REVIEW ARTICLE

Unexplained or Refractory Chronic Cough in Adults

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THE MANAGEMENT OF CHRONIC COUGH IS DESCRIBED IN EVIDENCE-based guidelines that appear to be effective for diagnosing and treating the many underlying causes of chronic cough. However, the management delineated in these guidelines is detailed and time-consuming,[1] challenging fidelity to effective management in many cases. These challenges may foster abbreviated evaluations, with some clinicians prematurely diagnosing "unexplained chronic cough" and "refractory chronic cough" in patients who have not been completely evaluated but who are thought to have in common a clinical condition termed cough hypersensitivity. This framework for chronic cough, centered on cough hypersensitivity, has been valuable and has propelled many efforts to find pharmacologic solutions targeting the neural signaling of cough hypersensitivity. The first and most extensively studied drug is the purinergic antagonist gefapixant. However, because gefapixant was only marginally more effective than placebo in treating unexplained or refractory chronic cough, the Food and Drug Administration (FDA) did not approve the drug.[2] For now, this has left clinicians without their hoped-for pharmacologic solution. Consequently, a review of the definitions, diagnostic evaluations, and treatment options for chronic cough, especially those for unexplained or refractory chronic cough, may be useful.

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N Engl J Med 2025;392:1203-14.
DOI: 10.1056/NEJMra2309906

BACKGROUND

DEFINITIONS

Categories of cough have been defined on the basis of data from empirical studies.[3] All coughs are acute at the outset; the duration of the cough is important because it suggests the likely cause. Acute cough lasts for less than 3 weeks, a subacute cough 3 to 8 weeks, and a chronic cough more than 8 weeks. The 8-week duration is based on data suggesting that postinfectious coughs due to viral, mycoplasma, or chlamydophila infections should not last longer,[4] and to mitigate the risk of a wide spectrum of cough-associated complications, an evaluation should not be delayed.[5]

According to an international expert panel in 2016,[6] an unexplained or refractory chronic cough can occur under three different circumstances. If a complete investigation is performed according to published guidelines but no underlying cause of the chronic cough is identified, the condition is termed unexplained chronic cough. If an underlying disorder known to be associated with chronic cough is diagnosed but the cough persists despite treatment of this disorder, the condition is termed explained but refractory chronic cough. If a diagnostic investigation for chronic cough does not reveal a cause and there is no response to empirical therapy, the condition is termed unexplained refractory chronic cough.

EFFECTS OF COUGH

The effects of an unexplained or refractory cough are important and multifaceted. The high intrathoracic pressures (up to 300 mm Hg),[7] velocity (up to 28,000 cm

KEY POINTS

UNEXPLAINED OR REFRACTORY CHRONIC COUGH IN ADULTS

- Unexplained chronic cough is diagnosed when patients undergo a comprehensive investigation according to published guidelines and the cough persists; refractory chronic cough is diagnosed when the cough persists after treatment for cough-associated conditions.
- Although some reviews have reported that up to 60% of adults with chronic cough have unexplained or refractory cough, a rigorous systematic review showed that the prevalence is closer to 10%.
- Confirmation of unexplained or refractory chronic cough should include an assessment for potential barriers in following updated guidelines.
- Patients should be referred to an interdisciplinary cough clinic, which can review the diagnostic examination and assess its adequacy and that of previous treatments.
- Confirmed cases of unexplained or refractory chronic cough are likely to be due to neuropathic changes in vagal signaling (i.e., cough hypersensitivity).
- Treatment options that have been shown to be helpful in randomized, controlled trials, such as multimodal speech therapy and pharmacologic neuromodulation, should be considered; reactive anxiety and depression should also be addressed.
- Neural signaling inhibitors are being investigated and may prove to be promising for the management of unexplained or refractory chronic cough.

per second or >500 miles per hour [>800 km per hour]),[8] and chest energy (up to 25 J)[9] produced during vigorous coughing in healthy persons are reasons that cough is an important defense mechanism that can help clear excessive secretions and foreign matter from airways and even maintain consciousness during potentially lethal arrhythmias (i.e., cough cardiopulmonary resuscitation[10]). These same biophysical properties are also responsible for cough spreading infections and leading to a variety of psychosocial, functional, and emotional complications, including fear about personal safety, as well as extreme physical symptoms[11] that can involve any organ system,[5] all of which can lead to a marked deterioration of the quality of life and, in rare cases, even death.[5]

As a result of these adverse occurrences, cough is a common symptom for which patients seek medical attention and for which an enormous amount of health care dollars is spent.[12-14] When retrospective surveys of general adult populations have been conducted in the United Kingdom, the prevalence of chronic cough has ranged between 2%[15] and 4.9%,[16] with women outnumbering men (57% vs. 43% in one analysis[15] and 58.2% vs. 41.8% in another[16]); these results are similar to values reported in clinics.[17] The effects and costs of cough have been recognized globally, with 12 countries publishing clinical practice guidelines on managing cough by 2014.[18] Although the prevalence of unexplained chronic cough has been widely and variably reported, the lowest prevalence of unexplained or refractory chronic cough among patients with chronic cough, 10.5% (382 of 3636 patients), was reported in a systematic review that focused on analyzing only articles that methodologically identified and putatively followed a specific clinical practice guideline.[19]

Why do women more frequently seek medical attention for chronic cough than men? Two explanations are likely: women with chronic cough have a more pronounced cough reflex sensitivity to inhaled capsaicin and citric acid than men,[20] and health-related quality of life is more adversely affected for women than for men because women are more apt to have cough-induced physical symptoms such as stress urinary incontinence, which has psychosocial repercussions, including embarrassment.[21] Irrespective of sex differences, chronic cough may have profound effects on the quality of life that are similar to the effects of shortness of breath due to disabling chronic obstructive pulmonary disease (COPD).[21]

NEUROANATOMY AND PHYSIOLOGY OF CHRONIC COUGH

There are important differences among species and frequent updates to our understanding of chronic cough, but we know that the human cough reflex is mediated by the vagus nerve innervating the lungs and may also be modulated by input from vagal afferents innervating other

visceral organs and possibly from trigeminal afferents innervating the nasal mucosa (Fig. 1).[22-32] Although direct evidence in humans is limited, vagal sensory afferents of airways, and possibly lung parenchyma, include thinly myelinated Aδ fibers of the nodose ganglion that are activated by mechanical and acidic stimulation, as well as nociceptive unmyelinated C fibers of the jugular ganglion that are activated by tissue damage, inflammation, and environmental irritants.[31-33] Vagal afferents mediating the cough reflex have multiple and sometimes overlapping types of membrane receptors that include, for example, the purinergic heteromeric P2X2/3 and homomeric P2X3 receptors, which sense extracellular ATP, an important mediator released by airway epithelial cells in response to tissue damage, inflammation, or inhaled irritants.[31]

The vagal afferents mediating the cough reflex terminate in the medulla oblongata, mainly at the nucleus of the solitary tract and also at the paratrigeminal nucleus.[31] However, cough evoked by a stimulus is not solely a brain-stem–mediated reflex response. Projections from brain-stem regions are modulated by subcortical and cortical brain activities that have been detected with the use of functional magnetic resonance imaging (fMRI) in persons inhaling cough-evoking stimuli.[26-29] Although much has been learned regarding the cough reflex, the pathophysiological distinction between a cough that responds to disorder-specific treatment and one that does not is still not known.

CHRONIC COUGH PHENOTYPES IN ADULTS

The main diagnostically useful characteristics of chronic cough in adults are the duration of the cough and a history of exposure to respiratory irritants.[34] A cough–vomit syndrome has a high specificity for suggesting the paroxysmal phase of a *Bordetella pertussis* infection in adults,[35] but the actual infection is over before the duration of the cough exceeds 8 weeks. Although productive or wet-sounding cough in children is a diagnostically helpful phenotype,[36] a carefully taken history that includes the character of the cough (dry or productive [no matter the quantity], honking or barking, paroxysmal, brassy, self-propagating, or loose), the timing (nocturnal, with meals, postprandial, with milk products, or on awakening), and complications (syncope or hemoptysis) has not been helpful in diagnosing the underlying cause of chronic cough in adults.[37] The absence or near absence of cough during sleep is a nonspecific finding because cough due to a variety of common diseases (e.g., chronic bronchitis and gastroesophageal reflux disease [GERD])[34] tends to be suppressed during sleep.[38]

Our experience is similar to that of Song and Morice[39] in that patients referred to us with a chronic cough nearly always report fits of coughing provoked by low levels of triggers and preceded by sensations in the pharynx and larynx such as a tickle or itch or an uncontrollable urge to cough. Although these symptoms are consistent with a neuropathic disorder that has been referred to as cough hypersensitivity syndrome (i.e., sensory vagal neuropathic cough or overactive cough reflex),[40] these sensations appear to be of limited value in diagnosing and predicting the outcome of treatment for a variety of causes of chronic cough.[41]

In a study by Mai et al. [41] involving patients who had chronic cough with these abnormal sensations, the cough responded to specific treatment for conditions known to commonly cause chronic cough. These findings[41] and our experience, which is similar,[34] suggest that cough hypersensitivity is more commonly transient than chronic and is not necessarily indicative of a distinctive chronic cough phenotype. Although some have stated that a cough triggered by singing or talking is also clinically suggestive of cough hypersensitivity syndrome,[39] there is an alternative explanation for cough being triggered by these activities. Since almost all our patients with chronic cough, no matter what the cause, report that singing or talking provokes coughing, these activities may further irritate vagal nerve endings in the vocal cords that have been severely traumatized by the act of coughing itself (Fig. 2),[42,43] with its violent oscillations of laryngeal structures.[44]

POSSIBLE EXPLANATIONS FOR DIAGNOSTIC AND TREATMENT FAILURES

It is important to consider the multiple reasons why the known underlying causes of chronic cough might have been missed by diagnostic testing and treatment trials.

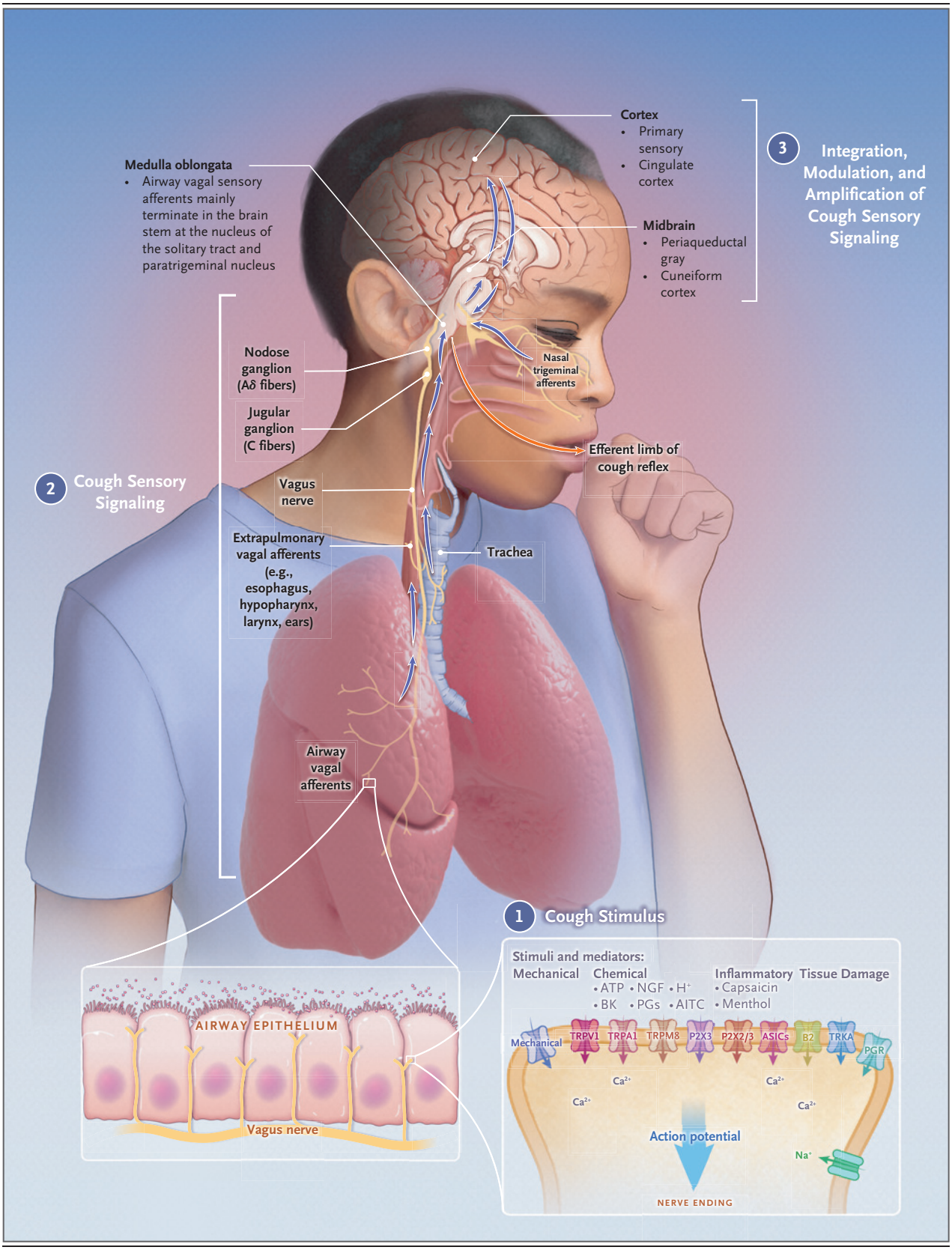

Figure 1 (facing page). Model of the Cough Reflex.
Mainly on the basis of studies in animals but with support from studies in humans,[22] reflexive cough appears to be primarily mediated and facilitated by stimulation of vagal sensory afferents. In the airways and possibly in lung parenchyma, the sensory afferents mediating the cough reflex include thinly myelinated Aδ fibers of the nodose ganglion and unmyelinated C fibers of the jugular ganglion. These sensory neurons have multiple, sometimes overlapping types of membrane channels and receptors that are needed to transduce signals for a variety of mediators and stimuli in the airways, including the extracellular mediator ATP. The Aδ fibers and C fibers terminate in the medulla oblongata of the brain stem at the nucleus of the solitary tract, a major sensory processing nucleus, but also at the paratrigeminal nucleus. Stimulation of the nasal mucosa does not initiate cough directly, but evidence suggests that trigeminal sensory afferents of the nose may modulate the cough reflex.[22-25] However, cough is not simply a brain-stem–mediated reflex response. On the basis of functional magnetic resonance imaging of the brain in humans, multiple higher brain regions, including the midbrain and the primary sensory cerebral cortex, are activated during cough evoked by stimuli, and these regions are likely to be critical in integrating, modulating, and amplifying the neural signaling underlying the cough reflex.[26-29] AITC denotes allyl isothiocyanate, ASICs acid-sensing ion-channel subtypes, B2 bradykinin type 2 receptor, BK bradykinin, NGF nerve growth factor, PG prostaglandin, PGR prostaglandin receptor, P2X3 and P2X2/3 ATP-gated (purine) cation-channel subtypes 3 and 2/3, TRKA tyrosine receptor kinase A, and TRPA1, TRPM8, and TRPV1 transient receptor potential cation-channel subtypes A1, M8, and V1.

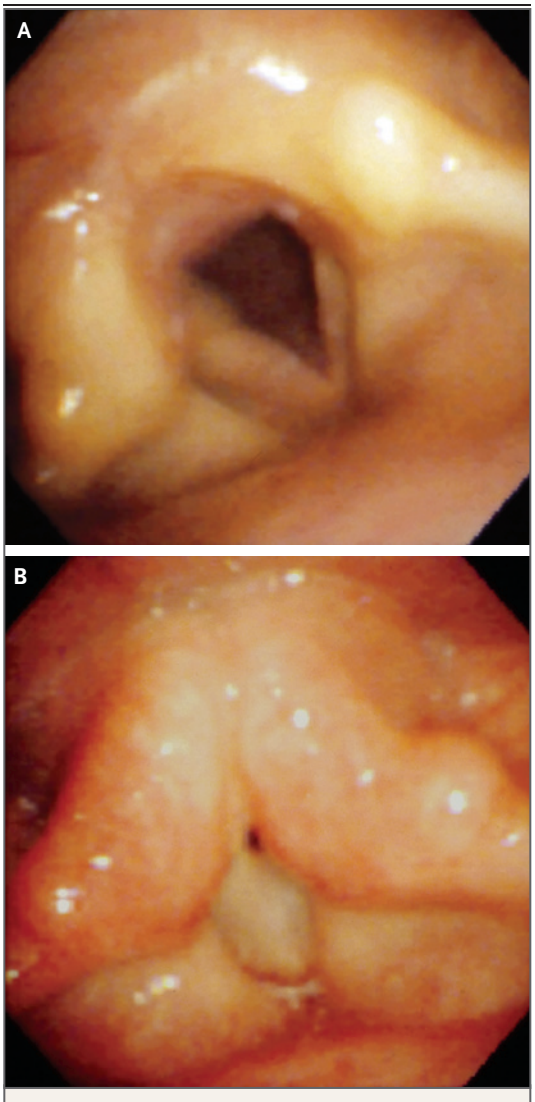

Figure 2. Endoscopic Views of Supraglottic and Glottic Structures Just before and Immediately after a Spontaneous Paroxysm of Violent Coughing.
Before an approximately 5-second paroxysm of coughing in a patient being evaluated for chronic cough of 5 years' duration, the mucosal surfaces are relatively normal, with the exception of thickening of the true vocal cords. Immediately after coughing, the mucosal surfaces appear erythematous and swollen. The brief fit of coughing was spontaneous and not provoked by the instillation of fluid, trauma from the endoscope, or regurgitation or vomiting. Reprinted from Irwin and French[43] with the permission of the publisher.

REGION-SPECIFIC SPECTRUM OF CAUSES

Worldwide, the overwhelming majority of cases of chronic cough in adults are caused by an upper-airway cough syndrome due to a variety of rhinosinus conditions, asthma, GERD, nonasthmatic eosinophilic bronchitis, or a combination of these disorders.[1] Moreover, even less common causes, such as broncholithiasis, tracheobronchomalacia, heart failure, and ear problems, are not so restricted to a specific geographic region that they would fail to be considered. Therefore, a spectrum of causes of chronic cough that is unique to a particular region of the world is not a likely explanation for most treatment failures.

USE OF OUT-OF-DATE EVIDENCE-BASED GUIDELINES

The use of clinical practice guidelines that have not been updated to reflect the latest advances in management is a potential reason for unsuccessful treatment of a chronic cough. This might have occurred in trials of gefapixant,[45] in which patients who did not have truly unexplained or refractory chronic cough may have been enrolled, which could have resulted in an observed placebo effect and regression to the mean.[46]

NEUROLOGIC, PSYCHOLOGICAL, OR PSYCHIATRIC CAUSES OF COUGHING

Adults with chronic cough have been reported to feign a coughing-associated illness for secondary gain as part of Munchausen's syndrome,[47] which is rare; to have recurrences in adulthood of tics (motor and phonic) due to Tourette's syndrome, a disorder that typically begins in childhood[48]; to have a primary motor or phonic tic disorder that develops in adulthood[49]; and to have somatic cough syndrome, a psychiatric disorder that has been reported to successfully respond to psychiatric treatments.[50] However, clinicians should resist presuming that depression and anxiety or other neuropsychological symptoms are the causes of cough, because all patients with troublesome chronic cough are at risk for multiple psychological symptoms as a direct complication of unresolved coughing.[5] Since depression and anxiety have been observed to abate or resolve when cough subsides, these psychological symptoms should always be considered and addressed.[51] The mistaken assumption that chronic cough in a patient with depression or anxiety must necessarily have a neuropsychological cause may be a reason for the true cause of chronic cough remaining elusive and unexplained in some patients.

The use of terminology appropriately aligned with the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, helps to avoid diagnostic pitfalls, inappropriate labeling of patients, and treatment failure.[52,53] These terms include somatic cough syndrome (previously called psychogenic cough) and tic cough (previously called habit cough) in adults and children with chronic cough. Misconceptions regarding the usefulness of historical clues may also contribute to misdiagnosis and treatment failure: the absence of coughing during sleep or cough with a barking or honking sound is not pathognomonic of somatic cough syndrome or tic cough or any other psychological or psychiatric diagnosis.[52]

FAILURE OF INTERVENTIONAL FIDELITY

The reported success in the management of chronic cough in adults varies. A structured evaluation of this variation[54] suggested that differences in interventional fidelity (i.e., the extent to which an intervention is administered as intended) that are due to both patient-related and provider-related factors may be the cause.[19] Provider-related factors contributing to this variation include differences in the use of treatments recommended in evidence-based guidelines, in the provision of standardized education and training for providers, and in verification that patients have been asked about their success in understanding and implementing recommendations. Patient-related variables include differences in the verification, receipt, and understanding of recommended treatments and the ability to enact them in daily activities.[19] Interventional fidelity has been especially poor for the management of GERD. Updated evidence-based guidelines[1] stress the importance of routine follow-up of patients in 4 to 6 weeks so that any patient-related factors accounting for poor interventional fidelity can be addressed.

NEUROPATHIC DISORDER AS A CAUSE OF TRULY UNEXPLAINED OR REFRACTORY COUGH

The importance of the vagus nerve in reflexive coughing is well established and explains, for example, why surgical disruption of the vagus nerve during lung transplantation causes loss of the cough reflex for as long as 6 to 12 months[55] and why palliative, ipsilateral vagotomy for unresectable lung cancer has alleviated cough.[56] Many researchers have speculated that a neuropathic change in vagal signaling underlies the transition from acute, transient coughing to chronic, persistent coughing. It has been suggested that in almost all patients with chronic cough, such neuropathic changes underlie a state of cough hypersensitivity, a condition that leads to coughing in response to even low levels of airway stimulation.[31,57] The loci of these neuropathic changes are not known, but they might not lie at the level of the peripheral vagus nerve.[26-28,31] When fMRI images of the brain were compared during inhalation of cough stimuli, patients with unexplained chronic cough had no increase — in fact, they had a decrease — in brain-stem activity in the medullary regions where cough sensory neurons project, but these patients did have increased activity in midbrain regions encompassing or adjacent to the periaqueductal gray and cuneiform nucleus.[28] One possible interpretation of these recent findings is that in patients with cough hypersensitivity, the neuropathic changes lie not in the vagal sensory afferents themselves but instead in midbrain regions that abnormally amplify low-level signals emanating from brain-stem nuclei.

Mai et al. reported that most thoroughly evaluated patients with chronic cough and cough hypersensitivity had a reduction in cough severity and an improvement in quality of life when specific underlying disorders were properly diagnosed and treated.[41] This finding suggests that even in the presence of cough hypersensitivity, when signaling is especially and persistently hypersensitive to minor stimuli, proper evidence-based treatment of the stimulus causing the cough (e.g., GERD) reduces that stimulus to levels below the cough threshold in most patients. Larger studies will be needed to substantiate the observation of Mai et al. that only a small fraction of patients have a truly unexplained or refractory chronic cough and do not have a response to specific treatment of an underlying disorder because the treatment fails to eliminate the stimulus to cough or because neural signaling is especially and persistently hypersensitive to minor or normally innocuous stimuli.

CURRENT MANAGEMENT STEPS AND TREATMENT OPTIONS

Nearly all patients referred to our cough clinic have previously received a diagnosis of unexplained or refractory chronic cough, but the diagnosis has been confirmed in only a small minority of those patients.[58] We therefore recommend that the first management step is to systematically determine whether there have been potential barriers (Table 1)[34] in carefully adhering to updated evidence-based clinical practice guidelines. Particular attention should be directed to properly managing chronic cough due to GERD or interstitial lung diseases. GERD is arguably the most difficult condition to treat successfully, especially because acid suppression alone is not likely to be helpful in treating chronic cough due to GERD,[59] and strictly following dietary and lifestyle recommendations requires behavior modifications that are hard for patients to make.

With respect to the interstitial lung diseases, a number of drugs appear to favorably affect cough. Findings from a small randomized, placebo-controlled clinical trial suggested that thalidomide may improve quality of life and reduce cough severity in patients with idiopathic pulmonary fibrosis.[60] A larger randomized, placebo-controlled trial has suggested that nintedanib can slow the worsening of fatigue, dyspnea, and cough severity more effectively than placebo over a period of 1 year in patients with a variety of fibrosing interstitial lung diseases other than idiopathic pulmonary fibrosis.[61] In addition, a prospective, observational, multicenter, international study suggested that pirfenidone can improve cough-related quality of life and reduce the frequency and severity of cough over a 12-week period in patients with idiopathic pulmonary fibrosis.[62] In considering these medications, however, it should be understood that a potential barrier to success in treating the cough is failure to consider that it may be due to common causes of chronic cough that are often treatable and unrelated to interstitial lung disease.[63]

The second step in management is to refer patients to an interdisciplinary cough clinic if such a referral has not already been made. The clinic can assess the adequacy of the assessment that has been performed and that of previous treatments, with a special focus on the management of GERD. Once the assessment has been determined to be adequate and the diagnosis of truly unexplained or refractory chronic cough has been confirmed, the third management step is to consider treatment options that have been found to be helpful in randomized, placebo-controlled trials.

MULTIMODAL SPEECH THERAPY

In two randomized, controlled trials[64,65] that compared multimodal speech therapy with advice on following a healthful lifestyle for patients with uncontrolled or refractory chronic cough, multimodal speech therapy led to greater decreases in cough-related symptoms and improvements in quality of life. As originally reported by Vertigan et al. in 2006,[64] the therapy consisted of education, cough suppression techniques, and breathing exercises. The presence of cortical activations that modulate subcortical and brain-stem activities in response to cough stimuli may explain the success of this intervention,[66] although the mechanism is not known.

PHARMACOLOGIC NEUROMODULATION

Centrally acting neuromodulators (e.g., amitriptyline,[67] gabapentin,[68] morphine,[69] baclofen,[70] and nalbuphine[71]), when used alone, have had positive effects on cough-related outcomes in randomized, controlled trials. In addition, a randomized,

Table 1. Factors to Consider for Successful Management of the Common Causes of Chronic Cough.*

UACS due to a rhinosinus condition

The disorder can manifest as a cough–phlegm syndrome and can be misdiagnosed as chronic bronchitis.

All histamine H_1 antagonists do not act similarly; those without anticholinergic properties are not likely to be effective in nonallergic rhinosinus disease, and those with anticholinergic properties may adversely affect coexisting memory disorder, glaucoma, and prostate conditions. In the latter clinical contexts, ipratropium bromide nasal therapy can be considered; in either situation, a sodium chloride–sodium bicarbonate sinus rinse can be considered as well.

UACS can be silent (i.e., the patient may not sense a postnasal drip or recognize their frequent throat clearing).

Allergic rhinitis or failing to avoid allergens should be considered even when symptoms occur throughout the year.

Sinusitis is not always clinically obvious.

Aspirin-exacerbated rhinosinus disease should be considered.

Upper respiratory endoscopy should be considered.

Asthma

Cough can be the sole presenting symptom of asthma (i.e., cough-variant asthma); asthma can also manifest as a cough–phlegm syndrome mimicking chronic bronchitis.

Inhaled medications may exacerbate cough.

A positive methacholine challenge test alone (i.e., without a positive confirmatory response to asthma treatment) may not be diagnostic of asthma.

Nonasthmatic eosinophilic bronchitis

The diagnosis should be considered, the correct test (e.g., F_ENO or sputum eosinophilia) should be ordered, and occupational or environmental causes should be investigated.

GERD

GERD can manifest as a cough–phlegm syndrome mimicking chronic bronchitis.

Cough can be the sole manifestation of GERD, without GI symptoms — that is, so-called silent reflux disease.

Successful medical therapy may require up to 3 mo of intensive treatment before cough starts to abate and may require up to 6 mo before cough resolves.

Acid suppression alone is not likely to improve cough due to GERD, even though it is very likely to decrease GI symptoms.

Cough can be due to non–acid reflux disease.

Cough may be due to GERD even if the cough remains unchanged when heartburn or other GI symptoms abate.

GERD cannot be diagnosed on the basis of the appearance of the vocal cords because inflammatory changes from coughing alone can mimic those due to reflux.

Coexisting conditions or their treatment may be making GERD worse.†

An antireflux diet and weight loss should be considered in order to enhance the function of the lower esophageal sphincter and decrease intraabdominal pressure, and intensive exercise that increases intraabdominal pressure should be avoided; adding GI prokinetic therapy should also be considered.

Cough by itself can provoke reflux events, so coexisting causes of cough that sustain the cycle of cough and reflux should be considered and adequately treated.

ILDs

ILD may not be the only cause of cough in a patient who has the condition; up to 54% of patients with ILD and chronic cough have a common non-ILD cause of the cough.[63]

Triad of UACS, GERD, and asthma or nonasthmatic eosinophilic bronchitis

Two or all three of these conditions may be simultaneous causes of cough.

One or more of these common conditions may be the cause rather than a seemingly obvious cause of cough (e.g., ILD or lung cancer).

All three of these common chronic conditions may intermittently flare, especially with viral respiratory tract infections.

Table 1. (Continued.)

Unsuspected upper and lower airway diseases
Bronchoscopy should be considered if cough persists, even when a chest radiograph and CT studies are normal; the transnasal route allows inspection of the upper as well as lower respiratory tract.

* The information provided is modified and updated from a report by Irwin et al.,[34] which contains additional details regarding diagnosis and treatment. CT denotes computed tomography, FeNO fractional exhaled nitric oxide, GERD gastroesophageal reflux disease, GI gastrointestinal, ILD interstitial lung disease, and UACS upper-airway cough syndrome.
† Coexisting conditions or their treatment that may exacerbate GERD include obstructive sleep apnea, diabetes mellitus with gastroparesis, nitrate treatment for coronary artery disease, calcium-channel blockers for essential hypertension, glucagon-like peptide 1 receptor agonists for diabetes, hormone replacement therapy with progesterone, and phosphodiesterase type 5 inhibitors for erectile dysfunction.

placebo-controlled trial showed favorable cough-related outcomes when multimodal speech therapy was combined with the neuromodulator pregabalin.[72] This combination therapy could be considered if speech therapy alone is not sufficiently successful. All the centrally acting neuromodulators that are promising enough to prescribe on a trial basis have potential adverse effects. Therefore, the risks and benefits of the drugs should be discussed with patients before the treatment is started and should be periodically reassessed and discussed again at well-defined intervals (e.g., monthly) before the treatment is continued. In a recent population-based cohort study involving patients with COPD, the risk of severe exacerbations was 39% higher among patients receiving the gabapentinoids gabapentin and pregabalin than in a matched group of patients who did not receive these agents.[73] Therefore, caution should be exercised in considering this therapy for patients with COPD.

The evidence for treating unexplained or refractory cough with superior laryngeal nerve block is very limited. A single randomized trial[74] suggested significantly improved cough-related quality of life at 27 days in 10 of 17 patients in the group assigned to a series of two nerve block injections, as compared with improvement in 1 of 10 patients in the placebo group. Although no adverse occurrences were reported during or after the trial, it was small and of short duration, and none of the patients completed multimodal cough-suppression speech therapy before or during the trial.

ADDRESSING REACTIVE ANXIETY AND DEPRESSION

Reactive anxiety, depression, or both can develop as complications of unresolved chronic cough[5,51,75,76] and should be addressed if present. These cough-related complications are ameliorated when the cough improves.[51]

PHARMACOLOGIC ANTAGONISTS

Effective pharmacologic antagonists of the vagal signaling underlying cough hypersensitivity would be highly desirable for patients with truly unexplained or refractory chronic cough, barring serious adverse effects.[77] Since heterogeneous mechanisms may underlie unexplained or refractory cough, multiple types of antagonists may be required to effectively treat different subpopulations of patients. Although antagonism of transient receptor potential cation channels (TRPV1 and TRPA1) on vagal C fibers showed initial promise in animal models, such antagonists did not significantly attenuate cough in clinical trials.[78-80]

More recently, antagonists of purinergic receptors (e.g., P2X3 and P2X2/3) have offered promise,[81] particularly gefapixant. However, gefapixant is associated with substantial taste disturbances, which are probably related to P2X2/3 antagonism,[45,82] and the FDA did not approve the drug for chronic cough because of its marginal effectiveness as compared with placebo, at least in the population studied.[2] Other purinergic antagonists, with varying selectivity for P2X3 and P2X2/3 receptors, have been or are being explored, although none have yet been approved for clinical use (Table 2).[83-90] The identification of a safe and effective pharmacologic treatment for cough hypersensitivity, which remains an unmet need, would have the potential to help address the challenging clinical problems posed by unexplained or refractory chronic cough.

SUMMARY

Chronic cough is an important clinical challenge worldwide. Although some reviews of the literature have reported that up to 60% of adults with chronic cough have unexplained or refractory cough,[82] the percentage, based on a rigorous,

Table 2. Purinergic Receptor Antagonists for Chronic Cough.*

Antagonist	Compound Name	Comments
Gefapixant[45]	AF-219, MK-7264	Low selectivity for P2X3 over P2X2/3; frequent taste disturbances; not FDA-approved as effective for chronic cough but licensed for clinical use in the European Union, Switzerland, and Japan
Eliapixant[83]	BAY-1817080	Decreased 24-hr cough counts in phase 2b trial; selectivity for P2X3 over P2X2/3; low rate of taste disturbances; clinical trials suspended for risk of hepatotoxicity
Camlipixant[84,85]	BLU-5937	High selectivity for P2X3 over P2X2/3; low rate of taste disturbances; clinical trials under way
Sivopixant[86]	S-600918	No significant decrease in 24-hr cough frequency in phase 2b trial; selectivity for P2X3 over P2X2/3; mild-to-moderate taste disturbances; 0in clinical trials, not approved for clinical use
Filapixant[87]	BAY-1902607	Decreased 24-hr cough frequency in phase 1–2a trial; high selectivity for P2X3 over P2X2/3; taste disturbances mild to moderate but frequent at higher doses; in clinical trials, not approved for clinical use
Aspirex[88]	DT-0111	Water-soluble inhalational drug candidate; antagonist of P2X2/3; studies in animals and in vitro
PSFL2915[89]	—	Nanomolar-affinity P2X3 inhibitor based on quercetin; no taste disturbance in animal model; studies in animals and in vitro
Quercetin[89]	—	P2X3 inhibitor; no taste disturbance in animal model; studies in animals and in vitro

* FDA denotes Food and Drug Administration.

systematic review,[19] appears to be much closer to 10% when patients are fully evaluated and treated for an underlying cause of cough. In this group of patients, unexplained or refractory cough may in rare cases be due to an underlying psychological or psychiatric condition. For the remaining patients, those with truly unexplained or refractory cough due to permanent cough hypersensitivity, treatment options are limited but include speech therapy, neuromodulatory pharmacotherapies, or both, as well as treatment of anxiety or depression. The hope is that further investigation of purinergic antagonists or other peripherally or centrally acting inhibitors of neural signaling (e.g., sodium-channel blockers, transient receptor potential cation-channel subtype M8 agonists, opioids, neurokinin 1 antagonists, and γ-aminobutyric acid B agonists) will prove promising and that such agents will help meet the clinical challenge of managing unexplained or refractory cough.[77]

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

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