CLINICAL PRACTICE

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Chronic Cough

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 63-year-old woman presents with a 1-year history of a chronic dry cough, associated with a sensation of "irritation" in the throat. Prolonged bouts of coughing are associated with stress urinary incontinence and occasionally end with retching and vomiting. The cough is triggered by changes in temperature, strong smells (e.g., the smell of cleaning products), laughing, and prolonged talking. She has no notable medical history, reports being otherwise well, and does not smoke. She has been prescribed a bronchodilator and inhaled and nasal glucocorticoids, but has had no benefit from any of these. The results of a physical examination, chest radiography, and spirometry are normal. How would you further evaluate and manage this condition?

THE CLINICAL PROBLEM

Cough is the most common symptom for which patients seek medical attention.[1] Estimates of the prevalence of cough vary, but as much as 12% of the general population report chronic coughing, defined as a cough lasting for more than 8 weeks.[2] Chronic cough is more common among women than among men, most commonly occurs in the fifth and sixth decades of life, and can persist for years, with substantial physical, social, and psychological effects.[3,4] The disabling effects of chronic cough are understandable, given that patients with the condition cough hundreds or even thousands of times per day; this is similar to the frequency of coughing that occurs in acute viral cough, but chronic cough can persist for months or years.[5,6] Most patients describe the cough as dry or productive of minimal amounts of sputum; excessive sputum suggests bronchiectasis or sinus disease.

Chronic cough is a feature of many common respiratory diseases (e.g., chronic obstructive pulmonary disease, asthma, and bronchiectasis) and of some common nonrespiratory conditions (e.g., gastroesophageal reflux and rhinosinusitis), and it may be the presenting symptom of patients with some rarer conditions (e.g., idiopathic pulmonary fibrosis and eosinophilic bronchitis). Cough is also listed as a side effect of many drug treatments but is most commonly associated with the use of angiotensin-converting–enzyme (ACE) inhibitors; cough occurs in approximately 20% of patients treated with ACE inhibitors.[7] Patients with chronic cough present to health care providers in a wide range of specialties, and if successful resolution is not rapidly achieved, these patients can pose diagnostic and management challenges to many clinical services and may see numerous doctors.[8] The natural history of chronic cough among patients in primary care settings has not been well studied. However, in a series of patients who had chronic cough that was

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KEY CLINICAL POINTS

CHRONIC COUGH

- Chronic cough (cough >8 weeks in duration) is common and can be disabling.
- Chronic cough is a feature of many respiratory diseases, and common triggers (asthma, esophageal reflux, and postnasal drip) should be routinely ruled out by testing or by treatment trials. Investigation and treatment algorithms are based largely on consensus opinion, and more data are needed from randomized trials.
- Limited data from clinical trials support a benefit of low-dose morphine, gabapentin or pregabalin, and speech therapy for patients with cough persisting after other investigations and empirical treatments.
- Newer evidence suggests that cough reflex hyperresponsiveness underlies chronic cough, although more research is needed into the mechanisms and associated potential treatments.

unexplained after evaluation at a specialty clinic and who were reevaluated more than 7 years later, cough had spontaneously resolved in 14% and had decreased in 26% of the patients.[9]

STRATEGIES AND EVIDENCE

Professional guidelines describe systematic approaches to the evaluation and management of chronic cough[10-13]; these guidelines are based largely on consensus opinion and observational data from the medical literature. Although there are national differences in the delivery of health care, the availability of diagnostic tests, and management strategies, the approach can be broadly simplified into four main steps (Fig. 1).

STEP 1: IDENTIFICATION AND TREATMENT OF OBVIOUS CAUSES

Initial evaluation of the patient, including a medical history, clinical examination, chest radiography, and spirometry, can identify or rule out a wide range of conditions that may underlie chronic cough, and the initial management of the condition should be guided by any positive findings. The history and physical examination should address medications such as ACE inhibitors, smoking or occupational exposures, and any symptoms or signs that suggest a serious underlying disease (e.g., weight loss or hemoptysis, either of which may raise concern regarding lung cancer). Asthma is often suggested by a history of wheezing; however, in some patients with asthma, wheezing is absent or trivial, a condition called "cough-variant asthma."[14] Spirometry in these cases may reveal an obstructed pattern that reverses with a bronchodilator. If there is any possibility of foreign-body inhalation, urgent investigation is warranted.

STEP 2: FOCUSED TESTING FOR AND TREATMENT OF ASTHMA, GASTROESOPHAGEAL REFLUX, AND RHINOSINUSITIS

In the context of normal results of chest radiography and spirometry, the most common conditions associated with chronic cough are asthma, gastroesophageal reflux disease, and rhinosinusitis,[15] although the prevalence of each of these varies substantially among cough clinics.[16]

Although most cases of asthma are associated with abnormalities on routine spirometry, methacholine challenge to assess for bronchial hyperreactivity is indicated for patients who have normal results and no other obvious cause of cough; levels of exhaled nitric oxide may also be elevated.[17] Although data from randomized trials to guide the management of cough-variant asthma are lacking, clinical experience suggests that this condition usually responds to treatment with inhaled glucocorticoids. Inhaled medications trigger the cough in some patients, which inevitably reduces the delivery of the treatment to the airways. In some patients, the cough responds well to a change of inhaler device (e.g., the use of a spacer device); in other patients, treatment with oral glucocorticoids for 1 to 2 weeks may be helpful.

The relationship between cough and esophageal reflux is complex but is becoming clearer.[18] Guidelines suggest a trial of treatment with acid-suppression therapy — for example, twice-daily treatment with proton-pump inhibitors (PPIs) for up to 3 months — in patients with chronic cough.[11,12,19] However, many patients with cough do not have symptomatic gastroesophageal reflux disease, and most randomized, controlled trials of reflux treatment for cough have not shown a significant improvement in association with this type of treatment.[20,21] There is likewise no good

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evidence that antireflux surgery (laparoscopic fundoplication) is an effective treatment for chronic cough, and its use should be limited to patients who meet the criteria for the surgery on the basis of symptoms of gastroesophageal reflux disease and assessments confirming that this condition is present.

A retrospective analysis of pooled data from trials of PPIs did not show an overall benefit, but the subgroup of patients with heartburn, regurgitation, or excessive acid reflux on esophageal pH monitoring appeared marginally more likely to have a response to PPI treatment.[21] However, complex tests of esophageal reflux — for example, pH or impedance tests — are poorly predictive of a response of cough to acid suppression, and most patients with chronic cough have levels of acid and nonacid reflux that are similar to those in controls, with little reflux reaching the proximal esophagus.[22] Current evidence does not support the notion that refluxate enters the larynx or pharynx or is microaspirated into the airways in chronic cough.[22-24] Inflammatory changes are often seen in the larynx of patients with cough and are interpreted as a sign of proximal gastroesophageal reflux ("laryngopharyngeal reflux"). However, patients with severe cough often have traumatic inflammatory changes in the larynx,[25] and there is poor agreement among observers with regard to the laryngeal signs of laryngopharyngeal reflux.[26,27] In approximately 50% of patients with chronic cough, there is a substantial temporal relationship between reflux and cough, with "physiological" episodes of distal reflux preceding individual bouts of coughing more often than would be expected by chance alone, irrespective of the acidity of the refluxate.[28,29] This implies that neuronal cross-talk between the distal esophagus and the airways can trigger coughing episodes in the absence of abnormal levels of distal or proximal reflux and therefore that sensitization of the vagal pathways may be the underlying abnormality.

Patients with chronic cough often report a sensation of postnasal drip. Guidelines recommend nasal glucocorticoids and antihistamines for patients with allergic rhinitis and chronic cough, but randomized, controlled trials to support this approach are lacking, and clinical experience indicates that the responses to this treatment are often disappointing. In cases in which chronic sinusitis is identified, patients may be offered antibiotics and sinus or septal surgery, but there are no objective data to indicate that surgical treatment of nasal disease results in an amelioration of cough.

STEP 3: INVESTIGATIONS TO RULE OUT RARER CAUSES OF COUGH

In patients in whom asthma, nasal disease, and reflux have been ruled out (on the basis of diagnostic testing or trials of treatment), other conditions that may manifest with chronic coughing and could respond to treatment should be considered, and referral should be made to a

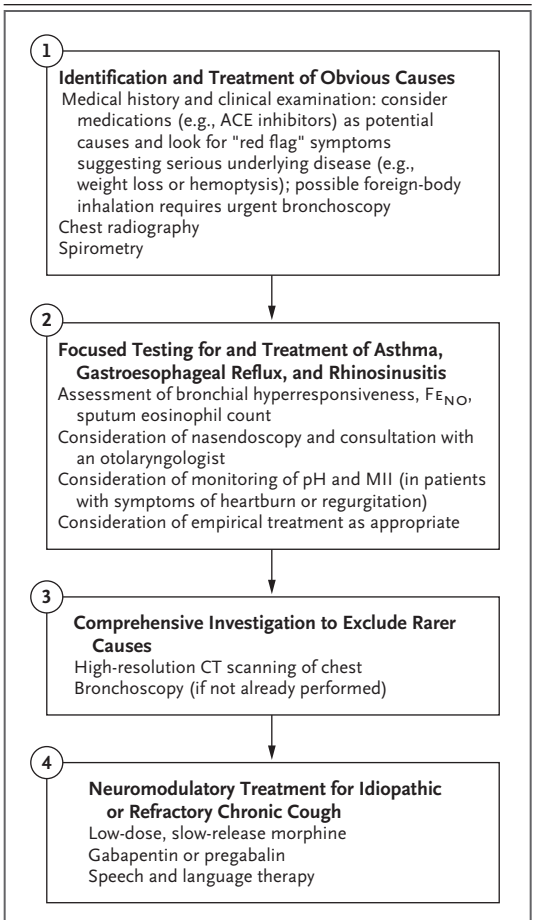

Figure 1. Steps for the Evaluation and Treatment of Patients with Chronic Cough.

National and international guidelines describe detailed and systematic approaches to the evaluation and treatment of patients presenting with chronic cough[10-12]; however the broad approach is consistent among the guidelines and can be simplified into four main steps. ACE denotes angiotensin-converting enzyme, CT computed tomography, Fe_{NO} fraction of exhaled nitric oxide, and MII multichannel intraluminal impedance.

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specialty cough clinic, if one is available. Conditions associated with chronic cough include obstructive sleep apnea,[30] eosinophilic bronchitis,[31] tonsillar enlargement and recurrent tonsillitis,[32] and external ear disease mediated through the auricular branch of the vagus nerve.[33] In cases in which cough remains refractory, high-resolution computed tomographic (CT) scanning of the thorax is recommended to rule out parenchymal lung disease that is not visible on plain chest radiographs (e.g., pulmonary fibrosis, bronchiectasis, or sarcoidosis). Bronchoscopy may be used to identify conditions such as tracheobronchomalacia, chronic bronchitis, and tracheopathia osteochondroplastica, which may be missed on CT scanning. In our specialty practice, among patients in whom the diagnosis remained unclear after plain chest radiography, pulmonary function testing (including methacholine challenge), empirical reflux treatment, and ear, nose, and throat evaluation, approximately 10% were found to have abnormalities on bronchoscopy,[34] although it is uncertain whether the abnormal findings explained the cough. Prompt bronchoscopy is indicated in cases in which there is any suspicion of cancer or to rule out inhalation of a foreign body. Bronchoscopy may also provide an opportunity to obtain samples to assess for eosinophilic bronchitis, if induced sputum is not available. Eosinophilic bronchitis is suggested by a sputum eosinophil count higher than 3% in the absence of bronchial hyperresponsiveness or variability in peak expiratory flow rate. This condition has been reported in up to 13% of patients who present to specialty cough clinics[31] and frequently responds to treatment with glucocorticoids. Any other conditions identified at this stage should be treated in accordance with standard guidelines for the identified condition, and the response of the cough to this treatment should be evaluated.

STEP 4: MANAGEMENT OF IDIOPATHIC OR REFRACTORY CHRONIC COUGH

In our experience, one or more conditions potentially underlying chronic cough are identified during steps 1 through 3.[15,28] However, despite treatment to address these potential causes, some patients continue to cough (up to 42% of patients presenting to specialty clinics,[35] although the frequency is unclear among patients seen in primary care practices). Patients with refractory chronic cough often seek relief from over-the-counter cough medicines. Some of these medicines contain no active ingredients whatsoever, whereas others have ingredients, like menthol, that may have minor antitussive effects.[36] These treatments are intended for use in acute viral cough, yet little evidence suggests that they are effective even for the treatment of that condition.[37] However, the swallowing associated with sucking lozenges (or sipping water) may transiently suppress cough, and the soothing, demulcent effects of lozenges, syrups, and even honey may provide a minor benefit by temporarily relieving the sensations of throat irritation.[38]

Although there are currently no treatments approved by the Food and Drug Administration or European Medicines Agency for treatment-refractory or idiopathic chronic cough, some interventions targeting neuronal hyperresponsiveness have been shown to be effective in randomized, placebo-controlled trials. In a placebo-controlled trial involving patients with chronic refractory cough, low-dose, slow-release morphine sulfate (5 mg twice daily) was found to be associated with lower cough severity (a difference of 1.6 points on a 9-point scale) and higher cough-specific quality of life than was placebo.[39] In a case series, the response was variable, with approximately 36% of patients reporting a clinically meaningful response but almost 50% having no response at all.[40] Reported side effects in the trial and the case series included constipation and occasionally drowsiness. The possibility of abuse or diversion is a serious concern, particularly in the United States in the context of the current epidemic of opioid abuse.

In a double-blind, placebo-controlled trial involving patients with chronic cough, the anticonvulsant gabapentin was associated with a greater improvement in cough-specific quality of life and a greater reduction in cough severity relative to baseline than was placebo (the between-group difference in the change in cough severity was 12 mm on a 100-mm visual-analogue scale).[41] Clinical experience suggests that the response is highly variable; for many patients, the adverse effects, including sedation and dizziness or unsteadiness, may outweigh any benefits. The risks associated with this medication also include depression and suicidal thoughts or behavior. Gabapentin and the related anticonvulsant pregabalin require individualized dose adjustments to establish a balance between adverse effects and efficacy. Amitriptyline (10 mg

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at bedtime) has been reported to be superior to codeine plus guaifenesin in improving cough-specific quality of life[42]; the sedative effect might also make it easier for patients with chronic cough to sleep.

In a randomized, sham-controlled trial, speech pathology treatment involving four components (education, reduction of laryngeal irritation, cough-control techniques, and psychoeducational counseling) was also shown to reduce cough severity and improve quality of life in patients with refractory chronic cough.[43] More data are needed to understand the essential components of successful therapy. A recent randomized, controlled trial assessing the effects of adding the anticonvulsant agent pregabalin to speech pathology treatment[44] showed significantly greater improvements among patients who received pregabalin than among those who received placebo, with respect to cough severity and cough-related quality of life but not with respect to cough frequency (the one nonsubjective primary outcome). Common adverse effects of pregabalin included dizziness, fatigue, and cognitive changes.

AREAS OF UNCERTAINTY

Whereas the "diagnostic triad" of asthma, gastroesophageal reflux, and postnasal drip have been considered to be the major causes of chronic cough, and high success rates have been claimed for treatments targeting these conditions,[45] several observations raise questions about this concept. First, the large majority of patients who present with these common conditions do not report coughing excessively. Second, despite careful guideline-driven testing and treatments, many patients with chronic cough either have no response to the treatment of the underlying conditions or have no identifiable cause of the cough, and the cough persists.[35] An alternative theory is that an abnormality of the neuronal pathways controlling cough is likely to be the primary disorder in these patients, with identified causes (including asthma, reflux, and postnasal drip) acting as triggers only in the context of neuronal cough hyperresponsiveness (Fig. 2). In support of this hypothesis, a study involving inhalation of capsaicin, an irritant aerosol, showed that this agent provoked a cough response in patients with chronic cough that was double the cough response in healthy controls.[48]

The concept that neuronal hyperresponsiveness underlies chronic coughing is also consistent with the clinical history described by these patients, who report that sensations of throat irritation, an urge to cough, and coughing bouts are triggered by low levels of environmental irritants (e.g., perfumes and dust), physical stimulation of the larynx (e.g., talking, singing, and eating), and changes in temperature and humidity.[49,50] Although the specific triggers of coughing differ among patients, most patients report sensations of airway irritation (75% report irritation in the throat and 15% report it in the chest) associated with an irresistible urge to cough.[50] The term "cough hypersensitivity syndrome" has recently been coined to describe this clinical picture,[51] but there is currently no consensus regarding clinical criteria or a discriminatory diagnostic test.

Mechanistically, chronic cough is probably not a single disorder. The neurologic mechanisms underlying cough hyperresponsiveness require further study, including studies of new drugs targeting specific neuronal receptors in both the peripheral and the central nervous system (e.g., P2X3,[52] neurokinin-1,[47] and transient receptor potential [TRP] vanilloid 1 [TRPV1], vanilloid 4 [TRPV4], and ankyrin 1 [TRPA1][53]) (Fig. 2). For example, in a recent randomized, controlled trial involving patients with refractory chronic cough, P2X3 antagonist treatment was associated with a 75% greater reduction in cough counts relative to baseline than was placebo,[52] although the potential role of this agent in clinical practice remains uncertain.

GUIDELINES

The American College of Chest Physicians has published guidelines for the management of chronic cough[10] that are currently being revised and updated[54] and are similar to those of other professional societies in European countries.[11,12] The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient with chronic cough who is described in the vignette has normal results of spirometry and chest radiography and no spe-

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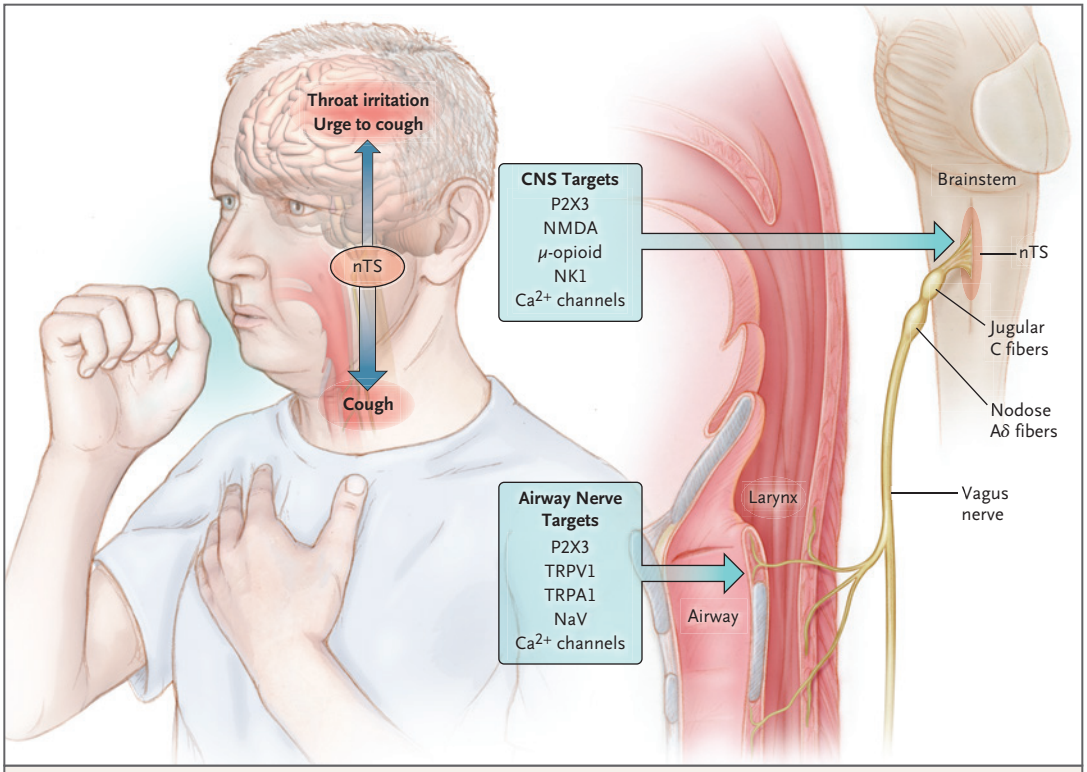

Figure 2. Neuronal Pathways Controlling Cough, and Targets of Available Antitussive Agents and of Those in Development.

C fibers, with bodies in the superior vagal (jugular) ganglion, and Aδ fibers, with cell bodies in the inferior vagal (nodose) ganglion, are the main vagal fibers mediating cough.[46] The key receptors and ion channels located on the terminals of airway sensory afferent vagal nerves that are capable of modulating cough are shown. P2X3 purinergic receptors are found mainly on peripheral sensory nerves, with some expression in the nucleus tractus solitarius (nTS) of the brainstem. Transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) are found on nerve terminals and are capable of initiating action potentials, and voltage-gated sodium channels (NaV) are responsible for action potential transmission. Antagonists for these targets are in development or early-phase clinical trials. In the central nervous system (CNS), the *N*-methyl-D-aspartate (NMDA) receptor is the main target for the over-the-counter therapy dextromethorphan. Morphine is thought to exert antitussive effects through the μ-opioid receptor, whereas gabapentin and pregabalin modulate calcium channels in central and peripheral pathways. The neurokinin-1 (NK1) receptor has been implicated in the sensitization of synapses in the nTS, and its antagonist (aprepitant) was recently found to reduce cough in patients with lung cancer.[47]

cific symptoms or signs to suggest the presence of an underlying pulmonary or extrapulmonary condition; trials of treatment for asthma and rhinitis have not been effective. In accordance with current guidelines, we would suggest a 2-month trial of acid-suppression therapy with a PPI. In practice, we have occasionally seen marked improvement in cough after such therapy, although it should be recognized that randomized trials of acid suppression have generally not shown a significant improvement in this population. We would discontinue treatment if there is no appreciable response. In parallel, we would initiate further testing to assess the possibility of reactive airways, including methacholine challenge and measurement of the fraction of exhaled nitric oxide ($F_{E_{NO}}$). If the results of these investigations are normal and the trial of acid suppression unsuccessful, high-resolution CT scanning of the thorax and bronchoscopy and nasendoscopy would be indicated. If all tests are negative, we would reassure the patient that there is no sinister underlying cause for the chronic cough and explain that a disorder of the nerves controlling the cough reflex is most likely the root of the prob-

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lem. We would explain that there are no currently licensed treatments for chronic cough but that limited clinical trial data have supported a benefit of treatment with slow-release low-dose morphine sulfate, gabapentin or pregabalin, or speech and language therapy; we would discuss with her the potential benefits and potential adverse effects of each option. We would reassure her that refractory chronic cough may resolve or decrease spontaneously over time.[9]

Dr. Smith reports receiving fees for serving on advisory boards from GlaxoSmithKline, Almirall, Reckitt Benckiser, Glenmark, Xention, Patara Pharma, Boehringer Ingelheim, and Vernalis, consulting fees from GlaxoSmithKline, Almirall, and Xention, and grant support from Afferent, Verona Pharma, Marie-Curie, MRC/Almirall, MRC/AstraZeneca, GlaxoSmithKline, Xention, and Nerre Therapeutics; and Dr. Woodcock, serving as chair of a trial steering committee for Afferent Pharmaceuticals and receiving fees for serving on an advisory board from Chiesi and lecture fees and travel support from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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