

Managed Care Considerations for Chronic Cough

HIGHLIGHTS

- › Understanding the Foundations of Chronic Cough
- › Updates in Treatment of Adults With Chronic Cough
- › Preparing for a New Era in Chronic Cough Management
- › CE Sample Posttest

Managed Care Considerations for Chronic Cough

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Intended Audience

Physicians, pulmonologists, respiratory specialists, nurses, pharmacists, managed care professionals.

Activity Overview

Chronic cough is the most common symptom for which individuals seek medical advice. This health issue has a substantial impact on a person's quality of life and can produce complications such as vomiting, fractures, muscle pain, syncope, and depression. Pharmacists and managed care professionals should recognize the complicated etiology of chronic cough and its difficult management. As there are currently no available therapies specifically indicated for this, the emerging treatment options that are targeted for patients with chronic cough have the promising potential to fulfill unmet needs in this population. They will resolve or minimize the significant burden on healthcare resources, families, work, and school, and improve patients' overall health.

Statement of Educational Need

Chronic cough is a highly debilitating condition that can result from multiple etiologies or is sometimes due to unknown causes. Further, there are no FDA-approved agents at this time that specifically address chronic cough. Combined with a lack of robust efficacy for agents used to treat acute cough, there is a significant unmet need for efficacious agents that provide relief for patients with chronic cough. To address these concerns, new agents with novel mechanisms of action are in development and, if found safe and effective, could become available in the United States. Therefore, healthcare professionals require continuing professional education and application of this knowledge to improve chronic cough management, clinical decision making, and the quality of life among patients affected.

Educational Objectives

At the completion of this activity, participants will be able to:

- Examine the etiologies of chronic cough, the burden, and the pathophysiology.
- Explain the treatment options for chronic cough including the emerging therapies.
- Identify opportunities to improve the management of chronic cough from a payer and patient perspective, as well as to integrate new treatments into the existing treatment algorithm.

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Managed Care Considerations for Chronic Cough

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] highlights the burden of chronic cough on the patient and healthcare system and identifies opportunities for healthcare and managed care professionals to improve the quality of care provided.

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Understanding the Foundations of Chronic Cough

Peter Dicpinigaitis, MD

Introduction

Cough continues to be one of the most common reasons that adults consult medical doctors in the United States, including both primary care physicians and specialists within pulmonology, allergy/immunology, otolaryngology, and gastroenterology.^{1,2} Within pulmonology clinics, up to 40% of patient visits are to evaluate chronic cough.³ Coughing is an essential reflex that is considered innate; however, in some patients, coughing can become a chronic, debilitating condition leading to negative outcomes. At its most extreme presentation, chronic cough can impact quality of life (QOL) and lead to depression, anxiety, urinary incontinence, and dysphonia.⁴ The impact of chronic cough on a patient's QOL is frequently underappreciated by healthcare professionals.

The impact of chronic cough is not isolated to the United States, with the global prevalence recently estimated to be close to 10% in a meta-analysis conducted by Song et al.⁵ Despite how frequently patients present with chronic cough, the exact underlying etiology can be challenging to diagnose, leading to multiple referrals and repeat office visits, along with extensive and often expensive testing. Results of a recent study published by Koskela et al found that 5.5% of patients with chronic cough underwent at least 3 consultations in the preceding 12 months.⁶ These patients accounted for approximately 50% of all physician consultations for cough, leading to a disproportionate usage of care.⁶ When evaluating a patient with chronic cough, physicians often repeat many unnecessary tests, are unaware of formal definitions of types of cough, and routinely stray from established professional society guidelines, which can complicate both current and future management.⁶

It is critical to understand the basics of chronic cough to accurately and appropriately make the underlying diagnosis as well as to identify effective treatments, especially as medications with new mechanisms of action are being increasingly developed. This review will focus on the definitions and epidemiology of chronic cough and the underlying pathophysiology that contributes to several etiologies and its impact on managed care in adult patients.

ABSTRACT

Despite chronic cough being one of the most frequent reasons for both primary care and specialty physician visits, its diagnosis and treatment remain challenging. The most common causes are upper airway cough syndrome, asthma, and gastroesophageal reflux disease; however, new research has implicated a cough hypersensitivity syndrome that may link many underlying etiologies. To accurately diagnose and treat patients with chronic cough, a thorough understanding of the various definitions, epidemiology, and pathophysiology is crucial. This article reviews these factors as well as the healthcare and socioeconomic burden of chronic cough.

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For author information and disclosures, see end of text.

Cough: Definitions

There is often confusion on how to define chronic cough, especially as many clinical trials have used varying definitions over the years. In a recent meta-analysis, Song et al reported 19 different definitions of chronic cough among 90 studies.⁵ However, both the American College of Chest Physicians (ACCP, or CHEST) and the European Respiratory Society define chronic cough as cough of greater than 8 weeks' duration.^{7,8} Therefore, when evaluating a patient with chronic cough, it is critical to stay consistent and follow guideline-established definitions. As new treatments for chronic cough are being developed, it is also important to be cognizant of these definitions as they will be routinely used in protocols and eventual prescribing information.

Based on the 2006 ACCP guidelines published by Irwin et al, cough can be defined based on duration of symptoms: (1) acute, less than 3 weeks; (2) subacute, 3 to 8 weeks; and (3) chronic, longer than 8 weeks.⁷ Therefore, the initial first step in evaluating someone for cough is to determine the duration, as this will help to narrow the differential diagnosis. In 2018, Irwin et al conducted a systematic review on the usefulness of the 2006 CHEST definitions in clinical studies and published their findings along with an updated guideline and expert panel report in *Chest*, further reviewing the critical nature of this determination and definition.⁹ Acute cough was most likely to be caused by infectious etiologies, especially with underlying viral causes; exacerbations of chronic medical conditions, such as asthma and chronic obstructive pulmonary disease (COPD); pneumonia; and environmental exposures.^{7,9} The most common causes of subacute cough included postinfectious cough, exacerbations of underlying conditions (eg, asthma, COPD), and upper airway cough syndrome (UACS). The predominant causes of chronic cough were found to be UACS, asthma, gastroesophageal reflux disease (GERD), and nonasthmatic eosinophilic bronchitis (NAEB), as well as a combination of these causes. Although considered a cause of chronic cough, allergies are typically considered a component within UACS and asthma. It is important to note that many of the studies included in this review are heterogeneous and associated with a degree of bias. The authors concluded that CHEST's 2006 definitions appeared useful when reviewing the literature.^{7,9} A more detailed review of etiologies of chronic cough will be covered in later sections.

Another subtype of chronic cough defined in the literature includes refractory chronic cough (RCC). RCC is defined as a persistent cough despite thorough investigation and treatment according to published practice guidelines.^{8,10,11} RCC has also been used interchangeably with chronic refractory cough (CRC) and unexplained chronic cough (UCC). The key component of RCC is the requirement of failure of guideline-based modalities, which may not always be followed in real-world settings. Therefore, it is paramount to obtain a thorough medication history from the

patient as well as prior records from referring physicians. It has been estimated that RCC can be seen in 20% to 46% of patients presenting to a specialist cough clinic.¹¹

Epidemiology of Chronic Cough

As noted, the global prevalence of chronic cough among 90 studies was reported as 9.6% (95% CI, 7.6%-11.7%) by Song et al.⁵ This meta-analysis was limited by varying definitions of chronic cough and had significant heterogeneity between studies but indicates the global burden that chronic cough has on the healthcare system. Chronic cough was found to be significantly more common in Europe and America compared with Africa and Asia.⁵ There are previously published data to support that there is no significant ethnic difference in cough reflex sensitivity among Caucasian, Indian, or Chinese patients using laboratory-measured, capsaicin-induced cough reflex sensitivity.¹² The regional variations in chronic cough observed in Song et al are most likely due to additional factors outside of ethnicity and may include environmental factors (eg, urbanization) as well as variations in diet and obesity.⁵

In addition to these regional variations, there is also a clear impact of gender on chronic cough. In an evaluation of 10,032 patients with chronic cough from 11 cough clinics worldwide, Morice et al found that approximately two-thirds were women.¹³ This female predominance was observed in each country studied, except for China, but was not as prominent in smaller cough clinics. The explanation for this gender difference has been postulated to be secondary to differences in the respiratory tract anatomy and increased sensitivity to the cough reflex in women. Within the same study, Morice et al evaluated the neural processing associated with cough in 10 healthy men and women to further investigate this difference.¹³ In addition to having a lower maximum tolerable dose of inhaled capsaicin compared with men, the healthy women also had significantly greater activation of the somatosensory cortex as measured on magnetic resonance imaging of the brain despite this lower stimulus. The somatosensory cortex has been established to receive airway sensory inputs, and its respective activation is closely correlated with a patient's perceived urge to cough.

This increased somatosensory response in healthy women may be similar to what is seen with lower cutaneous and visceral pain thresholds observed in chronic pain syndrome.¹³ Future studies can further aim to characterize this neural processing link specifically in patients with chronic cough. The heightened sensitivity of cough in women, specifically women of childbearing age, may have an evolutionary component by preventing aspiration in women who could potentially become pregnant.¹³ The specific hormonal pattern is most likely not the contributing factor in these clinical scenarios, based on the prominence of cough in postmenopausal women.¹³ In addition, the inherent, multifactorial pathophysiology underlying these gender differences can also be provoked

by certain medications, with prior studies showing that women are approximately twice as likely to develop cough while taking angiotensin-converting enzyme (ACE) inhibitors.¹⁴

Patients with chronic cough typically present later in life. Morice et al reported similar findings to prior studies, with the most common age for presentation being age 50 to 69 years.¹³ More than two-thirds of the patients were 50 years and older, with 20% aged 70 years and older, which somewhat mirrors the prevalence of other chronic conditions that can lead to chronic cough, such as GERD, but not asthma.¹³ Although the population evaluated was quite diverse, the similarities seen between the clinics indicated an underlying link that continues to be heavily researched: cough hypersensitivity syndrome (CHS).¹³ CHS could potentially link these patients through a proposed heightened response of afferent nociceptors within the upper airways of patients with chronic cough.¹⁵ This, as well as additional pathophysiologic mechanisms to explain chronic cough, will be reviewed in the following paragraphs.

Pathophysiology of Cough

As with any chronic condition, the pathophysiology associated with chronic cough is multifactorial and complex. It is also important to emphasize the underlying pathophysiologic differences between men and women that contribute to chronic cough. This review will focus on some basic pathophysiology while also covering some of the newer pathways that have become of increased interest in therapeutics; a complete review of all included pathways is beyond the scope of this review.

At its most basic premise, cough serves as a defense mechanism by helping to prevent aspiration and enhancing airway clearance.⁸ At its most extreme, loss of this reflex can lead to aspiration, infections, and nutritional deterioration, as is observed in patients with neurological deficits.⁸

Cough receptors can respond to either chemical or mechanical stimuli and are located both within and outside (eg, ear canals, eardrums, distal esophagus) the respiratory tract.¹⁶ Chemical receptors include transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin type 1 (TRPA1).¹⁶⁻¹⁸ Inhalation of capsaicin has been shown to induce cough via activation of TRPV1 receptors.¹⁸ TRPV1 receptors are not only activated by vanilloids such as capsaicin but also via other stimuli, including acidity and inflammatory mediators (eg, prostaglandins, bradykinin, and leukotrienes).¹⁸ Similarly, activating TRPA1 receptors can produce cough, with stimuli including cold temperatures, environmental irritants, and inflammatory mediators.¹⁷ P2X3 receptors are found on airway vagal afferent nerves, which, when stimulated, can lead to increased sensitivity to multiple stimuli and chronic cough.^{19,20}

Once the receptors are stimulated, the signal is carried to the brain for central processing and eventually leads to the actual motor act of a cough. Cough is a 3-phase expulsive motor act characterized

by an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase), and finally the expulsive phase, where the glottis opens and there is rapid expiratory airflow.²¹ This motor response is preceded by a complex interaction of sensory and chemical triggers that help form the cough reflex arc. This reflex arc is initially stimulated by the irritation of cough receptors found in the lining of the upper and lower respiratory tracts. The afferent pathways have cough receptors innervated by the vagus, glossopharyngeal, and trigeminal nerves.²² The highest concentration of cough receptors is found in the larynx, carina, and bifurcation of larger bronchi. These receptors respond to a multitude of stimuli, both intrinsic (eg, histamine, bradykinin, prostaglandins) and extrinsic (eg, smoke, environmental allergens). The afferent nerves then transmit signals to the cough center of the brain that is located in the nucleus tractus solitarius of the medulla. Impulses are then subsequently sent via the vagus nerve to the spinal motor and phrenic nerves that control the diaphragm, intercostal muscles, pelvic floor muscles, and abdominal wall that are responsible for generation of the cough.²²

A recently proposed concept developed to provide a mechanistic basis for RCC is that of CHS, which involves vagal nerve hypersensitivity enhancing the sensitivity of the cough reflex, thus rendering individuals with cough induced by certain ubiquitous triggers (cold air, strong smells, prolonged talking, laughing) that do not induce cough in the vast majority of the population.^{8,15,23} In 2011, Morice et al used the Hull Airway Reflux Questionnaire (HARQ) to evaluate both normal volunteers and patients with chronic cough. The authors concluded that patients with chronic cough could have an overall increased afferent hypersensitivity that predisposes them to chronic cough.¹⁵ The authors also proposed that gaseous nonacid reflux not detectable by testing at that time was a major driver of CHS, among other low levels of thermal, mechanical, or chemical exposures.^{15,23} This underlying hypersensitivity could also be explained by an underlying neuropathic condition that includes nerve damage as well as increased neuronal excitability via upregulated TRP nociceptors.²³ Upregulation of both central and peripheral components of neuronal mechanisms contribute to CHS as well.²³ The hypersensitivity seen in CHS is also different from the methacholine bronchial responsiveness in entities such as asthma, which reflects its afferent hypersensitivity to many different stimuli.²³ The entire range of receptors involved in CHS has not yet been fully elucidated, but TRPV1 and TRPA1 have been implicated. In addition, there may be a component of increased T2 inflammation in the airways also contributing to CHS.^{8,23} Patients with CHS may experience a dry, chronic cough with additional symptoms including persistent tickling or irritating sensation in the chest or throat, hoarse voice, dysphonia, and the perception of laryngeal obstruction that is provoked by low levels of environmental irritants.²³

Etiology

To identify the underlying etiology of a patient's chronic cough, a thorough history and physical examination must be performed. Cough duration, triggers, and preceding illnesses should be elicited. A detailed medical history should be obtained including both pulmonary and extrapulmonary conditions, such as GERD, hypertension, allergies, and immunological conditions. Surgical history is pertinent, especially within the cardiac, pulmonary, gastrointestinal, and otolaryngological organ systems. An extensive social history including recent travel, country of origin, potential sick contacts, occupational and environmental exposures, and smoking history should be completed.^{8,9} Interestingly, a majority of patients with chronic cough are either lifetime nonsmokers or former smokers.²⁴ After evaluating 1000 patients with chronic cough at a specialized cough center, it was found that 2.7% being evaluated were active smokers and 27% were former smokers.²⁴ A detailed medication reconciliation should be performed, with an emphasis on inquiring about medications specifically used for GERD, allergies, and hypertension (such as ACE inhibitors). In addition to this reconciliation, patients should be asked what medications have been tried for cough and if any have provided relief.

The review of systems should include both pulmonary and extrapulmonary symptoms. Based on the 2018 CHEST guidelines, there is an emphasis on specifically evaluating for hemoptysis, which is considered a red-flag symptom that should prompt a more expedited workup for infectious causes, such as tuberculosis as well as malignancy.⁹ Physicians should also make a concerted effort to decide on which validated cough severity tool will be used throughout their evaluation in order to stay consistent. Options include a simple cough score from 0 to 10, visual analog scale, cough QOL measures (eg, Leicester Cough Questionnaire [LCQ], Cough Quality of Life Questionnaire [CQLQ]), and additional, validated questionnaires (eg, HARQ).⁸

The CHEST 2018 guidelines recommend a routine follow-up 4 to 6 weeks after the initial evaluation.⁹ If patients have undergone prior evaluations by specialists, it is critical to obtain these medical records, including laboratory values, diagnostic reports, and treatments prescribed. After the history is completed, a thorough physical exam should be performed, with special attention to the respiratory, otolaryngological, cardiac, and gastrointestinal systems. An extensive review of all diagnostic tests to perform will not be the focus of this review; instead, the focus will be on the 3 most common causes of chronic cough, including UACS, asthma, and GERD.⁸ A patient's prior evaluations must be reviewed in order to determine if these etiologies have been accurately assessed, diagnosed, and treated. Many patients may not have been completely evaluated for these conditions yet diagnosed based on their response (or lack thereof) to certain medications, which is a critical part of the history to ascertain. There are a series of other etiologies of

chronic cough; however, these are beyond the scope of this review. Malignancy, infections, foreign body inhalation, and medications should always be kept on the differential diagnosis.⁸

UACS

UACS includes signs and symptoms referred to by similar names including postnasal drip syndrome, rhinitis, and rhinosinusitis.⁸ Patients can develop these symptoms secondary to allergies and infectious causes (eg, sinusitis, acute nasopharyngitis), which subsequently increase secretions in the upper airway and lead to stimulation of cough receptors within the laryngeal mucosa to stimulate a cough.⁸ Patients will frequently report increased nasal discharge, a sensation of liquid dripping into the back of the throat, and frequent throat clearing. As there are no formal diagnostic criteria, patients with suspected UACS may be prescribed and respond to first-generation oral antihistamines and/or nasal anticholinergics and steroids.

Asthma

Asthma, along with NAEB, is a clinical diagnosis with no clear-cut, absolute diagnostic test available to either rule asthma in or out as the cause of the patient's chronic cough.⁸ Asthma is mediated by eosinophilic inflammation, which can be challenging to objectively measure in real-world settings where testing, such as sputum eosinophilia and exhaled nitric oxide (NO), are not routinely available, time consuming, costly, not patient-friendly, and require expert evaluation.⁸ A complete blood count (CBC) with differential can be evaluated for eosinophilia; however, this is not a specific test and can vary based on season and time of day.⁸ Although nonspecific, an eosinophil count greater than 0.27 to 0.3 cells/ μ L may be representative of eosinophilic airway inflammation.^{8,25}

Within asthma, 3 subtypes of cough have been identified. Classic asthma is associated with bronchial hyperresponsiveness and airflow variability for which spirometry is indicated.⁸ Cough-variant asthma represents an entity where cough is the primary symptom and wheezing and dyspnea are not. In this clinical scenario, treatment with a combination of β -agonist bronchodilators, inhaled corticosteroids, and/or leukotriene receptor antagonists (LTRAs) can improve coughing.⁸ There are mixed opinions on whether performing bronchial provocation testing is indicated in these clinical scenarios. Eosinophilic bronchitis without bronchoconstriction or hyperresponsiveness, also termed NAEB, is the third and final type of asthmatic cough.⁸ A detailed review of medications used in chronic cough due to asthma will be the focus of future reviews; however, in general, the anti-inflammatory medications used in treating asthma include inhaled or oral steroids.

Reflux

Although established as a leading cause of chronic cough in the literature, there is some debate over the true contribution of reflux

to chronic cough.⁸ When evaluating a patient for reflux, it is important to inquire about both classic and atypical reflux symptoms, including chest pain and dysphagia.⁸ A patient's diet is also important to evaluate as well as how it correlates with their reflux and cough. Esophageal motility disorders may play a more integral part of reflux-mediated chronic cough than previously realized, especially in the setting of esophagopharyngeal reflux.⁸ In evaluation of reflux as a cause of chronic cough, many patients will undergo extensive and costly testing, including upper endoscopy, high resolution manometry, barium swallows, and pH monitoring. Similar to asthma, many of these tests require advanced facilities with gastroenterologists who have extensive experience evaluating the results.

Reflux likely contributes to chronic cough via several mechanisms, including aspiration of gastric contents leading to a proinflammatory reaction with mucus hypersecretion in the respiratory tract.²⁶ In addition, cough receptors in the upper respiratory tract can be stimulated by both acid and nonacid reflux.²⁷ Laryngopharyngeal reflux (LPR) can be considered a variant of GERD and occurs when gastric contents irritate the laryngopharynx.²⁸ Patients with LPR may not report classic GERD symptoms but rather experience dysphagia, frequent throat clearing without mucus, and dysphonia.

Results of a systematic review of 9 randomized controlled trials conducted by Kahrilas et al found modest benefit in using proton pump inhibitors (PPIs) in patients with acid reflux but no significant benefit over placebo in those patients without reflux.²⁷ Despite these findings, both acid and nonacid reflux have been implicated in chronic cough.²⁹ An underappreciated cause of chronic cough is nonacid reflux. Indeed, a trial of a combination of antacid and prokinetic/promotility therapy may be required to evaluate the role of nonacid reflux in a patient's chronic cough.⁸

A subgroup of patients with reflux-associated chronic cough are those with obesity. There is evidence in the literature that chronic cough is more common in patients who are obese, yet this link has not yet been fully elucidated.³⁰ Recently, a group led by Descazeaux et al noted a higher prevalence of GERD in obese versus nonobese patients with chronic cough (47.3% vs 34.6%, $P = .0188$) as well as obstructive sleep apnea (OSA) (9.8% vs 3.1%, $P = .0080$).³¹ There were no statistical differences in prevalence of asthma and UACS between the groups. Patients with suspected GERD-induced cough underwent at least 1 of the following tests: endoscopy, manometry, and/or pH monitoring. There was no statistical difference between the obese and nonobese patients with respect to normal and abnormal gastrointestinal testing. PPI therapy was also found to be more successful in obese patients compared with nonobese patients (32.5% vs 17.0%, $P < .05$); however, there was a trend toward an increased proportion of patients responding to PPI as body mass index increased, yet no statistical difference was found. In addition, obese patients treated with PPIs were less likely to report refractory cough at 12 months (22.3% vs 34.1%, $P < .05$). The authors

postulated that the underlying dysregulation in the neural and central processing associated with CHS may contribute to the 22.3% and will undoubtedly be of research interest in the future. This study reinforces the importance of assessing a patient with chronic cough for OSA and obesity as possible contributors. In addition to obesity itself leading to chronic cough, its downstream consequences can also contribute, including worsening hiatal hernia and increasing intragastric pressure and hypotensive lower esophageal sphincter.³¹ The authors also hypothesized that OSA worsens the main triggers of chronic cough, such as UACS, asthma, and GERD, and/or increases overall airway inflammation.

To further expand on the link between OSA and chronic cough, Sundar et al evaluated the impact of continuous positive airway pressure (CPAP) on patients with OSA who also had unexplained chronic cough.³² Patients with OSA and chronic cough treated with CPAP for 6 weeks had statistically significant improvements in their LCQ compared with sham CPAP. There were no differences found in the exhaled breath condensate markers of airway inflammation. Similar to results from Descazeaux et al, the authors proposed that OSA can lead to increased airway inflammation, laryngeal hypersensitivity, and rapid changes in oxygenation, all of which can lead to chronic cough. Although OSA is not within the top 3 etiologies of chronic cough, it is an important medical condition that may be concurrently present in certain patients with more classic etiologies. Therefore, CPAP may represent an adjunctive therapy in this population subset.

The role of PPI treatment in chronic cough will be covered more thoroughly in later sections; however, it is important to address all potential adverse effects (AEs) with the patient and thoroughly document this discussion in the patient's chart. A full review of these AEs is beyond the scope of this article, but they are increasingly important to discuss with patients. In addition, when reviewing a patient's medications, it is also crucial to evaluate whether or not the PPI is indicated and/or working for the patient's chronic cough or other indications; if not, consideration should be given to slowly tapering the PPI off to avoid unnecessary polypharmacy.

Healthcare and Socioeconomic Burden

As previously discussed, chronic cough represents one of the most common reasons for visits to both primary care providers and specialists, creating substantial socioeconomic impact as well as contributing to global healthcare burden. In the United States alone, there were 21 million outpatient consultations for cough in 2015 per the Centers for Disease Control and Prevention.³³ The impact of chronic cough on the healthcare system is multifactorial. Patients are often referred to several specialists and occasionally obtain multiple opinions from physicians within the same specialty. This can lead to unnecessary repeat testing, increased costs to both payers and patients, less time for patients with other symptoms,

and exposure to polypharmacy as well as possible AEs of these medications.⁶ Because there can be potentially life-threatening etiologies to explain the chronic cough, it is also not a symptom that should be easily dismissed.

To try to further understand this healthcare burden, a research group led by Koskela et al performed a cross-sectional email survey in Finland to try to determine the factors associated with repetitive doctor consultations for chronic cough.⁶ This was defined as at least 3 doctor consultations in the previous 12 months. Of 3695 patients who responded, 5.5% reported repetitive consultations, accounting for 50.4% of doctor consultations for cough. Repetitive consultations were most likely secondary to the presence of asthma and chronic rhinosinusitis. In addition, depression, smoking, presence of comorbidities, and low cough-related QOL scores were also associated with repetitive consultations. High medical costs associated with chronic cough have been traditionally attributed to acute care utilization, such as emergency department visits and inpatient stays; however, results of this study highlight the increasing burden of chronic cough on costs associated with outpatient care usage.

The impact of chronic cough on a patient's QOL is often overlooked or underappreciated by healthcare practitioners.^{23,34} Patients with chronic cough can develop anxiety and depression, which may lead to significant alterations in their social and family lives.³⁴ This is based on their symptoms being considered highly disruptive to the affected patient as well as their surrounding environment.⁸ Aside from the cough itself, this may lead to increased physician visits for insomnia, speech difficulties, anxiety, urinary incontinence, and depression.³⁵ In one study, 53% of patients undergoing evaluation for chronic cough were found to score positive for depression.³⁶ Improvement in cough score correlated with improvement in depression scores as well.

More physician visits may lead to additional testing, referrals, missed work or school, and more out-of-pocket expenses. Despite these additional visits, certain symptoms may be overlooked, including urinary incontinence experienced by women with chronic cough.⁸ This symptom may be embarrassing to many women, and it can lead to a delay in diagnosis as well as development of potential complications if care is delayed.^{8,35} This is a key symptom to review during a patient's evaluation. There are multiple cough-specific QOL tools, including the LCQ or CQLQ, that are frequently used in clinical studies, but may be challenging to use on a daily basis in real-world settings.^{37,38} Therefore, it may be more practical to use a simpler score, such as assessing the severity and impact on QOL using a "cough score" from 0 to 10 or a 100-unit visual analog scale.⁸

Conclusions

Chronic cough will undoubtedly continue to have a profound impact on patients, physicians, and the healthcare system. A thorough

evaluation with attention to evidence-based guidelines is critical to improving patient outcomes. Although there are similarities among patients with chronic cough as reviewed in epidemiology, pathophysiology, and etiology, each patient should be treated as an individual. The 3 most common etiologies, UACS, asthma, and GERD, must be systematically evaluated in all patients. Physicians must be cognizant of the predominance of women presenting with chronic cough and the subtleties associated with potential extrapulmonary symptoms. The foundations of chronic cough covered in this review can assist in both current evaluations of patients with chronic cough as well as prepare for future treatments. ■

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Updates in Treatment of Adults With Chronic Cough

Phung C. On, PharmD, BCPS

Introduction

Chronic cough is a severely debilitating condition that can result from multiple different etiologies. Historically, most treatments available to patients have been effective for the resolution of acute cough. Patients can purchase antitussives without a prescription and self-treat when needed. If self-treatment with over-the-counter therapy fails, patients may seek prescription medications for acute cough from their primary care physician, such as benzonatate or cough syrups with codeine.

However, patients whose cough persists beyond 8 weeks (refractory chronic cough [RCC] or unexplained chronic cough [UCC]) experience great irritation as they often cough in excess of hundreds to thousands of times daily.¹ Pharmacologic treatment for chronic cough has limited efficacy, resulting in decreased quality of life (QOL) for many patients affected. Recent advances over the past decade have improved the understanding of the pathophysiology of chronic cough and the suspected neurobiological role leading to the development of novel therapeutic agents to help address this debilitating condition.

Chronic Cough Guidelines for Adult Patients

Currently, 2 major treatment guidelines address the medical management of RCC and UCC: those of the American College of Chest Physicians (ACCP or CHEST) and the European Respiratory Society (ERS).^{2,3} Both guidelines recommend a thorough history and physical when evaluating patients who present with chronic cough.^{2,3} A CHEST guideline and expert panel also recommend focusing on the identification of red-flag symptoms (see [Table 1](#)⁴) and ruling out other conditions that either commonly or more rarely result in chronic cough.⁴

CHEST guidelines recommend that individuals with a known cause of their chronic cough have their therapy optimized for each diagnosis.^{2,3} Patients need to be assessed for adherence regularly, with frequent follow-up to monitor for barriers, efficacy of treatment, cough severity, and QOL. Education to avoid exposure to known environmental and occupational triggers should also be provided. A referral to a cough clinic should be considered in patients with RCC.^{2,3}

ABSTRACT

Chronic cough is a severely debilitating condition that results in individuals coughing hundreds to thousands of times per day. Unfortunately, at the time of this writing, the majority of treatments currently available address acute cough and have minimal efficacy for chronic cough. There are no current FDA-approved pharmacologic treatments for chronic cough, resulting in a large, unmet need for patients. Recent advancements in the understanding of the chronic cough reflex and suspected neurobiology have led to the development of novel therapeutic targets to bridge this unmet treatment need. Current American College of Chest Physicians and European guidelines recommend a thorough workup but differ in individual pharmacologic treatment recommendations. All patients should be evaluated for red-flag symptoms and any underlying conditions that may explain the patient's chronic cough. Historical treatments, such as opiates and neuromodulators, have been used with limited success. Emerging agents that target specific channel receptors have shown initial positive benefits concerning cough frequency, severity, and quality of life and may become available on the market as they have shown to be generally well tolerated without any safety concerns in clinical studies.

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For author information and disclosures, see end of text.

A comparison of CHEST and ERS guideline recommendations for the nonpharmacologic and pharmacologic treatment of chronic cough is outlined in **Table 2**.^{2,3} Both guidelines recommend a trial of speech pathology and gabapentin in patients with UCC and recommend against the use of proton pump inhibitors (PPIs) in the absence of gastroesophageal reflux disease (GERD). The guidelines differ in their recommendations of inhaled corticosteroids (ICS) and morphine.^{2,3} Current options for the management of RCC and UCC will be discussed in further detail in subsequent sections. Chronic cough management is often complex, requiring an individualized treatment plan. Therefore, treatment options discussed below include a summary of efficacy and tolerability data to guide clinical decision making.

Nonpharmacologic Treatment of Chronic Cough

Current CHEST guidelines recommend a trial of multimodality speech pathology therapy in patients with UCC.² This recommendation

was based on positive cough severity, randomized control trial data.^{5,6} Results of a systematic review by Chamberlain et al found 2 to 4 sessions of speech pathology that included education, cough suppression techniques, breathing exercises, laryngeal hygiene, and counseling resulted in decreased cough frequency, improved cough severity, and positive benefits on cough-related QOL.⁶

Speech pathology typically begins with measuring symptoms, assessing laryngeal physiology, and determining whether the individual is a good candidate for speech pathology treatment for chronic cough (SPTCC).⁷ The exact mechanism for chronic cough improvement after SPTCC is not fully elucidated. Individuals who present with a nonproductive cough; abnormal laryngeal sensations, such as tickle, itch, tightness, dryness, or globus; coughs triggered by nontussive stimuli, including perfumes, cold air, or talking; and low doses of tussive stimuli, such as chemical fumes or smoke, seem to improve the most from SPTCC. The desired outcomes for SPTCC include a reduced urge to cough, improved coping skills, decreased anxiety and depression, and reduced laryngeal constriction.⁷

Treatment of the Most Common Causes of Chronic Cough

Upper Airway Cough Syndrome (UACS)

Previously called postnasal drip syndrome, UACS is the most common cause of chronic cough in adults and should be addressed first when managing this condition.^{8,9} Patients may require further workups, such as allergy testing (allergic rhinitis) and computed tomography of the sinuses (sinusitis), as indicated on an individual patient basis.^{8,9}

The etiology of UACS will dictate the selection of treatment for affected patients. Managing exposure to environmental irritants, such as perfumes or pollution, and any other offending agents, including pollen, dust, or mites, is a standard first-line nonpharmacologic therapy approach.^{8,9} Sinusitis can be managed via saline lavage, nasal corticosteroids, antihistamines, and antibiotics as needed.^{8,9} If the cause of chronic cough is unknown, then initiation of a decongestant (eg, pseudoephedrine, phenylephrine) plus a first-generation antihistamine (eg, chlorpheniramine) may be started initially.¹⁰ Other therapies, such as intranasal corticosteroids (eg, fluticasone), saline lavage, nasal anticholinergics (eg, ipratropium), and antihistamines (eg, cetirizine, fexofenadine, loratadine), may also be

TABLE 1. Chronic Cough Red-Flag Symptoms⁴

- Hemoptysis, fever, weight loss, and/or peripheral edema **PLUS** weight gain
- Smoker aged >45 years with a new cough, change in cough, or coexisting voice disturbance
- Adults aged 55-80 years **PLUS** a 30 pack-year smoking history (current smoker or quit within past 15 years)
- Dyspnea (especially at rest or at night)
- Hoarseness; trouble swallowing, eating, or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam or chest radiograph coinciding with cough duration

TABLE 2. Comparison of CHEST and ERS Guideline Recommendations for Management of Chronic Cough^{2,3}

Recommendation	2016 CHEST Guidelines	2020 ERS Guidelines
Speech pathology therapy	✓	✓
Inhaled corticosteroid ^a	±	✓
Gabapentin ^b	✓	✓
Proton pump inhibitor ^c	±	±
Morphine ^d	±	✓

CHEST, American College of Chest Physicians; ERS, European Respiratory Society.

✓ Recommended ± Not Recommended

^aInhaled corticosteroid not recommended by CHEST guidelines in adult patients with unexplained chronic cough and negative tests for bronchial responsiveness and eosinophilia. ERS guidelines recommend a short-term trial (2-4 weeks) in adult patients with chronic cough.

^bGabapentin is recommended by CHEST guidelines with patient counseling on adverse effects and risk-benefit profile. ERS guidelines recommend a trial of gabapentin or pregabalin in adults with refractory chronic cough.

^cProton pump inhibitor therapy is not recommended by CHEST guidelines in adult patients with unexplained chronic cough and a negative workup for gastroesophageal reflux disease. Both proton pump inhibitors and histamine-2 receptor antagonists are not routinely recommended for chronic cough by ERS guidelines.

^dERS guidelines recommend a trial of low-dose morphine (5-10 mg twice daily) in adult patients with refractory chronic cough.

considered. Typically, clinical improvement is expected within days to weeks, with a maximum of 2 months for resolution of UACS.^{9,10}

Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Cough

ACE inhibitor-induced cough is a common cause among individuals on ACE inhibitor therapy.¹⁰ Upon discontinuation, the ACE inhibitor-induced cough typically resolves within 1 week to 3 months. Angiotensin receptor blockers (ARBs) are commonly prescribed as a replacement for patients who experience ACE inhibitor-induced coughs. Depending on the clinical circumstance, providers may choose to restart ACE inhibitor therapy, and the reoccurrence of cough may not occur in some patients.^{10,11}

Asthma

Asthma is another common cause of chronic cough, and treatment should begin with patient education on smoking cessation and the avoidance of potential triggers.^{9,10} Asthma treatment should then follow guidelines from the Global Initiative for Asthma (GINA) cycle of asthma care.^{12,13} The GINA control-based cycle of asthma care starts with the assessment of a patient's symptom control and risk factors, inhaler technique and adherence, and patient preferences. Treatment should be adjusted, taking into consideration modifiable risk factors, current asthma medications, and any nonpharmacologic strategies being employed. Then, the patient's response to the treatment plan is reviewed, addressing aspects including symptoms, exacerbations, adverse effects (AEs), patient satisfaction, and lung function, and the process continues with assessment.^{10,12}

Pharmacologic treatment usually consists of a bronchodilator (eg, albuterol) and an ICS (eg, budesonide). Leukotriene receptor antagonists (eg, montelukast, zafirlukast) are also sometimes added. Severe or refractory cough usually will require an oral corticosteroid (eg, prednisone, methylprednisolone) for 5 to 10 days.¹⁰

Chronic Obstructive Pulmonary Disease (COPD)

COPD frequently causes a chronic cough, but, unlike asthma, patients typically do not have undiagnosed COPD. Because symptoms of asthma and COPD can overlap, it is important to use spirometry to aid in the diagnosis, so proper treatment can be administered.

Treatment of COPD should follow the stepwise approach recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.¹⁴ Pharmacologic agents usually include an inhaled bronchodilator, inhaled anticholinergic, and ICS. A short course (5-7 days) of an oral corticosteroid (plus or minus antibiotics) may be used for acute management of exacerbations.¹⁴

Gastroesophageal Reflux Disease (GERD)

GERD has been associated with chronic cough in research, but treatment is considered controversial as the pathophysiology of cough

related to GERD is highly complex.^{10,15} The 2016 CHEST and expert panel guideline recommend individuals suspected to have reflux-cough syndrome first begin with diet modification to lose weight in patients who are overweight or obese, elevating the head of the bed, and avoiding meals within 3 hours of bedtime.¹⁵

Among individuals with reported acid reflux and regurgitation, antacid agents, such as histamine-2 receptor antagonists (H₂ RAs), PPIs, alginate, and calcium carbonate, are recommended to alleviate symptoms.¹⁵ PPI therapy is not recommended by CHEST among those who have chronic cough without acid reflux or regurgitation, as treatment is considered unlikely to be effective. Gastroesophageal symptoms typically respond within 4 to 8 weeks but may take up to 3 months. Chronic cough that persists beyond the 3-month antacid therapy trial should be further evaluated; additional diagnostic tests, such as esophageal manometry and/or pH-metry, should be conducted as indicated.¹⁵

Nonasthmatic Eosinophilic Bronchitis (NAEB)

NAEB is another common cause of chronic cough that is characterized by unresponsiveness to bronchodilators.¹⁰ Avoidance of inhaled allergens due to occupational exposure should be considered first when there is a known cause. ICS are usually effective for NAEB, and oral corticosteroids can be considered after failure of high-dose ICS.^{10,16}

Traditional Pharmacologic Agents for Chronic Cough

Nonprescription Products

The majority of products sold without a prescription for cough relief (eg, dextromethorphan, guaifenesin, diphenhydramine, and, in some states, low-dose codeine) are not considered more effective than placebo when studied in randomized clinical trials for cough suppression.^{17,18} These agents are readily available, inexpensive, and typically safe when used appropriately per nonprescription product labeling. Therefore, they are commonly used to address acute and chronic cough among patients who self-treat. However, none of these agents is indicated for chronic cough, so patients should be referred to their provider for further workup.

Opiates

Codeine and morphine are the most used opiate antitussives.¹⁹ Codeine has been used for more than 200 years to treat cough, including tuberculosis-induced cough. It has a rapid onset of action, and responders are easily identified from nonresponders within 1 to 2 weeks of initiation. Approximately 50% of patients with chronic cough will have a suboptimal cough suppression. Further, additional limitations, such as individual variability with codeine metabolism (CYP2D6) and potential safety concerns, are important considerations. Patients who are poor metabolizers

(little to no CYP2D6 activity) will have a decreased response to codeine. AEs, such as constipation and nausea, are common with codeine treatment.¹⁹ The efficacy of codeine is not well supported in clinical trials. Results of a trial by Smith and colleagues that investigated the use of 60 mg codeine phosphate daily did not find it to be more effective than placebo for reducing objective or subjective cough frequency or severity in individuals with COPD and cough.²⁰ Additional studies are needed to fully ascertain the utility of codeine in patients with chronic cough.

Morphine is an alternative opiate to codeine that is typically reserved for the most severe intractable coughs and is not recommended in current CHEST guidelines.^{2,19} In contrast with codeine, morphine does not exhibit the CYP2D6 variability in metabolism and is approximately 10 times more potent.¹⁹ Due to safety risks including respiratory depression, drowsiness, addiction, and accidental overdose, patients should be closely monitored. The efficacy and tolerability of morphine (5-10 mg) extended-release was evaluated in a 4-week randomized, placebo-controlled, crossover study (N = 27) in patients with chronic cough.²¹ Those who were treated with morphine reported a significant difference in the Leicester Cough Questionnaire (LCQ) score compared with placebo (mean difference, 2; $P < .02$) and daily cough severity score (range, 0; mean difference, -3.4 ± 1.8 ; $P < .01$). Although treatment was generally well tolerated and most effects were observed within the first week, 18 of 27 enrolled patients continued on to the extension study, and two-thirds opted to double their dose due to inadequate control of their cough during the core study.^{19,21}

Neuromodulator Agents

Gabapentin inhibits $\alpha 2\delta$ subunits on voltage-gated calcium channels and is approved for the treatment of seizures and neuropathic pain within the United States.²² It is now also considered a possible therapeutic option in patients with chronic cough based on improved understanding of chronic cough pathophysiology.^{23,24} The efficacy of gabapentin was evaluated in a 10-week randomized controlled trial (N = 62) in patients with RCC, and results indicated that gabapentin (1800 mg/day) significantly improved LCQ scores compared with placebo ($P = .004$). It also decreased cough severity scores ($P = .029$) and objective cough frequency ($P = .028$) by week 8. Once treatment was discontinued, the antitussive effects were not sustained.²³ Current CHEST guidelines recommend a trial of gabapentin as long as patients are educated on the potential for AEs and the risk-benefit profile along with a reassessment of risk-benefit at 6 months before continuing therapy.²

Pregabalin is a structural derivative of γ -aminobutyric acid and binds $\alpha 2\delta$ subunits on voltage-gated calcium channels.²⁵ Like gabapentin, pregabalin has also been evaluated for efficacy in RCC. A 14-week study evaluated pregabalin as adjunctive treatment to speech pathology therapy and demonstrated a significant improvement

in LCQ scores ($P = .024$) and decreased cough severity ($P = .002$) compared with just speech pathology alone.²⁶

Both gabapentin and pregabalin are associated with AEs, such as drowsiness, confusion, fatigue, and blurred vision, which have led to discontinuation.^{23,26} It has also been proposed that both gabapentin and pregabalin may just alter the perception of cough versus controlling cough.^{23,26} Therefore, additional randomized controlled trials are required to fully ascertain the utility of these agents in the treatment of chronic cough.

The tricyclic antidepressant amitriptyline is FDA approved for depression and is also frequently used for the treatment of anxiety, neuropathic pain, and potentially for chronic cough.^{27,28} At the time of this writing, no placebo-controlled randomized clinical trials are evaluating the efficacy of amitriptyline in the treatment of chronic cough. A small randomized trial (N = 28) evaluated the efficacy of amitriptyline 10 mg in patients with post-viral vagal neuropathy cough.²⁹ Amitriptyline was shown to be significantly more effective compared with the combination of codeine/guaifenesin in complete cough response and cough-specific QOL at 10 days.²⁹ A major limitation of this study was that neither objective cough frequency nor any safety outcomes were measured. Additional research is required to fully elucidate the role of amitriptyline in the treatment of chronic cough.

Novel Emerging Agents for Chronic Cough

The lack of efficacy of traditional antitussive agents combined with an improved understanding of the neurobiology of the cough reflex has led to an increased focus on the development of new agents to address this treatment gap.^{30,31} The new chronic cough agents target specific receptors or channels in the peripheral sensory neurons with the goal of reduced central nervous system AEs and control of hypersensitivity while reserving the protective cough response.³²

Transient Receptor Potential Receptor Vanilloid-1 (TRPV1) Antagonists

The TRPV1 channel was the first therapeutic target evaluated for chronic cough.³² TRPV1 channels are present in both peripheral neurons and nonneuronal cells.¹⁹ They are activated by hot temperatures ($>43^\circ\text{C}$), acidic pH, or inflammatory mediators and recognize capsaicin.³³ Two subsequent clinical trials in patients with chronic cough did not demonstrate that TRPV1 antagonists were clinically beneficial in the treatment of chronic cough.^{34,35} SB-705498, a highly selective and potent competitive antagonist for TRPV1 receptors, has shown to significantly affect the capsaicin cough reflex but had almost no effect on objective cough frequency, cough severity scores, or CQLQ scores.³⁵ XEN-D0501, which is significantly more potent than SB-705498 in vivo, exhibited similar results and failed to significantly reduce cough frequency in patients with chronic cough compared with placebo ($P = .41$).³⁴

Transient Receptor Potential Ankyrin-1 (TRPA1) Antagonist

TRPA1 is an environmental-sensing member of the transient receptor potential channel family.¹⁹ This channel family is activated by cold temperature (<17 °C), cigarette smoke, cinnamaldehyde, acrolein, and other various cough irritants.³⁶ Cold air is a common trigger observed clinically among patients with chronic cough, leading to optimism for this potential therapeutic target.³⁷⁻³⁹ An early-phase clinical trial investigating the potent TRPA1 antagonist GRC 17536 did not demonstrate a clinical benefit compared with placebo in patients with RCC.⁴⁰ At the current time of writing, there are no other TRPA1 antagonist clinical trials underway within the United States.

P2X3 Antagonists

P2X3 receptors play an important role in the activation of sensory neurons integral to the cough reflex (Aδ-fibres and C-fibres).⁴¹ Combined with an increased understanding of afferent sensitization in airway dysfunction among patients with chronic cough, P2X3 receptor antagonists are being investigated as a potential therapeutic option.¹

Gefapixant

Gefapixant (MK-7264/AF-219) is a novel, first-in-class, nonnarcotic, selective antagonist of the P2X3 receptor currently in clinical trials evaluating its safety and efficacy for treatment of chronic cough.⁴¹ Phase 1 and 2 clinical trials evaluated more than 300 patients and demonstrated positive results for decreased mean daytime cough frequency, 24-hour cough frequency, and awake cough frequency.⁴²⁻⁴⁴ Phase 1 trials used a significantly higher dose of gefapixant (600 mg), resulting in major taste disturbances due to inhibition of the P2X2/3 channels.⁴³ Subsequent dose-finding studies found an optimal dose of 30 mg to 50 mg twice daily.⁴³ Gefapixant was generally well tolerated in all phase 2 trials with no major safety concerns. Dose-dependent dysgeusia was the most common AE and should subside with discontinuation of gefapixant.⁴¹

Following the positive results from phase 1 and 2 trials, investigation of the utility of gefapixant was continued into phase 3 clinical trials. Two parallel, double-blind, randomized, placebo-controlled trials (ClinicalTrials.gov Identifiers: NCT03449134 [COUGH-1], NCT03449147 [COUGH-2]) were conducted to assess the efficacy and safety of gefapixant (15 mg or 45 mg twice daily) in patients with chronic cough.^{41,45-47} The primary efficacy outcomes included 24-hour cough frequency (at week 24), percentage of at least 1 AE during treatment and follow-up (up to 54 weeks), and percentage of participants who discontinued due to an AE (up to 52 weeks). The results of COUGH-1 and COUGH-2 were presented virtually at the European Respiratory Society International Congress in August 2020. Reported results found a statistically significant reduction in 24-hour cough frequency versus placebo at 12 weeks (COUGH-1

(18.45%, $P = .041$) and 24 weeks (COUGH-2) (14.64%, $P = .031$) in patients treated with gefapixant 45 mg twice daily.⁴⁷ Gefapixant 15 mg twice daily treatment arms did not meet the primary efficacy end point in either study. AEs reported were consistent with previous trials (dysgeusia occurring at a higher incidence with gefapixant 45 mg twice daily), and discontinuations of study drugs due to AEs were more frequent in the gefapixant 45 mg treatment arms compared to the gefapixant 15 mg and placebo arms.

BAY1817080, BLU-5937, and S-600918

Three additional P2X3 antagonists, BAY1817080, BLU-5937, and S-600918, are newer agents under investigation that are highly selective and may cause less dysgeusia compared with gefapixant. Each is discussed further in the following paragraphs (ClinicalTrials.gov identifiers NCT03310645, NCT03979638, and NCT04110054, respectively).⁴⁸⁻⁵⁰

The results from the BAY1817080 phase 1/2a double-blind, placebo-controlled, randomized, 2-way crossover trial (NCT03310645) was presented at the American Thoracic Society International conference virtually in August 2020.⁵¹ Reported results found BAY1817080 caused AEs in 41% to 49% of patients, with the majority being mild. Taste-disturbance AEs were dose dependent and occurred in 5% to 21% of patients. The 24-hour cough frequency counts were decreased with higher BAY1817080 doses compared with placebo (50 mg, $P = .054$; 200 mg, $P = .004$; 750 mg, $P = .002$). Cough frequency counts also decreased from baseline by 17% ($P = .025$) and patient-reported cough severity was significantly improved compared with placebo.⁵¹

The BLUE-5937 (RELIEF) trial was a phase 2, randomized, double-blind, placebo-controlled, crossover, dose-escalation study.⁴⁹ Individuals received two 16-day treatment periods with 4 escalating doses or matching placebo at 4-day intervals. The two 16-day treatment periods were separated by a 10- to 14-day washout period, with a 14-day follow-up period. The trial was terminated early in June 2020 due to the impact of the novel coronavirus 2019 (COVID-19) pandemic on clinical trial activities. There were 68 patients enrolled in the trial, and 52 completed the dosing trial.⁴⁹ Topline results from the RELIEF trial are expected to be released sometime in 2020.⁵²

The trial evaluating S-600918 is a phase 2b trial that is actively recruiting patients to determine the optimal dose of S-600918 in patients with RCC via a change in baseline in 24-hour cough frequency compared with placebo. The investigators expect to enroll 372 participants who will receive 50 mg, 150 mg, or 300 mg of S-600918, or placebo for 28 days. The anticipated study completion date is May 25, 2021.⁵⁰

Neurokinin-1 Receptor (NK-1) Antagonists

NK-1 and substance P (SP) are suspected of playing an important role in the induction and maintenance of cough reflex hypersensitivity.^{53,54}

This is evidenced by the increased SP concentrations in biological fluids and an increased cough response with inhaled SP in patients with idiopathic pulmonary fibrosis and acute cough.⁵⁵⁻⁶⁰

Evidence for the utility of NK-1 receptor antagonists first came from a randomized, double-blind, placebo-controlled, crossover pilot study (N = 20) evaluating aprepitant in patients with lung cancer-associated cough. Statistically significant improvements in cough frequency, cough severity, and QOL were observed.⁶¹

Recently, a phase 2, open-label, pilot study (VOLCANO-1) was conducted to evaluate efficacy and safety of orvepitant, a selective, centrally acting NK-1 receptor antagonist, in 13 patients with RCC.⁶¹⁻⁶³ Orvepitant demonstrated a statistically significant decrease in objective daytime cough frequency at week 4 ($P < .001$). The decreased cough frequency occurred early with a measurable improvement by week 1 ($P = .001$) and was sustained after discontinuation of orvepitant at week 8 ($P = .020$). Orvepitant also significantly improved severity scores and QOL, with a favorable safety profile.⁶³

VOLCANO-2 was a phase 2b, placebo-controlled trial (N = 275) conducted over 12 weeks in patients with RCC and a baseline awake cough frequency of at least 10 coughs/hour (ClinicalTrials.gov identifier NCT02993822).^{64,65} The primary cough frequency end point was not significant; however, an improved efficacy trend was observed among patients taking 30 mg orvepitant and a higher cough frequency (≈ 66.7 coughs/hour) compared with placebo ($P = .066$). The most common AEs included headache, dizziness, fatigue, and somnolence.^{65,66}

Other Agents Considered for Chronic Cough Treatment

Several other agents, such as esomeprazole, erythromycin, and ipratropium bromide, have been evaluated by CHEST guidelines for patients with chronic cough.² However, due to various factors including small sample size, lack of results replication, and lack of efficacy, among others, they are not currently recommended for the treatment of chronic cough.² Multiple other therapies are in various stages of investigation for their utility in the treatment of chronic cough, including TRPV4 antagonists, voltage-gated sodium channel blockers, γ -aminobutyric acid (GABA) B receptor agonists, nicotinic acetylcholine receptor $\alpha 7$ -subunit agonists, and inhaled sodium cromoglycate.¹⁹

Conclusions

In summary, RCC and UCC are disabling conditions that historically lacked effective treatment options. Any patient who presents with RCC or UCC must be thoroughly worked up (including a detailed medical and medication history), evaluated for any red-flag symptoms, and assessed by a differential diagnosis for common and uncommon causes of chronic cough before a treatment approach is developed. If a specific etiology is discovered, that condition should

be optimally treated first before treating the chronic cough. Current guidelines recommend nonpharmacologic and pharmacologic treatments based on individual patient circumstances and should follow a guideline/protocol process. Traditional treatments, such as speech therapy, opiates, and neuromodulators, have had limited success in improving cough frequency, severity, and QOL in patients affected. As a result, increased research has focused on the development of novel therapeutic targets based on an increased understanding of the neurobiology associated with the cough reflex. These new agents have demonstrated positive benefits for reducing cough frequency, severity, and QOL while being generally well tolerated in clinical trials. Therefore, it is likely that some of these agents may become available for treating patients and may help improve their QOL. ■

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Preparing for a New Era in Chronic Cough Management

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Introduction

Chronic cough, defined as cough lasting 8 weeks or more in adults or 4 weeks or more in children, accounts for about 16 million outpatient visits each year.^{1,2} The condition affects 8% to 10% of the population.³ Several underlying conditions are often responsible, including asthma, gastroesophageal reflux disease (GERD), and postnasal drip syndrome (PNDS). Despite comorbidities associated with chronic cough, up to 10% of patients experience unexplained chronic cough (UCC) in which no clear cause can be identified.⁴ The American College of Chest Physicians (CHEST) suggests using the term “unexplained” over “idiopathic” for these patients, as it is likely that there is more than 1 source of underlying disease. While it is a commonly used term, the European Respiratory Society (ERS) identifies this condition as refractory chronic cough (RCC), and this is the term that will be used throughout.⁵

Economic Burden of Chronic Cough

Chronic cough exerts a substantial economic burden due to multiple primary care and specialty office visits. The use of medications to manage symptoms and comorbid conditions, such as depression, anxiety, and insomnia, is also another factor that contributes to the significant burden of RCC. Some patients with a history of smoking may have a concomitant chronic cough diagnosis code.³ However, for many patients who have RCC, it is due to vagal hypersensitivity/enhanced cough reflex sensitivity. In a questionnaire survey, patients were a mean age of 65 years, although another survey revealed the condition was most common in patients aged 50 years and older.⁶ The most common age for presentation is shown to be between 50 and 69 years.⁷ Based on these age demographics, it is reasonable to infer that patients eligible for Medicare coverage may be more affected than those with other benefits.⁸

Chronic cough accounts for up to 38% of a pulmonologist's outpatient practice.^{9,10} RCC is a diagnosis of exclusion. Diagnosis of chronic cough can involve numerous tests for common causes and comorbidities. Most patients visit their physicians at least 3 times, and 53% are diagnosed with an underlying condition.¹¹ Patients may

ABSTRACT

Chronic cough, defined as cough lasting 8 weeks or more in adults, accounts for approximately 16 million outpatient visits per year. Chronic cough exerts a significant burden on the quality of life of patients, which is often why they initially seek treatment. Various factors have contributed to the high cost associated with the burden of chronic cough, from multiple referrals and unnecessary repeat testing to polypharmacy and development of comorbidities due to lack of proper treatment. Although treatment guidelines for chronic cough are available, they vary in their recommendations. There are no FDA-approved agents indicated specifically for chronic cough at this time, but medications such as inhaled corticosteroids and narcotic antitussives are frequently used for treatment, while speech and behavioral therapy have also been potential options. New targeted therapies in the clinical pipeline are expected to expand the treatment landscape and meet the unaddressed gaps for safe and efficacious agents that can provide relief and better management for patients. Access to appropriate care based on clinical guidelines is associated with favorable outcomes. Managed care organizations should consider treatment guidelines, patient factors, and emerging pharmacologic as well as nonpharmacologic treatment options to create a streamlined approach to managing chronic cough treatment in an evidence-based and cost-effective manner.

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For author information and disclosures, see end of text.

consult up to 6 medical providers while their symptoms persist for a median of almost 7 years.¹²

Cough is the most common reason for primary care visits, with up to 85% receiving prescriptions for treatment.^{3,12} Despite these high prescribing rates, the majority of patients report no symptom improvement.¹¹⁻¹³ For example, it is reported that almost 60% of patients receive codeine-containing antitussives; 45%, proton pump inhibitors; 26%, antidepressants; 15.5%, antianxiety medications; and 13.9%, neuromodulators, such as gabapentin.¹⁴ An average of \$3266 is attributed to annual medical costs per patient (including prescription medications, office visits, and hospitalizations).¹⁵ Emergency department visits and hospital utilization due to negative sequelae of continued coughing also contribute to the increased cost of managing chronic cough. Even annual costs for over-the-counter (OTC) antitussives, which only temporarily suppress symptoms, are estimated at as high as \$1 billion to \$3.5 billion.^{10,16}

Treatment of Chronic Cough With Underlying Conditions

Successful treatment of chronic cough is dependent on identifying the underlying cause. Given the known association between chronic cough diagnosis and history of smoking in patients, smoking-cessation treatment options should be offered first line for patients.¹⁷ Smoking was associated with \$168 billion in healthcare spending across all payers in the United States in 2010.¹⁸ In addition, another \$107.6 billion is attributed to loss of productivity in the United States each year due to smoking.¹⁹ Results of a study estimated that the return on investment (ROI) for providing up to 2 quit attempts per year with no patient cost sharing would increase to a positive value in the fourth year for commercial and Medicaid plans, and in the third year for Medicare plans. The ROI over 10 years would be \$1.18, \$2.50, and \$3.22 savings for every dollar spent on smoking cessation prescriptions for commercial, Medicaid, and Medicare plans, respectively.²⁰

Patients with asthma, especially cough-variant asthma (in which cough is the sole or predominant symptom), usually benefit from treatment with an oral or inhaled corticosteroid (ICS).²¹⁻²⁴ An analysis of managed care claims found that 38% of patients with chronic cough had been prescribed an ICS; 24%, an ICS/long-acting β -agonist combination; and 15.2%, ICS monotherapy.¹⁴ Results of a large international survey found that while 23% of patients with chronic cough had been diagnosed with asthma, 37% had been prescribed corticosteroids.¹¹ Another survey found similar results, with 24% of respondents reporting a preexisting diagnosis of asthma, and 32% prescribed an oral or ICS at some point.¹² Although more robust studies are lacking, antileukotrienes, such as montelukast and zafirlukast, have also shown beneficial effect in treating cough-variant asthma.²⁵ Medication costs for asthma treatment may also vary based on individual payer contracts and formulary status.

COPD can often cause a chronic cough, and symptoms can be similar between COPD and asthma. Patients with mild COPD frequently experience cough lasting an average of 1 year before they seek medical help and confirm a diagnosis.^{26,27} They also report nightly symptoms that affect sleep quality, which affects energy levels and the ability to perform daily tasks.⁶

Impact of Chronic Cough on Quality of Life (QOL)

Patients with chronic cough most often seek medical attention when it impacts their QOL. Patients with persistent symptoms can cough up to thousands of times a day, and their condition may persist for several years without diagnosis or effective treatment.¹⁴ These patients report that symptoms affect their daily activities, such as going up and down stairs and getting out of bed.²⁷ Depression and frustration are common among patients with chronic cough, and 94% reported that their cough disturbed or worried their friends and family.¹¹ A study conducted in a specialty center identified significant symptoms of depression in 53% of the 100 patients evaluated, noting a substantial improvement in depression as the patients' cough improved.²⁸

One of the first investigations of the impact of chronic cough on QOL enrolled 39 patients. Most sought medical care because they were afraid something was wrong, but about half sought care because of retching and exhaustion due to the cough, embarrassment, and because others thought something was wrong with them. They reported difficulty being heard during phone calls and giving up pleasurable activities, such as singing in church. Several reported that consistent coughing contributed to feelings of exhaustion as well as absenteeism from work and school.¹⁰ Another study demonstrated how many patients who sought medical care at specialty cough clinics took early retirement because of their cough but did not qualify for disability insurance coverage.²⁹

Other ways chronic cough has severely impacted the QOL of patients is through development of other comorbidities. Chronic cough is also linked to high rates of anxiety, as almost half of the patients evaluated in a specialty clinic reported in a study.³⁰ In another survey, participants reported that their cough interfered with their social life, causing anger, anxiety, and depression. They also experienced numerous physical effects, including breathlessness (55%), wheeze (37%), fatigue (72%), and disturbed sleep (70%). More than half of the women in the survey also reported incontinence.¹²

Managed Care Considerations for Chronic Cough Guideline Recommendations

Guideline development is complicated given limited evidence and access to standardized assessments and diagnostic tools.^{4,9,31,32} Finding effective treatment for chronic cough, especially RCC, poses a challenge. Although there are some differences, the CHEST and

ERS guidelines offer treatment algorithms to help appropriately diagnose and treat patients with chronic cough.^{3,4,31} These algorithms can be used to inform considerations for utilization management, prior authorization, and benefits coverage.

Diagnosis and Pharmacologic Treatment

Because RCC diagnosis is one of exclusion, testing for other common causes, such as asthma/COPD and GERD, should be reviewed in consideration for treatment coverage. For example, ICS should not be required in prior authorization criteria for patients who do not have signs or symptoms of chronic respiratory disease (eg, bronchial hyperresponsiveness, eosinophilia).⁴ Treatment response should also be reviewed on at least an annual basis, as many patients still report limited efficacy when medications are prescribed.^{33,34}

Some studies have explored various algorithms for their effectiveness and economic value. Lin et al conducted a cost-effectiveness analysis comparing 6 common treatment options for RCC involving a stepwise approach to testing for underlying conditions, then testing for PNDs, asthma, and GERD, and then treating each condition sequentially. The model assumed no overlap among the 3 diseases and a maximum treatment period of 12 weeks, with 1 week to receive the outcomes and no more than 2 weeks to judge the effectiveness of the treatment drug, which was considered 100% effective.³⁵ The authors found that a “test all, then treat” approach had the shortest treatment duration but the highest cost per treated patient (\$556), whereas empirical treatment (treat sequentially starting with PNDs) was the least costly approach (\$149).³⁵

The CHEST and ERS guidelines suggest a therapeutic trial of gabapentin for treating UCC, which has been associated with significant improvement in patient QOL with reduced cough frequency and severity.^{34,36,37} Common adverse effects associated with gabapentin use include confusion, dizziness, and dry mouth.^{34,36} For this reason, CHEST guidelines suggest assessing the risk-benefit profile of continued treatment with gabapentin every 6 months.⁴ In addition, managed care organizations may recommend adherence monitoring at least every 6 months to ensure appropriate use of the medication to continue coverage.

CHEST and ERS differ in their recommendations for morphine use in the treatment of UCC. Although a low dose is recommended by ERS for treatment, this recommendation should be weighed against policies regarding opioid utilization within the organization. Morphine is also commonly associated with constipation and drowsiness.^{35,36,38} These adverse reactions are even more concerning as the majority of patients who experience chronic cough are in the older adult population, making the medication potentially inappropriate for use.³⁹ Prescription drug monitoring programs should be reviewed to limit abuse and diversion. Patient education on opioid-reversal agents and techniques should also be performed on a regular basis.⁴⁰

Emerging Therapies

As highlighted in the second part of this supplement, several novel therapies that address chronic cough at the molecular level are in late-stage clinical trials. The phase 3 results of the P2X3 antagonist gefapixant, released in September 2020, suggest that it may be the first to reach the market.^{41,42} Phase 2 studies were also completed in spring 2020 for a second P2X3 antagonist, BLU-5937.⁴³ The emerging P2X3 antagonists are highly selective and may cause less dysgeusia.^{41,43-45} Additional agents include BAY1817080 and S-600918, which are in the pipeline.^{46,47} Clinical considerations, benefits coverage decisions, and monitoring requirements should be made based on available evidence, treatment guidelines, and consideration of cost-effectiveness of existing alternatives.

Nonpharmacologic Approaches

In addition to pharmacologic treatment, the CHEST guidelines suggest a trial of speech and language therapy for UCC.⁴ Behavioral treatment involves education, cough-suppression strategies, reducing laryngeal irritation, and psychoeducational counseling. This all occurs within 3 to 4 sessions.⁴⁴

The first randomized, placebo-controlled study of speech pathology therapy in patients (N = 87) with RCC compared a 4-session intervention involving education about the nature of chronic cough, strategies to control the cough, psychoeducational counseling, and vocal hygiene education to reduce laryngeal irritation with a 4-session placebo group that received healthy lifestyle education. Overall, 88% of participants in the interventional group demonstrated clinically significant improvements in cough frequency, dyspnea, voice, and upper airway symptoms compared with 14% in the placebo group ($P < .001$).⁴⁴

Results of a study in which behavioral therapy was instituted earlier in the treatment algorithm found it improved patients' QOL and condition faster than empirical treatment and reduced costs.⁵ In another study of behavioral therapy, results found it effectively resolved or showed marked improvement in cough symptoms in 84% of patients who were refractory to medical treatment.⁴⁸ While there is not yet a standardized tool to assess which patients are most likely to benefit from speech pathology interventions, results of a study found that patients with paradoxical vocal fold movement or muscle tension dysphonia may be most likely to experience symptom improvement (see [Table](#)).⁵

Although there is limited high-quality evidence, studies show that speech pathology-based treatment provides a positive benefit with no adverse effects.³ Despite positive evidence found in studies, speech therapy is significantly underused in clinical practice.⁵ Zeiger et al analyzed more than 11,000 managed care claims and found that 1.9% of patients had seen a speech therapist.¹⁴ Speech therapy may be recommended at any time during a patient's treatment, and should certainly be considered for patients who are refractory to multiple medications.

TABLE. Symptoms in Patients Most Likely to Improve With Speech Therapy⁵

Symptom	Manifestation
Paradoxical vocal fold movement	Dyspnea, audible inhalation, inspiratory stridor, tightness in neck muscles, sensation of restriction in the larynx/throat, tendency for more difficulty breathing in than out, and quick or no response to rescue inhalers
Muscle tension dysphonia	Strained voice quality, unpredictable voice pattern (eg, short or long periods of normal voicing without explanation)

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Conclusions

Diagnosis and treatment of UCC/RCC can lead to considerable patient frustration and increased costs due to extensive testing and numerous primary care and specialty visits. Emergency department and hospital utilization are additional cost drivers, as patients may experience additional complications from frequent coughing. Narcotic antitussives (eg, morphine) and gabapentin have been shown to be efficacious for chronic cough, particularly RCC. Opioid utilization management policies should be considered and the risk-benefit profile of using these medications should be frequently assessed to ensure patient safety during treatment. Educating patients about their disease and its management has been shown to enhance patient efficacy and engagement, leading to lower healthcare costs and greater adherence.⁴⁹ Speech and behavioral modification therapy are currently underutilized and may produce more favorable outcomes for patients, especially those who have tried several medications in the past.

Existing guidelines (eg, CHEST and ERS) may be used to inform organizational policies on diagnosis and continued treatment of UCC/RCC. Although some differences exist between guidelines, they serve as valuable resources to streamline patient care based on clinical evidence in a cost-effective manner.

The introduction of new, targeted therapies may dramatically change the treatment landscape. Consideration for their use should be evidence based and in examination of patient factors and existing alternatives. Managed care organizations have the potential to ensure a more systematic approach to the treatment of chronic cough through utilization management and prior authorization policies. Patient follow-up for therapy efficacy is also important to ensure adherence and continuity of treatment. ■

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Managed Care Considerations for Chronic Cough

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Sample of Online Posttest

Choose the best answer for each of the following:

1. The 3 most common causes of chronic cough are:

- A. Upper airway cough syndrome (UACS), reflux, medications
- B. UACS, asthma, medications
- C. UACS, asthma, reflux
- D. UACS, asthma, malignancy

2. Which statement is true regarding the epidemiology of chronic cough?

- A. The global prevalence of chronic cough is low at less than 1%.
- B. Men and women are equally affected.
- C. The most common age of presentation is typically 50 to 69 years.
- D. There have been no differences found in central processing of the cough reflex in men and women.

3. Which of the following is considered a red-flag symptom when reported by a patient with chronic cough?

- A. Hemoptysis
- B. Reflux
- C. Anxiety
- D. Fatigue

Please use the following case to answer questions 4 and 5.

You are conducting a medication therapy management session for a 65-year-old woman who has reported chronic cough for 1 year. She is a former smoker (30 pack-year) but quit smoking 5 years ago. She has seen multiple specialists and has had no successful treatments. She has started to become depressed, which has led her to gain weight, and she reports mild reflux at night. Her husband also states that he notices she has been snoring every night for the past 2 months, and when they went to a sleep clinic, she was found to have obstructive sleep apnea (OSA).

4. Which of the following is true regarding OSA and chronic cough?

- A. Patients with OSA and chronic cough may have improved cough scores with continuous positive airway pressure (CPAP).
- B. OSA predisposes to chronic cough via decreased airway inflammation.
- C. Rapid changes in oxygenation are not observed in OSA.
- D. OSA reduces the risk of UACS and gastroesophageal reflux disease.

5. Based on the current CHEST guideline recommendations, which of the following agents should patients with unexplained chronic cough initiate?

- A. Amitriptyline
- B. Gabapentin
- C. Morphine
- D. Pregabalin

6. These receptors play an important role in the activation of sensory neurons integral to the cough reflex (A δ -fibres and C-fibres). Which of the following are a class of drugs that are currently being investigated as a potential therapeutic option to target these receptors while being combined with an increased understanding of afferent sensitization in airway dysfunction?
- NK-1 antagonist
 - P2X3 antagonist
 - TRPA1 antagonist
 - TRPV1 antagonist
7. What treatment approach is associated with shorter treatment duration for refractory chronic cough (RCC)?
- Test all, then treat
 - Watch and wait
 - Complementary medicine
 - Empirical treatment
8. All of the following considerations should be made when considering RCC treatment from a managed care approach, EXCEPT:
- Opioid utilization management policies should be considered when narcotic antitussives are prescribed.
 - Medication adherence should be monitored and considered for continued coverage.
 - Speech therapy did not show differences in clinical improvements when compared with placebo in clinical trials.
 - Testing should be considered when recommending emerging therapies.
9. In the COUGH-1 and COUGH-2 trials, the primary efficacy outcomes that were evaluated for gefapixant included:
- 72-hour nighttime cough frequency
 - Change in Leicester Cough Questionnaire total score
 - Cough severity scores
 - 24-hour cough frequency
10. Untreated chronic cough is associated with a significant burden. All of the following are reasons for the high costs associated with the burden of chronic cough, EXCEPT:
- Patients with chronic cough are often referred to multiple specialists within the same specialty and can undergo unnecessary repeat testing.
 - Patients with chronic cough become exposed to polypharmacy and possible adverse effects of these medications because they end up being prescribed various therapies for acute cough instead.
 - Patients commonly miss days of work due to insomnia, anxiety, and depression from untreated chronic cough.
 - Patients with chronic cough are routinely admitted or have a significantly higher rate of readmissions.

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