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Review

Therapeutic and mechanistic advances in chronic cough

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Key Messages

- Chronic cough in adults is defined as a cough lasting more than 8 weeks.
- Refractory chronic cough is defined as a cough that persists despite a thorough evaluation, including guideline-driven workup and treatment.
- Chronic cough has a profound negative impact on patients' quality of life, affecting physical, psychological, and social aspects of daily living.
- Most cases of chronic cough in adults are due to 1 or more of the following 3 main underlying causes: upper airway cough syndrome, asthma or non-asthmatic eosinophilic bronchitis, and gastroesophageal reflux disease.
- Cough hypersensitivity syndrome is characterized by a cough that is often triggered by low levels of thermal, mechanical, or chemical exposure and typically accompanied by a tickle or itching sensation in the larynx leading to an urge to cough.

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ABSTRACT

Cough is one of the most common reasons patients seek medical care in the outpatient setting. Chronic cough (CC) in adults is defined as a cough lasting more than 8 weeks, with a global prevalence of approximately 10%. CC significantly impairs quality of life, affecting physical, social, and psychological well-being. In most cases, CC is attributed to 1 or more of the following 3 key conditions: upper airway cough syndrome, gastroesophageal or laryngopharyngeal reflux, and asthma or non-asthmatic eosinophilic bronchitis—assuming a normal chest x-ray result and no use of angiotensin-converting enzyme inhibitors. If the cough persists despite thorough guideline-based evaluation and treatment, it is classified as refractory CC (RCC). RCC is thought to arise from neuronal dysregulation involving both peripheral and central mechanisms, termed cough hypersensitivity syndrome. This is typically characterized by a tickle or itch sensation in the throat, leading to an urge to cough in response to seemingly harmless stimuli. Current treatment options for RCC include "off-label" use of centrally acting neuromodulators and speech therapy. In addition, a new peripherally acting oral P2×3 receptor antagonist, gefapixant, has been approved in the European Union, United Kingdom, Switzerland, and Japan, though not in the United States or Canada. Emerging treatments hold promise for improving management in the future.

Introduction

Chronic cough (CC) is characterized by a cough that persists more than 8 weeks in adults, and it affects almost 10% of the population.[1,2] In addition to physical symptoms, the burden of CC includes a significantly impaired quality of life (QoL) due to sleep disturbances, social embarrassment, and psychological distress.[3-6] Furthermore, the considerable economic impact of CC includes direct health care costs and indirect costs such as loss of productivity.[7]

Despite its significant prevalence, CC often presents diagnostic challenges and unmet clinical needs due to its diverse etiologies and impact on QoL. Common conditions associated with CC include asthma, non-asthmatic eosinophilic bronchitis (NAEB), gastroesophageal reflux

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disease (GERD), upper airway cough syndrome (UACS), and angiotensin-converting enzyme inhibitor (ACE-I) use.[8-12] Refractory CC (RCC) is defined as a cough that persists despite a thorough evaluation, including guideline-driven workup and treatment.[1,13] Another CC classification often used is unexplained CC, defined as a cough that persists longer than 8 weeks, and remains unexplained after investigation and guidelines recommended therapeutic trials. In this manuscript, we use RCC and cough hypersensitivity syndrome (CHS) to be consistent with the most recent guidelines. It is well accepted that CHS, a distinct condition, underlies the persistent RCC.[14] CHS is characterized by a cough that is often triggered by low levels of thermal, mechanical, or chemical exposure and typically accompanied by a tickle or itching sensation in the larynx leading to an urge to cough.[13,15] Epidemiologic studies suggest that CC affects all ages and sexes, with increasing prevalence in females and older populations.[1,16,17] The prevalence also varies by region globally with higher prevalence in Europe and North America than in Asia.[2,17-20] This review will evaluate the clinical approach to patients with CC, focusing on RCC and CHS, including QoL impact, multidisciplinary diagnostic workup, RCC pathophysiology, and currently available and emerging treatment options.

Alterations in Neuronal Pathways in Refractory Chronic Cough

An integrated network of peripheral and central sensory nerves control cough. Airways are densely innervated by peripheral sensory nerve fibers capable of provoking cough in response to a wide spectrum of tussive triggers.[21] Sensory fibers are broadly classified based on whether they respond to mechanical vs chemical stimuli, termed Aδ- and C-nerve fibers, respectively.[22] Airway sensory fibers send signals to the paratrigeminal nucleus and the nucleus of the solitary tract in the brainstem, which, in turn, relay input to cortical regions and to efferent brainstem centers (eg, central pattern generator) to provoke conscious and reflexive cough (Fig 1).[23] Changes in the neurons at each level of this network have been implicated in RCC, particularly in the development of a central feature of RCC known as cough hypersensitivity, in which noxious and innocuous stimuli provoke the urge to cough.

Peripheral Mechanisms

Changes in airway sensory nerves have been found in humans with RCC and in animal studies. For example, in the airways of patients with RCC, airway sensory nerve density is significantly increased, which is predicted to increase cough triggering.[24] Whether these changes precede the onset of RCC or develop because of frequent coughing that in turn contributes to the persistence of RCC is unknown. Sensory nerves express a spectrum of cough receptors and ion channels, including transient receptor potential (TRP) channels (-A1, -V1, and -M8), purinergic P2×3 receptors, voltage-gated sodium channels (subtypes 1.7 and 1.8), and neurokinin-1 (NK-1) receptors. Inflammatory mediators (eg, interferons and tumor necrosis factor alpha) and endogenous autocoids (eg, histamine, bradykinin, and prostaglandin E2) increase nerve responsiveness to tussive ligands of these receptors, and in some cases, directly provoke cough.[25-32] In this manner, conditions associated with coughing, such as respiratory virus infections and asthma, sensitize peripheral sensory nerves to increase cough generation.

Endogenous cough ligands may also play a prominent role in cough hypersensitivity. Of these, extracellular adenosine triphosphate (ATP) has emerged as an important target that triggers cough by activating sensory nerve P2×3 receptors and increasing cough sensitivity to other tussive agonists such as capsaicin.[33] ATP levels are increased in the airways of subjects with RCC associated with chronic obstructive pulmonary disease and asthma,[34,35] and cough sensitivity to ATP is increased in patients with idiopathic or unexplained CC.[36] Similarly, the sensory nerve NK-1 receptor ligand substance P provokes cough in RCC associated with idiopathic pulmonary fibrosis (IPF) but not in healthy volunteers,[37] and nasal substance P levels are increased in RCC.[38] Both P2×3 and NK-1 receptors have garnered interest as promising therapeutic targets.

Central Mechanisms

Functional magnetic resonance imaging has revealed that subjects with cough hypersensitivity exhibit increased activation of cortical regions responsible for cough generation, including left, right, and dorsal midbrain, on exposure to tussive stimuli.[39] Interestingly, activation of regions associated with cough suppression (eg, dorsomedial prefrontal cortex and anterior midcingulate cortex) was concurrently reduced.[39] Attenuation of voluntary cough suppression was similarly found in a cough challenge study, in which subjects with RCC were less able to suppress capsaicin-evoked cough compared with healthy volunteers.[40] Given that both the urge to cough and cough generation are modulated by voluntary cough suppression, loss of cortical cough suppression is central to cough hypersensitivity in RCC.

Cumulatively, the combination of structural and phenotypic remodeling of peripheral nerves, alterations in central control of cough, and an increase in endogenous tussive ligands are predicted to contribute to cough hypersensitivity in RCC synergistically.

Quality of Life

CC has a profound negative impact on patients' QoL, affecting physical, psychological, and social aspects of daily living.[3,5,41-43] The impact of CC on a patient stems from interrelated variables of cough frequency, intensity, and disruptiveness.[44,45]

Physical Impairment

Physical symptoms vary and can include sore throat, hoarseness, chest pain, sleep disturbance, fatigue, exhaustion, dizziness, vomiting, and urinary incontinence.[5,41] Notably, stress urinary incontinence can occur in up to 63% of female patients.[4] Because patients may fail to voluntarily share this symptom, providers should proactively inquire about it.

Cough syncope, although uncommon, reflects the intensity of the cough. Coughing can generate intrathoracic pressures of up to 300 mm Hg, leading to circulatory effects that may cause syncope.[46] Cough syncope can lead to self-injury, with even more severe consequences if the individual is driving or operating machinery during an attack. Rib fractures can result from the mechanical stress of repetitive coughing.[47]

Social Impairment

Patients with CC are often triggered by innocuous stimuli (eg, scents or talking), making social activities and communication challenging, which can strain relationships and lead to social isolation.[48] In one study, 57% of patients with refractory or unexplained CC reported communication difficulties and 30% had trouble socializing.[6] Patients frequently struggle with phone conversations, prolonged talking, and attending activities such as church, movies, or dining out.[5,6,41,49] Patients with CC often face negative reactions from others and feel that they are being perceived as ill or contagious.

Furthermore, patients with CC perceive their cough as bothersome to those around them. Many feel that their partner or roommate cannot tolerate it, sometimes resulting in sleeping in separate rooms.[5,50] At work, they worry about how their cough affects their colleagues, feeling embarrassed if they are hacking in a group setting.[48] These experiences highlight the challenges of functioning at work and can hinder productivity.

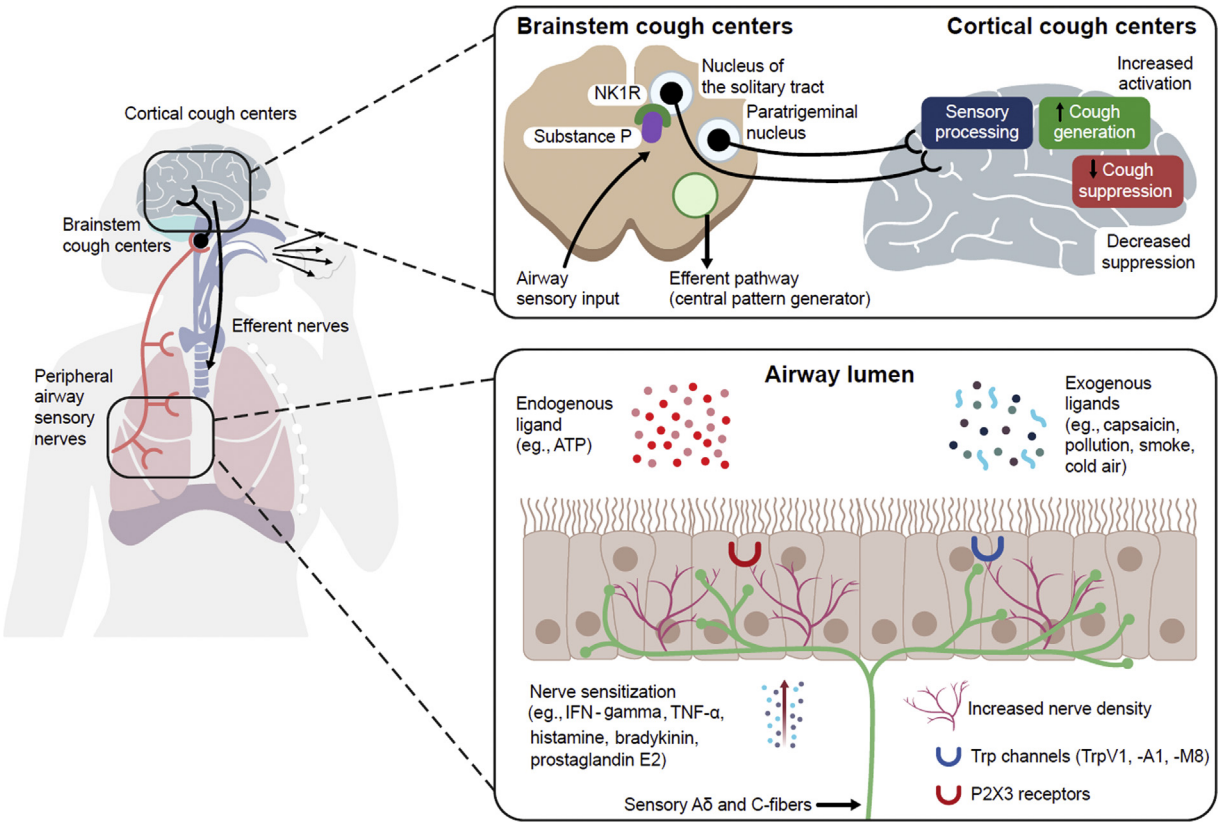

Figure 1. Cough mechanisms. Airway nerves detect exogenous and endogenous ligands and relay information to the nucleus of the solitary tract and paratrigeminal nucleus in the brainstem. These brainstem centers then relay information to brainstem reflexive cough centers and to cortical regions responsible for cough perception, generation, and suppression. ATP, adenosine triphosphate; IFN, interferon; TNF, tumor necrosis factor; Trp, transient receptor potential; NK1R, neurokinin 1 receptor.

Psychological

Patients with CC frequently experience a range of negative emotions, including anger, frustration, worry, anxiety, and depression.[41] A 2022 population-based study revealed that patients with CC report more depressive symptoms than those without CC.[51]

CC can also elicit fear due to concerns about the unknown underlying cause of the condition. French et al[5] found that up to 77% needed reassurance that their cough was not due to a serious medical condition. Patients frequently undergo numerous physician visits and extensive testing.[50] The uncertainty associated with the testing process can create a significant emotional and financial burden.

Cough-Specific Quality-of-Life Questionnaires

Cough-specific health-related QoL validated questionnaires can provide meaningful information regarding how cough affects multiple aspects of life. The Leicester Cough Questionnaire (LCQ) is the most widely used for evaluating all 3 physical, psychological, and social domains.[52] It was recently established that the content validity of LCQ is also appropriate for patients with RCC and unexplained CC.[53] The total score ranges from 3 to 21, with a higher score corresponding to a worse QoL. The minimal important difference is typically reported as 1.3 points for the LCQ; however, additional studies suggest that the minimal important difference may be closer to 1.5 to 2.0.[54,55] There is also the cough QoL questionnaire that can evaluate 6 domains of physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints, and personal safety fears.[56] The score ranges from 28 to 112, with a lower score indicating minimal impairment.

Differential Diagnoses

Multiple prospective studies have revealed that most cases of CC in adults are due to 1 or more of the following 3 main underlying causes: UACS (formerly postnasal drip syndrome; rhinitis), asthma or NAEB, and GERD.[57] Thus, the initial evaluation must include a thorough evaluation for the presence of these underlying, treatable causes after elimination of known contributing factors such as cigarette smoking and use of ACE-I (Fig 2).[58] A patient can have more than 1 underlying etiology of CC.[59] Thus, a partial but incomplete response to an empiric therapeutic trial may indicate that only 1 of multiple underlying causes of CC has been addressed.

Given prolonged wait times and barriers to subspecialty consultations,[60] a thorough initial evaluation by a primary care provider (PCP) can help identify treatable causes of CC or prompt a quicker subspecialist referral.

Pulmonary Etiologies of Chronic Cough

Although the evaluation of a patient with CC is often a multidisciplinary endeavor involving allergists, otorhinolaryngologists, and gastroenterologists, most patients are first referred to pulmonologists. The pulmonologist can determine whether further diagnostic evaluation beyond a chest radiograph and spirometry is indicated for a specific patient. Cough management guidelines published by the European Respiratory Society do not recommend routine performance of computed tomography of the chest in patients with normal chest radiograph and physical examination results.[1] The European Respiratory Society guidelines assigned a research recommendation with very low level of

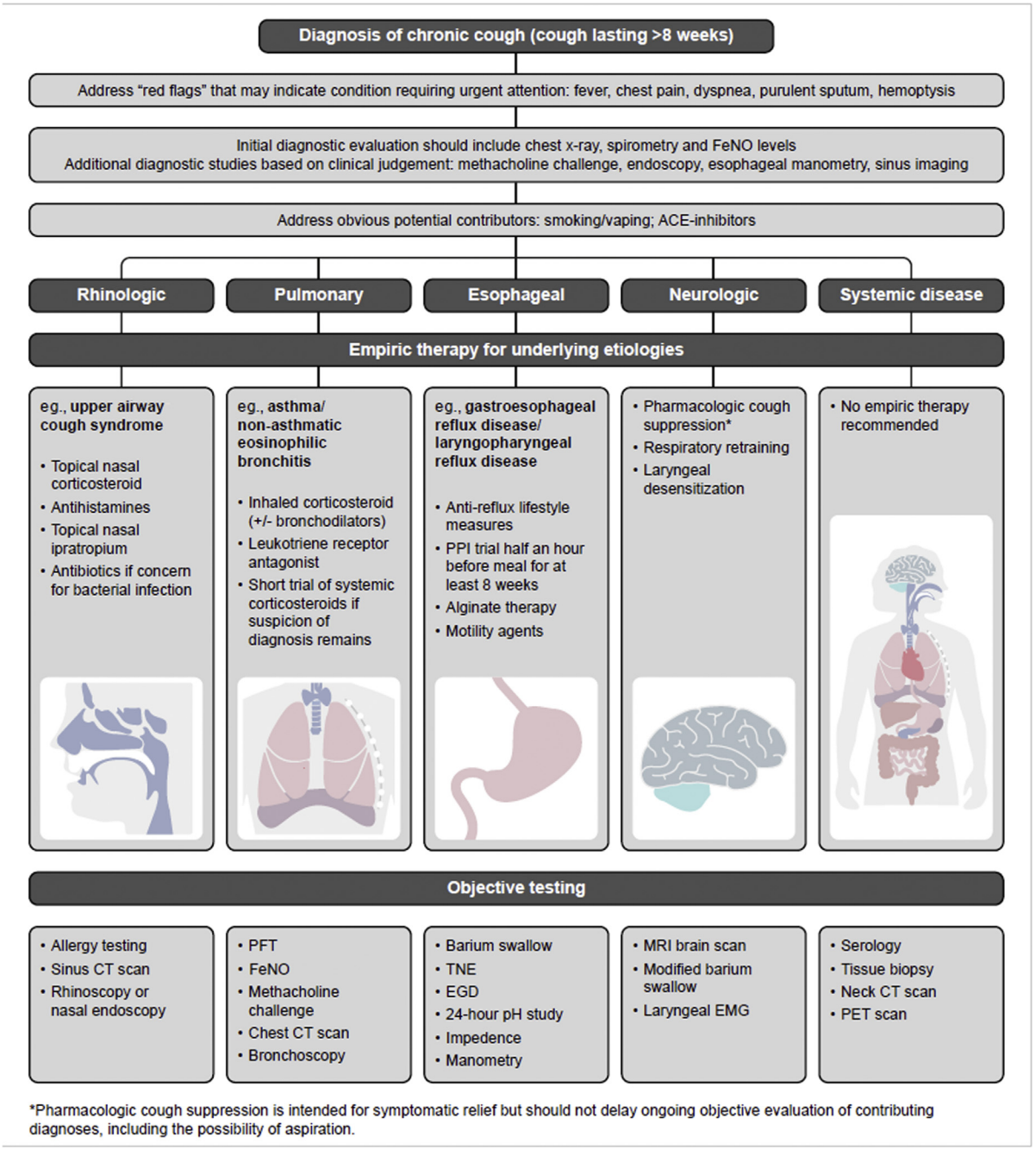

Figure 2. Example diagnostic-management protocol aimed at treatable underlying etiologies of chronic cough. ACE, angiotensin-converting enzyme; CT, computed tomography; EGD, esophagogastroduodenoscopy; EMG, electromyography; FeNO, fractional exhaled nitric oxide; MRI, magnetic resonance imaging; PET, positron emission tomography; PFT, pulmonary function test; PPI, proton pump inhibitor; TNE, transnasal esophagoscopy.

evidence for the use of fractional exhaled nitric oxide (FeNO) levels and blood eosinophil levels to predict response to inhaled corticosteroid or leukotriene-receptor antagonists, citing an absence of high-quality evidence in patients with CC.[1] In a prospective study of subjects with CC of unclear etiology and elevated FeNO levels more than or equal to 25 parts per billion, a 3-week trial of inhaled corticosteroid led to improvement in cough; however, this did not correlate with changes in FeNO levels.[61] Additional diagnostic studies including bronchoprovocation challenge and bronchoscopy are not recommended in published guidelines for routine implementation but are left to the physician's discretion.[1,57]

Upper Airway Cough Syndrome

The complex nature of CC is revealed by the interrelatedness of multiple disease states, which often confounds likely contributing factors.[62] Regardless of the triggers, it is universally recognized that cough is primarily centered in the larynx. Vocal fold closure is required to increase intrathoracic pressure, and relaxation of the vocal folds laterally is required to allow for air egress, permitting accelerative expulsion and producing the characteristic sound of a cough.

Overlapping physiology involved in the cough results in synergies that often magnify the effects of each disease (Fig 3). Rhinologic

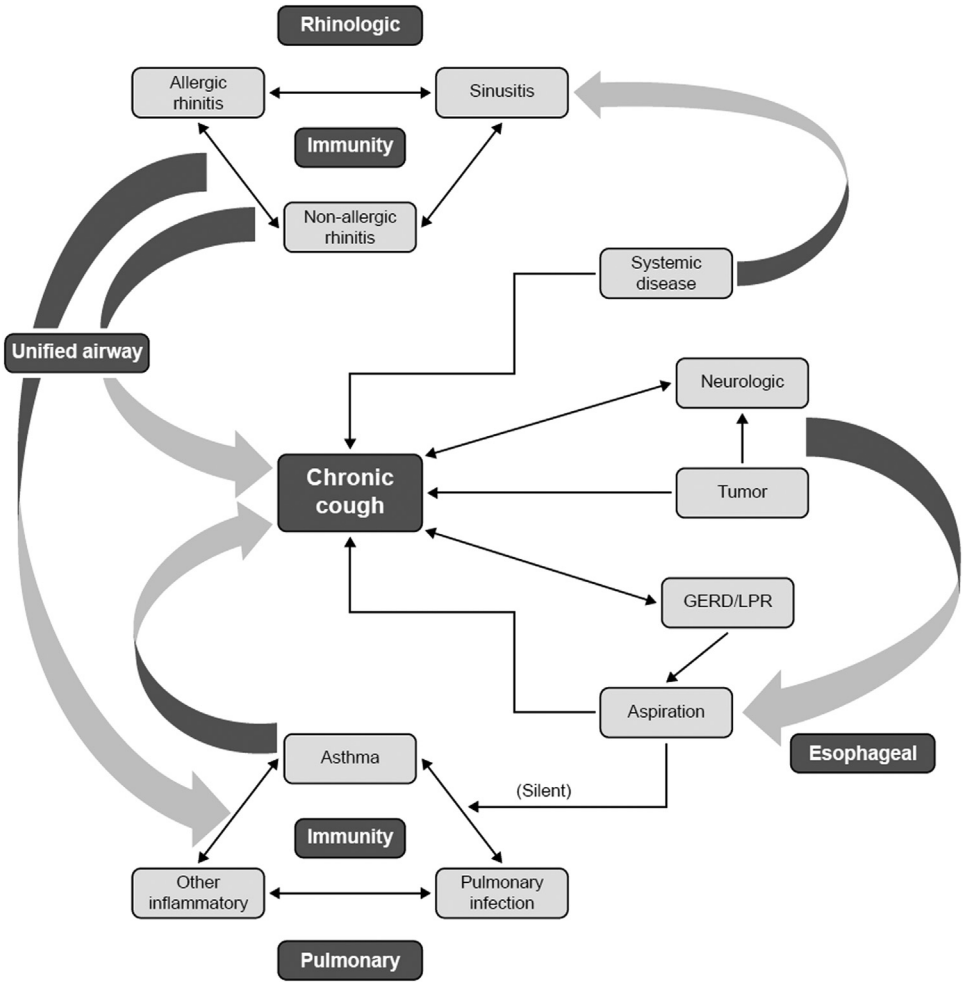

Figure 3. Factors contributing to chronic cough. GERD, gastroesophageal reflux disease; LPR, laryngopharyngeal reflux.

diseases associated with UACS include allergic rhinitis, rhinosinusitis, and non-allergic rhinitis. Mucosal edema, inflammatory cell and mediators,[63] altered mucus viscosity,[64] mechanical obstruction of the sinonasal outflow tracks, changes to the microbiome, and abnormal immune mechanisms[65] may be present in each of the UACS scenarios.

Rhinologic contributions are considered a dominant trigger for CC,[66] although there is a relative paucity of literature linking the two. Controversy remains because sinonasal-related postnasal drainage does not lead to CC in most patients, suggesting that airway hypersensitivity may play a more important role in some patients.[67] Nevertheless, the nose is often the first site of occupational and environmental exposures that can either trigger cough directly through mechanical and chemosensory mechanisms, or through any of the other combined secondary mechanisms.[68]

Mucus trafficking of altered airway surface liquid, epithelial cell type, ciliary function, and goblet cell mucus production are similar between the upper and lower airways.[65] Despite different microbiological environments in the nose and lungs, bacterial communication or chronic antibiotics may lead to shifts of the microbiome that are common to the upper and lower airways.[69,70] Also, the inflammatory, immune responses, and eventually, gene regulation drive this pathophysiological communication from the upper airway to the trachea and lungs.[71] New insights also offer possible learned mechanisms of cough sensitivity in patients with rhinitis.[72] Nevertheless, upper and lower airway communication likely exacerbates cough triggers beyond traditional UACS and pulmonary etiologies (Fig 3).

Management of UACS depends on clinical symptoms and examination findings and often starts with empiric therapy (Fig 2). Otolaryngologists, allergists, and others skilled in flexible nasopharyngeal laryngoscopy can identify specific findings. In the absence of convincing findings (such as pus from a sinus outflow track or in the subglottis), objective testing, such as formal allergy testing and a sinus computed tomography, is recommended after aggressive medical therapy.

Gastroesophageal Reflux Disease

An extra-esophageal manifestation of GERD, termed laryngopharyngeal reflux (LPR),[73] is often associated with CC. Both GERD and LPR involve regurgitation of gastric contents, but they may result in different symptom presentations or disease findings than the traditional GERD symptoms of heartburn, awareness of regurgitation, or dyspepsia.[74] CC can also be an extra-esophageal manifestation of eosinophilic esophagitis (EoE) even sometimes in the absence of typical gastrointestinal symptoms classic of EoE.[75-77]

Although the exact role of reflux in CC is unclear, typical patients with LPR present with nonproductive throat clearing, a cough-like behavior. This is often accompanied by a globus sensation near the cricoid cartilage, associated with increased cricopharyngeal tone on manometry.[78] Cricopharyngeal hypertonicity has also been linked to reflux.[79] These studies suggest that distal esophageal reflux may

precipitate a reflexive laryngeal cough response,[80] whereas esophageal hypersensitivity may heighten the cough reflex.[81]

The relationship between GERD and cough is complex, with multiple possible mechanisms and synergies (Fig 3). Direct refluxate to the larynx will precipitate cough as a protective mechanism, in part through mechanical and acid sensitivity of the cough receptors. Cough-induced reflux may result from diaphragmatic excursion during the cough, increased abdominal pressures, and lower esophageal sphincter relaxation.[82] This regurgitation to the larynx may result in gross aspiration or microaspiration, causing infectious or inflammatory pulmonary conditions that trigger cough.

A diagnosis of reflux-related cough may be aided by patient symptoms, such as with the "COuGH RefluX weighted score."[83] Suspicion increases when physical examination findings from flexible nasopharyngeal laryngoscopy align with a significant history of reflux disease occurring concomitant with the cough. The presence of posterior glottal edema may be sensitive, but it alone is not specific because edema can result from coughing itself. If patients present with CC and symptoms such as dysphagia, vomiting, or abdominal pain, then upper gastrointestinal endoscopy and biopsy should be considered to evaluate for EoE.

Initial Management of Chronic Cough

The initial evaluation needs not include an extensive battery of diagnostic tests; a chest x-ray and spirometry are often sufficient[1] unless there are specific signs suggesting need for further testing. Although published guidelines outline recommended management algorithms for patients with CC, including diagnostic-therapeutic trials of medications,[1,57] many patients experience CC for months or years without adequate exclusion of underlying, treatable causes. Common shortcomings in the evaluation of CC include the following: not considering a trial of an oral first-generation antihistamine, such as extended-release chlorpheniramine, before excluding UACS as an underlying etiology (first-generation antihistamine works as a centrally acting agent, although adverse effects of drowsiness and potential risk of dementia should be considered[84]); relying solely on an unsuccessful trial of inhaled corticosteroids and then not escalating to a short course of oral corticosteroids if history suggests asthma or NAEB, before excluding a steroid-responsive cough (asthma; NAEB); and, not performing an appropriate trial of anti-reflux therapy and reflux preventive measures in patients with a history of heartburn.[85] Long-term use of anti-reflux therapies is best guided by established clinical practice guidelines and a relative risk discussion with the patient.[86,87] In cases in which there is insufficient response to the cough with acid-suppressing medication, the latest CHEST Cough Guidelines recognize that objective testing for reflux is warranted in patients with suspected reflux disease who have symptoms despite treatment,[74] which will determine the presence of reflux disease, severity, and indications for more aggressive management.

Only when CC has not responded to a thorough diagnostic-therapeutic protocol (Fig 2) aimed at all treatable underlying etiologies is a subsequent diagnosis of RCC appropriate. Because there are currently no Food and Drug Administration–approved drugs for CC in the United States and many parts of the world, it is essential to uncover potential treatable causes of CC.

Treatment of Refractory Chronic Cough

In patients with CC, treatment targeting any underlying traits or conditions including asthma, NAEB, GERD, and UACS, or withdrawal of ACE-I and smoking cessation should be recommended.[88-91] However, despite these attempts, if coughing persists in patients with underlying conditions or investigations, do not reveal an underlying cause or trait, then we consider such patients to have RCC. At this point, the cough is often driven by neuronal dysfunction, and treatment is targeted toward suppressing the pathology, that is, neuronal hypersensitivity.[92] These include centrally acting neuromodulators which are used "off-label" and speech therapy (SP). A new peripherally acting oral P2×3 receptor antagonist, gefapixant, has also been licensed in the European Union, United Kingdom, Switzerland, and Japan, but not in the United States or Canada. Table 1[1,10,11,93-108] summarizes current options for RCC.

Centrally Acting Neuromodulators

Neuromodulator treatment includes low-dose morphine,[98] gabapentin,[103] and pregabalin.[94] Randomized controlled trials (RCTs) have revealed that all 3 therapies can improve symptoms and QoL. However, these studies were limited by small sample sizes, and the doses used were associated with notable adverse events, such as dizziness, somnolence, unsteadiness, and fatigue.

A trial of low-dose, slow-release opioid therapy may be considered for an initial period of 2 weeks after a discussion with the patient about the potential benefits and risks. Morphine doses of 5 to 10 mg of slow or modified release, administered twice daily, are typically sufficient in responders, with improvement often observed within 3 to 7 days.[98] A recent study has revealed that a 1-week course of treatment can reduce objective cough frequency by up to 72% in a responder group.[109] For those who do experience improvement, the dosage may be adjusted to minimize adverse effects and doses should not exceed 10 mg twice daily. Adjustments to the dose schedules, such as once-nightly or alternate day dosing or administering 3 to 4 hours before social or public engagements, may help reduce adverse effects. Codeine is generally not recommended, as studies have not supported its efficacy in acute cough or in chronic obstructive pulmonary disease.[110]

Gabapentinoids, such as gabapentin and pregabalin, are alternative options for patients with RCC, as they have been found to alleviate symptoms and improve QoL.[103] However, concerns about misuse and dependency necessitate careful dose titration and close monitoring. Gabapentin is typically initiated at a low dose of 100 mg 3 times daily and titrated to a maximum dose of 600 mg 3 times daily. A placebo-controlled trial found that gabapentin improved LCQ scores by 1.80 (95% CI: 0.56-3.04; P = .004), with a number needed to treat of 3.58.[103] Pregabalin can be trialed at an initial dose of 25 mg twice daily, with gradual increases to a target dose of 75 mg twice daily (maximum dose 150 mg twice daily), if needed. In one study, a combination of pregabalin and SP produced significantly greater improvements in LCQ scores than SP combined with placebo (mean LCQ difference = 3.5 [1.2]; 95% CI of difference: 1.1-5.8; P = .024).[94] Notably, although LCQ scores improved, no significant reduction in cough frequency was observed using the Leicester Cough Monitor. There is also limited evidence supporting the use of amitriptyline, with one unblinded study using 10 mg at bedtime revealing some symptomatic benefit, though the absence of a placebo control and validated outcome measures limits the study's conclusions.[104] Baclofen, a peripheral and central gamma-aminobutyric acid (GABA) agonist, has been trialed in small studies[111]; however, there is limited value of these agents in clinical practice due to adverse effects and tolerability.[112]

Peripheral Antagonist

Gefapixant (formerly AF-219) is a novel oral purinergic antagonist that inhibits the P2X3 receptor on vagal afferent nerves. Two phase 3 studies confirmed that a 45-mg twice-daily dose achieved the primary end point of a statistical reduction in 24-hour cough frequency compared with placebo.[113] A dose-response meta-analysis from 9

Table 1
Treatment Options for Patients Presenting With Refractory Chronic Cough

Therapy type	Dosage/frequency	Mechanism	Pros	Cons
Non-pharmacologic				
Speech therapy or PSALTI[93]	Variation in frequency and duration[93]	Education on cough triggers and suppression, teaches breathing exercises and laryngeal hydration strategies, provides counseling and throat massage[93]	• No adverse effects reported[93] • Patient led[93] • Can be combined with pregabalin[94] • Reduces cough hypersensitivity[95]	• Requires patient motivation[93] • Limited evidence of subjective improvement beyond initial treatment period[96] • Therapist dependent[93] • Multicomponent intervention; difficult to standardize[93] • Limited evidence from RCTs, no difference in 24-h cough frequency beyond 4 wk,[96] small sample sizes[93] • Limited access to therapy[1,96,97]
Pharmacologic				
Low-dose morphine[98]	5-10 mg MR twice a day[98]	Mu-opioid receptor agonist[97]	• Rapid reduction in cough score observed in responders to treatment; potential to improve cough-specific quality of life[98] • Short trial duration feasible (4 wk)[98] • Acts directly on cough hypersensitivity[1]	• Adverse effects include constipation and drowsiness[98] • Approximately half of patients have response to opiates[1] • Limited evidence of efficacy from RCTs based on cough severity (0-9 numerical rating scale)[98]
Pregabalin[94]	Up to 300 mg (maximum daily dose)[94]	Calcium channel modulator acting on α2δ-1 subunits[99,100]	• Can be prescribed at low dose with potential for dose escalation[94] • Acts directly on cough hypersensitivity[1] • Potential to improve cough-specific quality of life (LCQ) and cough severity when combined with speech therapy[94]	• Common adverse effects include weight gain, drowsiness,[101] dizziness, fatigue, cognitive changes, nausea, and blurred vision[1,94] • Hallucinations, suicidal ideation,[101] and issues with withdrawal[102] have also been observed in some cases • Limited evidence of efficacy from RCTs: no improvement in objective cough frequency[94]
Gabapentin[103]	1800 mg (maximum tolerable daily dose)[11]	Calcium channel modulator[98] acting on α2δ-1[99]	• Can be prescribed at low dose with potential for dose escalation[11,103] • Acts directly on cough hypersensitivity[1] • Potential to improve cough-specific quality of life (LCQ) and reduce cough frequency and severity[1,103]	• CNS-associated adverse effects may occur, such as sedation and unsteadiness[97] • Other adverse effects include dizziness, fatigue, dry mouth, disorientation, confusion, nausea, or blurred vision[1,103] • Limited evidence of efficacy from RCTs: subjective end points based on LCQ score, cough monitored for 1 h[103]
Amitriptyline[104]	10 mg every day[104]	Tricyclic antidepressant and serotonin reuptake inhibitor[105]	• Potential to improve cough-specific quality of life,[104] depression, and anxiety[106]	• Adverse effects include dry mouth, fatigue,[107] tremor, and weight gain[108] • Limited evidence of efficacy from RCTs: no placebo arm, only 10 d of therapy, subjective end points based on quality-of-life cough questionnaire (CQLQ)[104]

Abbreviations: CNS, central nervous system; CQLQ, Cough Quality-of-Life Questionnaire; LCQ Leicester Cough Questionnaire; MR, modified release; PSALTI, Physiotherapy, Speech and Language Therapy Intervention; RCT, randomized controlled trial.

RCTs concluded that gefapixant reduced cough frequency by 17.6% (95% CI: 10.6%-24.0%), reduced cough severity on a 100-mm visual analog scale (mean difference: −6.2 mm; 95% CI: −4.1 to −8.4), and improved cough-specific QoL on the LCQ (mean difference: 1.0 point; 95% CI: 0.7-1.4).[114] However, taste-related adverse effects occurred in 69% of patients, with 12% discontinuing due to these adverse effects. On the basis of these data, gefapixant was the first ever licensed drug for RCC and unexplained CC by the European Medicines Agency and regulatory authorities in the United Kingdom, Switzerland, and Japan. However, the Food and Drug Administration did not approve the medication in the United States. Clinicians in approved regions should engage in informed discussions with patients regarding its benefits and risks. Importantly, taste adverse effects improved in 25% of patients during treatment and resolved in nearly all after discontinuation or even on treatment, and there was no associated weight loss.

Speech and Language Therapy

Non-pharmacologic interventions, typically delivered by speech and language therapists or physiotherapists, focus on actively suppressing or controlling cough. These treatments can be used independently or alongside pharmacologic therapies, particularly for patients with RCC. Interventions include educating patients about their cough, teaching cough suppression techniques, incorporating breathing exercises, improving laryngeal hydration, and offering psychoeducational counseling to enhance cough control.[115] Six studies have been completed, consistently revealing non-pharmacologic interventions help reduce cough frequency and improve QoL and cough hypersensitivity.[115] In a multicenter RCT (PSALTI [Physiotherapy, Speech and Language Therapy Intervention)], there was a 41% reduction in cough frequency assessed objectively with the Leicester Cough Monitor, and a clinically significant improvement in QoL was sustained after therapy was completed at 3 months, but long-term data beyond this are not available.[116] The combination of SP with neuromodulators, such as pregabalin, has been evaluated, revealing clinically significant QoL improvements, which were also maintained after therapy. Furthermore, SP is particularly useful for patients with coexisting laryngeal disorders, such as muscle tension dysphonia, inducible laryngeal obstruction or vocal cord dysfunction, and voice disturbances, whereas physiotherapy is beneficial for those with disordered breathing patterns.[94] However, the main limitations of non-pharmacologic treatments include limited availability in primary and secondary care settings, a shortage of trained staff, and issues with patient adherence. Future research should focus on optimal referral timing, the most effective components of therapy, and their best modes of delivery. In addition, ongoing work is investigating the benefits of delivering these therapies virtually or in group sessions, which

may improve accessibility, reduce waiting times, and offer more convenience to patients.

Laryngeal Procedures

A recent meta-analysis reviewed 4 retrospective studies involving a total of 73 patients.[117] The experimental interventions included superior laryngeal nerve block with local anesthetic (lidocaine or bupivacaine) and corticosteroid (triamcinolone acetonide or methylprednisolone), bilateral thyroarytenoid botulinum toxin injection, and vocal fold augmentation with methylcellulose or hyaluronic acid.[117] These studies were limited by high bias risk, lack of control groups, and weaknesses such as imprecision and indirectness. These procedures have potential adverse effects. Patients undergoing bilateral thyroarytenoid botulinum toxin injections reported temporary liquid dysphagia and dysphonia. Superior laryngeal nerve block recipients experienced brief episodes of laryngospasm and temporary throat paresthesia. In addition, there is a risk of serious complications such as blindness or stroke due to potential steroid embolization into the arterial circulation.[118]

Emerging Therapies

Camlipixant (BLU-5937) is a more specific P2X3 receptor antagonist found to have promising results in a phase 2b trial, reducing cough frequency by 30% with minimal taste adverse effects, and is now in phase 3 trials. Other P2X3 antagonists, such as eliapixant, were discontinued due to liver toxicity, and sivopixant failed to have significant benefit in a phase 2b parallel group study design.[119] Pharmacologic modulation of TRP channels has been investigated for the treatment of CC.[120,121] However, the two phase 2 double-blind studies of TRP vanilloid 1 did not reveal improvements in spontaneous cough frequency.[122,123] Nalbuphine is a centrally acting mixed opioid agonist-antagonist at the mu and kappa receptors found to have positive phase 2a results in patients with RCC with IPF.[124] Phase 2a study in patients with RCC without IPF and a larger and longer phase 2b in RCC with IPF are currently ongoing.

Conclusion

There is significant unmet need in understanding and managing CC, especially RCC. Current treatments often do not result in sufficient improvement in coughing or patients' QoL. Future targeted therapies that address the underlying heterogeneous mechanisms hold promise for more effective symptom control.[125] In addition, increased awareness among health care providers and the general public about the impact of RCC is necessary to treat this chronic vexing medical problem effectively.

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References

1. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*. 2020;55(1):1901136.
2. Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J*. 2015;45(5):1479–1481.
3. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. *Lung*. 2008;186(suppl 1):S55–S58.
4. Dicpinigaitis PV. Prevalence of stress urinary incontinence in women presenting for evaluation of chronic cough. *ERJ Open Res*. 2021;7(1):00012–02021.
5. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med*. 1998;158(15):1657–1661.
6. Bali V, Schelfhout J, Sher MR, Tripathi Peters A, Patel GB, Mayorga M, et al. Patient-reported experiences with refractory or unexplained chronic cough: a qualitative analysis. *Ther Adv Respir Dis*. 2024;18:17534666241236025.
7. Birring SS, Holden SE, Jenkins-Jones S, Jones BI, Berni ER, Topaloudi V, et al. Healthcare utilization and cost associated with chronic cough in the United Kingdom: a retrospective observational study. *Eur Respir J*. 2020;56:3822.
8. Cote A, Russell RJ, Boulet LP, Gibson PG, Lai K, Irwin RS, et al. Managing chronic cough due to asthma and NAEB in adults and adolescents: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158(1):68–96.
9. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet*. 2008;371(9621):1364–1374.
10. Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. *Eur Respir J*. 2004;24(3):481–492.
11. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, et al. Treatment of unexplained chronic cough: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(1):27–44.
12. Morice AH. Post-nasal drip syndrome—a symptom to be sniffed at? *Pulm Pharmacol Ther*. 2004;17(6):343–345.
13. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J*. 2014;44(5):1132–1148.
14. Morice AH, McGarvey LP, Dicpinigaitis PV. Cough hypersensitivity syndrome is an important clinical concept: a pro/con debate. *Lung*. 2012;190(1):3–9.
15. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. *Respir Med*. 2015;109(6):701–707.
16. Ringus DL, Li SH, Vu TT, Guo A, Yuksel S, Arch RS, et al. Management and referral patterns for new-onset chronic cough in primary care patients. *Allergy Asthma Proc*. 2022;43(6):e72–e79.
17. Wang G, Hallberg J, Um Bergstrom P, Janson C, Pershagen G, Gruzieva O, et al. Assessment of chronic bronchitis and risk factors in young adults: results from BAMSE. *Eur Respir J*. 2021;57(3):2002120.
18. Satia I, Mayhew AJ, Sohel N, Kurmi O, Killian KJ, O'Byrne PM, et al. Prevalence, incidence and characteristics of chronic cough among adults from the Canadian Longitudinal Study on Aging. *ERJ Open Res*. 2021;7(2):00160–02021.
19. Abozid H, Baxter CA, Hartl S, Braun E, Salomonsson S, Breyer-Kohansal R, et al. Distribution of chronic cough phenotypes in the general population: a cross-sectional analysis of the LEAD cohort in Austria. *Respir Med*. 2022;192:106726.
20. Huang K, Gu X, Yang T, Xu J, Yang L, Zhao J, et al. Prevalence and burden of chronic cough in China: a national cross-sectional study. *ERJ Open Res*. 2022;8(3):00075–02022.
21. West PW, Canning BJ, Merlo-Pich E, Woodcock AA, Smith JA. Morphologic characterization of nerves in whole-mount airway biopsies. *Am J Respir Crit Care Med*. 2015;192(1):30–39.
22. Drake MG, Cook M, Fryer AD, Jacoby DB, Scott GD. Airway sensory nerve plasticity in asthma and chronic cough. *Front Physiol*. 2021;12:720538.
23. Taylor-Clark TE, Undem BJ. Neural control of the lower airways: role in cough and airway inflammatory disease. *Handb Clin Neurol*. 2022;188:373–391.
24. Shapiro CO, Proskocil BJ, Oppegard LJ, Blum ED, Kappel NL, Chang CH, et al. Airway sensory nerve density is increased in chronic cough. *Am J Respir Crit Care Med*. 2021;203(3):348–355.
25. Deng Z, Zhou W, Sun J, Li C, Zhong B, Lai K. IFN-gamma enhances the cough reflex sensitivity via calcium influx in vagal sensory neurons. *Am J Respir Crit Care Med*. 2018;198(7):868–879.

26. Hsu CC, Lin YS, Lin RL, Lee LY. Immediate and delayed potentiating effects of tumor necrosis factor-alpha on TRPV1 sensitivity of rat vagal pulmonary sensory neurons. *Am J Physiol Lung Cell Mol Physiol*. 2017;313(2):L293–L304.
27. Lin RL, Gu Q, Lee LY. Hypersensitivity of vagal pulmonary afferents induced tumor necrosis factor alpha in mice. *Front Physiol*. 2017;8:411.
28. Hewitt MM, Adams Jr G, Mazzone SB, Mori N, Yu L, Canning BJ. Pharmacology of bradykinin-evoked coughing in guinea pigs. *J Pharmacol Exp Ther*. 2016;357 (3):620–628.
29. Kamei J, Takahashi Y. Involvement of ionotropic purinergic receptors in the histamine-induced enhancement of the cough reflex sensitivity in guinea pigs. *Eur J Pharmacol*. 2006;547(1-3):160–164.
30. Patil MJ, Ru F, Sun H, Wang J, Kolbeck RR, Dong X, et al. Acute activation of bronchopulmonary vagal nociceptors by type I interferons. *J Physiol*. 2020;598 (23):5541–5554.
31. Al-Kandery AA, Rao MS, El-Hashim AZ. Prostaglandin E2 sensitizes the cough reflex centrally via EP3 receptor-dependent activation of NaV 1.8 channels. *Respir Res*. 2021;22(1):296.
32. Kollarik M, Ru F, Pavelkova N, Mulcahy J, Hunter J, Undem BJ. Role of NaV 1.7 in action potential conduction along human bronchial vagal afferent C-fibres. *Br J Pharmacol*. 2022;179(2):242–251.
33. Kamei J, Takahashi Y, Yoshikawa Y, Saitoh A. Involvement of P2X receptor subtypes in ATP-induced enhancement of the cough reflex sensitivity. *Eur J Pharmacol*. 2005;528(1-3):158–161.
34. Basoglu OK, Barnes PJ, Kharitonov SA, Pelleg A. Effects of aerosolized adenosine 5′-triphosphate in smokers and patients with COPD. *Chest*. 2015;148 (2):430–435.
35. Basoglu OK, Pelleg A, Essilfie-Quaye S, Brindicci C, Barnes PJ, Kharitonov SA. Effects of aerosolized adenosine 5′-triphosphate vs adenosine 5′-monophosphate on dyspnea and airway caliber in healthy nonsmokers and patients with asthma. *Chest*. 2005;128(4):1905–1909.
36. Fowles HE, Rowland T, Wright C, Morice A. Tussive challenge with ATP and AMP: does it reveal cough hypersensitivity? *Eur Respir J*. 2017;49(2):1601452.
37. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003;168 (8):995–1002.
38. Lim KG, Rank MA, Kita H, Patel A, Moore E. Neuropeptide levels in nasal secretions from patients with and without chronic cough. *Ann Allergy Asthma Immunol*. 2011;107(4):360–363.
39. Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ. Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax*. 2016;71(4):323–329.
40. Cho PSP, Fletcher HV, Turner RD, Jolley CJ, Birring SS. Impaired cough suppression in chronic refractory cough. *Eur Respir J*. 2019;53(5):1802203.
41. Everett CF, Kastelik JA, Thompson RH, Morice AH. Chronic persistent cough in the community: a questionnaire survey. *Cough*. 2007;3:5.
42. Bali V, Adriano A, Byrne A, Akers KG, Frederickson A, Schelfhout J. Chronic cough: more than just a persistent cough: a systematic literature review to understand the impact of chronic cough on quality of life. *Qual Life Res*. 2024;33(4):903–916.
43. Abdelhay A, Mahmoud AA, Al Ali O, Hashem A, Orakzai A, Jamshed S. Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006-19: a national, retrospective cohort study. *EClinicalMedicine*. 2023;62:102143.
44. Vernon M, Leidy NK, Nacson A, Nelsen L. Measuring cough severity: perspectives from the literature and from patients with chronic cough. *Cough*. 2009;5:5.
45. Meltzer EO, Zeiger RS, Dicpinigaitis P, Bernstein JA, Oppenheimer JJ, Way NA, et al. Prevalence and burden of chronic cough in the United States. *J Allergy Clin Immunol Pract*. 2021;9(11):4037–4044.e2.
46. Sharpey-Schafer EP. The mechanism of syncope after coughing. *Br Med J*. 1953;2 (4841):860–863.
47. Hanak V, Hartman TE, Ryu JH. Cough-induced rib fractures. *Mayo Clin Proc*. 2005;80(7):879–882.
48. Brindle K, Morice A, Carter N, Sykes D, Zhang M, Hilton A. The “vicious circle” of chronic cough: the patient experience - qualitative synthesis. *ERJ Open Res*. 2023;9(3):00094–02023.
49. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. *Chest*. 2006;130(6):1839–1843.
50. Kuzniar TJ, Morgenthaler TI, Afessa B, Lim KG. Chronic cough from the patient's perspective. *Mayo Clin Proc*. 2007;82(1):56–60.
51. Arinze JT, Hofman A, de Roos EW, de Ridder MAJ, Verhamme KMC, Stricker B, et al. The interrelationship of chronic cough and depression: a prospective population-based study. *ERJ Open Res*. 2022;8(2):00069–02022.
52. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58(4):339–343.
53. Martin Nguyen A, La Rosa C, Cornell AG, Sher MR, Bernstein JA, Birring SS, et al. Content validity of the Leicester Cough Questionnaire in adults with refractory or unexplained chronic cough: a qualitative interview study. *Ther Adv Respir Dis*. 2024;18:17534666241274261.
54. Birring S, Muccino D, Bacci ED, Vernon MK, Nguyen AM, Nguyen AM. Defining Minimal Clinically Important Differences (MCID) on the Leicester Cough Questionnaire (LCQ): analyses of a phase 2 randomized controlled trial in chronic cough. *J Allergy Clin Immunol*. 2019;143(2):AB52.
55. Raj AA, Pavord DI, Birring SS. Clinical cough:what is the minimal important difference for the Leicester Cough Questionnaire? *Handb Exp Pharmacol*. 2009;IV (187):311–320.
56. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality-of-life questionnaire. *Chest*. 2002;121(4):1123–1131.
57. Irwin RS, French CL, Chang AB, Altman KW, Chest Expert Cough Panel. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. *Chest*. 2018;153(1):196–209.
58. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1)(suppl):169S–173S.
59. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3):640–647.
60. Dicpinigaitis PV, Altman KW, Ulger Isci I, Ke X, Blaiss M. Interdisciplinary collaboration in the diagnosis and management of chronic cough: the role and importance of primary care providers. *Curr Med Res Opin*. 2023;39(10):1375–1381.
61. Lee JH, Kang SY, Yu I, Park KE, Oh JY, Lee JH, et al. Cough response to high-dose inhaled corticosteroids in patients with chronic cough and fractional exhaled nitric oxide levels >/= 25 ppb: a prospective study. *Lung*. 2024;202(3):275–280.
62. Irwin RS, French CT, Lewis SZ, Diekemper RL, Gold PM. Chest Expert Cough Panel. Overview of the management of cough: CHEST Guideline and Expert Panel Report. *Chest*. 2014;146(4):885–889.
63. Schleimer RP, Berdnikovs S. Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. *J Allergy Clin Immunol*. 2017;139(6):1752–1761.
64. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010;363(23):2233–2247.
65. London Jr NR, Lane AP. Innate immunity and chronic rhinosinusitis: what we have learned from animal models. *Laryngoscope Investig Otolaryngol*. 2016;1 (3):49–56.
66. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP Evidence-Based Clinical Practice Guidelines. *Chest*. 2006;129(1)(suppl):63S–71S.
67. Yu JL, Becker SS. Postnasal drip and postnasal drip-related cough. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24(1):15–19.
68. Tarlo SM, Altman KW, Oppenheimer J, Lim K, Vertigan A, Prezant D, et al. Occupational and environmental contributions to chronic cough in adults: Chest Expert Panel Report. *Chest*. 2016;150(4):894–907.
69. Halderman AA, Lane AP. Organism and microbiome analysis: techniques and implications for chronic rhinosinusitis. *Otolaryngol Clin North Am*. 2017;50 (3):521–532.
70. Natalini JG, Singh S, Segal LN. The dynamic lung microbiome in health and disease. *Nat Rev Microbiol*. 2023;21(4):222–235.
71. Halderman A, Lane AP. Genetic and immune dysregulation in chronic rhinosinusitis. *Otolaryngol Clin North Am*. 2017;50(1):13–28.
72. Janssens T, Dupont L, Goossens S, Sterckx Y. Van den Bergh O. Acquisition and generalization of cough trigger beliefs in allergic rhinitis. *J Behav Med*. 2020;43 (2):286–296.
73. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991;101(4 Pt 2)(suppl 53):1–78.
74. Kahrilas PJ, Altman KW, Chang AB, Field SK, Harding SM, Lane AP, et al. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. *Chest*. 2016;150(6):1341–1360.
75. Greifer M, Santiago MT, Tsirilakis K, Cheng JC, Smith LP. Pediatric patients with chronic cough and recurrent croup: the case for a multidisciplinary approach. *Int J Pediatr Otorhinolaryngol*. 2015;79(5):749–752.
76. Orizio P, Cinquini M, Minetti S, Alberti D, Paolo CD, Villanacci V, et al. Chronic cough and eosinophilic esophagitis: an uncommon association. *Case Rep Gastroenterol*. 2011;5(2):497–501.
77. Rubinstein E, Rosen RL. Respiratory symptoms associated with eosinophilic esophagitis. *Pediatr Pulmonol*. 2018;53(11):1587–1591.
78. Peng L, Patel A, Kushnir V, Gyawali CP. Assessment of upper esophageal sphincter function on high-resolution manometry: identification of predictors of globus symptoms. *J Clin Gastroenterol*. 2015;49(2):95–100.
79. Kwiatek MA, Mirza F, Kahrilas PJ, Pandolfino JE. Hyperdynamic upper esophageal sphincter pressure: a manometric observation in patients reporting globus sensation. *Am J Gastroenterol*. 2009;104(2):289–298.
80. Canning BJ. Afferent nerves regulating the cough reflex: mechanisms and mediators of cough in disease. *Otolaryngol Clin North Am*. 2010;43(1). 15-25, vii.
81. Javorkova N, Varechova S, Pecova R, Tatar M, Balaz D, Demeter M, et al. Acidification of the oesophagus acutely increases the cough sensitivity in patients with gastro-oesophageal reflux and chronic cough. *Neurogastroenterol Motil*. 2008;20 (2):119–124.
82. Herregods TVK, Pauwels A, Jafari J, Sifrim D, Bredenoord AJ, Tack J, et al. Determinants of reflux-induced chronic cough. *Gut*. 2017;66(12):2057–2062.
83. Krause AJ, Kaizer AM, Carlson DA, Chan WW, Chen CL, Gyawali CP, et al. Validated clinical score to predict gastroesophageal reflux in patients with chronic laryngeal symptoms: COuGH RefluX. *Clin Gastroenterol Hepatol*. 2024;22(6):1200–1209.e1.
84. Su CH, Huang KH, Yang Y, Gau SY, Chung NJ, Wu PT, et al. Cumulative dose effects of H1 antihistamine use on the risk of dementia in patients with allergic rhinitis. *J Allergy Clin Immunol Pract*. 2024;12(8):2155–2165.
85. Dicpinigaitis PV. Thoughts on one thousand chronic cough patients. *Lung*. 2012;190(6):593–596.
86. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal gastroesophageal reflux Disease: expert review. *Clin Gastroenterol Hepatol*. 2023;21(6):1414–1421.e3.

87. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology*. 2017;152(4):706–715.
88. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, et al. ERS guidelines on the assessment of cough. *Eur Respir J*. 2007;29(6):1256–1276.
89. Satia I, Badri H, Al-Sheklly B, Smith JA, Woodcock AA. Towards understanding and managing chronic cough. *Clin Med (Lond)*. 2016;16(suppl 6):s92–s97.
90. Satia I, Wahab M, Kum E, Kim H, Lin P, Kaplan A, et al. Chronic cough: investigations, management, current and future treatments. *Can J Respir Crit Care Sleep Med*. 2021;5(6):404–416.
91. Wu Z, Spencer LG, Banya W, Westoby J, Tudor VA, Rivera-Ortega P, et al. Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial. *Lancet Respir Med*. 2024;12(4):273–280.
92. Smith JA, Satia I, Badri H, Marsden P. Mini-review: hypertussivity and allotussivity in chronic cough endotypes. *Neurosci Lett*. 2023;792:136934.
93. Chamberlain Mitchell SAF, Ellis J, Ludlow S, Pandyan A, Birring SS. Non-pharmacological interventions for chronic cough: the past, present and future. *Pulm Pharmacol Ther*. 2019;56:29–38.
94. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. *Chest*. 2016;149(3):639–648.
95. Slinger C, Mehdi SB, Milan SJ, Dodd S, Matthews J, Vyas A, et al. Speech and language therapy for management of chronic cough. *Cochrane Database Syst Rev*. 2019;7(7):CD013067.
96. Chamberlain Mitchell SA, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax*. 2017;72(2):129–136.
97. Smith JA. The therapeutic landscape in chronic cough. *Lung*. 2024;202(1):5–16.
98. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med*. 2007;175(4):312–315.
99. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. *Br J Pain*. 2020;14(2):104–114.
100. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel α2-d (alpha2-delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res*. 2007;73(2):137–150.
101. European Medicines Agency. Lyrica SmPC. Accessed September 24, 2024. Available at: https://www.medicines.org.uk/emc/product/5539/smpc.
102. Ishikawa H, Takeshima M, Ishikawa H, Ayabe N, Ohta H, Mishima K. Pregabalin withdrawal in patients without psychiatric disorders taking a regular dose of pregabalin: a case series and literature review. *Neuropsychopharmacol Rep*. 2021;41(3):434–439.
103. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9853):1583–1589.
104. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. *Laryngoscope*. 2006;116(12):2108–2112.
105. Visca D, Beghe B, Fabbri LM, Papi A, Spanevello A. Management of chronic refractory cough in adults. *Eur J Intern Med*. 2020;81:15–21.
106. On PC. Updates in treatment of adults with chronic cough. *Am J Manag Care*. 2020;26(11)(suppl):S239–S245.
107. Ryan NM, Vertigan AE, Birring SS. An update and systematic review on drug therapies for the treatment of refractory chronic cough. *Expert Opin Pharmacother*. 2018;19(7):687–711.
108. European Medicines Agency. Amitriptyline SmPC. Accessed September 24, 2024. Available at: https://www.medicines.org.uk/emc/product/10849/smpc#about-medicine.
109. Al-Sheklly B, Mitchell J, Issa B, Badri H, Satia I, Collier T, et al. Randomised control trial quantifying the efficacy of low dose morphine in a responder group of patients with refractory chronic cough. *Thorax*. 2017;72:A24–A25.
110. Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2006;117(4):831–835.
111. Dicpinigaitis PV, Rauf K. Treatment of chronic, refractory cough with baclofen. *Respiration*. 1998;65(1):86–88.
112. Dong R, Xu X, Yu L, Ding H, Pan J, Yu Y, et al. Randomised clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-oesophageal reflux-induced chronic cough. *Aliment Pharmacol Ther*. 2019;49(6):714–722.
113. McGarvey LP, Birring SS, Morice AH, Dicpinigaitis PV, Pavord ID, Schelfhout J, et al. Efficacy and safety of gefapixant, a receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet*. 2022;399(10328):909–923.
114. Kum E, Patel M, Diab N, Wahab M, Zeraatkar D, Chu DK, et al. Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose-response meta-analysis. *JAMA*. 2023;330(14):1359–1369.
115. Birring SS, Floyd S, Reilly CC, Cho PSP. Physiotherapy and speech and language therapy intervention for chronic cough. *Pulm Pharmacol Ther*. 2017;47:84–87.
116. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax*. 2006;61(12):1065–1069.
117. Wamkpah NS, Peterson AM, Lee JJ, Jia L, Hardi A, Stoll C, et al. Curbing the cough: multimodal treatments for neurogenic cough: a systematic review and meta-analysis. *Laryngoscope*. 2022;132(1):107–123.
118. Liu OG, Chunming L, Juanjuan W, Xiaoyan X. Central retinal artery occlusion and cerebral inrfaction following forehead injection with a corticosteroid suspension for vitiligo. *Indian J Dermatol Venereol Leprol*. 2014;80(2):177–179.
119. Sykes DL, Zhang M, Morice AH. Treatment of chronic cough: P2×3 receptor antagonists and beyond. *Pharmacol Ther*. 2022;237:108166.
120. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Sulaiman Al-Ahmad M, et al. WAO-ARIA consensus on chronic cough - part 1: role of TRP channels in neurogenic inflammation of cough neuronal pathways. *World Allergy Organ J*. 2021;14(12):100617.
121. Tekulapally KR, Lee JY, Kim DS, Rahman MM, Park CK, Kim YH. Dual role of transient receptor potential ankyrin 1 in respiratory and gastrointestinal physiology: from molecular mechanisms to therapeutic targets. *Front Physiol*. 2024;15:1413902.
122. Belvisi MG, Birrell MA, Wortley MA, Maher SA, Satia I, Badri H, et al. XEN-D0501, a novel transient receptor potential vanilloid 1 antagonist, does not reduce cough in patients with refractory cough. *Am J Respir Crit Care Med*. 2017;196(10):1255–1263.
123. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *J Allergy Clin Immunol*. 2014;134(1):56–62.
124. Maher TM, Avram C, Bortey E, Hart SP, Hirani N, Molyneux PL, et al. Nalbuphine tablets for cough in patients with idiopathic pulmonary fibrosis. *NEJM Evid*. 2023;2(8):EVIDoa2300083.
125. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. *Lancet Respir Med*. 2018;6(8):636–646.