Chronic Cough in Adults

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Faculty

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Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants/associates, and nurses involved in the care of patients with chronic cough.

Accreditations & Approvals

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Course Objective

Chronic cough is difficult to effectively assess and treat, leading to extended periods before diagnosis and significant negative impact on patients' quality of life. The purpose of this course is to provide clinicians with the knowledge and skills necessary to identify and treat patients with chronic cough, regardless of underlying etiology, in accordance with clinical guidelines.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the background and terminology related to chronic cough.
2. Compare and contrast available cough severity measures.
3. Outline the epidemiology of chronic cough and underlying etiologies.
4. Evaluate the impact of chronic cough on various dimensions of patients' lives.
5. Discuss the natural history and course of chronic cough.
6. Describe the pathophysiology of chronic cough.
7. Outline components of the initial evaluation of patients with chronic cough.
8. Identify potential underlying etiologies of chronic cough as well as appropriate management approaches for these conditions.
9. Analyze available treatment modalities for chronic cough of various underlying causes, including upper respiratory, lower respiratory, and reflux-associated cough.
10. Identify appropriate modalities for the treatment of refractory chronic cough, including pharmacotherapy, nonpharmacologic approaches, and investigational agents.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Chronic cough, or cough lasting longer than eight weeks, is a debilitating disease that can result in patients coughing hundreds to thousands of times every day. This physically exhausting and socially isolating condition can persist for years or decades, and degrade the quality of life in nearly every domain, and result in numerous medical and psychosocial consequences, yet its adverse impact on patients is often overlooked or underappreciated by clinicians. While acute cough is typically transient and self-limited, chronic cough often poses a diagnostic and therapeutic challenge; both non-treatment and over-treatment with ineffective medication are common [1; 2]. Cough that persists despite investigation and treatment is especially vexing for patients and clinicians [3].

BACKGROUND

The anatomic, diagnostic protocol (ADP) established in the late 1970s that chronic cough in patients with negative chest x-ray findings is a symptom of asthma, postnasal drip, or acid reflux. Later refined to asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD, it was believed that treating these underlying etiologies led to a favorable outcome in 90% of patients with chronic cough [4; 5; 6].

However, a large proportion of patients with these conditions do not have chronic cough [7]. Moreover, in many patients, cough persists despite treatment of its presumed cause (referred to as refractory chronic cough) or an underlying cause cannot be identified (referred to as unexplained chronic cough) [8]. This suggested that additional pathophysiological processes were involved [7].

In 2014, the European Respiratory Society (ERS) introduced cough hypersensitivity syndrome, defining chronic cough as a distinct clinical entity [9]. The 2020 ERS clinical practice guideline for chronic cough was pivotal in establishing cough hypersensitivity syndrome, influencing subsequent national and international chronic cough guidelines [10; 11; 12; 13].

In 2016, the "treatable traits approach" was introduced to improve the outcomes of pulmonary patients with complex clinical syndromes (e.g., asthma and COPD) and variable treatment responses by moving beyond practice guidelines directed at diagnostic categories as a single disease entity, to identify and treat relevant phenotypic and endotypic "traits" instead [14; 15; 16]. The treatable traits approach gained rapid acceptance in pulmonary medicine and endorsement in chronic cough guidelines [5; 17; 18].

Cough performs an essential physiological function, mediated by cough reflex pathways in the airways and brain. In some individuals, irritation or inflammation of vagal afferent nerves in the airway leads to cough reflex hypersensitivity, the cardinal feature of cough hypersensitivity syndrome, peripheral and central sensitization, and clinical manifestations of allotussia, hypertussia, and/or laryngeal paresthesia (***Table 1***) [3; 19; 20]. The demographic, pathophysiological, and clinical similarities between cough hypersensitivity syndrome and chronic neuropathic pain are numerous. Chronic pain research has substantially informed how chronic cough and cough hypersensitivity syndrome are understood; both are disorders of sensory processing [4; 21; 22].

Sensitization of cough pathways may persist long after resolution of the inciting acute or subacute event. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity. Cough hypersensitivity syndrome may improve with the targeted intervention of other treatable traits. If chronic cough persists, the patient has refractory chronic cough [5].

CHRONIC COUGH TERMINOLOGY	
Term	**Definition**
Acute cough	Cough lasting less than 3 weeks
Subacute cough	Cough lasting 3 to 8 weeks
Chronic cough	Cough lasting more than 8 weeks
Refractory chronic cough	Cough that persists despite guideline-based treatment of the presumed underlying cause(s)
Unexplained chronic cough	No diagnosable cause of cough is found despite extensive investigation for common and uncommon causes
Allotussia	Cough triggered by innocuous stimuli (e.g., laughing, talking, changes in ambient temperature)
Hypertussia	Exaggerated coughing triggered by mildly tussive stimuli (e.g., strong odors, second-hand cigarette smoke)
Urge to cough (laryngeal paresthesia)	A distinct, often debilitating sensation of irritation or "itch" in the throat or chest that precede cough and is not satiated by coughing
Cough reflex hypersensitivity	The cardinal feature of cough hypersensitivity syndrome
Cough hypersensitivity syndrome	Disorder characterized by cough triggered by mildly tussive or innocuous stimuli, with features of allotussia, hypertussia, and/or laryngeal paresthesia

Source: [5; 9; 26] *Table 1*

Refractory and unexplained chronic cough are diagnoses of exclusion. A thorough, systematic clinical workup is required so that non-obvious and obvious causes of chronic coughing can be identified. The treatable traits approach may significantly expand clinically important intervention targets. After a diagnosis of refractory/unexplained chronic cough is made, therapeutic attention shifts to downregulating the hypersensitive cough reflex [5].

Maturation in research and practice has led to novel and emerging therapeutic options for patients with refractory chronic cough. Randomized controlled trials of existing centrally acting agents have identified the efficacy of low-dose morphine and gabapentin [10; 23; 24]. The development of P2X3 receptor antagonists, a novel peripherally acting drug class, has led to the approval of gefapixant for the treatment of refractory chronic cough in the European Union, Japan, and Switzerland, with U.S. Food and Drug Administration (FDA) advisory committee review believed imminent as of 2024 [25]. In a given patient, refractory/unexplained chronic cough may primarily involve peripheral mechanisms, central mechanisms, or both, and no tool is available for predicting therapeutic response to peripherally or centrally acting antitussive agents.

As of 2024, there are no FDA-approved treatments for chronic cough or for refractory chronic cough. When chronic cough persists after potential underlying causes are identified and treated according to current practice guidelines (e.g., for chronic cough related to nonasthmatic eosinophilic bronchitis or GERD), all therapeutic options for refractory chronic cough are prescribed off-label.

Important knowledge advances in this rapidly evolving field are not reaching healthcare professionals in the United States because chronic cough guidelines published for domestic consumption have become outdated. From this course, clinicians will gain current information on chronic cough and refractory/unexplained chronic cough, including the pathophysiology, differential diagnosis, and clinical management, essential for healthcare professionals in primary care, respiratory medicine, and ear/nose/throat (ENT) settings.

COUGH SEVERITY MEASURES

Patients with chronic cough experience cough-related physical, psychological, and social burdens, which can result from different aspects of cough severity, including cough frequency, cough intensity, disruption of daily activities due to cough, and cough-specific health-related quality of life. The severity and impact of chronic cough on physical, psychological, and social domains can be quantified through several validated objective and subjective measures [27].

Patient-reported outcome measures obtain a comprehensive understanding of the impact across these domains [27]. Patient-reported outcomes capture many issues that cannot be assessed effectively by objective measures and are also inexpensive, readily available, convenient, and easy to use for the patient [28]. A minimal clinically importance difference, the smallest change in an outcome that patients would perceive as important, is established for both objective and patient-reported outcome tools [29]. Cough measures mentioned throughout this course are summarized in ***Table 2***. Cough frequencies of greater than 700 over an hour have been recorded [28].

EPIDEMIOLOGY

PREVALENCE

Cough is a frequent reason for seeking outpatient medical attention in the United States, accounting for as many as 30 million clinical visits per year, up to 40% of which result in specialist referral [31].

Chronic cough has a prevalence among U.S. adults of roughly 10%, of whom 92% visited healthcare clinicians in the past six months [32]. Chronic cough is estimated to cost $6.8 billion annually in the United States, and an estimated $3.6 billion is spent annually on over-the-counter therapies [33].

The economic implications of chronic cough include the cost of outpatient visits, plus diagnostic work-ups, prescription medications to treat cough, and lost work and lost school productivity [1]. While inconsistent definitions prohibit direct comparisons of chronic cough prevalence between different countries or ethnicities, chronic cough appears to be more common in Europe, North America, and Australia than in Asian countries [32; 34].

In KNHANES, a nationally representative study of the Korean adult population, the point prevalence of acute (<3 weeks), subacute (3 to 8 weeks), and chronic (>8 weeks) cough was 2.5%, 0.8% and 2.6%, respectively. The modal durations of current cough were less than one week (31.1%), and more than one year (27.7%); this bimodal distribution reflects the different pathophysiology of acute and chronic cough [35].

REFRACTORY AND UNEXPLAINED CHRONIC COUGH

Refractory chronic cough is seen in 20% to 59% of patients presenting to specialist cough clinics [36]. At Kaiser Permanente Southern California, 11,290 patients with specialist-diagnosed chronic cough were treated and followed for one year; 40.6% continued coughing despite etiological treatment by specialists (i.e., refractory chronic cough) [37].

Roughly 10% of patients with chronic cough lack an identifiable cause despite thorough evaluation (i.e., unexplained chronic cough), including 17% of patients with chronic cough in the Kaiser Permanente cohort [1; 37]. Of 43,453 patients receiving primary care for chronic cough in the UK, 31% had ongoing chronic cough in the absence of associated comorbidities (i.e., no causal explanation or unexplained chronic cough) [4].

COUGH MEASURES		
Name	**Domains/Items, Rating and Minimal Clinically Importance Difference (MCID)**	**Comments**
Health-related quality of life patient-reported outcome tools		
Leicester Cough Questionnaire (LCQ)	Seven-point Likert scale (1=all of the time; 7=none of the time); 19 items in 3 domains: physical, psychological, and social. Total score range: 3 (maximal impairment) to 21 (no quality-of-life impairment). MCID: 1.5 to 2.5 increase	The most widely used tool for assessing quality of life impact of chronic cough
Cough Quality of Life Questionnaire (CQLQ)	Four-point Likert scale (1=strongly disagree; 4=strongly agree); 28 items over 6 domains: physical and extreme physical complaints, psychosocial issues, emotional well-being, safety fears, and functional abilities. Total score range: 28 (no adverse effect of cough) to 112 (worst possible impact). MCID: 10.6 to 21.9	Contains more items on physical impact of chronic cough (e.g., fractured ribs, headaches, immune deficiency, tuberculosis)
Hull Airway Reflux Questionnaire (HARQ)	Six-point scale (0=no symptoms; 5=most severe) of 14 items that measure airway hypersensitivity in chronic cough. Total score range: 0 to 70 Normal is <14 MCID: 16	Also used as a diagnostic tool for airway reflux, and to assess unexplained respiratory symptoms
Cough Severity Diary (CSD)	11-point scale (0=never; 10=constantly) of 7 items on frequency; intensity; disruptiveness MCID ≥1.3 total score, −1.4 to −1.1 domain scores	Captures the severity and impact of chronic cough. Developed in response to patient feedback.
Objective assessment tools		
VitaloJAK Cough Monitor Leicester Cough Monitor (LCM)	Electronic cough recording monitors worn by patients to measure cough frequency, typically as coughs per hour over 24 hours MCID: ≥20% to 30% decrease	Does not capture the episodic nature of chronic cough, a primary factor in patients' disease burden
Subjective tools		
Visual Analogue Scale (VAS)	Score range 0 (no cough) to 100 mm (worst cough ever) MCID: 30-mm reduction on the 100-mm cough severity VAS	—
Numerical Rating Scale (NRS)	Score range 0 (no cough) to 10 (worst cough ever)	

Source: [28; 29; 30] *Table 2*

DISEASE BURDEN AND HEALTHCARE UTILIZATION

The Kaiser Permanente study examined the disease burden of chronic cough in comorbidities, medication use, and exacerbations [37]. Diagnoses included GERD (44%), hypertension (42%), allergic rhinitis (33%), chronic rhinitis (31.5%), asthma (31%), chronic sinusitis (24.4%), obesity (24%), upper airway cough syndrome (20.4%), depression (20%), and cough complications (19%). Nearly 40% of patients with unexplained chronic cough consulted at least two different specialist departments. In the previous three years, about half of the patients with emergency department visits (28.5%) or hospitalizations (10%) were for respiratory events [37]. Medications were respiratory: nasal corticosteroids (55%), short-acting b2-agonists (50.5%), inhaled corticosteroids/long-acting b2-agonist (27%), inhaled corticosteroid monotherapy (24%), and leukotriene modifiers (18.6%); non-respiratory: antitussive codeine (59%), proton pump inhibitors (PPIs) (45%), antidepressants (26%), anxiolytics (15.5%), and gabapentinoids (14%); and other: systemic antibiotics (72.4%) and oral corticosteroids (47%).

Over one year, patients with emergency department visits (26%) and hospitalizations (12%) remained high; more than 50% were respiratory-related. Antitussive and psychotherapeutic drugs were dispensed at a frequency similar to the baseline year. The clinical and economic burden was especially high in patients with both respiratory disease and GERD, but chronic cough persistence (40.6%) was similar between subgroups [37].

A subsequent Kaiser Permanente study of patient-level burden used patient-related outcomes (average chronic cough 8 years) [38]. Mean scores were 11 on LCQ (maximum: 21), 33 on HARQ (normal: ≤13), and 57 on CQLQ (maximum: 112). Correlations were high between LCQ and HARQ (–0.65), LCQ and CQLQ (–0.80), and HARQ and CQLQ (0.69). Patients with chronic cough-related respiratory and gastrointestinal disorders were generally similar. Treatment responses were suboptimal. Women (compared with men) and non-White individuals (compared with White individuals) reported significantly worse cough severity and poorer LCQ, HARQ, and CQLQ scores.

The patient-reported burden of chronic cough was substantial, with long duration, high severity, poor health status, high degree of cough hypersensitivity, low quality of life, multiple cough triggers, and frequent laboratory testing, specialist care, and medications. The study provides strong evidence that patients with chronic cough exhibit frequent poor responses to medications and overall control [38].

The objective and patient-reported burden of chronic cough is substantial, particularly in women and non-White minorities, which markedly affects daily living with inadequate response to treatments.

RISK FACTORS

Risk factors of chronic cough include smoking, female sex, older age, obesity, asthma, allergic rhinitis, rhinosinusitis, and angiotensin-converting enzyme (ACE) inhibitor use for hypertension treatment [34; 39].

In the United States, 18% of adults who smoke cigarettes have chronic coughs [39]. Cigarette smokers are three times more likely to report chronic cough than never-smokers and ex-smokers, and the cough is usually due to chronic bronchitis. However, most patients in cough specialist clinics are nonsmokers [19]. Among 1,000 patients evaluated at a cough center in the Bronx, 2.7% were active smokers and 27% former smokers [40]. Of 11,290 Kaiser Permanente patients with chronic cough, 65% were never-smokers and 2.3% were current smokers [37].

Age and sex underlie the burden and prevalence of chronic cough; more than 67% of patients presenting with chronic cough to specialist clinics are female, likely due to gender differences in cough reflex sensitivity [1; 19]. Cough reflex sensitivity was assessed in individuals from China, India, and northwest Europe. No differences between ethnic groups were found, suggesting that racial variation in chronic cough prevalence may not reflect differences

in cough reflex sensitivity and may be influenced by asthma, allergy, or environmental factors [34; 39; 41]. Women in all three ethnic groups demonstrated lower cough thresholds [41].

While chronic cough can occur at any age, the rate rises substantially in women who are 40 years of age or older and is highest in the 60 to 69 age group. The highest rates in men occur between 50 and 69 years of age [1]. In KNHANES, chronic cough increased significantly with age. The odds ratio of 2.20 suggests a substantial increase in chronic cough likelihood for individuals 65 years of age or older (compared with those 18 to 39 years of age). The associations with older age were independent of current smoking and comorbidities [35].

In separate longitudinal European population studies, chronic cough was associated with low educational level and lower socioeconomic status [34]. A systematic review found a significant association between low education level and risk of chronic cough [42].

In South Korea and China, higher male prevalence of chronic cough was attributed to differences in smoking habits and air pollution exposures, respectively [28]. Occupational irritants, such as fumes, gases, cleaning products or dust, may cause cough by triggering cough reflex or by inducing oxidative stress and eosinophilic inflammation, but the effect of such factors on chronic cough remains elusive. Air pollution is an important risk factor for chronic cough. Levels of fine particulate matter ≤2.5 mcm in diameter (or PM2.5) are higher in East Asian than in European or North American countries but the prevalence of chronic cough is lower, suggesting potential host-environment interactions in developing chronic cough [19].

Persistent cough is a class-wide adverse effect of ACE inhibitors, and the 5% to 35% prevalence is much higher in East Asian than in other populations. In genotype studies, the genetic polymorphisms ACE I/D and SLCO1B1 were related to ACE inhibitor-induced cough and were more common in East Asian populations, which may account for the ethnic differences and possibly predict risk of ACE inhibitor-induced cough [43].

PATIENT IMPACT OF CHRONIC COUGH

Patients report numerous cough-related physical and psychosocial effects, most commonly fatigue, sleep disturbance, exhaustion, breathlessness, headache, dizziness, musculoskeletal pain, wheezing, impairment of speech, vomiting, excessive perspiration, self-consciousness, and interference with daily activities [28; 44]. These effects have a significant impact on patients' quality of life.

PHYSICAL IMPACT

During vigorous coughing, intrathoracic pressures may reach 300 mm Hg and expiratory velocities approach 500 miles per hour (mph) (85% of the speed of sound). These physical forces cause many of the cardiovascular, gastrointestinal, genitourinary, quality of life, musculoskeletal, neurologic, ophthalmologic, psychosocial, and respiratory complications of chronic cough, ranging from the relatively minor to life-threatening or even fatal. Comorbid illnesses or older age can magnify these effects [44; 45].

Surgical Complications and Hernia

Surgical complications from uncontrolled coughing include extrusion (i.e., expulsion) of ocular contents during eye surgery, and wound dehiscence (i.e., splitting or bursting open) following cardiac or abdominal surgery. Similarly, severe coughing can cause inguinal, femoral, umbilical, lumbar, or abdominal wall hernia [45].

Fracture

Cough-induced rib fractures, another painful and potentially serious complication of chronic cough, often involve multiple ribs, particularly ribs 5 through 7. The number of ribs fractured is associated with higher mortality rates, particularly in older patients who often have decreased bone density due to osteoporosis (also an adverse effect of long-term corticosteroid treatment). However, rib fractures can also occur in patients with normal bone density [44; 46].

Stress Urinary Incontinence

Stress urinary incontinence, defined as the unintentional loss of urine during or following a bout of coughing or other physical activity, significantly contributes to quality-of-life disruption caused by chronic cough in women. Of 210 consecutive adult women evaluated at a cough center for chronic cough, 63.3% reported stress urinary incontinence induced by cough episodes; stress urinary incontinence developed after the onset of chronic cough and solely occurred during or after coughing in 92.5% and at least daily in 47.3%. For context, 3.5% of similarly aged women in the community experience stress urinary incontinence, while only 5% of men with chronic cough report stress urinary incontinence as an issue significantly impacting their quality of life [28; 47].

Surveys have reported lower rates of urinary incontinence in women with chronic cough, but most women will not volunteer a history of cough-induced stress urinary incontinence unless specifically asked. This may explain the higher prevalence in this study, because the establishment of trust between patient and physician may have encouraged sharing such information. After discussion ensues, patients are often relieved to learn this is a common problem faced by women with chronic cough [47].

Cough Syncope

Cough-evoked syncope is a serious and potentially fatal consequence of coughing. Numerous reports of motor vehicle accidents resulting from cough syncope include the deaths of drivers and pedestrians. While the exact mechanism of remains debated, the required generation of very high intrathoracic pressures likely explains the nearly uniform profile of patients with cough syncope as large male subjects with obstructive airway disease [48]. Cough syncope is considered relatively uncommon, although 10% of subjects with chronic cough in a community sample reported experiencing cough syncope [5; 49]. The mandatory loss of driver's license in some countries (e.g., the UK) has a major impact on employment prospects for these patients [28].

PSYCHOSOCIAL AND QUALITY OF LIFE IMPACT

Chronic cough can interfere with all aspects of patients' lives, including daily living activities, social interactions, home management, recreational activities, and employment. Importantly, when triggers of coughing bouts are very difficult to avoid, the psychosocial impact can be substantial. Chronic cough has a negative impact on relationships, with spouses not being able to tolerate the cough as a key reason for patients' health-related dysfunction [28]. In a multinational European survey of 1,120 persons with chronic cough, most reported that coughing affected their quality of life (96%), disturbed their family and friends (94%), and affected activities they enjoyed (81%) [51].

The psychological effects associated with chronic cough are highly prevalent, with an impact on mental health comparable to that of stroke or Parkinson disease. Studies of patients with chronic cough have reported high rates of anxiety (33% to 52%) and depression (16% to 91%) [28].

Patients may avoid or be uncomfortable in social situations due to the embarrassment of coughing, its effects (e.g., stress urinary incontinence, retching), and/or the perception by others that they have a contagious condition or are a heavy smoker [28]. The COVID-19 pandemic increased the social stigma of persistent coughing due to its association with contagious respiratory diseases [50].

NATURAL HISTORY AND DISEASE COURSE

Little is known about the natural history of cough hypersensitivity, but the available evidence suggests that patients often suffer from it for many years [4]. In a longitudinal study of patients with unexplained chronic cough, cough severity worsened (36%) or was unchanged (23%) over 7 to 10 years. Predictors of cough persistence or improvement could not be identified. Unexpectedly, longitudinal spirometry data showed declines in forced expiratory volumes over one second (FEV1) that were well above population norms for similarly aged nonsmokers.

The striking magnitude of decline argued against a chance finding. Around 10% of patients developed spirometric features of COPD [52].

The abnormally rapid decline in FEV1 and a significant minority of patients developing COPD raise the possibility that unexplained chronic cough is associated with a persistent damaging airway process and could be a risk factor for COPD [52]. A 2023 study confirmed that chronic cough is highly associated with FEV1 decline, regardless of COPD presence, while chronic cough in patients suffering from COPD is associated with lower FEV1, more dyspnea, worse health status, and is an independent risk factor for exacerbations of COPD possibly linked to altered transient receptor potential (TRP) channel function [53].

Cough is often the most bothersome and intractable symptom reported by patients with asthma, and the significant disease burden of chronic cough was described in a prospective cohort of 323 consecutive adult participants with asthma who received optimized asthma therapy. After 12 months, those with chronic cough had more airflow obstruction; worse asthma control and quality of life; increased airway inflammation; upper respiratory tract infection as a trigger; more psychological, rhinitis, and COPD comorbidities; greater work productivity loss and daily activity impairment; and increased exacerbations. These findings call for more attention to chronic cough in asthma [54].

In summary, chronic cough is related to an accelerated FEV1 decline over time, regardless of smoking history or COPD diagnosis, but the relationship between chronic cough and worse clinical outcomes lacks a clear pathophysiological explanation [55].

PATHOPHYSIOLOGY OF CHRONIC COUGH

NORMAL PHYSIOLOGY

The Cough Reflex

Cough is an innate reflex that protects the airways from foreign objects, clears excess secretions, and preserves airway patency. The cough reflex consists of peripheral airway receptors of afferent nerves, cough control centers in the central nervous system (CNS), and efferent nerves.

Cough occurs in three phases [31; 56]. The first is inspiratory, during which the glottis opens widely followed by rapid inhalation sufficient for generating enough air movement to be productive. The second phase is compression. This phase is characterized by the rapid closure of the glottic apparatus and contraction of abdominal and other respiratory muscles compresses the alveoli and bronchiole, increasing intrathoracic pressure to greater than 300 mm Hg. The final phase is expiration, or the sudden opening of the epiglottis and vocal cords results in rapid, high-volume expiratory airflow that may exceed 500 mph in velocity. The force of this process loosens and expels mucous secretions from the airway wall, while the rapid airflow vibrates the larynx and pharynx, inducing the characteristic sounds of cough.

Vagal Afferents

The cough reflex is activated by vagal afferent A-δ and C fibers, sensory neurons originating from brainstem vagal ganglia that innervate the larynx and proximal airways. A-δ fibers are mechanoreceptors, activated by airway mucus, inhaled foreign bodies, and low pH (i.e., acidity). C-fibers are nociceptive chemoreceptors, activated by signaling molecules and mediators of inflammation or tissue damage within the airway [19; 25; 57; 58].

Neurobiological Processes

Complex neurobiological processes in the peripheral nervous system, brainstem, and higher cerebral cortex mediate coughing [59]. Receptors (e.g., P2X3 purinergic receptors, voltage-gated sodium channels [NaV], bradykinin receptors, and transient receptor potential [TRP] ion channels) and neuropeptides (e.g., substance P, calcitonin gene-related peptide [CGRP]) play important roles [60].

Noxious mechanochemical stimuli in the airways activate ligand-gated ion channels and G protein-coupled receptors on vagal nerve endings; NaV channels depolarize, propagating the signal up the vagus nerve to first-order synapses in brainstem nuclei. From there, the signal is relayed by second-order neurons to brainstem and spinal motor neurons to reflexively modify breathing; to third-order neurons of the primary somatosensory cortex where the unpleasant urge-to-cough sensation is mediated; and to higher-order cortical neurons that mediate conscious perception of cough [23; 60].

These ascending third-order pathways enable perception of airway irritation, and regulatory control of descending motor pathways that terminate in the brainstem and in spinal respiratory circuits [22; 61]. Under physiologic conditions, higher inhibitory brain processes permit the modification of coughing behavior, and the urge to cough may be suppressed [21].

Extrapulmonary airways (i.e., larynx, trachea, and mainstem bronchi) are also reflexogenic sites essential for preventing aspiration, inhalation of noxious chemicals, and accumulation of excessive mucus; all can induce reflex coughing with irritation of vagal afferent nerves [21].

Coughing is a reflex and a voluntary behavior with or without the sensation of an urge to cough. Reflex cough, behavioral cough, and the urge to cough (which precedes the motor act of coughing) are three separate entities, each dependent on their own neural processes [21; 22]. The relevance of these neurophysiological processes is apparent when considering the development of cough hypersensitivity syndrome [21].

PATHOPHYSIOLOGY OF CHRONIC COUGH AND COUGH REFLEX HYPERSENSITIVITY

Chronic cough, unlike protective cough, is a pathologic state that no longer serves a physiologic role [60]. Excessive coughing is a consequence of increased activation of neuronal cough-mediating pathways due to [62; 63]:

- Excessive activation of airway vagal afferent terminals by chemical or mechanical irritants
- Neuroplastic changes in vagal afferent fibers
- Neuroplastic changes in the CNS

Nervous system plasticity, or malleability, dictates that excessive stimulation of peripheral nerve fibers can reshape their excitability through changes in receptor expression; synaptic transmission in the CNS is subsequently altered, further increasing the gain within the system [62].

Chronic cough is most associated with and traditionally considered a symptomatic byproduct of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and/or GERD, but most patients with these chronic inflammatory diseases do not have chronic cough. Further, cough severity correlates poorly with cough-associated disease severity, and chronic cough can occur in the absence of these conditions as unexplained chronic cough or unexplained chronic cough [19; 20; 64]. This implies individual differences in cough reflex sensitivity and that hypersensitivity of airway sensory nerves may underlie chronic cough [65].

Cough hypersensitivity, defined as repeated episodes of coughing often in response to minimal or no discernible triggers, is common to all persons with chronic cough [66]. Extracellular adenosine triphosphate (ATP) may play a prominent role in cough hypersensitivity. During cellular injury or inflammation, cells release ATP to alert neighboring cells to damage. In respiratory conditions associated with chronic cough and airway inflammation, such as COPD and asthma, extracellular ATP may be elevated and sensitivity to ATP is heightened [33].

The NK-1 receptor and its ligand, substance P, may also be involved in inducing and maintaining cough hypersensitivity, both peripherally and centrally, either indirectly through inflammatory mediators or directly by stimulating sensory nerve fibers [33].

Cough Hypersensitivity Syndrome

Cough hypersensitivity syndrome frames chronic cough as a hypersensitivity disorder, akin to chronic pain. Sensitization of vagal afferents by upper or lower airway inflammation leads to increased cough sensitivity to normally anodyne stimuli, the cardinal feature of cough hypersensitivity syndrome [22; 58].

In chronic cough, as in chronic pain, peripheral sensitization is necessary but probably insufficient without central sensitization, which alters the efficacy of neurotransmission in the brainstem and regulation of cough reflex-mediating brain pathways [21]. Patients with cough hypersensitivity or chronic pain have shown abnormal activity in the same midbrain areas that amplify incoming cough (or pain) signals [58; 67; 68].

Chronic pain research substantially informs the conceptual transformation in how chronic cough and refractory chronic cough are understood. Both disorders involve abnormal sensory processing. Taking inspiration from chronic pain, hypertussia describes abnormal excessive coughing in response to airway irritation. Allotussia describes coughing in response to innocuous stimuli. Laryngeal paresthesia describes noxious sensations in the throat or chest associated with an "urge to cough." Peripheral and central sensitization describe processes that alter cough pathway function [62; 63].

Peripheral Sensitization

Dysregulation of airway innervation contributes to chronic coughing and is considered the main driver of cough in refractory chronic cough [63].

In airway inflammation, vagal neuron sensitization and plasticity is shown by increased production of neuropeptides, upregulation of glutamate receptors and nociceptive ion channels (e.g., TRPV1), and lower thresholds for activating sensory-evoked cough responses. Neuropeptide upregulation occurs in airway sensory neurons where they are not normally expressed. These effects underlie hypertussia by expanding the cough-evoking stimuli field [21].

For example, bronchoscopic biopsies of patients with chronic cough demonstrated increases in airway epithelial nerve length and branching. The remodeling of these vagal C fibers may contribute to airway hypersensitivity through increased density of fiber terminals and enlargement of their receptive fields. The shearing forces of chronically coughing and/or the resultant release of inflammatory mediators (e.g., ATP) may explain the increased density of epithelial innervation [69].

Whether the primary stimulus for peripheral sensitization is cellular damage, mechanical stress, or nociceptor stimulation is unclear, as all three can trigger ATP release, activating P2X3 receptors [59].

Central Mechanisms

While peripheral nervous system dysfunction is the most-described component of cough hypersensitivity, central dysfunction plays a fundamental role [70]. Patients with cough hypersensitivity attempting to voluntarily suppress coughing show reduced activity in dorsomedial prefrontal and anterior midcingulate cortices, suggesting diminished ability to inhibit cough reflex activation [66; 67; 71].

Patients with refractory chronic cough demonstrate structural and functional alterations in the left frontal brain regions, including lower gray matter volume and enhanced frontoparietal functional connectivity, which may underlie the higher cough scores, greater psychosocial impact, longer disease duration, and impaired cough inhibition in these patients [72].

Studies of chronic cough in asthma and nonasthmatic eosinophilic bronchitis identified increased neuronal sensitivity and subsequent central sensitization via mechanisms of inflammatory-mediated nociceptor sensitization and altered afferent nerve terminal excitability, phenotypic changes in vagal afferent neurons, and central neuroplasticity resulting from increased synaptic signaling from peripheral afferents [73].

The contribution of CNS mechanisms accounts for the efficacy of centrally acting medications (e.g., gabapentin and low-dose morphine) in patients with refractory chronic cough [58].

Laryngeal Hypersensitivity

A study of refractory/unexplained chronic cough patients with cough hypersensitivity referred to a cough clinic suggests highly prevalent laryngeal dysfunction. The 12-month cohort of all referred patients showed high rates of cough hypersensitivity (100%), multiple cough triggers (75%), laryngeal paresthesias (95%), voice abnormalities (50%), upper airway dyspnea (25%), and laryngeal functional abnormalities on nasoendoscopy (73%). Given the frequent constellation of symptoms typifying laryngeal dysfunction and cough hypersensitivity, the authors suggest designating laryngeal hypersensitivity as a specific cough phenotype [74].

Many refractory chronic cough cases have a sensory neuropathic etiology in the hypopharynx and larynx, with laryngeal hypersensitivity a key mechanism [75]. Pharyngeal/laryngeal sensations (e.g., irritation, tickle, throat-clearing), frequently associated with upper airway cough syndrome and reflux cough, may represent sensory neuron dysfunction of vagal afferents in the upper airways and a phenotype of cough hypersensitivity syndrome. Dysphonia, dysphagia, dyspnea, and abnormalities of vocal fold motion on laryngoscopy may present with chronic cough as part of the pharyngeal/laryngeal nerve dysfunction seen in cough hypersensitivity syndrome [76].

Autonomic Dysregulation

There is also evidence of broader autonomic nervous system dysregulation. Compared with healthy controls, patients with chronic cough report more frequent and severe autonomic symptoms in gastrointestinal, orthostatic intolerance, bladder, and pupillomotor domains, primarily in parasympathetically mediated systems, suggesting this population may suffer from dysautonomia. Whether this results from coughing, or if both the cough and dysfunction are part of wider vagal pathology, is unclear [70].

SUMMARY

Functional changes in TRPV1, TRPA1, and P2X3 nerve channels and the development of peripheral and central sensitization are thought to turn cough from a defensive reflex into a cough hypersensitivity syndrome [77]. Hypersensitivity of the cough reflex and deterioration in central inhibition of the cough explain cough persistence [78].

Cough hypersensitivity syndrome is identified by symptoms of allotussia, hypertussia, and/or laryngeal paresthesia and may improve with the treatment of other treatable traits. If the chronic cough persists, the patient has refractory chronic cough [5].

Owing to nervous system plasticity, sensitization of cough pathways may persist long after resolution of the inciting event, such as acute viral airway infection. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity [5].

Currently, there are no available methods to identify susceptibility to nervous system plasticity and sensitization, objectively diagnose cough hypersensitivity syndrome, or predict treatable versus refractory chronic cough.

According to the European Respiratory Society, cough hypersensitivity through cell damage and inflammation underlies much of the increased cough seen in other pathologies. The different pathological processes in individual conditions contribute to the disease-specific heterogeneous etiology of cough in other lung disease.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Level of Evidence: Expert Opinion/Consensus Statement

INITIAL EVALUATION OF CHRONIC COUGH

When initially encountering a patient with chronic cough, the primary task is to perform a thorough evaluation that seeks potential underlying treatable causes of chronic cough and to treat the cause(s) according to current clinical practice guidelines [99]. These patients typically undergo extensive medical workup and treatment across multiple subspecialties without improvements in their symptoms, and clinicians should try to break the often-repetitive cycle of investigations, empirical treatment, and worry experienced by these patients [75]. The degree to which patients have been investigated varies, so basic tests may be required. Further investigations depend on the individual's presentation [5]. After a diagnosis of refractory chronic cough is made, the therapeutic focus shifts from identification and treatment of underlying causes to suppression of the hypersensitive cough reflex [99].

The initial evaluation (detailed history and physical examination) accomplishes the key tasks of identifying or ruling out a wide range of diseases underlying the chronic cough and identifying any danger signs that may indicate a diagnosis that needs urgent attention. Any positive findings should guide the initial management [8; 44].

DEFINITIONS OF COUGH

To eliminate confusion on how to define cough, the American College of Chest Physicians (ACCP) and the ERS have standardized the definition of cough according to its duration [10; 100]. Consistently applying these guideline-established definitions is crucial [2].

Thus, the first step in evaluating cough is to determine its duration. This also helps to narrow the differential diagnosis based on the most common underlying causes [10; 100]:

- Acute (<3 weeks) cough:
  - Infectious etiologies, especially with viral causes
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Pneumonia
  - Environmental exposures
- Subacute (3 to 8 weeks) cough:
  - Postinfectious cough
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Upper airway cough syndrome
- Chronic (>8 weeks) cough:
  - Upper airway cough syndrome
  - Asthma
  - Nonasthmatic eosinophilic bronchitis
  - GERD

In chronic cough, allergies are considered secondary to upper airway cough syndrome or asthma.

When cough has lasted three or more weeks and is not postinfectious, some experts recommend not waiting for eight weeks to begin a chronic cough workup [6].

PATIENT HISTORY

A detailed evaluation is performed and should include the following [2; 5; 6; 8; 10; 100]:

- Presenting symptoms or cough characteristics:
  - Duration
  - Productive or nonproductive
  - Associated symptoms (e.g., rhinorrhea, nasal congestion, sneeze, fever, sputum production, hemoptysis, dyspnea, weight loss, dysphonia, dysphagia, peripheral edema)
  - Prior episodes
  - Preceding illnesses (e.g., recent viral infection)
  - Clarify whether the patient is coughing, throat-clearing, or both.
- Medical history, including pulmonary and extrapulmonary (e.g., GERD, hypertension, allergic, immune) conditions

- Surgical history, especially involving cardiac, pulmonary, gastrointestinal, and otolaryngological organ systems
- Family history of atopic disease
- Exposure history
  - Tobacco and cannabis smoking or vaping (e.g., electronic cigarettes)
  - Occupational and environmental exposures
  - Recent travel
  - Country of origin
  - Potential sick contacts
- Review current medications for potential iatrogenic cause. Ask about current use of both prescribed and over-the-counter NSAIDs and aspirin.

It is important to always rule out culprit medications by assessing whether the patient is taking an ACE inhibitor antihypertensive, NSAID, sitagliptin, or any medication that may be suspected of inducing the cough. A dry persistent cough from ACE inhibitor use is caused by bradykinin, substance P, and prostaglandins that accumulate in the upper respiratory tract or lung when ACE is inhibited, enhancing the cough reflex. Stopping the drug typically resolves coughing within four weeks or improves it sufficiently for a diagnosis of iatrogenic cough. Switching to angiotensin II receptor blockers (ARBs) provides antihypertensive control without provoking coughing [6; 101].

PHYSICAL EXAMINATION

The physical examination of a patient presenting with chronic should assess for nasal congestion, pharyngeal erythema, tonsillar swelling, hoarseness, stridor, wheeze (particularly focal wheeze), crackles, and other adventitious sounds.

MANDATORY INITIAL TESTS

Initial diagnostic testing should include chest radiography (usually x-ray). Spirometry testing of pulmonary function is recommended pre- and post-bronchodilator to evaluate possible asthma or COPD.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Respiratory Society suggests that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have normal chest radiograph and physical examination.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, very low-quality evidence

"RED FLAG" ASSESSMENT OF SERIOUS UNDERLYING CAUSES OF COUGH

In cough of any duration, the initial evaluation should identify any danger signs that may indicate a diagnosis requiring urgent attention. Important danger signs that will need further evaluation with chest x-ray and possibly laboratory testing and computed tomography (CT) include [44; 100]:

- Systemic symptoms (raises suspicion for chronic infection or rheumatic disease):
  - Fever
  - Night sweats
  - Weight loss
  - Peripheral edema with weight gain
- Hemoptysis, an indicator of infection (e.g., bronchiectasis, lung abscess, tuberculosis), cancer (e.g., lung, bronchus, or larynx), rheumatologic diseases, heart failure, or foreign body inhalation
- Prominent dyspnea, especially at rest or at night, a possible clue to airway obstruction or lung parenchymal disease
- Possible foreign-body inhalation (requires urgent bronchoscopy)
- Smoker older than 45 years of age with a new cough, change in cough, or co-occurring voice disturbance
- Hoarseness
- Trouble swallowing when eating or drinking

- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

RECORDS REVIEW

If patients have undergone prior evaluations for upper airway cough syndrome, asthma, GERD, or nonasthmatic eosinophilic bronchitis, obtain and review these medical records, including laboratory values, diagnostic reports, and treatments prescribed, to determine if these etiologies have been accurately assessed, diagnosed, and treated. Patients may not have been completely evaluated for these conditions yet diagnosed based on their response (or lack thereof) to empiric trials, which is important to ascertain [2].

THE ANATOMIC DIAGNOSTIC PROTOCOL (ADP)

Even in current international guidelines that emphasize treatable traits, the anatomic diagnostic protocol (ADP) remains useful in the clinical workup of patients with chronic cough for identifying possible treatable conditions, while recognizing that treatment of the presumed cause(s) does not always improve the cough [19]. Consistent with the ADP, this section organizes chronic cough etiologies and management by their lower airway, upper airway, and gastroesophageal origin.

In nonsmoking, immunocompetent patients not taking an ACE inhibitor and with unremarkable chest radiography, cough lasting longer than eight weeks is considered a symptom of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, GERD, or any combination [6]. These four common causes to consider should be evaluated (***Table 3***).

The ADP has been modified to simplify the clinical workup by emphasizing empiric treatment trials for suspected, but not fully investigated or confirmed, disease [77]. According to the rationale, objective diagnostic methods for upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and GERD are technically demanding, sometimes difficult for patients, and require specialized instruments and personnel. Further, with GERD, discerning causal and temporal relationships between acid reflux and cough is difficult. Thus, sequential empirical therapy is frequently considered and is advised by some before embarking on extensive workup [39; 102]. Because symptom reduction is said to confirm a diagnosis, empiric treatment has been called a diagnostic-therapeutic trial [1].

DIAGNOSTIC TESTS

If airway disease is suspected, the treatable traits approach is advocated to identify and optimize treatment of pulmonary, extrapulmonary, and behavioral traits (***Table 4***). Optimizing airway disease treatment is usually the key to managing cough in these patients. Cough hypersensitivity may be a trait in airway disease and require additional specific treatment [5].

Classic asthma, cough-variant asthma, and nonasthmatic eosinophilic bronchitis are clinical diagnoses with no clear-cut, absolute diagnostic test available to either rule asthma in or out as the cause of a patient's chronic cough [10]. In a stepwise diagnostic approach, initial abnormal lung function testing suggests classic asthma or COPD; normal testing is inclusive of cough-variant asthma, nonasthmatic eosinophilic bronchitis, or chronic bronchitis. Absence of bronchial hyperreactivity to methacholine challenge in patients with normal physical exam and spirometry findings suggests nonasthmatic eosinophilic bronchitis. Negative airway responsiveness can exclude cough-variant asthma. Abnormal spirometry contraindicates bronchial challenge testing [104].

Lung Function Tests

Spirometry can reveal airflow obstruction, variability (>20%) in peak expiratory flow measurements, or an improvement in threshold testing (FEV1 >12%, improvement from baseline of >200 mL) in response to bronchodilators (b-2 agonists). Abnormal spirometry can be seen in patients with classic asthma and COPD, but not cough-variant asthma or nonasthmatic eosinophilic bronchitis [104].

EVALUATION OF COMMON CAUSES OF CHRONIC COUGH				
Evaluation	**Common Causes**			
	Asthma	**NAEB**	**UACS**	**GERD**
Spirometry	X			
Bronchodilator reversibility	X			
Bronchoprovocation challenge	X			
Allergy evaluation	X	X	X	
Sputum eosinophilia		X		
Blood eosinophilia		X		
Fractional exhaled nitric oxide (FeNO)		X		
Sinus imaging			X	
Nasopharyngoscopy			X	
Empiric treatment trials[a]	X	X	X	X
[a]Diagnostic-Therapeutic Trials				
UACS	First-generation oral antihistamines Inhaled corticosteroids Inhaled ipratropium			
Asthma or NAEB	Inhaled corticosteroids Systemic (oral) corticosteroids Leukotriene receptor antagonist			
GERD	High-dose proton pump inhibitor (PPI) acid-suppression therapy Anti-reflux lifestyle measures Pro-kinetic agent: metoclopramide			
GERD = gastroesophageal reflux disease; NAEB = nonasthmatic eosinophilic bronchitis; UACS = upper airway cough syndrome.				
Source: [1; 82; 83; 100]				*Table 3*

Spirometry

An FEV1/forced vital capacity (FVC) ratio of <70% (or below the lower limit of normal, if available) is a positive test for obstructive airway disease (obstructive spirometry) [103].

Bronchodilator Reversibility Test

Bronchodilator reversibility testing is recommended in patients with obstructive spirometry (FEV1/FVC ratio <70%). Following short-acting beta-agonist bronchodilator administration, improvement in FEV1 of ≥12%, together with an increase in volume of ≥200 mL, is a positive test [103].

Airway Inflammation Measures

Asthma is often, but not always, mediated by eosinophilic inflammation, and measurement of airway inflammation has clinical utility because eosinophilic airway inflammation is associated with favorable inhaled corticosteroid response. Fractional exhaled nitric oxide (FeNO) levels and peripheral blood eosinophil count indirectly estimate airway eosinophilia [5; 10; 84]

Significant (>3%) sputum eosinophilia is the criterion standard for eosinophilic inflammation, but sputum eosinophilia may not be routinely available. Blood eosinophil count is simple and readily available but has diurnal and seasonal variability so multiple assessments should be performed. A blood eosinophil count >0.3 cells/mcL may indicate eosinophilic airway inflammation.

AIRWAY INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	**Description**	**Utility**
Lower Airway		
Chest radiograph	Plain radiograph of the chest from anterior or posterior aspect (occasionally lateral view)	**Mandatory**. Abnormal findings should be pursued first as potential cause of chronic cough.
Spirometry	Maximal inhalation and exhalation into a spirometer measures forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)	**Mandatory** test for airflow obstruction. FEV1 ≤80% or FEV1/FVC ratio <70% predicted for age and sex prompts reversibility testing.
Bronchodilator reversibility test	Pre- and post-bronchodilator spirometry in patients with obstructive airflow to measure change 10 to 15 minutes after SABA (e.g., albuterol)	Increase in FEV1 ≥12%, or ≥200 mL, after SABA indicates reversibility. Ideally, perform before starting asthma therapy.
Fractional exhaled nitric oxide (FeNO)	Measurement of nitric oxide levels in exhaled breath to indicate eosinophilic airway inflammation	Increased FeNO levels correlate with type 2 airway inflammation in asthma or nonasthmatic eosinophilic bronchitis. High FeNO (>30 ppb) may predict corticosteroids response.
Induced airway sputum	Patient inhales nebulized hypertonic saline (3% to 5%), inducing sputum expectoration for differential cell count analysis.	The criterion standard assessment of eosinophilic airway, routinely used in cough clinics but not widely adopted
Bronchial challenge/ provocation test	Patient inhales histamine or methacholine; a ≥20% drop in FEV1 confirms bronchial hyperresponsiveness (positive test).	Positive test with isolated cough and normal spirometry indicates an anti-asthma therapy trial. A negative test makes asthma improbable.
Chest computed tomography (CT)	Provides better resolution of lung parenchymal and mediastinal structures than chest x-ray	In productive cough, may identify early lung fibrosis or confirm bronchiectasis. Low utility in chronic cough with normal physical exam and chest x-ray.
Bronchoscopy (fiberoptic)	Allows direct visualization of the upper and lower airways and bronchoalveolar lavage to obtain specimens	**Mandatory** in all patients with suspected inhaled foreign body. Endobronchial appearance typically normal in chronic cough with normal chest x-ray.
Upper Airway		
Laryngoscopy (fiberoptic)	Allows direct inspection of laryngopharyngeal area including epiglottis and vocal cords	Typically unremarkable, but may reveal laryngopharyngeal reflux. Suspected laryngeal dysfunction prompts challenge laryngoscopy.
Sinus CT imaging	Visualizes the frontal, ethmoid, and maxillary sinuses and nasal passages	May provide evidence of sinus opacification or mucosal thickening. Unclear role in patients with chronic cough without nasal symptoms.
Other		
Peripheral blood eosinophil count	Measures absolute number or relative percentage of eosinophils in peripheral blood	May help predict corticosteroid response in respiratory diseases; utility in chronic cough not established.
ppb = parts per billion, SABA = short-acting beta-agonist.		
Source: [10; 19; 103]		*Table 4*

FeNO is a surrogate marker of eosinophilic airway inflammation and inhaled corticosteroid response in classic asthma. FeNO has a relatively high specificity in predicting asthma among patients with chronic cough, but a cut-off level for diagnosis lacks consensus. Elevated FeNO levels (>40 ppb) support a diagnosis of asthma with typical symptoms, but the usefulness in predicting inhaled corticosteroid response in chronic cough is uncertain [5].

A meta-analysis of studies in patients with chronic cough reported significantly higher inhaled corticosteroid response rates in high (>25 ppb) compared with low FeNO (87.4% vs. 46.3%) [105]. After three weeks of high-dose inhaled corticosteroids, the response rate (defined as a ≥1.3-point increase in LCQ) was 68% in patients with high FeNO and no other apparent etiology; LCQ scores and FeNO significantly improved. However, improvements in cough were unrelated to changes in FeNO levels, challenging their direct mechanistic link [106]. Thus, an inhaled corticosteroid trial should be prompted with FeNO >25 ppb but avoided with FeNO <25 ppb unless other factors suggest eosinophilic airway disease [5]. Treatment decisions should not solely hinge on FeNO values [6].

Airway Hyper-Reactivity Measures

In patients with negative physical examination and spirometry findings, bronchial challenge testing (e.g., methacholine) should be performed to confirm airway hyper-reactivity consistent with symptomatic asthma [84]. Bronchial challenge testing is recommended in patients with reactive airway diseases to help diagnosis of asthma and nonasthmatic eosinophilic bronchitis as a cause of chronic cough. A negative bronchial challenge test (defined as an FEV1 decrease of <20% at the highest methacholine challenge dose [10 mg/mL]) has a high negative predictive value of asthma as an etiological diagnosis in chronic cough [104].

Airway eosinophilic inflammation can be present in both asthma and nonasthmatic eosinophilic bronchitis but can be distinguished by a methacholine inhalational challenge (positive in asthma, negative in nonasthmatic eosinophilic bronchitis) because substantially more mast cells localize in the smooth muscle layer in asthma compared with nonasthmatic eosinophilic bronchitis [6].

IDENTIFICATION AND MANAGEMENT OF UNDERLYING ETIOLOGIES

The concept that chronic cough is a disease in its own right has only recently gained acceptance. Different phenotypes of this condition are recognized (e.g., asthmatic cough, reflux cough), but the underlying pathology involves hypersensitivity of the vagus nerve and its central projections. The paradigm of asthma, GERD, and postnasal drip causing the symptom of chronic cough was promulgated from the 1980s onwards. However, after it became apparent that many patients suffering from chronic cough with a particular disease label (e.g., asthma, GERD) failed to respond to treatments for that condition, clinical practice guidance changed [79].

Systematic evaluation and treatment guidelines for chronic cough, based on the anatomic locations of receptors and afferent pathways in the cough reflex, first appeared in 1977 [80]. Using such an approach was estimated to determine the cause of chronic cough in 100% of patients, and the subsequent cause-specific treatment was reportedly almost always successful. Termed the ADP, this stepwise diagnostic approach involves a targeted patient history and physical examination to investigate the possible cause/s of their cough. This information is then used to initiate a stepwise treatment approach until resolution of the cough symptoms [77].

The AACCP recommended the ADP in their comprehensive clinical practice guideline on cough in 1998 and in 2006 [81; 82]. More recent ACCP guidelines evaluate ADP components and provide treatment recommendations on the major causes of cough, including chronic cough due to GERD in 2016, asthma and nonasthmatic eosinophilic bronchitis in 2020, stable chronic bronchitis in 2020, and unexplained/refractory chronic cough in 2016 [77; 83; 84; 85; 86].

However, the understanding of chronic cough has evolved beyond the ADP, especially since 2020 with incorporation of cough hypersensitivity and the treatable traits approach into clinical practice guidelines and endotyping of many cough-associated chronic inflammatory conditions. These knowledge advances are not efficiently reaching U.S. clinicians, because ACCP guidelines on chronic cough have not kept pace. While the ADP remains an important structure of the diagnostic workup for chronic cough patients, its assumptions have been supplanted in recent international chronic cough guidelines.

THE "TREATABLE TRAITS" APPROACH IN CHRONIC AIRWAY DISEASES

In the late 19th century, Sir William Osler established the modern approach to the diagnosis and treatment of disease, based on the principal organ system where symptoms and signs manifest, with some biological correlates. The Oslerian paradigm of disease classification using diagnostic categories has been in use for more than 100 years, with substantial merit, but limitations of the diagnostic label approach have become evident [16].

As noted, in 2016, the treatable traits approach was introduced to pulmonary medicine to overcome the shortcomings of the diagnostic label approach, which does not consider the biological complexity of airway diseases, the distinct endotypes present in each patient, or common patterns of disease such as chronic cough [14; 17].

The treatable traits approach addresses the complexity of chronic airway diseases as heterogeneous, frequently overlapping, and often comorbid conditions. In clinical trials of patients with asthma and COPD, the treatable traits approach led to significantly greater improvements in health-related quality of life and biological outcomes and reductions in primary care visits (compared with usual care) [16].

A trait is defined as clinically relevant, measurable, and treatable. These traits can be identified by their phenotypes and/or endotypes in pulmonary, extrapulmonary, and behavioral/environmental domains, and can coexist, interact, and change over time in the same patient. The treatable traits approach is agnostic to the traditional diagnostic labels of asthma or COPD and can be used in any patient with airway disease. The treatable traits approach often extends beyond the diagnostic label itself to find more treatment targets, especially in complex patients with suboptimal response to conventional guideline-based treatment [87; 88]. In other words, the treatable traits approach represents a transdiagnostic model.

In asthma, many extrapulmonary traits present as connected comorbidities, meaning they coexist with asthma and may share mechanisms. Extrapulmonary traits (e.g., chronic rhinosinusitis, GERD, anxiety, atopic dermatitis) are clinically relevant as they predict poor outcomes, confound the management of asthma, and are treatable themselves. Through multidimensional assessment of pulmonary, extrapulmonary, and behavioral/environmental domains, the treatable traits approach identifies and targets extrapulmonary traits with effective treatments, improving both asthma and the comorbidity [89].

In the 1970s, the ADP extended the Oslerian classification system to cough, addressing the three common causes (asthma, postnasal drip, reflux) arising from three different anatomical areas. Refined to four causes (asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD), this approach benefitted many patients,

but in 30% to 40% of these patients, the coughing continues or a presumed cause cannot be identified [16; 90]. In 2023, COPD was added to become a fifth common potential underlying cause of chronic cough [24].

Chronic cough is associated with airway and reflux diseases that are heterogeneous, frequently overlapping, and often comorbid, the same characteristics the treatable traits approach addresses [14; 17]. For instance, asthma is a clinical syndrome with varying phenotypes and endotypes, rather than a single disease entity. COPD is an umbrella term encompassing different respiratory conditions sharing airflow obstruction. Asthma is not always eosinophilic, and GERD is not necessarily acidic [15]. Despite its relatively recent appearance, the treatable traits paradigm is endorsed throughout pulmonary medicine and in post-2019 (international) clinical practice guidelines on chronic cough.

ENDOTYPES OF COUGH-RELATED CHRONIC INFLAMMATORY DISEASES

A phenotype is an observed characteristic resulting from interactions between genotype and environment. An endotype is a specific biological pathway that forms the basis of observable traits in the phenotype [56].

In the 2016 treatable traits paper, the authors broadly call for a shift away from the classical Oslerian top-to-bottom approach (i.e., from symptoms to mechanisms) to reclassifying airway diseases bottom-up, by linking causal molecular pathways (i.e., endotypes) to disease phenotypes (i.e., from molecules to symptoms) [14].

This has been unfolding in allergy and immunology, and these advances are highly relevant to pulmonary medicine and to chronic cough. For instance, the chronic inflammatory diseases of asthma, allergic rhinitis, chronic rhinosinusitis with or without nasal polyposis, eosinophilic esophagitis, and atopic dermatitis, are now defined by a constellation of symptoms that may result from different pathological mechanisms and not as homogeneous diseases [91].

The discovery of new endotypes in allergic and immune diseases has prompted the transition from symptom-focused disease descriptions to biomarkers and pathogenetic pathways—from phenotypes to endotypes [91]. The imperative for transitioning to endotypes is heightened by FDA approval of several biologicals that target specific inflammatory pathways important in disease pathophysiology [92]. These include the most common chronic cough-associated disorders.

Immune dysregulation has been endotyped as type 1, type 2, and type 3 responses. Asthma has been commonly dichotomized as type 2 and non-type 2. Type 2 inflammation is the best-characterized endotype [91; 93; 94; 95].

Type 2 inflammation involves eosinophils as the key players, which contribute to chronic allergic inflammation by producing cytokines, or interleukins (IL), with specific roles in the inflammatory pathway. IL-5 promotes eosinophil recruitment to sites of inflammation. IL-4 and IL-13 promote immunoglobulin E (IgE) production and immune cell trafficking to tissue, driving and sustaining the type 2 response, tissue damage, and chronic inflammation. IL-31 activates binding sites on sensory neurons, which release CGRP and nerve growth factor, causing neurogenic inflammation. In non-type 2 asthma, Th2 cells migrate to asthmatic bronchi and change their phenotype to produce T1 effector cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), inducing bronchial epithelial apoptosis and remodeling. TNF-α promotes neutrophilic inflammation, which correlates with sputum TNF-α levels in patients with severe asthma. In type 3 inflammation, innate lymphoid cells type 3 (ILC3), T helper lymphocyte type 17 (Th17), and Th22 cells produce cytokines IL-17, IL-22, and IL-23. This mechanism is particularly relevant in the pathogenesis of chronic rhinosinusitis with nasal polyps and neutrophilic asthma [91; 93; 94; 95].

In 2023, the European Academy of Allergy and Clinical Immunology (EAACI) published an updated disease taxonomy with advances in biomarkers, pathogenetic and metabolic pathways, and pathogenic genetic variants. This expanded nomenclature characterizes the following types with relevance to chronic cough [91].

Type V: Epithelial Barrier Defect

The epithelial barrier defect and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation and release of inflammatory cytokines, chemokines and inflammatory mediators (histamine, leukotrienes, reactive oxygen species). The sequence of events eventually leads to tissue damage in asthma, chronic allergic rhinitis, chronic rhinosinusitis, and chronic rhinosinusitis with nasal polyps.

Type VI: Metabolic-Induced Immune Dysregulation

Obesity is a distinguishing variable for clustering and classifying asthma subtypes, and the number of obese patients with asthma has risen dramatically with increasing obesity rates. The obese asthmatic, more likely to be female with adult-onset asthma and to become corticosteroid resistant, has a higher risk of being hospitalized and more frequently presents with severe disease. Higher body mass index (BMI) is associated with increased circulating inflammatory mediators, blood neutrophils, and eosinophils. An additive effect of asthma and obesity further increases inflammatory mediators and airway inflammation.

An asthma endotype introduced in 2020, IL-6-high asthma, is characterized by elevated plasma IL-6 levels, increased markers of systemic inflammation, metabolic dysfunction, and obesity [96].

Type VII: Inflammatory Drug Reactions

These idiosyncratic reactions include hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) and phenotypes such as NSAIDs-exacerbated respiratory disease in patients with asthma and/or chronic rhinosinusitis ± nasal polyposis. NSAIDs-exacerbated respiratory disease is a chronic inflammatory condition characterized by the triad of asthma, recurrent nasal polyps and hypersensitivity to NSAIDs/aspirin. In the underlying mechanism, cyclooxygenase (COX)-1 inhibition releases eicosanoid mediators, causing bronchoconstriction, increased vascular permeability, mucus production and recruitment of inflammatory cells.

These advances in endotyping chronic inflammatory diseases associated with chronic cough have not yet appeared in practice guidelines on chronic cough, with the exception of eosinophilic airway inflammation, but this science is being translated into practice. For example, cough is the most troublesome symptom for patients with asthma. Older patients with asthma and chronic cough show worse clinical outcomes in asthma control, quality of life, and airway obstruction, and more frequent moderate-to-severe exacerbations, partly explained by the interaction of chronic coughing with aging [97]. Non-type 2 inflammation (e.g., increased neutrophils) is associated with cough in older patients with asthma with chronic cough. Interferon-γ is a non-type 2 biomarker that enhances cough reflex sensitivity by inducing calcium influx in vagal sensory neurons and is associated with increased cough in patients with refractory chronic cough. Older patients with asthma show increased levels of sputum IFN-γ. Non-type 2 inflammation (i.e., neutrophils and IFN-γ) is also associated with reduced inhaled corticosteroid response [54; 97; 98].

TREATMENT

CHRONIC AIRWAY INFLAMMATION

Treatment of chronic airway inflammation includes inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic antagonists, leukotriene receptor antagonists, systemic corticosteroids, and biologicals. Confirmation that chronic cough is due to asthma (or another chronic cough-associated condition) requires a beneficial response to therapy for asthma, as patients with asthma can also have chronic cough due to non-asthmatic causes [44].

For chronic cough due to cough-variant asthma or nonasthmatic eosinophilic bronchitis, the ACCP recommends inhaled corticosteroids as first-line treatment [84]. With incomplete response, the inhaled corticosteroid dose should be escalated and adding a leukotriene receptor antagonist should be considered. Other causes of cough should be reconsidered as well. For cough-variant asthma, adding beta-agonists should be considered.

In patients with chronic cough in asthma, the first-line treatment is inhaled corticosteroid with or without long-acting beta-agonist [6]. A leukotriene receptor antagonist or long-acting muscarinic antagonist may be added in for those who do not fully respond to initial treatment. Whether biologics can treat chronic cough related to asthma has not been studied.

In adult and adolescent patients with chronic cough due to non-asthmatic eosinophilic bronchitis (NAEB), we suggest inhaled corticosteroids as first-choice treatment

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Strength of Recommendation/Level of Evidence: 2B (Weak recommendation based on moderate-quality evidence)

When an offending allergen cannot be identified or avoided, chronic cough associated with nonasthmatic eosinophilic bronchitis should be treated with an inhaled corticosteroid. Second-line therapy calls for escalation of the inhaled corticosteroid dose; if response remains incomplete, the patient should be assessed for other causes of cough and a trial of leukotriene receptor antagonist initiated. Occasionally, systemic corticosteroids may be needed.

Tiotropium may be another therapeutic option. In 17 patients with chronic asthmatic cough refractory to inhaled corticosteroid/long-acting beta-agonist, four to eight weeks of tiotropium (5 mcg/day) significantly improved cough reflex sensitivity and cough severity in a subgroup of 11 patients [107]. These results were replicated in a randomized comparison to theophylline 400 mg/day over four weeks. Both drugs improved cough severity and cough-specific quality of life. Tiotropium decreased cough reflex sensitivity, which correlated with changes in cough severity, and higher baseline cough reflex sensitivity predicted greater tiotropium response. The authors conclude that tiotropium may modulate cough reflex sensitivity to alleviate chronic cough in asthma refractory to inhaled corticosteroid/long-acting beta-agonist [108].

EMPIRIC TREATMENT APPROACH

Empiric treatment of chronic cough is systematically directed at the four most common causes of cough, starting with upper airway cough syndrome. In its 2006 guideline, the ACCP states that therapy should be given in sequential and additive steps, because more than one cause of cough may be present [82]. Initial empiric treatment should begin with an oral first-generation antihistamine/decongestant.

If chronic cough persists after treatment for upper airway cough syndrome, asthma as the possible cause should be worked up next. If spirometry does not indicate reversible airflow obstruction, bronchoprovocation testing is performed in the evaluation for asthma.

With the diagnoses of upper airway cough syndrome and asthma ruled out or treated without the elimination of cough, nonasthmatic eosinophilic bronchitis should be considered next, with a properly performed induced sputum test for eosinophils. In most patients with suspected cough due to asthma, a bronchoprovocation challenge should be performed and, if the result is positive, some combination of inhaled corticosteroids, inhaled beta-agonists, and/or oral leukotriene inhibitors should be administered.

In patients whose cough responds only partially or not at all to interventions for upper airway cough syndrome and asthma or nonasthmatic eosinophilic bronchitis, treatment for GERD should be instituted next. In patients with cough whose condition remains undiagnosed after all of these conditions has been worked up, referral to a cough specialist is indicated.

When the cause of chronic cough is identified or suspected, there are two options [26; 44; 57; 109]. The first is to pursue one diagnostic and treatment path at a time; with incomplete response of the cough to one line of therapy, adding therapy for the next most likely diagnosis is reasonable. The second option in patients with more than one suspected cause and a cough that is especially disruptive is to empirically treat or evaluate the likely causes simultaneously. After the cough resolves, treatments can be stopped sequentially, starting with the least likely to have been helpful, observing the patient for any return of cough.

BEHAVIORAL TREATABLE TRAITS

Nonadherence and poor inhalation technique strongly influence outcomes in airway disease. Despite their critical importance, the proportion of patients with poor technique is high, unimproved over the past 40 years, and often unaddressed by clinicians. These behavioral treatable traits can be improved using strategies such as patient-centered communication, motivational interviewing, shared decision-making, and simplification of drug regimens; and should be assessed in every follow-up visit [110].

Smoking cessation improves cough by resolving chronic bronchitis. Nicotine suppresses the cough reflex, and nicotine withdrawal due to smoking cessation may enhancement cough hypersensitivity; hence, patients may experience more coughing for a period after quitting. This can be attenuated and quit rates improved by using nicotine replacement [5].

LOWER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND MANAGEMENT

Lower airway diseases commonly associated with chronic cough are classic asthma, cough-variant asthma, nonasthmatic eosinophilic bronchitis, and COPD [20].

Chronic cough is a central feature that develops in diverse pulmonary pathologies, such as asthma (an inflammatory airway disease) and idiopathic pulmonary fibrosis (an alveolar fibrosing disease), highlighting the significant role of dysregulated cough pathways in lung disease phenotypes [60]. Chronic cough prevalences have been reported for asthma (8% to 58%), COPD (10% to 74%), bronchiectasis (82% to 98%), interstitial lung disease (50% to 89%) and sarcoidosis (3% to 64%); in all five diseases, patients demonstrate cough reflex hypersensitivity, a cardinal feature of cough hypersensitivity syndrome [111].

Presence of chronic cough generally predicts impaired health status and more severe respiratory disease and is associated with greater symptom burden and disease severity in asthma, COPD, bronchiectasis, and interstitial lung disease. It has also been linked to greater exacerbations in asthma and bronchiectasis and increased mortality and lung transplantation in idiopathic pulmonary fibrosis [111].

Asthma and Nonasthmatic Eosinophilic Bronchitis

Asthma is a complex, chronic airway inflammatory disease of bronchial hyper-responsiveness, intermittent airflow obstruction, and symptoms of wheeze and dyspnea that impacts 26 million people in the United States, results in approximately 10,000 deaths annually, incurs an estimated $56 billion

annually in medical care and lost productivity costs, and accounts for cough in 24% to 32% of adult nonsmokers with chronic cough [84; 112; 113]. Asthma prevalence has increased with rising obesity rates. Obesity often precedes an asthma diagnosis, making it an important modifiable risk factor (or treatable trait) [5; 113].

In atopic asthma, the most common type (affecting approximately 50% of adults with asthma), allergens trigger innate and adaptive immune activity, releasing inflammatory mediators such as histamine, prostaglandins, and leukotrienes that promote bronchoconstriction and cough [20; 114]. Classic asthma describes symptoms of wheezing, chest tightness, and dyspnea. In these patients, immune response to allergen exposure results in airway inflammation, airflow obstruction, and characteristic symptoms. Increased mucous secretions in narrowing airways induce cough [31; 112].

Cough-variant asthma, in contrast, presents with persistent cough as the primary or only symptom. Cough receptor density is highest in the proximal airways, decreasing as the airways get smaller. In cough-variant asthma, inflammation is primarily in the proximal airways, where cough is stimulated, and less so distally, where inflammation and narrowing cause wheezing and dyspnea in classic asthma [31; 56]. Some have suggested that asthma-variant cough is a more appropriate term than cough-variant asthma, given that cough hypersensitivity symptoms are the chief complaints, while asthmatic features act as triggers and treatable traits of chronic cough in these patients [115].

Nonasthmatic eosinophilic bronchitis was first described in 1989 as corticosteroid-responsive chronic cough in nonsmokers with airway eosinophilia, but without variable airway obstruction or bronchial hyper-responsiveness [116]. Nonasthmatic eosinophilic bronchitis accounts for 10% to 30% of specialist referrals for chronic cough, but nonasthmatic eosinophilic bronchitis prevalence is uncertain, as its diagnosis requires assessment of eosinophilic airway inflammation [44; 84; 117].

In nonasthmatic eosinophilic bronchitis, patients have chronic cough, no symptoms or evidence of variable airflow obstruction, sputum eosinophilia, and normal bronchial provocation tests [56; 117].

Chronic cough in asthma is mechanistically complex, involving IgE or non-IgE mediated eosinophilic airway (i.e., atopic or nonatopic) inflammation, abnormal neuromechanical properties of the lungs, and presence of cough reflex hypersensitivity independently of airway eosinophilia or bronchial hyper-responsiveness [20].

Nonasthmatic eosinophilic bronchitis and asthma share airway eosinophilia and similar basal membrane thickening, but inflammatory mast cells primarily infiltrate the superficial airway epithelium in nonasthmatic eosinophilic bronchitis versus airway smooth muscle in asthma. Along with lower IL-13 expression in nonasthmatic eosinophilic bronchitis, this partially explains bronchitis and cough with normal airway responsiveness in nonasthmatic eosinophilic bronchitis [116; 118]. Nonasthmatic eosinophilic bronchitis lacks the airway hyperresponsiveness of cough-variant asthma, but both share atopic features of eosinophilia and airway inflammation [109].

Eosinophilic airway inflammation in cough-variant asthma is linked to more severe disease. Cough-variant asthma may be a precursor of classic asthma, and both cough phenotypes can manifest overlapping symptoms, airway inflammation, and bronchial hyper-responsiveness [20]. Chronic dry cough, eosinophilic inflammation, and chronic airflow obstruction can present in both cough-variant asthma and nonasthmatic eosinophilic bronchitis [56].

Chronic Obstructive Pulmonary Disease (COPD)

COPD comprises several lung diseases, including emphysema and chronic bronchitis, with persistent and usually progressive airflow limitation associated with an enhanced chronic inflammatory response in the airways and lungs. Exacerbations and comorbidities contribute to the overall severity, while airway and systemic inflammation in COPD is related to disease progression and mortality [119; 120].

In the United States, 14.2 million adults had diagnosed COPD in 2021, of whom 25% were never-smokers, and COPD accounted for 354,000 deaths in 2020 [121; 122]. Among patients with COPD, 70% experience persistent cough and many consider it extremely severe and impairing [64].

Chronic bronchitis describes productive cough on most days of the week for at least three months total duration in two successive years. Chronic obstructive bronchitis is chronic bronchitis with spirometric evidence of airflow obstruction. Chronic asthmatic bronchitis is a similar condition with chronic productive cough, wheezing, and partially reversible airflow obstruction mostly found in smokers with a history of asthma [123].

Emphysema is defined as the permanent enlargement and damage of the lung air sacs with destruction of the airspace walls, causing symptoms of breathlessness. Emphysema can exist without airflow obstruction but is more common in patients with moderate or severe airflow obstruction [119].

COPD manifests as productive cough with airflow limitation and occasional bronchial hyper-responsiveness [20]. COPD and asthma share symptoms of cough, wheeze, and difficulty breathing. The blurred distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is termed asthma-COPD overlap [123].

Cigarette smoking is the primary risk factor, but only 15% of smokers develop clinically apparent COPD. Smokers with pre-existing airway reactivity, even in the absence of clinical asthma, have greater risk of developing COPD. Inflammation in the large and small airways can persist after smoking cessation. The genetic disorder alpha-1 antitrypsin deficiency is an important cause of emphysema in nonsmokers and markedly increases susceptibility to COPD in smokers [120; 123].

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is an interstitial lung disease, a group of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea frequently resulting in end-stage respiratory failure. Interstitial lung disease affects 650,000 people and causes 25,000 to 30,000 deaths per year in the United States [124].

Idiopathic pulmonary fibrosis, the most common interstitial lung disease accounting for 35% to 61% of all patients, is a chronic, progressive, invariably fatal fibrotic lung disease [111; 124]. Despite approvals of two antifibrotic therapies, the five-year survival rate remains 25%, far worse than many common cancers. Pharmacotherapies slow the disease progression, but none address the significant symptoms of chronic cough, fatigue, and dyspnea suffered by 85% to 95% of patients with idiopathic pulmonary fibrosis [125].

Chronic cough in idiopathic pulmonary fibrosis predicts disease progression and mortality, is as distressing as breathlessness for patients, and remains one of the most difficult symptoms to control [64; 125]. Among 1,447 patients with idiopathic pulmonary fibrosis cough, every 1-point decrease in LCQ score increased the risk of respiratory-related hospitalization by 6.5%, death by 7.4%, and lung transplantation by 8.7% over 12 months. Worse cough-specific quality of life independently associated with increased risk of respiratory hospitalization, death, and lung transplantation [126].

Two breakthrough studies demonstrated that low-dose morphine and nalbuphine can safely decrease coughing in idiopathic pulmonary fibrosis patients, as will be described later in this course.

Bronchiectasis

Bronchiectasis is a heterogenous disorder characterized by infection, airway inflammation, failure of mucociliary clearance, and airway structural damage. Absolute suppression of cough is not recommended because bronchiectasis is a suppurative condition with an increased risk of infection. However, much of the cough exceeds what is physiologically needed for sputum clearance and is thus maladaptive or pathological [111]. Cough is a central clinical feature of bronchiectasis that contributes to impaired health status and may be an early indicator of disease exacerbation, but it is almost never evaluated [64].

DISTINGUISHING CHARACTERISTICS OF RHINITIS PHENOTYPES				
Rhinitis Phenotype	**Primary Symptoms**	**Associated Features**	**More Responsive to**	**Less Responsive to**
Allergic	Sneezing, nasal pruritis, clear rhinitis	Ocular itching, wheezing, atopic dermatitis	INCS, INAH, FGAH, SGAH, SCS, AIT	Decongestants, ABX
Nonallergic noninfectious	Intermittent congestion, clear rhinitis	Physical triggers (temperature changes, food, irritants)	INCA, INAH, INAC	FGAH, SGAH, SCS, AIT, ABX
GERD-associated	Postnasal drip, throat clearing	Epigastric pain, heartburn, dysphagia	GERD diet and lifestyle changes, INAC	FGAH, SGAH, INCS, INAH, SCS, ABX, AIT
Chronic rhinosinusitis with or without nasal polyposis	Anosmia/hyposmia, unremitting congestion, facial pain/pressure	Wheezing, NSAID hypersensitivity	SCS, biologics, intermittent INCS	FGAH, SGAH, INAH
Infectious	Acute onset, sinus pressure, nasal congestion with purulent discharge	Viral prodrome, episodic nature lasting <2 weeks	Saline nasal lavage, INAH, decongestants, INAC	FGAH, SGAH, INCS, SCS, ABX, AIT
ABX = antibiotics; AIT = allergen immunotherapy; FGAH = first-generation oral antihistamines; GERD = gastroesophageal reflux disease; INAC = intranasal anticholinergics; INAH = intranasal antihistamines; INCS = intranasal corticosteroids, SCS = systemic corticosteroids; SGAH = second-generation oral antihistamines.				
Source: [6]				*Table 5*

UPPER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In upper airway cough syndrome, diverse chronic infectious, inflammatory, or neurogenic upper airway diseases induce chronic cough [20; 127]. While upper airway cough syndrome lacks a uniform definition, its prevalence in chronic cough patients is probably comparable to other major causes like asthma and GERD; in some studies, it is the first or second leading cause [39; 127].

Rhinitis, comprising most chronic upper airway diseases in upper airway cough syndrome, has a lifetime prevalence up to 33% in the United States [6]. Nasal mucosa inflammation due to allergic or non-allergic cause leads to mucus secretion, sneezing, nasal pruritus, and postnasal drip that irritates the airways and stimulates coughing [31]. In chronic rhinitis, these symptoms persist at least three months, inducing nasal obstruction and increased nasal discharge [119].

Rhinitis has numerous phenotypes and the nomenclature is not straightforward (***Table 5***). Allergic rhinitis requires immunoglobulin E (IgE)-mediated sensitization to an allergen exposure [6]. Chronic cough in patients with allergic rhinitis is often related to undiagnosed asthma or nonspecific bronchial hyperreactivity. Bronchial biopsy studies of patients with allergic rhinitis without asthma have shown inflammatory cell infiltration and active structural remodeling of the lower airways similar to that of patients with asthma, thereby potentially contributing to cough in these patients [128].

Chronic nonallergic rhinitis syndromes include chronic nonallergic rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), atrophic rhinitis, and drug-induced rhinitis; nonallergic rhinitis accounts for up to 80% of cases [129]. Nonallergic rhinitis phenotypes include [6]:

- Vasomotor
- Irritant
- Infectious
- GERD-associated
- Chronic rhinosinusitis with or without nasal polyposis

Rhinosinusitis is preferred to sinusitis because purulent sinus disease without similar rhinitis is rare [130].

Chronic rhinosinusitis is an inflammatory disease of the sinonasal mucosal lining secondary to infectious and allergic etiology, with symptoms of anosmia, nasal obstruction, thick nasal drainage, and facial pressure [92]. Retention of sinus secretions, the key event in chronic rhinosinusitis development, fosters infection and is caused by obstruction or narrowing of sinus ostia, mucociliary dysfunction, or altered mucus composition; 90% of sinus infections involve the maxillary sinus [119]. Cough, one of the important symptoms of chronic rhinosinusitis, occurs in 1% to 5% of U.S. adults [131].

Chronic rhinosinusitis with nasal polyposis, representing up to 20% of chronic rhinosinusitis cases, is more debilitating than the phenotype without nasal polyposis. Comorbidities in chronic rhinosinusitis with nasal polyps are asthma (55% to 56%), allergy (12% to 77%), and allergic rhinitis (17% to 76%). Asthma with nasal polyps is harder to control and more prone to severe exacerbations [92; 93].

Chronic cough pathogenesis in upper airway cough syndrome was previously tied to postnasal drip, because the nose and sinuses lack vagal sensory innervation. However, only a minority of patients with postnasal drip have chronic cough, some patients with upper airway cough syndrome do not have postnasal drip, and the pathophysiology is more complex [11; 127].

In chronic rhinitis and rhinosinusitis, inflammatory mediators are transmitted via glossopharyngeal and vagal receptors in the pharynx and larynx, and via afferent fibers of the trigeminal nerve, sensitizing the cough reflex centrally [11]. Direct irritation of nasolaryngeal mucosa and stimulation of vagal afferents by postnasal drip lead to hematogenous spread of inflammatory mediators and neurogenic or systemic communication between upper and lower airways, resulting in airway sensory nerve inflammation, cough reflex hypersensitivity, and chronic cough [10; 39].

Convergence of trigeminal and vagal afferents in central cough pathways provides a mechanistic/neuronal link between upper airway disease and the development of cough hypersensitivity [5]. In general, upper airway diseases lead to chronic cough only if the cough reflex becomes hypersensitive; therefore, they are generally considered a trigger rather than a cause of chronic cough [11].

In 2024, nonallergic rhinopathy was introduced to replace vasomotor rhinitis as the term describing 80% of the larger nonallergic rhinitis category, prompted by evidence that neuroinflammation and TRPV1 receptor activation play important roles, rather than blood vessels. TRPV1 also contributes to nasal hyper-reactivity in allergic rhinitis, an entity called mixed rhinitis. The management of nonallergic rhinitis requires the correct diagnosis; rhinopathy draws attention to the underlying neuro-immune endotype [129; 132].

Chronic cough is triggered in many patients with chronic upper airway disease (usually allergic rhinitis or chronic rhinosinusitis with or without nasal polyps) with common symptoms and signs of postnasal drip, compulsive throat-clearing, nasal stuffiness, globus feeling, headache/facial pain, loss of smell and taste, recurrent hoarseness, and cobblestone appearance of the pharyngeal mucosa on inspection [11]. The most commonly used tool is the SinoNasal Outcome Test (SNOT) [92].

With numerous symptoms and unclear diagnostic criteria, upper airway cough syndrome diagnosis has been based on first-generation oral antihistamine response, which may have central antitussive effects. Upper airway and other airway disease is frequent in patients with chronic cough, making it unclear whether coughing arises from upper or lower airways [5].

A large case series found allergic rhinitis, classic asthma, chronic rhinosinusitis, and nasal polyposis in 46%, 31%, 12%, and 9% of patients with chronic cough, respectively. The high predictive value for concomitant asthma in upper airway cough syndrome calls for investigating lower airway pathology in chronic cough of upper airway origin [20].

Rhinitis is a principal contributor to upper airway cough syndrome. The lengthy differential diagnosis of rhinitis in upper airway cough syndrome includes both allergic and nonallergic diseases; many patients have a combination of both or mixed rhinitis. Distinguishing these will increase treatment success and decrease the time before symptoms improve [6].

Radiological investigations may be useful and are guided by nasal symptoms. Incidental sinus changes may be present in up to 33% of CT and 67% of MRI scans. PPIs should not be used to treat upper airway symptoms [5].

Laryngeal dysfunction and hypersensitivity are common in chronic cough [5]. Consider treatment of laryngeal hypersensitivity as a symptom of cough hypersensitivity. Laryngitis often leads to chronic cough with voice changes (e.g., hoarseness, aphonia). Chronic cough is frequent in functional voice disorders, (e.g., muscle tension dysphonia) [11].

In vocal cord dysfunction, laryngeal hypersensitivity leads to persistent laryngospasm due to different triggering factors, manifesting as cough, wheeze, breathlessness, and voice disturbance. Coughing can be both a trigger and a symptom. Symptoms may be episodic. Diagnosis is based on findings in history, laryngoscopy, and, if possible, spirometry during an attack [5; 11]. In a refractory chronic cough population, vocal cord dysfunction is a common finding and may be a manifestation of laryngeal hypersensitivity. Treatment is by speech and language therapy intervention [5].

REFLUX DISORDER ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In GERD, retrograde transit of gastric contents into the esophagus leads to troublesome symptoms of heartburn, esophageal chest pain, and regurgitation (i.e., "typical" esophageal symptoms) [133; 134]. Cough is an extraesophageal symptom of reflux disease [11]. Chronic cough has a low, but potential, pathophysiological relationship to reflux disease [133]. Estimated chronic cough due to GERD vary widely (7% to 85%), with higher prevalence in Western than Asian countries [20]. Chronic cough and GERD are both very common conditions and can therefore co-appear without being causally related [99].

GERD was previously considered a leading chronic cough etiology directly caused by the acidity of proximal esophageal refluxate, but patients with chronic cough and healthy controls show similar proximal reflux events [58; 135]. Many patients with chronic cough report GERD symptoms, but PPI therapy is ineffective in those without acidic reflux and only modestly benefit those with typical esophageal symptoms [109].

Reflux can be acidic or non-acidic, liquid or gaseous, and proximal or distal in location. Reflux can trigger cough, coughing can induce reflux, and chronic cough may also cause GERD or increase reflux episodes [20; 134]. PPIs decrease reflux acidity but not reflux events and work poorly in patients with airway or extraesophageal reflux [136]. PPI failure in chronic cough treatment suggests the acidic component of reflux has little effect on chronic cough or its etiology [58].

In extraesophageal reflux, troublesome symptoms not normally considered esophageal manifest in the lower and upper airways as chronic cough, asthma, laryngitis, dysphonia, pulmonary fibrosis, sinus disease, ear disease, postnasal drip, throat clearing, non-cardiac chest pain, or dental erosion [20; 134].

Laryngopharyngeal reflux is defined as the backflow of weakly or non-acidic "mist" or liquid above the upper esophageal sphincter into the upper airways. Due to weaker mucosal defenses in the upper respiratory tract, inflammation of the mucous membranes and epithelial tissue damage occur with exposure to fewer, and less acidic, reflux events. A significant negative effect from pepsin, a gastric enzyme, on oropharyngeal and respiratory tract tissues is also demonstrated [58; 137].

Airway reflux is interchangeably used for laryngopharyngeal, non-acid esophageal, extraesophageal, and silent reflux. But it is important to remember that airway reflux is not GERD. Defined by the symptoms of heartburn and dyspepsia, and associated with esophagitis, GERD is a peptic condition predominantly of liquid acidic reflux [59]. The majority of patients with airway reflux/laryngopharyngeal reflux do not have esophagitis or heartburn [137].

Airway reflux shifts the paradigm from traditional GERD to cough hypersensitivity through sensitization of vagal afferents. Evidence that esophageal irritation by acid and non-acid reflux may directly initiate cough led to the concept of an esophagobronchial reflex based on crosstalk at the nucleus tractus solitarius between esophageal and airway sensory neurons converging in this brainstem area [58].

This led to gastroesophageal reflux-associated cough, a cough-predominant phenotype of GERD, as a chronic airway inflammatory disease. Epithelial damage and airway inflammation in gastroesophageal reflux-associated cough patients suggest micro-aspiration, and the esophagobronchial reflex mediated by distal esophageal vagal afferents [136].

Chronic cough may result from GERD/extraesophageal reflux-induced airway inflammation and supraesophageal pathology. Whether refluxate causes damage leading to extraesophageal reflux, needs to be acidic or merely contain pepsin, or whether neurogenic signaling leads to inflammation and subsequent symptoms remains unclear [134; 136].

In sum, GERD can directly affect the airways when gastric acid backflows into the esophagus, irritating the proximal esophagus and laryngopharyngeal areas, triggering the cough reflex to clear the airways. Gastric content can indirectly cause chronic cough by stimulating the distal esophagus, resulting in vagus nerve irritation and cough reflex sensitization. Airway reflux may comprise most cases of reflux-induced cough, its extraesophageal symptom hampering diagnosis based on symptoms alone [39].

Management

As discussed, the role of reflux, esophageal dysmotility, and aspiration in chronic cough is controversial. Studies suggest non-acidic reflux, both liquid and gaseous, may be an etiological factor. However, no tool reliably detects such reflux and diagnosis relies on clinical history supported by validated questionnaires (e.g., the HARQ). Moreover, the high prevalence of esophageal dysmotility in patients with chronic cough suggests esophagopharyngeal reflux rather than GERD may be the problem [10].

Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration, including voice change, nasal symptoms, and dysgeusia. Frequent chest infection bronchitis, even frank bronchiectasis, may be the consequence rather than the cause of cough via repeated aspiration. Unsurprisingly, following aspiration of GI contents there is a neutrophilic or eosinophilic inflammatory response that might be giving rise to asthmatic cough and mucus hypersecretion [10].

The 2016 ACCP clinical practice guideline for reflux-associated chronic cough suggests that esophageal manometry and pH-metry be performed in patients with suspected reflux cough refractory to

REFLUX INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	**Description**	**Utility**
24-hour esophageal pH testing	A catheter is inserted nasally into the esophagus with two pH sensors for 24-hour measurement of proximal and distal acid reflux	Does not reliably predict response to PPI therapy
Barium meal	Radiographic test that visualizes the movement of barium liquid. Can detect structural and motility abnormalities of the esophagus, stomach, and duodenum.	May demonstrate a hiatal hernia and document the extent of non-acid reflux not identified on 24-hour pH testing
Manometry	A catheter is inserted to assess motility patterns by measuring the amplitude of contractile events in the esophagus and its sphincters	Impaired peristalsis is more prevalent in patients with chronic cough, consistent with symptoms of esophageal dysmotility
Impedance testing	Intraesophageal probes measure impedance and pH to record acid, weakly acidic, and non-acid reflux events	Non-acid refluxate may be important in chronic cough etiology, but impedance testing is not validated to investigate chronic cough
Upper GI endoscopy	Allows direct inspection of the upper GI tract and biopsy of stomach and duodenum	Often unrevealing; endoscopic evidence of GERD less common with atypical (e.g., chronic cough) vs. typical symptoms
Source: [19]		*Table 6*

a three-month antireflux trial and being evaluated for surgical management (antireflux or bariatric); or with strong clinical suspicion warranting diagnostic testing for gastroesophageal reflux (***Table 6***). Esophageal manometry assesses for major motility disorder. It involves placing the pH electrode 5 cm above the lower esophageal sphincter in the pH monitoring study after the patient is off PPIs for seven days and histamine H2-receptor antagonists for three days [83].

For overweight and obese patients, treatment of suspected reflux-cough should include diet change to promote weight loss. In all patients, recommended diet and lifestyle modifications include [6]:

- Eliminate coffee, tea, soda, other carbonated beverages, fish oil supplements, chocolate, mints, alcohol, and energy drinks, sports, or other drinks containing citric acid
- Consume no more than 45 grams of fat daily
- Avoid smoking and vaping
- Avoid exercising that markedly increases intra-abdominal pressure
- Elevate the head of the bed and avoid meals within three hours of bedtime

In patients with heartburn and regurgitation, PPIs, histamine H2-receptor antagonists, alginate, or antacid therapy is often sufficient to control these symptoms. Gastrointestinal symptoms respond within 4 to 8 weeks, but cough may take 12 weeks to improve [83]. PPI monotherapy is not recommended for chronic cough with solely extraesophageal symptoms, as it is unlikely to resolve the cough.

The ACCP suggests against antireflux surgery for patients with chronic cough patients with a major motility disorder and/or normal acid exposure time in the distal esophagus, as the procedural risks and lack of supporting evidence make the risk-benefit ratio unacceptable [83]. However, surgery may be considered for presumed reflux-cough in patients with normal peristalsis, abnormal esophageal acid exposure on pH-metry, and refractory to medical therapy.

PITFALLS IN THE MANAGEMENT OF CHRONIC COUGH
Upper Airway Cough Syndrome
Failing to recognize that upper airway cough syndrome (also asthma or GERD) can present as a cough-phlegm syndrome, misdiagnosed as chronic bronchitis. Assuming that all histamine H1 receptor antagonists (H1RAs) are the same. H1RAs without anticholinergic activity do not help nonallergic rhinitis conditions. Further, anticholinergic H1RAs may adversely affect memory, glaucoma, and prostate problems. Instead, consider ipratropium bromide nasal therapy. Failing to consider: • "Silent" upper airway cough syndrome when a patient does not sense a postnasal drip or realize their frequent throat clearing • Allergic rhinitis and recommend the avoidance of allergens because symptoms are perennial • Sinusitis because it is nonobvious • NSAID-exacerbated disease • The potentially beneficial role of upper respiratory endoscopy
Asthma
Failing to recognize that: • Asthma can present as cough alone (i.e., cough-variant asthma) • Inhaled medications may exacerbate cough • Positive methacholine challenge alone is not diagnostic of asthma
Nonasthmatic Eosinophilic Bronchitis
Failing to consider the diagnosis, occupational/environmental causes, or order the correct test
GERD
Failing to recognize that: • "Silent" reflux disease can be causal and that it may take two to three months of intensive treatment before cough starts to improve and five to six months to resolve • GERD can be worsened by comorbidities (e.g., obstructive sleep apnea) or their treatment (e.g., nitrates or calcium channel blockers for coronary artery disease, progesterone for hormone replacement) Assuming that: • Cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve • Vocal cords' appearance can diagnose GERD, when inflammatory changes from coughing can mimic those of reflux Being unaware that acid suppression alone will not improve cough Failing to consider: • Non-acid reflux disease • The role of diet, intense exercise, and prokinetic therapy • Adequately treat co-existing causes of cough that perpetuate the cycle of cough and reflux because cough can provoke reflux
Triad of Upper Airway Cough Syndrome, Asthma, and GERD
Failing to consider that more than one condition may be contributing simultaneously to cough, or failing to consider additional contributing conditions because of another "obvious" cause (e.g., COPD) Failing to appreciate: • These chronic disorders cannot be cured and will periodically flare, especially with viral illness • When cough flares after a period of remission, re-evaluate as if a new problem • Asthma may become a problem when it was not before
Unsuspected Airway Diseases
Failing to perform bronchoscopy when chest x-ray and CT are normal. Transnasal route allows inspection of both upper and lower respiratory tracts. Failing to appreciate that prolonged IV therapy for suppurative airway disease may succeed when the same drug given orally failed
Source: [6; 80] *Table 7*

TREATABLE TRAITS AND THOROUGHNESS

The variable success in managing chronic cough may be due, in part, to guidelines or protocols not being implemented as planned (***Table 7***) [6; 80]. Failure to recognize the complexity of airway diseases can lead to suboptimal outcomes, as diseases with different endotypes can require different therapeutic strategies (precision medicine). Because the treatable traits approach is a label-free approach, it does not start on the assumption that the diagnosis (e.g., asthma, COPD) is well-established and clear, a situation that is not the case in many instances in clinical practice, particularly in primary care. This is a fundamental, but often overlooked, issue in the current guideline-directed management of airway diseases [14; 16].

Pulmonary and Extrapulmonary Traits as "Connected Comorbidities"

As discussed, the treatable traits approach encourages transdiagnostic thinking about chronic cough and associated diseases to identify distinct endotypes and phenotypes within traditional diagnostic categories, as well as shared mechanisms across diagnostic boundaries. For example, asthma and severe chronic rhinosinusitis with nasal polyposis are frequently associated with other, coexisting type 2 inflammatory diseases, such as NSAID-exacerbated respiratory disease, allergic rhinitis, eosinophilic esophagitis, atopic dermatitis, and type 2 eosinophilic COPD [114]. Chronic rhinosinusitis with nasal polyposis has a 7% prevalence in patients with asthma, increasing to 40% in NSAIDs-exacerbated respiratory disease [138]. In predisposed subjects, a dysregulated type-2 inflammation can develop in epithelial barriers (e.g., airways, intestine, skin) in response to various antigens, such as allergens, micro-organisms, and pollutants. This dysregulated epithelial response leads to diseases such as asthma, rhinitis/rhinosinusitis, eosinophilic gastrointestinal disorders, and atopic dermatitis [95].

Allergens are not the only antigens that trigger inflammation. Rather than allergic disorders, type 2 disorders would be a more appropriate definition, also including non-allergic eosinophilic diseases such as nonasthmatic eosinophilic bronchitis, chronic rhinosinusitis, and eosinophilic disorders of the gastrointestinal tract [95].

Targeted biological therapies can also address conditions with shared type 2 pathophysiology. Biologics with FDA approval targeting type 2 inflammatory disease pathophysiology include dupilumab (anti-IL-4 and IL-13), omalizumab (anti-IgE), mepolizumab (anti-IL-5), and benralizumab (anti-IL-5R) [92]. Mepolizumab has proven effective in chronic rhinosinusitis with nasal polyposis and asthma with high eosinophil levels in sputum. Dual targeting of IL-4 and IL-13 by dupilumab has shown efficacy across chronic rhinosinusitis with nasal polyposis, asthma, eosinophilic esophagitis, and atopic dermatitis, and in uncontrolled COPD with high eosinophil counts [93]. Chronic cough, it should be stressed, has not been examined in any study of biological therapies.

The Argument for Thoroughness

The optimal clinical approach in chronic cough and refractory chronic cough continues to evolve. The ERS guideline suggests simplifying the diagnostic process to shorten a patient's journey to a diagnosis of refractory/unexplained chronic cough and limiting sequential empiric trials to two to four weeks unless responses are observed [10]. However, the 2023 BTS guideline and others argue for a more assertive approach to identify all treatable traits and maximize therapy response before diagnosing refractory/unexplained chronic cough [5; 78]. This would be the counterargument to the diagnostic-therapeutic empiric trials approach.

In a 2024 study, all 201 patients presenting to a cough center in 2018–2022 were prospectively studied. Refractory chronic cough (defined as persistent cough severity VAS ≥40 with little improvement after at least two treatment attempts) was diagnosed in 30.7% and unexplained chronic cough in 1.5% [78]. The authors suggest a thorough diagnostic algorithm, with frequent second-step investigations, enabled diagnoses of less common cough etiologies and the low (1.5%) unexplained chronic cough rate. As many therapeutic trials as necessary were engaged in order to target all identifiable treatable traits of chronic cough. Treatment followed a stepwise intensification of therapy and introduced add-on treatment of all cough causes, but this was time-consuming and related to difficulties in keeping patients' adherence. In routine practice, the authors usually recommend more than two therapeutic trials before diagnosing refractory chronic cough. When refractory/unexplained chronic cough is diagnosed, additional treatments should be initiated. These patients require nonpharmacologic and/or drug therapies with opioids, neuromodulators, or novel refractory chronic cough agents.

In a separate study conducted at a clinic in China, experts found that among 1,554 patients with chronic cough patients with negative chest x-rays, 58.8% were attributable to common causes, including nonasthmatic eosinophilic bronchitis (18.3%), cough-variant asthma (16.3%), gastroesophageal reflux-associated cough (13.2%), and upper airway cough syndrome (11.1%) [139]. In addition, 18.4% of cases were attributable to other causes: chronic bronchitis (6.1%), bronchiectasis (4.5%), atopic (4.4%), and postinfectious (3.5%) cough; 9.6% had chronic cough of unexplained etiology. Finally, 13.1% of cases were due to rare causes (e.g., bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, obstructive sleep apnea, and interstitial lung disease). These findings suggest that special examinations should be considered after excluding common causes of chronic cough.

It is important to remember that the workup to rule out refractory/unexplained chronic cough is not complete until bronchoscopy has been performed [6]. A study of bronchoscopy involving 54 patients with refractory/unexplained chronic cough with sputum production (more than 1 tbsp/day), atypical urge-to-cough sensations in chest, and unremarkable chest CT revealed bronchoalveolar neutrophilia in 84% and excessive dynamic airway collapse in 31% [140]. Bronchoscopy influenced or changed the management in 89% of patients. Bronchoscopy findings in this specific population have rarely been described, and treatment strategies in these patients differ from typical refractory/unexplained chronic cough. Bronchoscopy provides high diagnostic value in refractory/unexplained chronic cough with mucus production, identifying specific treatable traits of neutrophilic airway inflammation and excessive dynamic airway collapse [140].

Another argument for moving away from the routine use of empiric therapeutic-diagnostic trials is to spare patients with chronic cough from exposure to minimally helpful or unhelpful medications with potentially adverse effects. For example, PPIs are recommended against for chronic cough in patients who lack classic GERD symptoms. Cumulative doses of PPIs dose-dependently increase the risk of developing hypomagnesemia and other side effects. Both hypomagnesemia and its consequent decrease in melatonin production can decrease lower esophageal sphincter tone and trigger a paradoxical iatrogenic cough. Rather than PPI dose escalation for partial responders, magnesium and melatonin supplementation is recommended to curtail side effects of long-term PPIs [104].

Oral corticosteroids, due to their substantial cumulative side effects, are now recommended only as a last resort in the most recent asthma treatment guidelines [141; 142]. Even occasional short courses of oral corticosteroids are associated with significant short-term and cumulative long-term adverse effects, with a pronounced dose-response. Short-term adverse effects of oral corticosteroids include sleep disturbance, increased appetite, reflux, mood changes, sepsis, pneumonia, and thromboembolism.

GUIDELINE RECOMMENDATIONS FOR NEUROMODULATOR TREATMENT OF REFRACTORY/UNEXPLAINED CHRONIC COUGH						
Drug	**Guideline Organization (Year)**					
	ACCP (2016)	**ERS (2020)**	**GRS (2020)[a]**	**FRS (2023)**	**BTS (2023)**	**NEURO-COUGH (2023)**
Low-dose morphine slow-release	Not reported[b]	Strong recommendation	Strong recommendation	Recommended: Grade B	Recommended	Recommended, very high consensus
Codeine	Not reported	Not recommended	Not reported	Not reported	Recommended against	Not reported
Gabapentin	Recommended	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Recommended, high consensus
Pregabalin	Not reported	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Not reported
Amitriptyline	Not reported	Not reported	Can be used	Recommended: Grade C	Not reported	Recommended, high consensus
Baclofen	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

[a]"Can be used" is a weaker endorsement than "recommendation" (i.e., "should be used").
[b]75% of expert panelists endorsed a recommendation of morphine, falling short of 80% required for inclusion; thus, morphine is neither recommended for nor against.
ACCP = American College of Chest Physicians; BTS = British Thoracic Society; ERS = European Respiratory Society; FRS = French-Speaking Society of Respiratory Diseases; GRS = German Respiratory Society; NEURO-COUGH = New Understanding in the treatment Of COUGH Clinical Research Collaboration; SR = sustained-release.

Source: [5; 10; 11; 12; 18; 86] *Table 8*

As few as four to five lifetime courses of oral corticosteroids are associated with a significantly increased dose-dependent risk of diabetes, cataracts, heart failure, osteoporosis, and several other conditions [142].

TREATMENT OF REFRACTORY CHRONIC COUGH

Refractory and unexplained chronic cough are diagnoses of exclusion. For cases with no clear etiology after an extensive workup, or when guideline-based treatment improves the presumed underlying cause of coughing but not the chronic cough itself, cough hypersensitivity syndrome is the most likely explanation [39].

A variety of organizations have published guideline recommendations for the treatment of refractory and/or unexplained chronic cough (***Table 8***). The British Thoracic Society asserts that cough hypersensitivity is a treatable trait of many conditions and often the foremost problem in patients with chronic dry/unproductive cough [5]. However, there are currently no tools to positively identify cough hypersensitivity. If the condition does not improve with treatment of treatable traits, it is considered refractory chronic cough. In these patients, the most effective treatments are those addressing cough hypersensitivity and include low-dose morphine, gabapentin, and nonpharmacological therapy. In addition, novel therapies are in development, with P2X3 antagonists the most promising [5].

PHARMACOTHERAPY

Neuromodulators are centrally acting agents for refractory chronic cough that can downregulate the hypersensitive cough reflex to decrease coughing. Neuromodulators are first-line options for refractory chronic cough [39; 57]. However, some of the literature on neuromodulator use in patients with refractory chronic cough might seem counterintuitive.

Clinical trials of P2X3 antagonists have shown efficacy in reducing cough frequency in many patients with refractory/unexplained chronic cough, but the exact mechanisms underlying refractory/unexplained chronic cough remain poorly understood. Although data also suggest central mechanisms may be a key component in the pathophysiology of refractory/unexplained chronic cough, antitussive drug development has focused on peripheral targets [143].

Among patients with unexplained chronic cough started on amitriptyline and contacted by mail two to three years later, 64% had stopped the medication due to no improvement (40%) and/or side effects (48%). The most common side effects triggering treatment nonadherence were sedation (18%), dry mouth (18%), anxiety (8%), difficulty sleeping (8%), and dizziness (5%). Combining patients who continued and stopped amitriptyline, 53% reported cough improvement of at least 50%. There is some evidence that as treatment duration increases, amitriptyline efficacy may decrease [144].

Opioid Medications

The concept of chronic cough as a neuropathic condition, treated with neuromodulators, is not new. In 1856, Edward Smith described chronic cough as a "disease in itself" due to "irritability of the nerves" that could be treated with "morphia," 164 years before expert consensus in the European Respiratory Society chronic cough guidelines concluded the same, albeit for refractory chronic cough [10; 111]. Opioids are thought to exert antitussive effects through opioid receptors within inhibitory cortical descending pathways [59].

Codeine

Codeine is a weak opioid that is metabolized to morphine (5% to 10%) by the enzyme cytochrome P450 2D6 (CYP2D6) in the liver to produce its antitussive effects [145]. Codeine has long been used as an antitussive, but a minority of the population possess a genetic variation in CYP2D6 activity, with variable and unpredictable metabolism that increases unpleasant side effects and decreases efficacy. Codeine is now considered an unreliable antitussive and should not be used in chronic cough [5].

Low-Dose Morphine Slow-Release (SR)

Morphine is not affected by interindividual variability in CYP2D6 metabolism; thus, its biological effects are more predictable than codeine [146]. In the first positive results from a double-blind randomized controlled trial for any drug therapy of refractory chronic cough, morphine was selected to minimize the variability of codeine [25; 147]. This study compared twice-daily slow-release morphine 5 mg with placebo for four weeks, followed by four weeks of crossover to the alternate treatment. A three-month open-labeled extension of the randomized controlled trial allowed dose escalation to 10 mg twice per day if patients thought their cough was inadequately controlled [147].

The mean LCQ score significantly improved on morphine but not placebo, with significant improvement in physical, psychological, and social subdomains. A 40% reduction in daily cough scores was noted with morphine; placebo had no discernable effect over baseline. Of patients entering the extension, 67% opted for dose escalation and, after three months, had cough outcome improvements similar to 5-mg full-responder patients. Side-effects of constipation (40%) and drowsiness (25%) were tolerable; no patient dropped out from adverse events. Sedation, previously believed to explain the antitussive action of morphine, was transient, but the antitussive effect continued throughout the core and extension study phases [147].

The authors of this study state that side effects and dependence are obvious concerns with opioid therapy for what is a disabling but non-life-threatening condition. However, they note that the risk-benefit ratio makes low-dose slow-release morphine a credible therapeutic option in patients with refractory chronic cough for whom other treatments have failed. Comparisons of similar therapeutic options were made with patients who require long-term oral corticosteroids for severe nonasthmatic eosinophilic bronchitis or cough-variant asthma with a consequently worse adverse event profile [147].

Another double-blind crossover study randomized previous morphine responders to slow-release morphine 5–10 mg twice daily or placebo. After five days, morphine reduced 24-hour cough frequency by 72% over placebo, including overnight (83%) and daytime (71%) cough frequency [148]. Morphine also significantly reduced noxious somatic sensations driving the urge to cough, suggesting this may be an important component of opioid modality in refractory chronic cough [149].

In a real-world effectiveness and tolerability study of long-term, low-dose opioids, 100 patients were prescribed twice daily slow-release morphine 5–10 mg (72%), oxycodone, or oxycodone/naloxone for a median 52 weeks for refractory/unexplained chronic cough. Median cough severity score (CSS, on a 0–10 scale) decreased from 8 pre-treatment to 4. In all, 60% had good-to-excellent response, while 25% had no response. Side effects (present in 38%) were most commonly constipation (25%), which was managed with dose reduction or constipation therapy; however, 15% stopped treatment due to side effect intolerance. Low-dose opioids improved long-term cough outcomes and were tolerated by most patients with refractory/unexplained chronic cough, but managing constipation allowed more patients to continue therapy [150].

Clinical experience with low-dose, slow-release morphine suggests that up to 50% to 60% of patients with refractory chronic cough obtain benefit [5; 59; 150]. Response dichotomizes into either a large effect on cough symptoms or no effect at all and is usually apparent within five days. The main side effect, constipation, can be managed with laxatives or adding oral low-dose naloxone. Once-daily dosing may be sufficient if cough symptoms are mainly troublesome during waking hours or overnight. Antitussive tolerance does not seem to develop. Unlike in severe chronic pain, there appears to be a dose ceiling for slow-release morphine of twice daily 10 mg, with no further antitussive effect beyond this. Concerns remain about misuse/addiction potential, and patients must be carefully monitored [5; 59]. As noted in a 2024 review, it is unclear why such low doses, compared with those used for analgesia, are effective in some patients with refractory chronic cough [25].

Gabapentinoids

Gabapentin and pregabalin are synthetic analogs of gamma-aminobutyric acid (GABA) that bind the α2δ subunit of voltage-gated calcium channels to block excitatory neurotransmitter release. Both were developed originally for epilepsy treatment and subsequently found to ameliorate chronic neuropathic pain, which is associated with central sensitization. The similar pathophysiologic mechanisms of chronic neuropathic pain and chronic cough suggested that gabapentin and pregabalin may also be beneficial in patients with refractory chronic cough [151].

Gabapentin (1,800 mg/day or the maximum tolerable dose) was compared with placebo for eight weeks in a double-blind randomized controlled trial of 62 patients with refractory chronic cough. Gabapentin significantly improved LCQ score over placebo by 1.8 points, and significantly reduced objective cough frequency and cough severity over placebo. Gabapentin response was greater in patients with symptoms of central sensitization (e.g., laryngeal paresthesia, allotussia, hypertussia). The onset of action of gabapentin took up to four weeks [152].

It was subsequently noted that cough frequency differed between gabapentin and placebo groups at baseline (45.3 vs. 68.8 coughs per hour) and was measured only for one hour at each assessment visit, making interpretation of cough frequency outcomes difficult [25; 146].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Respiratory Society suggests a trial of gabapentin or pregabalin in adults with chronic refractory cough.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, low-quality evidence

An open-label randomized trial compared gabapentin (300 mg three times per day) to baclofen (20 mg three times per day), an antispasticity drug, in 234 patients with refractory gastroesophageal reflux-associated cough over nine weeks. Compared with baseline, gabapentin and baclofen similarly led to decreased cough symptom scores and patients with success for cough resolution (57.3% vs. 53.0%). Gabapentin led to lower side effect rates than baclofen of somnolence (20% vs. 35%) and dizziness (11% vs. 24%) [151]. In addition to other burdensome side effects, sudden discontinuation of baclofen can result in seizures [5].

In another study, twice daily pregabalin 75 mg was prescribed to 50 consecutive patients with refractory or unexplained chronic cough for three months. Pregabalin response, defined as LCQ total score improvement of ≥1.3, was attained by 56% of patients. Responders were more likely to have refractory (with underlying pulmonary disease) than unexplained chronic cough, and on average were more symptomatic at baseline. There was no information on side effects or dropout [153].

In another study, 40 patients with refractory chronic cough were randomized to speech pathology treatment plus pregabalin 300 mg/day or speech pathology treatment plus placebo for four weeks. Compared with the placebo group, those who received speech pathology treatment/pregabalin experienced a statistically significant improvement [154]. However, CNS adverse effects (e.g., dizziness, disorientation, confusion, fatigue, blurred vision) were common and sometimes intolerable. The effects of pregabalin on 24-hour cough frequency outcome were non-significant [146].

Because gabapentinoids have beneficial effects on anxiety, improvements in mood may contribute to the apparent benefit or changes in symptom perception or cough intensity. Side effects are common, wide ranging, and can be difficult for patients to tolerate. Slow dose escalation may help minimize this, and maximal doses may not be needed to afford some improvement in cough. Gabapentin and pregabalin may have abuse potential in susceptible patients [5].

Gabapentin should be started at a low dose (e.g., 100 mg three times per day) and titrated up to a maximum dose (600 mg three times per day), depending on clinical effects and tolerability. The usual starting dose of pregabalin for chronic cough is 25 mg twice daily, with increases in increments to a maximum 75 mg twice daily. Patients should be reassessed during dose titration and therapy stopped if there are significant side effects or inadequate response to treatment [5].

In clinical experience, the minority of patients who achieve cough suppression often do so at the expense of intolerable adverse effects, usually sedation [57]. Among 38 patients prescribed gabapentin (maximum: 1,800 mg per day) or pregabalin (maximum: 300 mg per day) for refractory chronic cough, 24% developed immediate intolerable side effects and 37% tolerated the drugs but had no response and stopped the medication. Among the 39% with an initial favorable response, 18% eventually developed intolerable side effects and 21% were able to continue with therapy long-term. The most common side effect was drowsiness/sedation. In real-world practice, gabapentinoids are effective in a subgroup of patients with refractory chronic cough, but side effects may outweigh their potential benefits, which were intolerable for 42% of patients [155].

Tricyclic Antidepressants

Amitriptyline and nortriptyline are tricyclic antidepressants with a broad range of pharmacologic actions effecting adrenergic, serotonergic, muscarinic, and histaminergic systems. Amitriptyline is also used in chronic neuropathic pain (e.g., migraine, postherpetic neuralgia, painful diabetic neuropathy) and has been suggested to be effective in the treatment of chronic cough, with anticholinergic properties thought to underlie the antitussive effect [57; 156]. However, clinical experience with amitriptyline in refractory chronic cough suggests more limited value [5].

In a small randomized trial of patients attending an otolaryngology clinic with postviral refractory chronic cough, amitriptyline 10 mg per day was compared with codeine 10 mg/guaifenesin 100 mg combined in a syrup taken every six hours. The majority of patients reported a 75% to 100% improvement in cough with amitriptyline, while most reported no improvement with codeine/guaifenesin. Compared with the control arm, amitriptyline was significantly associated with a response greater than 50% [157]. In a randomized controlled trial of patients with chronic pharyngolaryngeal neuropathy, 67% had subjective improvement with amitriptyline (up to 50 mg/day), compared with 44% with placebo. The mean Voice Handicap Index-10 (VHI-10) score worsened with amitriptyline but was unchanged with placebo. Attrition over the eight-week trial was 40% [158].

Nortriptyline was studied in 42 patients with neurogenic chronic cough, of whom 45% discontinued nortriptyline due to side effect intolerance or lack of response. The average time to clinical response was 5.5 months. The average minimum effective dose was 21 mg per day in responders. Laryngeal asymmetry was present in 85.7% of all patients. Side effects included sedation, xerostomia, and anxiety. The intolerability was surprising, because nortriptyline is both a metabolite of amitriptyline and reported to be better tolerated [159].

Pharmacotherapy for Chronic Cough in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a chronic, progressive, and invariably fatal fibrotic lung disease, and 85% of patients with idiopathic pulmonary fibrosis experience cough, a distressing symptom associated with rapid disease progression. Available treatments for idiopathic pulmonary fibrosis slow disease progression but do not improve symptoms or quality of life. Thalidomide benefitted idiopathic pulmonary fibrosis cough in one randomized controlled trial, but its side effect profile renders it practically useless, as only 20% of patients were able to tolerate it [125]. Worse still, the potentially severe adverse effect of peripheral neuropathy suggests it may damage sensory nerves (vagal afferents). Thalidomide should not be considered even as second-line therapy for idiopathic pulmonary fibrosis cough until further evaluation of the benefit/risk ratio has been undertaken [160].

Although studies on refractory chronic cough can help inform the treatment of idiopathic pulmonary fibrosis cough, the biological mechanisms that contribute to cough probably differ in these conditions, as evidenced by the contrasting results with gefapixant, a P2X3 receptor antagonist, in refractory chronic cough (positive findings) and idiopathic pulmonary fibrosis cough (negative findings) [161].

Nalbuphine

Nalbuphine extended-release (ER) is an opioid agonist-antagonist. In a double-blind randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, nalbuphine ER tablets (titrated up to 162 mg twice daily) led to 75.1% reduction in daytime objective cough frequency, compared with 22.6% with placebo, a 50.8% placebo-adjusted reduction in 24-hour cough frequency, and similar improvements in patient reported outcomes [162]. Nalbuphine ER was the first therapy to show robust effects on chronic cough in idiopathic pulmonary fibrosis [25]. However, nalbuphine side effects of nausea (42.1%), fatigue (31.6%), constipation (28.9%), and dizziness (26.3%) led to a 24% dropout during the drug initiation phase, partially attributed to the inflexible forced-titration study design [162].

Low-Dose Morphine SR

In a multicenter randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, low-dose, slow-release morphine (5 mg twice daily) reduced objective awake cough frequency by 39.4% over placebo, and all cough-related patient-reported outcomes remained significantly improved when adjusted for placebo. Morphine side effects of nausea (14%) and constipation (21%) resulted in only one participant discontinuing morphine, indicating tolerability for these patients. The authors note that the safety assessments during study visits were reassuring and there appeared to be no changes in mood or excessive fatigue with morphine [161]. The authors advocate for rapid implementation in clinical practice due to the well-established safety profile and worldwide availability [163].

A 2024 study reported variable effectiveness of slow-release morphine (8–32 mg per day) in reducing breathlessness in patients with COPD. But, it provided reassuring safety data by observing no evidence of harm and no worsening of subjective daytime sleepiness, alertness, or sleep quality at one and four weeks in these severely ill patients [164].

INVESTIGATIONAL PHARMACOTHERAPIES

Low-dose, slow-release morphine has the strongest observational and empirical evidence of antitussive benefit in refractory chronic cough of any commercially available (although off-label) medication and may be used safely in this population when patients are carefully screened and monitored. Because as many as 50% of patients with refractory chronic cough have no response to low-dose morphine and with substantial restrictions on opioid prescribing in the United States, effective peripherally acting antitussives are an urgent priority for investigators.

P2X3 Receptor Antagonists

P2X3 receptors form ion channels containing ATP-binding sites. In the lungs and airway, ATP activates P2X3 receptors localized on vagal sensory nerve terminals, resulting in bronchoconstriction, cough, and localized release of inflammatory neuropeptides [165].

A breakthrough occurred when gefapixant, a P2X3 receptor antagonist, demonstrated a dramatic reduction in chronic cough. Other P2X3 antagonists confirmed the efficacy of this drug class in refractory chronic cough. The endogenous ligand for P2X3 is ATP. Epithelial damage is believed to release ATP. Evidence suggests that ATP largely mediates peripheral hypersensitivity; therefore, gefapixant is peripherally acting in refractory chronic cough [166].

P2X3 receptors are ion channels found on sensory afferent nerve fibers, activated by ATP. In preclinical studies, vagal C fibers, including those thought to be important in mediating cough, have been shown to express P2X3 and P2X2. At present, it is unclear whether ATP concentrations are elevated or P2X3 receptor expression increased in the airways of patients with refractory chronic cough, or how antagonism of P2X3 plays a role in reducing coughing to a range of chemical irritants, temperature changes, and mechanical stimuli. Nonetheless, in clinical trials, P2X3 receptor antagonism has provided robust reductions in cough frequency and patient-reported outcomes [25].

Gefapixant

The first novel therapy to have significant effects in patients with refractory chronic cough was gefapixant, a first-in-class P2X3 antagonist that was originally planned to be developed as an analgesic. Gefapixant has become the first therapeutic to undergo systematic development as a treatment for refractory chronic cough following unprecedented reductions in cough frequency.

In a landmark study, twice daily gefapixant 600 mg showed remarkable therapeutic effects in patients with refractory chronic cough [167]. Objective 24-hour cough frequency was reduced 74% compared with placebo, and daytime cough severity VAS score and CQLQ score reduced by −25.6 and −9.2, respectively. However, another important finding was that virtually all treated patients reported ageusia, or loss of taste, and 24% withdrew because of the adverse effect. These taste side effects are likely attributable to the inhibition of P2X2/3 channels on the nerve fibers innervating the taste buds by high-dose gefapixant [146].

Subsequent studies suggest that antitussive effects are retained at much lower doses (30–50 mg twice daily), at which taste was altered rather than lost and hence the therapy was better tolerated. Larger multi-center parallel group studies were performed in the UK and the United States followed by the first-ever global phase 3 trials of an antitussive treatment for refractory chronic cough, which reported positive findings over placebo for a 45-mg twice daily dose [25].

Eliapixant and Filapixant

Following the taste side effects reported for gefapixant, more selective P2X3 antagonists were evaluated for the treatment of refractory chronic cough; however, there was some uncertainty about whether effects at both P2X3 and P2X2/3 channels were both contributing to antitussive efficacy and hence whether more selective agents would have similar efficacy. Eliapixant and filapixant both demonstrated efficacy in dose-ranging studies, but eliapixant appeared to cause less taste disturbance (up to 21% of patients) and was therefore progressed to a phase 2b parallel trial. Although this trial reported positive findings, a small number of cases of liver toxicity prevented further development of this therapy for refractory chronic cough [25].

Sivopixant

Another more selective P2X3 antagonist, sivopixant, exhibited promising findings in a single-dose crossover study, very similar in design to the first gefapixant study. The reduction in daytime cough frequency of 32% over placebo (the primary endpoint) was not quite statistically significant, but taste adverse effects were only reported in 6.4% of patients. In a follow-up, multicenter parallel group study assessing a range of doses for four weeks, no dose of sivopixant could be discriminated from the very large placebo effect—there was 60% placebo reduction in cough frequency from baseline. The largest absolute change in cough frequency was observed for the highest dose (300 mg), but 30% of patients reported taste adverse effects. No further studies of sivopixant in refractory chronic cough have been planned [25].

Camlipixant

Finally, thought to be the most selective P2X3 antagonist, camlipixant is the second compound in this class to be evaluated in phase 3 trials. The first double-blind randomized controlled crossover trial of camlipixant studied escalating doses from 25 mg to 200 mg versus matched placebo. Although the primary endpoint of awake cough frequency did not reach statistical significance, preplanned subgroup analysis in patients with a cough frequency of at least 20 coughs per hour (80% of patients) and those with greater than the median cough frequency (≥32 coughs per hour, 50% of patients) exhibited significant improvements versus placebo for all doses tested. This preplanned analysis was based on observations from several of the gefapixant studies that suggested P2X3 antagonism was most efficacious in patients with the highest baseline cough frequency [25].

In post-hoc analysis of a phase 2a study, among patients who reported cough-related urinary incontinence at baseline, 11%, 15%, and 21% of those treated with 12.5 mg, 50 mg, and 200 mg camlipixant, respectively, reported no cough-related urinary incontinence at day 29 (compared with 3% with placebo) [168]. As of 2024, camlipixant is being evaluated in two large-scale phase 3 studies, again in patients selected for higher cough frequencies [25].

Other Novel Antitussives Under Investigation

The studies completed to date investigating P2X3 antagonists have typically found that between one-quarter and one-third of patients do not experience the 30% reduction in cough frequency thought to be the meaningful clinical threshold, suggesting some heterogeneity in the mechanisms underlying refractory chronic cough. Furthermore, patients with less frequent/severe coughing than those recruited to these trials may not benefit from treatments interrupting the ATP-P2X3 axis. Therefore, treatments with alternative modes of action are required to optimally manage patients with refractory chronic cough [25].

Sodium Channel Blockade

Lidocaine non-selectively blocks voltage-gated sodium channels important in the initiation of action potentials and their conduction and is a local anesthetic agent in routine topical use to reduce coughing during bronchoscopy. Case reports and case series have also described the use of nebulized lidocaine as an antitussive to treat refractory chronic cough [169].

In a three-way crossover study of single-dose lidocaine in refractory chronic cough, lidocaine throat spray reduced coughing by about 50% and was more effective than nebulized lidocaine, probably because nebulization into the lower airways has an irritant effect and evokes coughing initially [169]. The antitussive effects of lidocaine spray are relatively short lived and also associated with numbness in the mouth and lips, preventing patients from safely eating after treatment. Efforts have been made to develop similar therapies with a longer duration of action and without loss of sensation [25].

A novel approach to sodium channel blockade has been developed using a compound that is only active in blocking sodium channels after entering neurons via large-pore ion channels, such as P2X3 channels. As of 2024, a phase 2a clinical trial has been performed but the results are not yet published.

TRPM8 Agonism

Activation of TRPM8 ion channels produces cooling sensations. One new therapy has used an orally dissolving tablet containing a TRPM8 agonist (AX-8) placed on the back of the tongue to act as a counter irritant to the sensations of throat irritation reported by many patients with refractory chronic cough. In a randomized controlled trial, AX-8 reduced cough frequency, but not significantly over eight hours, the duration of action suggested by a previous open-label study. However, the effect was significant over four hours and exaggerated in those patients reporting greater throat discomfort, consistent with the proposed mechanism of action. Further studies in this subgroup of patients are hoped to confirm efficacy [25].

On day 1, AX-8 reduced cough frequency within 15 minutes and more than placebo over two and four hours, but not eight hours. In participants with baseline throat discomfort, reduction in cough frequency was significant over 24 hours, with a maximum reduction compared to placebo of 43% over two hours. Over 14 days, AX-8 significantly improved patient-reported outcomes and the safety profile was good with no serious adverse events. This suggests that TRPM8 agonism has potential for control of refractory/unexplained chronic cough as an alternative or adjunct to other therapies, especially in those patients complaining of cough driven by throat sensations [170].

NK-1 Antagonism

Following a positive study testing aprepitant as a cough treatment in patients with lung cancer, there has been interest in the potential antitussive effects of centrally acting neurokinin-1 (NK-1) antagonists. Following a negative trial in refractory chronic cough, a double-blind randomized controlled trial is in progress testing the effects of orvepitant in patients with cough associated with idiopathic pulmonary fibrosis [25].

NONPHARMACOLOGIC THERAPY

Speech and Language Therapy

Speech and language therapy techniques were first described as improving chronic cough in a randomized controlled trial in 87 patients with refractory chronic cough. The intervention appeared to have positive impact on cough, voice, throat symptoms, and symptom limitation after four therapy sessions over two months. Another study investigated a similar intervention delivered by speech and language therapists and physiotherapists. Compared with sham therapy, LCQ score improved by 1.5 points. Cough frequency improved by 40% more than in the sham-treated arm at four weeks and seemed to be maintained at three months. No larger-scale trials have been completed [25].

Speech and language therapy is a complex intervention, comprising components of education, cough suppression techniques, vocal hygiene, and psychoeducational counseling. Thus, it is difficult to standardize the intervention, and it is not clear whether all or just some of the components are essential for efficacy. In practice, the therapy seems to be most effective when delivered by experienced therapists, who may not be widely available. There is also a question about the durability of the effects over longer timescales when patients may not continue to practice the techniques [25].

The European Respiratory Society suggests a trial of cough control therapy (physiotherapy/speech and language therapy) in adult patients with chronic cough.

(https://erj.ersjournals.com/content/55/1/1901136. Last accessed August 12, 2024.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, moderate-quality evidence

The speech and language therapy approach to the management of chronic cough involves four steps: education, vocal hygiene, cough control/suppression training, and psychoeducational counseling [19].

Education

Patients are provided education on the biology of coughing, chronic cough, and cough hypersensitivity. The negative effects of repeated coughing and throat clearing are explained [19].

Vocal Hygiene

Vocal and laryngeal hygiene and hydration are advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation [19].

Cough Control/Suppression Training

Following identification of patient cough triggers, patients are taught a range of suppression strategies, including forced/dry swallow, sipping water, chewing gum, or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing while inhaling through the nose [19].

Psychoeducational Counseling

Behavior modification is used to reduce overawareness of the need to cough and facilitate an individual's internalization of control over their cough and to help manage stress and anxiety [19].

Local Injection Therapies

The experience of superior laryngeal nerve block by the injection of local anesthetic agents and corticosteroids has been described retrospectively following implementation in several clinics. In 2024, a small single-blind placebo-controlled study was performed comparing this treatment in 10 patients injected with active treatment and 7 with placebo, finding improvements in cough VAS and LCQ scores. Transient sensations of globus (lump in the throat) and soreness at the site of inject were the main adverse effects. Laryngeal botulinum toxin injections have also been reported to produce improvements in series of patients in clinical care, but no controlled studies have been performed. The broad safety of these interventions and duration of any effect currently remains unclear [25].

CONCLUSION

Chronic cough affects roughly 10% of adults in the United States [32]. These individuals can cough hundreds to thousands of times every day, often with uncontrollable bouts of coughing triggered by laughing, speaking, or changes in ambient temperature. This can continue for many years or decades, leading to substantial physical and emotional symptoms, including fatigue, urinary incontinence, cough syncope, dysphonia, depression, anxiety, embarrassment, social isolation, and severely diminished quality of life [28; 40; 64].

In 20% to 59% of patients with chronic cough, coughing persists despite extensive guideline-recommended evaluation and treatment of comorbidities or an underlying cause of cough cannot be identified. In these cases, a diagnosis of refractory or unexplained chronic cough is rendered [7; 36].

Chronic cough is a distinct pathologic entity (cough hypersensitivity syndrome) that develops when repetitive activation of airway cough receptors (typically by inflammatory mediators) induces neuroplastic changes, resulting in peripheral and central sensitization with symptoms of allotussia, hypertussia, and/or laryngeal paresthesia [3; 19; 20]. Hypersensitivity of vagal afferent neurons in the airways and their central projections, and deterioration in cortical inhibitory control of cough, explain the chronicity characteristics of this condition [33; 78].

According to current best evidence, clinical management of patients with chronic cough requires that clinicians perform thorough history, physical examination, and diagnostic testing to identify any potential underlying causes, with asthma, COPD, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD the top diagnoses to consider. After assessment is complete, clinicians should treat any identified airway and esophageal conditions according to practice guidelines. As part of the treatment approach, behavioral treatable traits, including cigarette smoking, use of ACE inhibitors and NSAIDs, poor inhaler technique (when relevant), and treatment adherence in general should be identified and addressed [5; 6; 10; 18; 24; 25; 79; 171].

It is important to recognize that cough hypersensitivity syndrome is present when cough persists despite etiologically based treatment or no etiology can be identified. Clinicians can make a diagnosis of refractory or unexplained chronic cough and refocus management to downregulating a hyper-reactive cough reflex using commercially available medication prescribed off-label and cough-specific speech and language therapy [5; 6; 10; 18; 24; 25; 79; 171].

Despite showing the best effectiveness, safety, and tolerability of commercially available medications evaluated in patients with refractory/unexplained chronic cough patients and despite recommended by international clinical practice guidelines, use of low-dose, slow-release morphine may be untenable or unrealistic. In light of this fact, gabapentin, pregabalin, and amitriptyline remain options for effective pharmacotherapy. Clinicians should also stay informed about possible FDA approval of gafapixant, the first-ever drug approved for refractory/unexplained chronic cough in several other countries, and about phase 3 trials of campilixant. Approval of these agents could expand the treatment options for these patients and potentially improve patient quality of life.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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