>21,23,26</sup>
- Failure to recognise typical clinical and pathological patterns of disease in patients with cough thought to be due to different causes<sup>13,27,28</sup>
- The observation that non-eosinophilic chronic cough largely arises in middle-aged women, irrespective of the potential cause<sup>1,29</sup>

	Eosinophilic airway diseases	Non-eosinophilic chronic cough
Age	Any	40–60 years
Sex	Equal	Female predominant
Response to corticosteroids	Good	Poor
Pathology	Eosinophilic	Non-eosinophilic
Exhaled (NO)	Raised	Low
Variable airflow obstruction	Present in asthma	Absent
Airway hyper-responsiveness	Present in asthma	Absent

NO=nitric oxide.

**Table 1: Differences between the two major types of chronic cough**



**Figure 1: Model for pathogenesis of non-asthmatic chronic cough**

Cough depends on combined effect of a pre-existing, intrinsic abnormality of cough reflex, and effects of aggravating factors. When effects of an aggravating factor are large (ie, ACE-inhibitor therapy, smoking), benefits of its withdrawal are likely to be large. When the aggravating factor has a small effect (ie, active rhinitis, gastro-oesophageal reflux disease), benefits of treatment or removal of that factor will be smaller.

substantial differences in epidemiology, pathology, and expectation of treatment responses between these groups (table 1). We believe that no preconceptions should exist about the underlying causes of non-eosinophilic cough. Moreover, extrapulmonary factors such as rhinitis and gastro-oesophageal reflux, in which the evidence of a causal association with chronic cough is weak, are best viewed as potential aggravating factors of any underlying abnormality of the cough reflex, especially prevalent in middle-aged women, rather than causes. The model in figure 1 has the advantage of providing a basis for an understanding of the incomplete response to treatment

seen in many patients. This is important because it will stimulate rather than inhibit research into other causes of a heightened cough reflex, which in turn could result in the development of improved treatment.<sup>30</sup>

**Investigations**

An important first step, especially in a primary-care setting, is to establish why the patient has requested a review, and what their expectation of that review is. Sometimes the chronic cough itself will clearly not be a substantial problem, and concern about the potential cause has driven the consultation. In such patients, reassurance might be all that is needed. Studies<sup>1–19</sup> have shown a low frequency of serious pulmonary conditions, such as lung cancer and tuberculosis, in patients who have an isolated chronic dry cough and normal physical examination, chest radiograph, and spirogram, suggesting that these simple tests are an effective screening strategy. Therefore, strong reassurance could be offered if no diagnosis is apparent after these investigations have proved to be normal.

Detailed inquiry of the circumstances of the onset of cough is important: an abrupt onset of coughing when eating or chewing should raise the possibility of an inhaled foreign body and the onset of cough shortly after introduction of ACE-inhibitor therapy should raise the possibility of ACE-inhibitor associated cough. The presence of haemoptysis, substantial quantities of sputum, systemic symptoms, prominent breathlessness, wheeze, or abnormal physical signs increases the probability of lung disease and should trigger appropriate investigations, which could include high-resolution CT scan of the chest and bronchoscopy,<sup>18</sup> even if more simple investigations reveal no suggestive findings. Onset of cough with symptoms suggestive of an upper or lower respiratory tract infection raises the possibility of a postinfectious cough; prominent whoops, a very troublesome nocturnal cough, and cough associated with vomiting are all associated with pertussis—a condition that is increasingly recognised in schoolchildren and adults.<sup>31,32</sup> Otherwise, little evidence exists to show that information about timing, nature, complications, and potential aggravating factors is predictive of the underlying cause of cough.<sup>13</sup>

An important next step is to assess objectively cough severity. This step can inform decision making about the intensity of the diagnostic work-up and allow objective assessment of the response to treatment, trial of withdrawal of treatment, or trial of removal of a potentially relevant environmental factor (table 2). Table 3 shows potential methods for objective assessment of cough and their measurement characteristics. There are no properly validated cough symptom scores. Moreover, little is known about how these scores relate to objective cough frequency and cough reflex sensitivity. Cough visual analogue scores are most commonly used in clinical trials. Typically, these scores assess cough according to the patient's own experience—eg, the patient will be asked to rate their cough on a 10-cm scale fixed at both ends by no cough and

	History	Examination	Investigations	Treatment
Smoking-related cough	Typically productive morning cough >3 months per year for more than 1 year. History of smoking	Coarse crackles	n/a	Stop smoking. Remove other potential irritants
ACE cough	Cough onset often, but not always temporarily related to starting ACE inhibitor	n/a	n/a	Drug withdrawal. Substitution with alternative if appropriate
Eosinophilic airway diseases	Nocturnal cough, cough after exercise in asthma. Wheeze might be heard in asthma	Possible signs of airflow obstruction in asthma	Sputum eosinophil count >3%. Raised exhaled NO. In asthma, one or more of the following: >15% increase in FEV <sub>1</sub> after inhaled salbutamol 200 µg; within day PEF variability over 2 weeks >20%; or PC <sub>20</sub> <8 mg/mL, or both	Inhaled corticosteroid. Prednisolone 30 mg daily for 14 days in selected cases. Bronchodilator therapy for asthma
Rhinitis	Rhinorrhoea, nasal obstruction, sinus pain, sneezing, nasal itch, postnasal drip	Nasal secretions, nasal or pharyngeal mucosal inflammation	Sinus radiograph or CT showing mucosal thickening or fluid amount, or both*	Topical corticosteroid. In selected cases: topical ipratropium bromide 40 µg twice daily, oral antihistamine
Gastro-oesophageal reflux	Heartburn, flatulence, water brash. Cough might be the only manifestation	n/a	Barium swallow, endoscopy, oesophageal manometry, and 24 h pH monitoring*	Weight reduction, raising of head in bed, avoid eating within 2 h of bedtime, acid suppression with PPI. Prokinetic agent in selected cases
Postinfection	Onset after viral upper respiratory tract infection	n/a	n/a	Observation

ACE=angiotensin-converting enzyme. PC<sub>20</sub>=provocative concentration of methacholine needed to cause a 20% fall in FEV<sub>1</sub>. PEF=peak expiratory flow. PPI=proton-pump inhibitors. NO=nitric oxide. \*These investigations are not predictive of the success of subsequent treatment. n/a=not applicable.

**Table 2: Clinical features, investigation, and treatment of common conditions associated with chronic cough**

the worst cough ever. Assessments are responsive and repeatable,<sup>33,34</sup> but they are of no value when comparing cough severity between individuals or populations.

Another limitation of cough symptom scores is in the inability to identify many different components of impaired health status seen in patients with chronic cough. Two research groups have attempted to address this limitation by developing cough-specific quality-of-life questionnaires.<sup>33,35</sup> The Leicester cough questionnaire (LCQ) consists of 19 items and three domains made of physical, psychological, and social attributes, with a seven-point Likert response scale,<sup>33</sup> whereas the cough-specific quality-of-life questionnaire (CQLQ) has 28 items in six domains.<sup>35</sup> Responsiveness to treatment has been shown in a group of patients with cough that

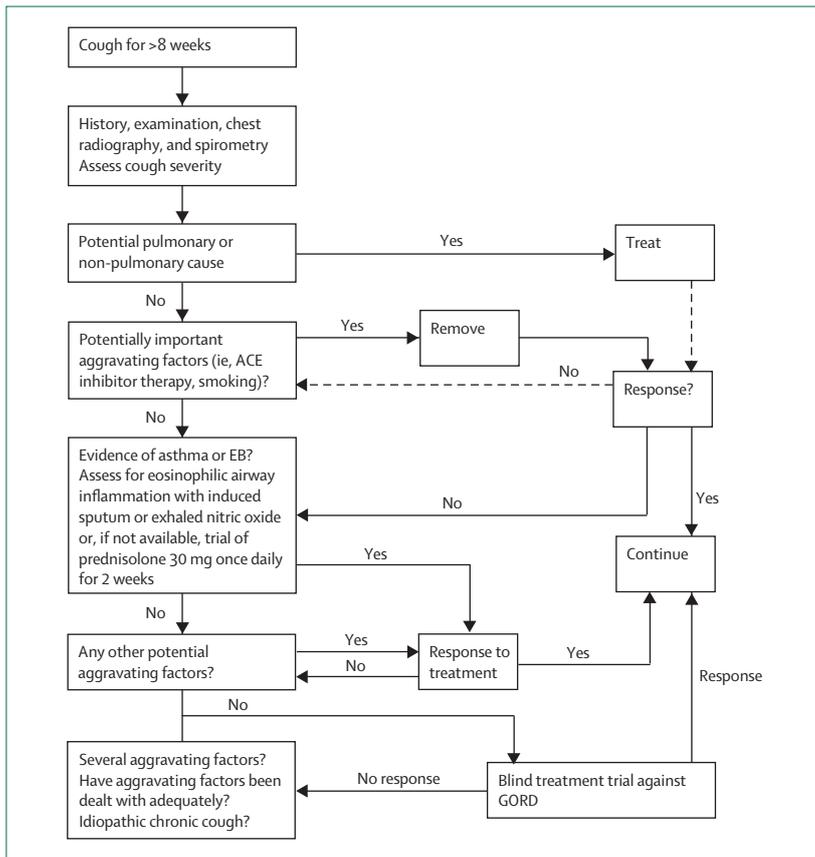
was successfully treated and the LCQ score has been shown to correlate with cough visual analogue scores,<sup>33</sup> and the cough frequency assessed by a sound-based cough monitor.<sup>36</sup> However, more work is needed to show the potential sensitivity of these questionnaires to changes in cough severity, and the relation between cough-specific quality of life and other measures of cough severity.

Perhaps the ultimate objective assessment of cough is to measure its frequency and intensity;<sup>37</sup> there has been interest in this area for more than 50 years. The main difficulties relate to reliably distinguishing cough from other related sounds, such as clearing of the throat or laughing. Many of the earlier systems attempted to identify cough as a distinct sound associated with a

Method	Measurement characteristic	Comment	
Cough visual analogue scores <sup>33,34</sup>	10-cm line fixed at both ends by no cough and the worst cough ever	Between participant SD 4 mm; within participant SD 7-8 mm	Good for measuring change within participant; cannot be used for between patient comparison
Cough-specific quality-of-life scores: LCQ and CQLQ <sup>33,35</sup>	LCQ: 19 items in three domains, seven-point Likert response scale; CQLQ: 28 items in six domains, four-point Likert response scale	LCQ: Between participant SD 4-5; within participant SD 1; CQLQ: Between participant SD 13; intraclass correlation coefficient 0-89	Assesses broader range of health issues associated with cough. Useful for between and within patient comparisons
Cough reflex sensitivity with inhaled capsaicin <sup>49</sup>	Doubling concentrations of capsaicin inhaled by a dosimeter. Concentrations needed to cause two (C2) and five coughs (C5) calculated	Normal ranges (µmol/L) C2: women >1-6, men >1-9; C5: women >7-8, men >14-4. Between participant SD (log <sub>10</sub> units) C2 0-5, C5 0-6. Within participant SD C2 0-3, C5 0-6	Large overlap between health and disease. Responsive to change
Cough counts <sup>36</sup>	Mainly sound-based recording and some form of computerised analysis of sounds	Normal range <3 coughs/h. Mean cough frequency in patients with chronic cough up to 43/h. Between participant SD 36, within participant SD 23 coughs/h	Clear differences between healthy controls and patients with cough, although only few data on 6-h daytime monitoring available—24-h cough monitors are now in development

CQLQ=Cough-specific quality-of-life questionnaire. LCQ=Leicester cough questionnaire.

**Table 3: Methods to assess chronic cough**



**Figure 2: Algorithm for investigation of chronic cough**  
ACE=angiotensin-converting enzyme. EB=eosinophilic bronchitis. GORD=gastro-oesophageal reflux disease.

simultaneous event, such as activation of respiratory muscles assessed with an electromyogram.<sup>38,39</sup> Some workers<sup>40</sup> have described automation of cough recognition with probabilistic neural network systems, differentiating cough from other events by modifications of voice-recognition algorithms<sup>36,41</sup> or by probability statistics.<sup>42</sup> Telemetry has been used to transmit the cough sound to a computer.<sup>43</sup>

Cough has been quantified by counting coughs,<sup>36</sup> or the number of seconds spent coughing;<sup>44,45</sup> the clinical value of measuring other aspects of cough, such as effort and intensity, is unclear. In small studies of patients with chronic cough, daytime cough frequency was substantially higher in patients with chronic cough than in age-matched and sex-matched controls,<sup>36</sup> and a correlation was noted between cough counts and clinical cough scoring systems.<sup>38,45</sup> Other investigators have explored the use of automated cough monitors in clinical trials.<sup>44,46</sup> Such monitoring is likely to develop substantially in the next few years.

Assessment of cough sensitivity probably represents a measurement of the degree of sensitisation of the cough reflex. Measurement of the cough reflex has been studied most often by inhalation of citric acid or capsaicin; both techniques have been well validated, and methods are

well standardised. Cough sensitivity to capsaicin is probably the most widely used test, since this substance induces cough reliably, and assessments of cough reflex with inhaled capsaicin are reproducible (table 3).<sup>47,48</sup> An increase in cough sensitivity has been reported in most conditions associated with chronic cough,<sup>49</sup> with decreases in cough sensitivity seen in successfully treated patients with chronic cough.<sup>50</sup> However, substantial overlap is present between capsaicin cough reflex sensitivity in healthy volunteers and in patients with chronic cough, suggesting that the technique is of little value in validating the presence of a problem or in quantifying it.<sup>49</sup>

In a study of patients with bronchiectasis, investigators noted a significant correlation between scores on the LCQ, and cough sensitivity to capsaicin.<sup>51</sup> In patients with COPD, the coughing detected by an ambulatory cough monitor, quantified as cough seconds per hour, correlated with the cough sensitivity to citric acid.<sup>45</sup> However, in a more diverse population of patients with chronic cough, the relation between cough reflex sensitivity, assessed with inhaled capsaicin, and 6-h daytime cough counts was not close, suggesting that these measures assess different, potentially complementary aspects of chronic cough.<sup>36</sup>

Cough-specific, health-related quality-of-life questionnaires coupled with a simple cough scoring system or a visual analogue scale would probably be the most practical way to assess severity of cough in the clinic. In specialised cough clinics, ambulatory cough monitoring and cough challenges with citric acid or capsaicin might be used in selected patients to confirm cough severity or study the response to treatments.

## Management

After assessment of cough severity, some questions should be addressed (figure 2). First, are there important aggravating factors? Treatment with ACE inhibitors and exposure to cigarette smoke are the most important potential aggravating factors. Removal of these factors is often associated with a substantial improvement in cough. Persistence of cough after withdrawal of ACE inhibitors raises the possibility of another cause of cough, such as asthma, the onset of which has been linked to the use of ACE inhibitors.<sup>52</sup> A temporal association between the introduction of ACE-inhibitor treatment and the onset of cough is frequently present, but its absence does not exclude ACE-inhibitor therapy as a cause, and treatment should be discontinued in all patients with a troublesome, dry cough irrespective of the timing or characteristics of the cough.<sup>1,4,5</sup>

Community studies have shown that active smoking is associated with a 2-fold to 3-fold and passive smoking a 1.3-fold to 1.6-fold increase in the prevalence of cough and other respiratory symptoms.<sup>53-56</sup> There is good evidence of a dose-response relation; prevalence of cough is reduced to near normal in ex-smokers,<sup>53-56</sup> which strongly suggests that the effect of smoking on cough is reversible. Observational studies provide some support

for this view.<sup>57</sup> However, the mechanism and time course of the effect of smoking cessation on cough needs further study, since there is evidence of a short-term increase in cough reflex sensitivity after smoking cessation.<sup>58</sup> Nevertheless, smoking cessation is essential in all patients with a troublesome chronic cough.

Second, is chronic cough due to eosinophilic airway disease? Table 1 shows some of the important differences between cough due to eosinophilic airway diseases and non-eosinophilic cough. A discussion of the different types of eosinophilic airway diseases is presented in the first part of this Series. Asthma, unlike eosinophilic bronchitis, is associated with variable airflow obstruction and airway hyper-responsiveness.<sup>59</sup> How important the distinction is from a clinical standpoint is unclear, since most patients with cough due to asthma or eosinophilic bronchitis respond well to corticosteroid therapy. Some patients with asthma might have a bronchodilator-responsive, corticosteroid-resistant cough, but this pattern of treatment response has not been clearly documented. Test results suggesting the presence of eosinophilic airway inflammation, such as a raised induced sputum eosinophil count<sup>59,60,61</sup> or increased exhaled nitric oxide concentration,<sup>62</sup> are associated with the success of corticosteroid therapy; they are most helpful in distinguishing between cough due to eosinophilic airway disease and non-eosinophilic cough. In the absence of these tests, present guidelines recommend a carefully controlled 2-week trial of oral prednisolone.<sup>1</sup> Management of identified cases of asthma or eosinophilic bronchitis should then be along the lines suggested by these guidelines (table 2). Persistent cough despite treatment with corticosteroids could indicate inadequate control of lower airway inflammation, untreatable factors related to irreversible airway remodelling, or the presence of other aggravating factors. How important these factors are has not been clearly established.

Third, are there other potential aggravating factors? Evidence for successful treatment of factors other than ACE-inhibitor therapy, smoking, and eosinophilic airway diseases is weak. At this stage some patients, generally seen in primary care, whose cough is not too troublesome can be sufficiently reassured that there is no evidence of a serious illness or that an easily treatable cause requires no further assessment. However, other aggravating factors might exist in the remainder of patients.

Persistent cough can be a consequence of occupational exposures, although good epidemiological evidence for such an association is often absent. Cough in farm workers,<sup>63</sup> workers exposed to hot acidic conditions in a bottle factory,<sup>64</sup> and workers exposed to hot chilli peppers<sup>65</sup> are notable exceptions. The relation between work and coughing should be suspected if there is a history of improvement in cough over the weekend or when on holiday. In some cases, a carefully controlled trial of removal of the worker from workplace exposures will be necessary.

Rhinitis, often associated with sinusitis and postnasal drip, is frequently identified as a common cause of chronic cough. However, some believe that there might have been overdiagnosis of rhinitis in earlier studies, perhaps because a response to non-selective anti-histamines was assumed to indicate a specific effect on rhinitis-associated cough, when it might have been due to the antitussive effect of these agents.<sup>19,66</sup> Moreover, there is no evidence that upper airway symptoms are reported more commonly in patients with chronic cough than in controls, or that specific findings are predictive of successful resolution of cough after treatment is directed against rhinitis. Finally, no controlled double-blind studies have shown that interventions against rhinitis are associated with a reduction in cough frequency in a general population with cough. Thus, rhinitis could be an event not directly causally linked to cough.

Other upper airway conditions associated with chronic cough include viral upper respiratory tract infection,<sup>67</sup> chronic tonsillar enlargement,<sup>68</sup> disease of the external auditory canal,<sup>69</sup> obstructive sleep apnoea,<sup>70</sup> and chronic snoring,<sup>71</sup> supporting the notion that structural and inflammatory conditions of the upper airway disease can aggravate coughing. Therefore, we can reasonably suppose that structural abnormalities and chronic inflammation of the upper airway are potential, albeit unproven, aggravating factors for chronic cough, and therefore offer appropriate treatment to patients with suggestive symptoms or clinical findings. An approach to treatment of rhinitis is set out in table 2.

Symptoms suggesting gastro-oesophageal reflux or abnormalities of oesophageal function are common in patients with chronic cough,<sup>72</sup> and the frequent clinical observation that effective treatment of gastro-oesophageal reflux is associated with improvement of cough supports a causal association. We reviewed potential mechanisms in the first part of this Series. Gastro-oesophageal reflux is associated with relaxation of the lower oesophageal sphincter, and often arises during eating, while talking, or on waking, and it is notable that many patients with chronic cough report increased coughing during these activities.<sup>1</sup> The presence of symptoms such as heartburn, dysphagia, sore throat, globus pharyngeus, and dysphonia might not be a good guide to the success of antireflux treatment, since some believe that cough is the sole clinical manifestation of gastro-oesophageal reflux in up to 75% of patients.<sup>73</sup>

Many of the problems with cough due to rhinitis that we have described also apply to cough associated with gastro-oesophageal reflux. There is good evidence that reflux symptoms and abnormalities of oesophageal function arise more commonly in patients with cough than in controls,<sup>72</sup> but also in other airway diseases such as asthma and COPD, making it difficult to make a specific link between cough and gastro-oesophageal reflux. Moreover, investigators have not been able to identify specific features that predict the success of treatment of

gastro-oesophageal reflux,<sup>26</sup> and randomised trials of acid-suppression therapy in cough associated with gastro-oesophageal reflux have been disappointing.<sup>22–25</sup>

A meta-analysis of six small randomised controlled trials of proton-pump inhibitor therapy showed very small effects of treatment on cough severity in adults with chronic cough,<sup>24</sup> questioning the importance of acid reflux in cough. Potentially the link between reflux and cough is more dependent on the volume of reflux than on its acidity, and therapeutic strategies that reduce reflux volume by addressing gastro-oesophageal sphincter function might be more effective. However, excess gastro-oesophageal reflux in cough could also be a function of coughing itself or a manifestation of a general abnormality of upper aerodigestive reflexes, in which case there would be no direct causal link between reflux and cough.<sup>49</sup> The current state of knowledge is such that a trial of treatment with acid-suppression therapy with a proton-pump inhibitor and an alginate for 2–3 months would be reasonable in patients with otherwise unexplained cough, even when there are no suggestive upper gastrointestinal symptoms. A suggested treatment regimen is outlined in table 2. More work is needed before more invasive treatments, such as Nissen fundoplication, with potentially greater effect than conventional treatment on the volume of reflux, can be recommended in patients with cough suspected to be caused by reflux, if the sole motive is to improve cough.

Community surveys suggest that most coughs related to upper respiratory tract infections resolve within 3 weeks. However, cough takes several months to resolve in a small proportion of patients. Infection in most cases remains unidentified; *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* have been among the organisms implicated in adults. Persistent cough due to infection might be more likely in patients with pre-existing airway problems.<sup>74</sup>

Observational studies of patients with otherwise unexplained cough and fixed airflow obstruction have consistently shown a high frequency of chronic inflammatory conditions elsewhere,<sup>16,17,75,76</sup> suggesting that these conditions are associated with airway involvement. The physiological, radiological, and pathological features of airway disease seen in association with chronic inflammatory disorders are similar to those seen in obliterative bronchiolitis complicating chronic rejection in lung transplant recipients and chronic graft-versus-host disease.<sup>75,76</sup> The most striking associations are seen with chronic inflammatory conditions affecting organs whose embryological development is related to the development of the lungs. Such conditions include inflammatory bowel disease,<sup>77</sup> chronic hepatitis C infection,<sup>78</sup> autoimmune thyroid disease,<sup>16,77</sup> and *Helicobacter pylori*-induced gastritis.<sup>79</sup> However, airway disease is also commonly seen in more generalised inflammatory disorders such as rheumatoid arthritis,<sup>76</sup> Sjögren's syndrome,<sup>80</sup> and scleroderma.<sup>81</sup> Cough might be the sole or most obvious clinical manifestation of

airway inflammation, especially if the inflammation is mild or in its early stages. However, more information is needed about the importance of airway complications of systemic inflammatory conditions.

Diffuse panbronchiolitis is a well recognised cause of corticosteroid-resistant adult-onset chronic productive cough in Japan. It is an important diagnosis to consider because treatment with low-dose macrolide antibiotics is associated with a lasting improvement, which seems to be independent of the antimicrobial effects of these drugs.<sup>82</sup> Patients with diffuse panbronchiolitis typically have sinusitis and show prominent small-airway changes on imaging. Whether less clinically overt cases occur in a general population with cough is unclear; this possibility should be explored, and clinical trials of low-dose macrolide antibiotics should be done in a wider population of patients with otherwise unexplained chronic cough.

Some investigators<sup>14</sup> have suggested that up to 20% of patients with chronic cough have more than one potential aggravating factor, and all factors need to be addressed before satisfactory control can be achieved. Other possible explanations for failure to control cough include inadequate treatment of the potential aggravating factor. Validation of the success of an intervention against a potential aggravating factor might be necessary before concluding that the factor does not contribute to the cough.

### Antitussive treatment

Clearly, in a substantial number of patients, the cause of heightened cough reflex will probably remain at least partly unexplained, and treatments directed against potential aggravating factors will not achieve perfect results. In many such patients, antitussive therapies are needed. Codeine is probably the most commonly prescribed opioid-derived antitussive agent. As with other opioids, it mainly acts centrally on the cough network in the brainstem, but might also inhibit peripheral activation of cough receptors. Although previous studies have recorded antitussive activities against induced cough in healthy volunteers<sup>83</sup> and in spontaneous cough in patients,<sup>84,85</sup> more recent ones have shown that such therapies are ineffective against acute cough of the common cold,<sup>86</sup> and against cough in patients with COPD.<sup>44</sup> A non-narcotic antitussive, dextromethorphan, has proved to have some effect on cough associated with upper respiratory tract infections, although the effect on cough frequency was small and of uncertain clinical relevance.<sup>87</sup> The use of morphine and diamorphine has been restricted to severe distressing cough in malignant disease, in which cough is often associated with pain and distress. There is evidence of the effectiveness of a slow-release formulation of morphine in a population with distressing, unexplained cough.<sup>88</sup> More information on the risks and benefits of this approach is needed before this treatment can be widely recommended. Chronic cough has been treated with lidocaine delivered by

	Agent	Comment
Peripheral opioid receptors	BW443C ( $\mu$ -opioid receptor agonist), SB-221122 ( $\delta$ -opioid receptor agonist)	BW443C effective in animals; not effective against capsaicin-induced cough in man. <sup>94</sup> SB-221122 inhibits citric acid induced cough in guinea pigs. <sup>95</sup> No data in man
NOP1 receptor	Nociceptin	Effective against mechanical and capsaicin-induced cough in animal models. <sup>96</sup> No data in man
Transient receptor potential vanilloid receptor-1	Capsazepine, iodoresiniferatoxin	Activated by capsaicin and protons. Expression is increased in airway nerves of patients with chronic cough. <sup>97</sup> Capsazepine blocks capsaicin and citric acid-induced cough in animal models; <sup>98</sup> iodo-resiniferatoxin is more potent. <sup>99</sup> No data in man
Bradykinin B2 receptor	Icatibant and HOE-140 (both B2 receptor antagonists)	Icatibant inhibits cough induced by citric acid <sup>100</sup> and HOE-140 inhibits ACE inhibitor associated increase in the cough reflex in animal models. <sup>101</sup> No data in man
Tachykinin receptor	CP-99994 (NK1 antagonist), SR-48968 (NK2 antagonist), SB-235375 (NK3 antagonist)	CP-99994 ineffective against hypertonic saline-induced cough in asthma. <sup>102</sup> SR-48968 and SB-235375 inhibit citric acid induced cough in animals <sup>103,104</sup>
Cannabinoids	JWH-133 (CB2 agonist)	Inhibits citric acid induced cough in animals. <sup>105</sup> No data in man
Ion channel modulators	NS-1619 (opens large-conductance $Ca^{2+}$ -activated channel), pinacidil ( $K^+$ channel opener), furosemide (Na or Cl co-transport inhibitor)	NS-1619 inhibits citric acid induced cough <sup>106</sup> and pinacidil capsaicin induced cough <sup>107</sup> in animal models. Inhaled furosemide inhibits cough induced by low chloride solutions but not by capsaicin in man. <sup>108</sup> Mode of action is unknown
GABA receptor	Baclofen (GABA agonist)	Baclofen inhibits capsaicin induced cough via a central effect in animals; <sup>109</sup> also active in man <sup>110</sup>

ACE=angiotensin-converting enzyme. GABA=Gamma-aminobutyric acid. NOP1=opioid receptor-like 1. NK=neurokinin.

**Table 4: Potential new antitussive agents**

aerosol<sup>89</sup> or nebuliser,<sup>90</sup> although good evidence of the effectiveness and safety of this approach is absent; and, in a clinical trial of 62 patients with COPD, nebulised terbutaline was equally effective.<sup>90</sup>

Other workers<sup>91</sup> have shown, in a randomised placebo-controlled trial, that speech therapy improved chronic cough; similar benefits were noted in an uncontrolled study of outpatient physiotherapy.<sup>92</sup> We do not know what the key components of these interventions are. An important part of the advice is voluntary cough suppression, suggesting that excess coughing might partly be due to the continuation of a vicious cycle in which coughing leads to airway trauma and activation of the cough reflex.

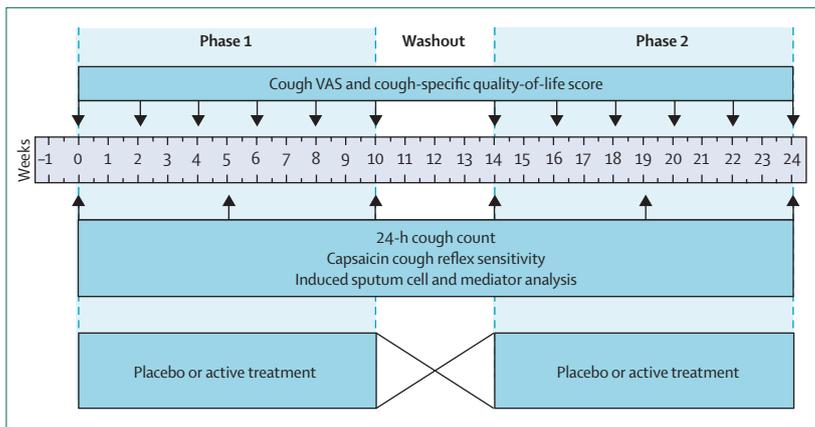
Potentially new antitussive treatments have been reviewed;<sup>93</sup> some of the most promising approaches are summarised in table 4. Much of the existing work assessing pharmacological manipulation of the cough reflex is limited, because it has been done in animals that poorly predict effects in man. Moreover, the agents that have been investigated in man have been tested against models of questionable relevance to the population in need, including simple capsaicin-challenge protocols in healthy volunteers and subjective assessment of cough in patients with COPD. We urgently need clinical trials of new drugs with objective measures of cough severity and frequency, as well as cough-specific quality-of-life and symptom indices.

The difficulty in providing strong, evidence-based advice on the treatment of chronic cough has been highlighted by the recently updated guidelines of the American College of Chest Physicians on the investigation and management of cough in adults and children. These guidelines note that many of the recommendations, including those of treatments, are based more on opinion than on evidence.<sup>5</sup> Potential explanations for this

drawback include a perceived absence of unmet need in chronic cough, a perceived lack of potential antitussive drugs, a feeling that no good endpoints can be reliably measured, and an absence of interest from clinicians and pharmacologists to develop antitussives. Table 4 shows that there are many potential agents that could be tried, and, as we have emphasised in this Series, clinicians and pharmacologists should be interested in developing more effective indirect antitussives, since many patients have chronic cough that cannot be controlled with available management guidelines.

So in whom and how should antitussives be assessed? We think that the population that needs to be studied should include patients with persistent cough, despite adequate treatment of any associated potential aggravating factors, or in the absence of aggravating factors. Participants should have a heightened cough reflex, and excess coughing, measured with a portable cough counter. People with postviral acute cough are a less appealing population to study, since cough is usually transient and the mechanisms of acute cough are likely to be different from those of chronic cough. In conditions typically associated with a productive cough, such as COPD and bronchiectasis, suppression of cough might lead to sputum retention and infection. The high frequency of pneumonia in patients with ineffective cough, and reports<sup>111,112</sup> that ACE-inhibitor therapy is associated with reduced death from pneumonia in racial groups that are prone to developing ACE-inhibitor associated cough, emphasises that, in some circumstances, a heightened cough reflex improves health.

An important hurdle to the assessment of antitussive therapy has been the uncertainty of outcome measures for clinical trials. Assessment of cough has often been on the basis of poorly validated measures of patients'



**Figure 3:** Model for assessment of antitussive therapies in a placebo-controlled, double blind, crossover study. Treatment duration, washout duration, and assessments done during and after treatment will depend on the probable mode of action of the agent under investigation. VAS=visual analogue score.

perception of their cough. In the past 5–10 years, several methods for the assessment of cough have been developed and validated, including cough-specific quality-of-life questionnaires,<sup>33,35</sup> objective cough counts,<sup>36,44,45</sup> and cough challenges<sup>49</sup> that can be used in clinical trials. The relation between these different measures of cough seems to be complex,<sup>33,36,45</sup> and the clinical significance of changes in these measures has not been clearly defined. For these reasons, we recommend the use of several methods of assessment of cough in future clinical trials. In assessing treatments for chronic cough, since the antitussive agent will generally suppress rather than cure the cough, a crossover trial will often be the trial design of choice, although researchers need to bear in mind the possibility of period, order, and carry-over effects. A suggested model of the crossover design is shown in figure 3. Crossover trials are not appropriate for assessment of treatments to suppress acute cough, or when the intervention might have a longlasting effect on cough; in such situations a parallel-group comparison is recommended.

### Cough in the community

The strong, dose-related relation between environmental exposure to tobacco smoke and chronic cough,<sup>55,56</sup> and evidence that reported cough is related to exposure to environmental pollution,<sup>113,114</sup> especially particulates, suggests that interventions to remove these factors would be associated with a substantial gain to the community. Studies have shown a rapid reduction in reported cough in former smokers,<sup>55</sup> and a reduction in cough prevalence in Swiss cities where particulate concentrations have fallen.<sup>114</sup>

### Conclusions

Chronic cough is often viewed as a difficult clinical problem. Clinicians are frequently struck by the discrepancy between their own experience of managing chronic cough, and the high cure rates suggested by reported case series. Patients might become frustrated

by the absence of substantial progress; their fear that they have a serious illness might be fuelled by endless investigations and unsuccessful treatment trials. We hope that the approach suggested here will lead to a more balanced understanding of the problem, ultimately leading to more satisfactory outcomes. Large-scale recognition is needed of the substantial numbers of patients whose chronic cough cannot be diagnosed or controlled with present investigation and treatment protocols. Hence, we need more research and better treatments. Recognition of this large unmet need and the development of a number of well validated techniques to measure chronic cough can only help in this effort.

### Conflict of interest statement

IDP was one of the developers the Leicester Cough Questionnaire. He receives occasional payments for the use of the questionnaire in commercially sponsored clinical trials. He declares that he has no other conflict of interest. KFC is co-Editor-in-Chief of an online journal, *Cough*. He was co-organiser of a Cough Symposium in London, which received educational grants from AstraZeneca, GlaxoSmithKline, and Novartis. He declares no other conflict of interest.

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