REVIEW ARTICLE

Investigations and management of chronic cough: a 2020 update from the European Respiratory Society Chronic Cough Task Force

Mohammed A. M. Farooqi[1], Vicky Cheng[1], Mustafaa Wahab[1], Izza Shahid[1], Paul M. O'Byrne[1,2], Imran Satia[1,2]

1 Division of Respirology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
2 Firestone Institute for Respiratory Health, St Joseph's Healthcare, Hamilton, Ontario, Canada

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ABSTRACT

Chronic cough affects approximately 10% of the general population, is highest amongst people aged 50 to 60 years, and is twice as common in women than men. It is described to last 8 weeks or longer in adults and does not respond well to treatment with over-the-counter medications and those targeting potential associated conditions. This is a debilitating condition with physical, social, and psychological consequences. The purpose of this review was to highlight the key messages on the management of chronic cough from the task force commissioned by the European Respiratory Society. The assessment of patients with chronic cough should include a thorough detailed history and examination to identify potential causes. The impact and severity can be assessed in a clinic using questionnaires. Potential causes of the condition vary and include, for example, angiotensin-converting enzyme inhibitors, smoking, asthma, nonasthmatic eosinophilic bronchitis, gastroesophageal reflux disease, and upper airways cough syndrome. In many patients, coughing is persistent despite optimum medical therapy of the underlying medical condition and is hence referred to as refractory chronic cough. In some cases, no cause can be found and the cough is classified as unexplained chronic cough. If treatment of any underlying disease is unsuccessful at controlling cough, then neuromodulatory treatment such as a low-dose opioid, gabapentin, pregabalin or speech and language therapy may be considered. There is no licensed treatment for chronic cough, but a new class of treatment targeting the purinergic P2X3 receptor is currently in phase 2 and 3 of development.

Correspondence to:
Imran Satia, MD, McMaster University Medical Centre, 3U 21–26, 1280 Main St West, Hamilton, L8S 4LA Ontario, Canada, phone: +1 905 525 2100 (76 228), email: satiai@mcmaster.ca
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Introduction Chronic cough is a common condition that affects 7% to 11% of adults worldwide, and accounts for a major burden of primary care visits in both developed and developing countries.[1,2] In adults, it is defined as a cough that lasts for 8 weeks or longer, is twice as common in women, and peaks in the sixth and seventh decade of life.[3] Refractory symptoms can be distressing, leading to incontinence, dysphonia, and social isolation, with resultant detriment in the quality of life.[4] Chronic cough can be challenging to treat, with most over-the-counter therapies being ineffective.[5,6] As a result, a comprehensive approach to the diagnosis and management of chronic cough is critical to optimize care of patients with this condition with a significant clinical burden. The European Respiratory Society (ERS) recently commissioned a task force on the management of chronic cough and the purpose of this review is to highlight the key messages from the most recent guideline.[7]

Causes of chronic cough Chronic cough can occur with respiratory conditions such as asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, and occasionally with lung cancer. The most common causes of chronic cough in patients with a normal chest x-ray are medications (specifically, angiotensin-converting enzyme [ACE]–inhibitors, approximately 15%)[8], asthma, nonasthmatic eosinophilic bronchitis, gastroesophageal reflux disease (GERD), and upper airways cough syndrome (UACS) (TABLE 1). These conditions, either alone or

TABLE 1 Investigations for the differential diagnostic workup of chronic cough

Disorders to exclude	Investigation
• Malignancy • Parenchymal lung disease	Chest x-ray
Asthma	• Blood eosinophil count[a] • Spirometry with postbronchodilator measurement if airflow obstruction is present • Bronchoprovocation challenge (methacholine challenge test) • Exhaled nitric oxide[b]
Nonasthmatic eosinophilic bronchitis	Induced sputum for cell count and differential[a] (eosinophil cutoff ≥3%)
Allergy	Skin prick testing
Upper airway cough syndrome	• Nasopharyngoscopy[a] • Laryngoscopy[a] • CT of the sinuses[a]
Gastroesophageal reflux disease	• 24-hour pH impedance monitoring[a] • High-resolution manometry[a] • Barium swallow[a] • Video fluoroscopic evaluation[a] • Upper GI endoscopy[a]
Interstitial lung disease/bronchiectasis	High-resolution CT scan[a]
• Vocal cord dysfunction • Central airway lesion	Bronchoscopy[a]

a Investigation not routinely recommended by the ERS task force for evaluating.

Abbreviations: CT, computed tomography; GI, gastrointestinal

in combination, account for a large proportion of chronic cough cases.[9] However, there are large variations amongst clinicians in the prevalence of associated conditions due to the availability of testing, for example, sputum induction, 24-hour pH impedance/manometry, or the expertise of the consulting specialist.[10] Cough prevalence varies by age and usually correlates with the age-related prevalence and distribution of diseases associated with chronic cough. For example, asthma and UACS are more common in younger adults, compared with chronic obstructive pulmonary disease (COPD) and GERD, which are more common in older patients.[11] It is unclear why chronic cough is more prevalent in women, although age-related hormonal changes may contribute. This, however, is yet to be fully elucidated.[12,13] Cough that persists despite guideline-based treatment for the above conditions is classified as refractory chronic cough. Cough with no clear identifiable cause is considered as unexplained chronic cough.[14]

Mechanisms of cough Chronic cough has also been described as cough hypersensitivity syndrome as many patients experience cough which is triggered by exposure to low levels of thermal, chemical, or mechanical stimulation.[15,16] Patients often describe a sensation of itchiness, irritation, and unpleasantness in the throat region or even describe it as "something physically stuck in the throat." Cough is often triggered by changes in temperature, perfumes, aerosols, strong smells, talking, laughing, and singing.[17,18] The concept of cough hypersensitivity syndrome has been endorsed as an overarching syndromic diagnosis and can be found with any of the other abovementioned causes of chronic cough. The etiological mechanisms for cough hypersensitivity syndrome remain controversial, and both central and peripheral sensitization mechanisms have been suggested.[15]

Coughing, like breathing and swallowing, can be under both voluntary and automatic control at the same time, but it is widely accepted that the cough reflex is the archetypal airway defensive reflex. Numerous studies have used different inhaled stimuli to evoke cough to study the mechanisms of coughing.[3] The objective of cough challenge studies is to stimulate the vagal afferent nerves (tenth cranial nerve) in the larynx and airways which bind onto ligand gated ion channels and G protein–coupled receptors.[19] Upon activation, sodium and calcium ions flow inside the nerve membrane resulting in depolarization. If sufficient depolarization is achieved, an action potential is generated and transmission to the brainstem occurs via voltage-gated ion channels. Once the signal reaches the first order synapse in the nucleus tractus solitarius and paratrigeminal nuclei, second order neurons relay the signal to the thalamus, and third order neurons to the primary somatosensory cortex. This is where patients may feel the unpleasant sensation of an urge to cough, which if great enough, will evoke coughing. The most common example of a cough challenge agent is capsaicin, the active substance found in hot chili peppers, which specifically binds transient receptor potential vanilloid type 1 (TRPV1). Other challenge agents, such as citric acid, are likely to activate multiple ion channels including TRPV1, transient receptor potential ankyrin 1, and acid-sensing ion channels.[20,21] Challenges of different osmolarities have also been used, for example, water, normal saline, hypertonic saline, and mannitol.[22,24]

Cough challenge studies have revealed that patients with refractory chronic cough have a more sensitive and hyper-responsive cough reflex in comparison with healthy controls. This has been demonstrated by showing that a lower concentration of substance is required to cause 2 coughs or 5 coughs.[21] More recently, other studies have shown that a higher maximum evoked cough is reached (Emax), and the dose evoking half the maximum (ED50), is much lower, that is, the cough dose response curve reaches a higher plateau and is left shifted.[25] These studies lend support to the concept that the peripheral nerves are sensitized in various associated conditions, particularly asthma, eosinophilic bronchitis, COPD, and GERD.[21,25-31] However, it should be noted that these cough challenge studies are testing the entire reflex, and hence the role of the central nervous system, in particular, the brainstem and higher cortical centers, is

TABLE 2 Summary of treatments options

Cause	Treatment options
Medication (ie, ACEI)	Discontinue medication (if on ACEI can try ARB)
Asthma	• Inhaled corticosteroid ±LABA • Leukotriene receptor antagonist • Systemic glucocorticoids
COPD	LAMA
Nonasthmatic eosinophilic bronchitis	• Inhaled corticosteroids • Systemic glucocorticoids
Gastroesophageal reflux disease	• Antireflux diet • PPI or H2 antagonist (recommend an 8-week trial)
Nasal disease	• Antihistamine • Decongestant • Nasal corticosteroid
Unexplained chronic cough	• Low-dose morphine (5–10 mg orally twice daily) • Gabapentin (up to 300 mg orally 3 times a day); start with 100 mg 3 times a day • Pregabalin (up to 150 mg orally twice daily); start with 50 to 75 mg twice daily • Amitriptyline (10 mg orally at night) • Speech and language therapy

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; PPI, proton pump inhibitor

often ignored and poorly understood. There is currently a small number of studies in healthy controls and in patients with chronic cough that investigated the central cortical pathways in chronic cough using functional magnetic resonance imaging.[32,33]

Key questions in patient history A detailed history is integral in the evaluation of chronic cough and involves defining the characteristics of the cough as well as associated features which may point to an underlying trigger. The cough history should focus on identifying the common triggers of cough such as GERD, UACS, asthma, occupational and smoking history, as well as red flags such as hemoptysis, weights loss, fevers, dysphonia, and dysphagia. Interestingly, studies have not shown the characteristics and timing of cough, or presence and absence of sputum production to be of diagnostic value.[9,27] Nevertheless, a history of wheeze, dyspnea, allergies, nocturnal cough, or cough triggered by exercise or cold air may be suggestive of asthma. In patients with UACS, there may be a history of postnasal drip, sinusitis, rhinorrhea, nasal congestion, and an examination of the posterior pharynx possibly revealing a "cobblestone" appearance. Patients with GERD may experience heartburn, dyspepsia, dysphonia, or hoarseness, often worse when lying down or bending forwards. A productive cough may prompt consideration of other diagnoses including bronchiectasis, chronic bronchitis, eosinophilic bronchitis, or pneumonia, keeping in mind the most common causes of chronic cough in this population remain asthma, eosinophilic bronchitis, GERD, UACS, or a combination of the 3.[34] In patients with a smoking history, COPD should be considered as a cause of cough. Frequently, cough is strongly associated with cigarette consumption.[35] Cough may be dry or productive, and patients with a productive cough are at an increased risk of exacerbations.[36] Congestive heart failure is an uncommon cause of chronic cough but should be considered in an appropriate clinical context.[37]

Severity of cough may be assessed by using a visual analog scale or cough questionnaires such as the Leicester Cough Questionnaire or Cough Specific Quality of Life Questionnaire that can be useful tools in tracking patient's response to therapy.[38,39]

The most widely recognized drugs causing chronic cough are ACE inhibitors which are associated with a dry cough in up to 15% of patients. The cough occurs days to months after the initiation, with 1 population study showing a median time from introduction of an ACE inhibitor to the onset of cough of 156 days (95% CI, 85–242 days).[40] Other drugs reported to cause cough include calcium channel blockers and fentanyl when administered as an intravenous bolus. There are also case reports of topiramate and phenytoin causing cough.[41] There was also one case series suggesting sitagliptin may cause cough; however, there was insufficient evidence associated with sitagliptin from large phase 3 randomized controlled trials (RCTs).[42]

Clinicians should inquire about symptoms of aspiration (dysphagia, coughing with liquids/solids), gastrointestinal symptoms of inflammatory bowel disease, thyroid disease, and an autoimmune screen for connective tissue diseases.[43] A comprehensive review of systems may help detect rare causes of cough such as Holmes–Adie syndrome.[44,45] This is a rare condition presenting with anisocoria, tendon areflexia, and autonomic dysfunction, and has been described to be associated with a dry chronic cough.

Investigations A systematic approach to the evaluation of chronic cough is recommended, initially focusing on evaluating and applying guideline-based management of common causes of chronic cough, specifically asthma, nonasthmatic eosinophilic bronchitis, UACS, and GERD (TABLE 2). Empiric treatment for these conditions may be considered in conjunction with diagnostic workup depending on clinical suspicion. The assessment should begin with chest x-ray to exclude any obvious structural cause of lung disease. If chest x-ray is normal, then a CT scan of the thorax is not recommended. Spirometry should be considered, with postbronchodilator measurements in the presence of airflow obstruction to evaluate for asthma and COPD. Bronchoprovocation tests with methacholine challenge and sputum induction for airway eosinophilia can be considered based on clinical suspicion for asthma, but they are often not available outside specialist centers. Sputum eosinophilia can help in the diagnostic

workup of nonasthmatic eosinophilic bronchitis as well.[30] Blood tests are not usually helpful, although the presence of peripheral eosinophilia may support a diagnosis of asthma and initiation of inhaled corticosteroids. Likewise, exhaled nitric oxide is not currently recommended for routine use in the diagnostic workup of chronic cough. The ERS task force, however, does recognize that this is due to the lack of quality evidence and that placebo-controlled trials are needed to assess their utility and optimum cutoff values. Bronchoscopy is also not routinely recommended in the evaluation of chronic cough, unless there are red flag signs (weight loss or hemoptysis) or sputum induction for cell count and differential diagnosis is needed. Bronchoscopy or laryngoscopy may also be of help in the assessment of vocal cord dysfunction, muscle tension dysphonia, inducible laryngeal obstruction.[46,47] If UACS is being considered, sinus imaging and nasopharyngoscopy may be helpful, but this is not routinely recommended by the ERS task force. For GERD, 24-hour pH impedance monitoring, high-resolution manometry, barium swallow, video fluoroscopic evaluation, and endoscopy are usually reserved after a trial of empiric therapy has failed in the context of high-suspicion of reflux. These tests are invasive and usually difficult to access.[48]

In patients with presyncope or syncope secondary to cough, further assessment for arrhythmias or autonomic dysfunction may be warranted. This may include electrocardiography, 48- to 72-hour Holter monitoring, echocardiogram, and tilt-table testing. If all tests remain negative or inconclusive, patients are considered to have unexplained chronic cough.

Treatment Treatment of chronic cough starts with addressing triggers. Offending medications should be stopped, particularly ACE inhibitors. Patients should be counselled on smoking cessation and any unresolved infections and red flag symptoms should be addressed.

Asthma, nonasthmatic eosinophilic bronchitis, and chronic obstructive pulmonary disease In patients with chronic cough and asthma, a short-term trial of inhaled corticosteroid (ICS) for 2 to 4 weeks should be attempted.[49] It should be noted that inhalers can sometimes trigger cough which may reduce delivery of the medication to the airways.[50] In patients who do not respond to inhaler therapy, a 1 to 2 week trial of oral glucocorticoids may be attempted.[11] For patients with nonasthmatic chronic cough, ICS has not been shown to reduce the severity of cough compared with placebo and is not recommended.[51,52] However, it may be reasonable to trial an ICS in a patient with unknown airway hyperresponsiveness and unknown sputum eosinophilia if testing is unavailable. Patients with nonasthmatic eosinophilic bronchitis should be treated with ICS and / or oral glucocorticoids. Leukotriene receptor antagonists have also shown efficacy in cough variant asthma in 2 small RCTs and have been recommended in recent guidelines.[53-55] ICS have not been shown to reduce cough frequency in COPD,[56] but long-acting muscarinic antagonists, such as aclidinium, have been shown to reduce cough and breathlessness in moderate COPD on a symptom severity questionnaire.[57] A randomized placebo-controlled study on codeine in COPD also failed to show improvements in objective cough frequency.[58]

Gastroesophageal reflux disease The ERS guidelines do not suggest a trial of medications reducing stomach acid production for 2 months (proton pump inhibitors [PPIs] and H2 antagonists) unless there is objective evidence of reflux or at least symptoms of acid reflux.[7] Randomized controlled trials of PPIs in chronic cough are small and systematic reviews of PPI trials have not shown significant benefit in reducing severity of cough in patients without evidence of GERD.[59,60] In subgroup analyses, patients with symptoms of reflux or objective evidence of reflux on esophageal pH monitoring may have a modest benefit from PPI therapy. The duration of PPI trial has not been well defined; however, a minimum of 8 weeks is likely required to derive benefit.[61] Guidelines also recommend an antireflux diet including elimination of coffee, tea, alcohol, chocolate, mints, and citrus products based on an expert opinion.[11]

Promotility agents There are no RCTs for treatment with metoclopramide or domperidone, in patients with chronic cough. There is very limited evidence of the effect of long-term low-dose macrolides in chronic cough and hence they are generally not recommended.[7] In patients with features of chronic bronchitis with COPD, one study showed significant benefit of a 12-week low-dose azithromycin.[62] In 2 other trials of refractory or unexplained chronic cough, low-dose erythromycin or azithromycin did not provide any significant benefits over placebo on cough frequency, cough severity, and quality of life.[63,64]

Upper airway cough syndromes This broadly encompasses allergic and nonallergic rhinitis (most commonly vasomotor), chronic rhinosinusitis and often presents in patients with a sensation of liquid dripping into the posterior naso- and laryngo-pharynx. This is commonly described as postnasal drip. There is no strong evidence to guide therapy, however, guidelines recommend a trial of antihistamine and decongestant.[65]

Cough induced by angiotensin-converting enzyme inhibitors The only effective treatment of cough induced by an ACE inhibitor is the discontinuation of the drug. Improvement is usually seen in 1 to 4 weeks, although some cases have documented cough lasting up to 6 months after discontinuation.[66] Patients are recommended to switch to angiotensin receptor blockers, which are not associated with increased risk of cough.[67]

Refractory or unexplained chronic cough Patients in whom the above therapies do not result in remission of their chronic cough are considered to have refractory or unexplained chronic cough. In these cases, neuromodulatory treatment may be considered in conjunction with speech and language therapy. Neuromodulatory treatment is currently off-label and includes the following: 1) low-dose morphine, typically 5 to 10 mg twice a day[68]; 2) gabapentin titrated up to a maximum of 300 mg 3 times a day[69]; 3) pregabalin up to 150 mg twice a day[70]; and 4) amitriptyline 10 mg at night.[71] All 4 therapies have shown positive results in improving symptoms in RCTs; however, these trials have been small (all less than 100 patients) and the doses used in the RCTs were associated with high rates of adverse events such as dizziness, drowsiness, unsteadiness, and fatigue. In clinical practice, most patients are unable to tolerate such high dosage used in RCTs, hence it is recommended to start at 100 mg 3 times a day with gabapentin and 50 to 75 mg twice a day with pregabalin and to increase slowly on a weekly basis. Speech and language therapy is a safe and effective add-on or alternate therapy in patients who do not wish to take neuromodulatory medications or for those who develop side effects. However, access to therapists adequately trained in the management of chronic refractory cough can be challenging, and patient adherence is necessary to achieve optimal effect, similar to all other therapies.

Future treatments Blocking airway nerves with TRPV1 antagonist has failed;[72,73] however, there have been encouraging results from recent studies of a new compound called gefapixant (formerly AF-219), a novel oral purinergic antagonist, which blocks the P2X3 receptor. The initial phase 2a of proof-of-concept study using 600 mg twice per day demonstrated an unprecedented 75% reduction in objective cough rates compared with placebo.[74] More recently, after completing a dose finding study,[75] the 12-week study showed an approximate 37% reduction in cough rates compared with placebo with 50 mg twice per day.[76] The full results of the phase 3 studies are eagerly awaited. Other similar P2X3 antagonists are also in development and it is likely that in the coming years, we will see a number of compounds available for managing patients with chronic cough.[77-79]

Conclusions Chronic cough is a common trouble symptom which is twice as common in women than men and can severely affect the physical, social, and psychological well-being of patients. Investigations are often all normal, and there are no licensed treatments. Current guidelines recommended treatment of any identifiable conditions, but if the cough is refractory or unexplained, then neuromodulatory treatment such as low-dose opioids, pregabalin, gabapentin, or speech and language therapy can be trialed. Clinicians are advised to err on the side of caution with the dose and length of treatment with centrally acting neuromodulatory treatment. However, there is potential hope with the ongoing development of novel oral P2X3 antagonists.

CORRECTIONS

This article was corrected on February 26, 2021. The list of corrections is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST IS reports receiving grants from BMA James Trust Award, ERS Respire 3 Marie Curie fellowship, North West Lung Centre, Merck; personal fees from Educational Talks for GPs, sponsorship to attend conference meetings, outside the submitted work. POB reports grants and personal fees from AstraZeneca, personal fees from GSK, grants from Novartis, grants and personal fees from Medimmune, personal fees from Chiesi, outside the submitted work. Other authors declare no conflict of interest.

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