Medicina Clínica 166 (2026) 107289

Contents lists available at ScienceDirect

Medicina Clínica

journal homepage: www.elsevier.es/medicinaclinica

Review

Chronic cough as a disease: A mechanism-based framework for diagnosis and management

La tos crónica como enfermedad: diagnóstico y tratamiento basado en estudio de mecanismos

Miguel Jiménez-Gómez

Pulmonology Department, 12th of October University Hospital, 28041 Madrid, Spain

ARTICLE INFO

Keywords:
Cough hypersensitivity
Refractory chronic cough
Questionnaires
P2X3 antagonists
Speech pathology and language therapy
Patient-reported outcomes

ABSTRACT

Chronic cough (CC) has traditionally been attributed to asthma, rhinosinusitis, and gastroesophageal reflux disease. Yet in many patients, symptoms persist despite targeted treatment, revealing a mismatch between clinical need and current strategies.

A new paradigm has emerged: refractory and unexplained CC are increasingly recognized as manifestations of cough hypersensitivity syndrome. Diagnosis should follow a lean pathway emphasizing focused history, exclusion of red flags, essential baseline tests, and addressing treatable traits. Recognition of hypersensitivity features (allotussia, hypertussia, laryngeal paresthesia) is supported by validated tools such as the CHQ and TOPIC. Severity assessment requires integrating objective cough counts with robust patient-reported outcomes (MCSQ, CSD, LCQ, CQLQ), which capture clinical burden and guide referral.

Management should be mechanism-based: early access to multimodal speech therapy, judicious neuromodulators, and emerging peripherally targeted therapies such as P2X3 antagonists.

Establishing CC as a disease entity is essential to align research, regulation, and care with patient suffering.

Palabras clave:
Hipersensibilidad tusígena
Tos crónica refractaria
Cuestionarios
Antagonistas P2X3
Logopedia
Resultados referidos por el paciente

RESUMEN

La tos crónica (TC) se ha relacionado tradicionalmente con el asma, la rinosinusitis y el reflujo gastroesofágico. Sin embargo, a pesar de un tratamiento dirigido, los síntomas persisten en muchos pacientes, lo que evidencia un desajuste entre las necesidades clínicas y las estrategias actuales.

La TC refractaria se reconoce cada vez más como una manifestación del síndrome de hipersensibilidad tusígena. El diagnóstico se basa en una historia clínica detallada, la exclusión de signos de alarma y pruebas básicas. Se pueden aplicar escalas que ayuden al diagnóstico, así como la gravedad.

El manejo debe basarse en la fisiopatología, con un acceso temprano a terapias de logopedia o fármacos neuromoduladores y terapias emergentes como los antagonistas de P2X3.

Reconocer la TC como una entidad independiente es esencial para alinear la investigación, la regulación y la atención clínica con el sufrimiento de los pacientes.

Introduction

Cough is a vital defense reflex. When it becomes chronic—persisting beyond 8 weeks, as defined by the European Respiratory Society (ERS)[1]—, it evolves into one of the most frequent and challenging complaints in respiratory practice. Although the 8-week threshold is somewhat arbitrary, it aligns with the expected resolution of post-infectious coughs (typically following viral, Mycoplasma, or Chlamydia) and has become the standard entry criterion for clinical trials.[2,3]

Chronic cough (CC) affects up to 10% of adults worldwide.[4,5] In the United Kingdom, nearly 60% of respiratory specialists report that at least one-quarter of their consultations are driven primarily by CC.[2] A multinational European survey found that almost one third of patients with chronic cough meet criteria for possible refractory or unexplained CC, usually with moderate-to-severe symptoms and poor response to conventional therapies.[5] The condition is roughly twice as common in women, peaking between 50 and 60 years of age.[6] The

E-mail address: migueljimenezgomez@gmail.com

https://doi.org/10.1016/j.medcli.2025.107289
Received 25 August 2025; Accepted 12 November 2025
0025-7753/© 2025 Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

burden is substantial: CC causes psychosocial distress, functional limitations, and stigma, with quality-of-life decrements greater than those reported in stroke or Parkinson's disease. Approximately half of patients develop depression, and two-thirds of women report cough-related urinary incontinence.[3,7]

For decades, diagnostic algorithms revolved around three "usual suspects": asthma, postnasal drip and gastro-esophageal reflux disease (GERD). These conditions have often been over-attributed as direct causes, despite weak causal evidence.[4] In fact, cough persists in more than 40% of patients even after systematic management of these comorbidities.[4,5] CC is far from universal in those with asthma (present in only about two-thirds of uncontrolled asthma patients) or postnasal drip (present in fewer than 10%).[4] Yet many patients either fail to fit these categories (unexplained CC) or remain symptomatic despite targeted therapy of the underlying condition (refractory CC).[8]

This recognition has driven a paradigm shift. ERS guidelines[1] now define refractory and unexplained CC as distinct clinical entities driven by cough hypersensitivity syndrome.[9] Contributing factors such as smoking, angiotensin-converting enzyme inhibitors (ACEi), airway disease, GERD, among others are better regarded as treatable traits that interact with the primary disease process rather than as direct causes of cough.[4] Establishing CC as a disease in its own right—paralleling the reconceptualization of chronic pain—is increasingly seen as a clinical and research priority.[10] National initiatives have also contributed to this shift: the recent French guidelines provide practical recommendations for the diagnosis and management of CC.[11]

Despite this progress, practice remains heterogenous.[2,12] Surveys across Europe, including more than 770 physicians (general practitioners, pulmonologists, and allergists) demonstrate wide variation in diagnostic strategies: chest radiography, spirometry, and bronchodilator testing are nearly universal, while advanced tests such as computed tomography scan and bronchial provocation are applied inconsistently.[2] The combination of limited treatment effectiveness and delayed access to care frequently leads to suboptimal management.[4]

These observations mirror patient-reported experiences. In a Canadian survey, over half of individuals with persistent CC expressed dissatisfaction with prescribed therapies, and one-third discontinued further medical consultations due to lack of benefit.[13] Similarly, a European community survey of more than 1100 patients revealed that only 30% felt their doctor had "dealt with their cough thoroughly".[14] Together, these data highlight a persistent mismatch between clinical need and available management strategies, underscoring the limitations of current treatments and the urgent need for a unified, mechanism-based approach. Recent studies estimate that 10–50% of adults referred for specialist evaluation ultimately have refractory cough, often after 5–10 years of symptoms before receiving appropriate recognition.[15]

Against this background, there is an urgent need for a unified, mechanism-based framework for the evaluation and management of CC. In this context, real-world research using well-designed population-based studies can provide critical insights into disease characteristics and generate evidence that informs standardized and effective management strategies.[16]

This review synthesizes recent conceptual and therapeutic advances, aiming to provide clinicians with a practical pathway that improves both recognition and patient-centered outcomes.

Physiopatohology

The cough reflex in humans is primarily mediated by the vagus nerve, with inputs from vagal afferents innervating other visceral organs and trigeminal fibers supplying the nasal mucosa. Within the airways (possible extending into the lung parenchyma), two main sensory fiber populations have been described: thinly myelinated Aδ fibers arising from the nodose ganglion, responsive to mechanical or acidic stimuli; and unmyelinated C fibers from the jugular ganglion, responsive to harmful signals such as tissue injury, inflammation, or environmental irritants. These afferent fibers express multiple, often overlapping membrane receptors. Among the most relevant are the purinergic P2X2/3 heteromeric and P2X3 homomeric receptors, which detect extracellular adenosine triphosphate (ATP) released by epithelial cells in response to injury, inflammation, or irritant exposure. Centrally, vagal afferents project to the medulla oblongata, particularly to the nucleus tractus solitarius and the paratrigeminal nucleus.[3] The pivotal role of the vagus in cough control is underscored by clinical observations: interruption of the nerve during lung transplantation abolishes the cough reflex for 6 to 12 months, and ipsilateral vagotomy in patients with unresectable lung cancer can markedly reduce cough.[3]

The initial evidence of increased cough reflex sensitivity came from findings that ACEi-induced CC was associated with the accumulation of substance P. ACE metabolizes small peptides, activating bradykinin while degrading substance P. Therefore, ACEi leads to elevated synaptic levels of substance P, contributing to CC. This was later supported by studies showing that microinjection of substance P into the nucleus tractus solitarius, caused an upregulation of cough responses.[17]

Cough hypersensitivity, sometimes referred as neuropathic cough, is thought to result from heightened excitability of vagal afferents to otherwise innocuous stimuli, combined with abnormal central processing of cough and sensory perception.[4,8] This model closely parallels the mechanisms of chronic pain, where peripheral sensitization (e.g., upregulation of vagal C-fiber receptors and P2X3 signaling) interacts with central amplification of sensory inputs. Central to this understanding is the concept of interoception—the brain's ability to perceive and interpret internal bodily signals.[7] Neuroimaging studies in refractory CC patients demonstrate abnormalities in brain linked to interoception and inhibitory control, providing a neurobiological basis for impaired suppression of CC.[7] Together, these findings establish cough reflex hypersensitivity as the unifying pathophysiological mechanism in adults with CC.[18]

Diagnosis

Although apparently straightforward, defining CC as a disease remains challenging.[4] Current guidelines increasingly recognize CC as more than a symptom, yet in routine care it is still approached as a diagnosis of exclusion, confirmed only after systematic evaluation and treatment of other potential causes.[19]

Thorough clinical history remains the cornerstone of diagnosis.[8] Key elements include duration, onset, severity, potential triggers or complications of cough.[6] Important conditions to consider include asthma, GERD, and postnasal drip, along with a detailed occupational and smoking history. Symptoms such as sudden breathlessness, dysphonia, choking, or swallowing difficulties may point to vocal cord dysfunction. A chronic productive cough can suggest bronchiectasis, chronic bronchitis, or eosinophilic bronchitis. Careful documentation of drug exposure is also essential, with particular attention to ACEIs. Furthermore, somatic cough syndrome (previously termed psychogenic cough) and tic cough (formerly habit cough) should be considered in both adults and children presenting with CC.[3] Family history provides further diagnostic insight: after adjustment for confounding factors, children of parents with chronic dry cough showed a 7% prevalence of similar symptoms, rising to 14% for productive cough.[8] Moreover, genetic predisposition may play a role, as a high prevalence of mutations in the RFC1 gene—responsible for CANVAS syndrome (Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome)—has been linked to CC.[8]

Red flags such as hemoptysis, weight loss, progressive dyspnea and fever should also be noted and prompt further investigations if present. In the absence of red flags or risk factors, initial investigations should be limited to essential tests: chest radiography, spirometry with bronchodilator challenge, and blood eosinophilia; further studies such as

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

fractional exhaled nitric oxide, bronchial provocation, computed tomography scan or induced sputum depend on clinical context.[4]

Patients with unexplained or refractory CC frequently report describe hypersensitivity symptoms such as allotussia (exaggerated cough response to mild stimuli such as cold air, perfumes, or eating), hypertussia (increased sensitivity to tussigenic agents) and laryngeal paresthesia (abnormal throat sensations such as itching, tickling or an irresistible urge to cough).[3,18] These phenomena mirror the sensory disturbances observed in neuropathic pain: allodynia, hyperalgesia and paresthesia respectively.[20] Additional triggers frequently reported include talking, laughing or singing, which are less specific and may result from mechanical irritation of vagal afferents caused by repetitive coughing itself.[3] Importantly, cough hypersensitivity does not always represent a fixed phenotype. This suggests that hypersensitivity is a dynamic process, potentially reversible, rather than a permanent characteristic of all patients with CC.[3]

Despite advancements in understanding these phenomena, tools for its assessment remain limited. Objective tools, such as tussive inhalation tests with diluted capsaicin, are restricted to research settings. These tests consistently show that patients with CC have a lower threshold for cough induction and a diminished ability to suppress the reflex compared with healthy individuals.[4]

In routine practice, identifying a patient's trigger profile can provide valuable diagnostic clues. However, these sensations are rarely volunteered spontaneously and are easily overlooked unless actively explored. To systematize this assessment, the 22-item Cough Hypersensitivity Questionnaire (CHQ) was developed through a rigorous process combining literature review and patient interviews.[20] The CHQ is brief—requiring about one minute to complete—yet offers a structured, reproducible evaluation of hypersensitivity symptoms. Recent studies have validated the CHQ in CC populations, demonstrating high reliability, internal consistency, and responsiveness, which supports its use both in clinical practice and research.[18] A longitudinal analysis further confirmed its stability across cough phenotypes: patients with asthmatic cough and those with refractory CC achieved comparable scores (8.3 vs. 8.9; $p = 0.215$), reinforcing the concept of a shared underlying hypersensitivity mechanism and consolidating the CHQ as a valuable cross-context tool.[21] No studies to date have established validated cut-off points for its interpretation; despite this, the CHQ remains a useful instrument to support diagnosis and characterize cough hypersensitivity in practice.

More recently, the Triggers and Sensations Provoking Cough (TOPIC) questionnaire was developed as a 15-item questionnaire specifically designed to capture the sensory experiences and triggers associated with CC. Its structures approach allows better discrimination between refractory CC and other causes of CC.[19]

Other instruments have been developed to assess abnormal throat sensations potentially linked to CC. The Newcastle Laryngeal Hypersensitivity Questionnaire evaluates and categorizes laryngeal symptoms across a spectrum of conditions associated with laryngeal dysfunction. The Hull Airway Reflux Questionnaire (HARQ), a validated 14-item self-administered tool, was originally designed to assess laryngeal and airway reflux in patients with significant GERD. However, its scope is narrower and does not adequately capture the wider range of triggers and sensory disturbances typically reported in refractory CC.[19]

Observational studies suggest that many patients with CC attending referral clinics continue to experience persistent symptoms despite appropriate treatment, and that the presence of multiple cough hypersensitivity features is associated with cough persistence. These findings support the concept of cough hypersensitivity as a treatable trait influencing long-term outcomes.[22]

Severity assessment

Quantifying cough is essential in both clinical trials and in evaluating treatment response in practice.[23]

Objective assessment relies mainly on cough frequency monitoring. Several devices have been developed, including the Leicester Cough Monitor®, VitaloJAK®, Hull Automated Cough Counter®, Hyfe Cough Monitor System®, Strados Remote Electronic Stethoscope Platform®, and SIVA®.[23,24] These devices provide reproducible frequency counts with good correlation to clinical observation. However, their utility is limited by day-to-day variability and the Hawthorne effect (patients may suppress or exaggerate their cough, either consciously or subconsciously). Importantly, frequency alone does not capture the impact on patient's lives, as it ignores other dimensions such as timing, intensity, and the disruptive impact of cough.[23]

For this reason, patient-reported outcomes (PROs) are essential complements for assessing the efficacy and harms of interventions. They capture aspects that objective tools cannot measure: the distress of persistent coughing, fatigue, voice disruption, social embarrassment, and anxiety about losing control in public situations.[23] For this reason, various tools have been developed to evaluate cough from the patient's perspective.

Cough severity scales, quantifying patients' direct perception of cough severity:

- Cough severity visual analog scale (VAS): quick and simple, but limited by poor repeatability and responsiveness.
- McMaster Cough Severity Questionnaire (MCSQ).[25] developed in 2024 with rigorous methodology aligned to regulatory standards. It includes eight Likert-scaled items covering cough frequency and intensity, with strong validity confirmed through cognitive debriefing interviews.
- Cough Severity Diary (CSD): slightly shorter than MCSQ, but proprietary, limiting access.
- Cough Severity Questionnaire (CSQ)[24]: a nine-item tool developed by expert consensus within the Catalan Society of Pulmonology, aimed at identifying severe cases for timely referral. Psychometric validation is ongoing.

Cough-related quality of life (QoL) instruments capture the downstream impact of cough (e.g., chest discomfort, fatigue, low mood, social embarrassment), rather than the act of coughing itself. In some cases, they are even more responsive to treatment than severity scores alone.[23] Commonly used instruments include:

- Cough-related quality of life scale (CQLQ). Minimal important difference: 10.6 points.[6]
- Leicester cough questionnaire (LCQ).[26] Widely used in research since 2003 but less so in routine practice. A recent large community-based study demonstrated strong associations between lower LCQ scores and greater healthcare utilization, independent of age and sex. Based on this, thresholds for mild, moderate, and severe disease have been proposed, which may guide referral and health-system planning.[27] Minimal important difference: 1.3 points.[6]

Emerging evidence shows that higher scores on hypersensitivity questionnaires such as CHQ and TOPIC correlate with lower LCQ scores and worse quality of life, reinforcing the central role of cough hypersensitivity in driving clinical burden.[19,20]

A practical framework integrating diagnostic steps and tools for severity assessment is summarized in Table 1 .

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

Table 1
Diagnostic and severity assessment framework for refractory or unexplained chronic cough.

Refractory chronic cough or unexplained chronic cough management	
Diagnosis	Assessing severity
Probability of cough reflex hypersensitivity • Cough Hypersensitivity Questionnaire (CHQ) • Triggers and Sensations Provoking Cough (TOPIC) • Newcastle Laryngeal Hypersensitivity Questionnaire • Hull Airway Reflux Questionnaire **Identify "red flags"**: abnormal X-ray, haemoptysis, weight loss, fever or progressive dyspnea. **Rule out** (clinical history, chest X-Ray and spirometry) • Asthma and eosinophilic bronchitis • GERD • Postnasal drip • ACEi • Smoking • Anxiety/depression • CANVAS syndrome • Vocal cord dysfunction. • OSA	**Objective tools**: Leicester Cough Monitor®, VitaloJAK Cough Monitor®, Hull Automated Cough Counter®, Hyfe Cough Monitor System®, Strados Remote Electronic Stethoscope Platform®, and SIVA® **Subjective tools** (gold standard): patient reported outcomes • Severity scales: McMaster Cough Severity Questionnaire (MCSQ), Cough Severity Questionnaire (CSQ), Cough Severity Diary (CSD), Cough severity visual analog scale (VAS) • Quality of life: Cough-related quality of life scale (CQLQ), Leicester cough questionnaire (LCQ)

ACEi: angiotensin-converting enzyme inhibitor; CANVAS: Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome; GERD: gastroesophageal reflux; OSA: obstructive sleep apnea.

Treatment

For years CC has imposed a major physical, psychological, and social burden, yet no approved therapies have been available.

Assessing treatment response in CC is notoriously challenging, given the strong placebo effect, regression to the mean, and the natural resolution of cough over time, even when cough is measured objectively.[4] In clinical trials, placebo alone has reduced cough frequency by more than 60%,[28] a phenomenon that confounds efficacy signals and complicates regulatory approval.[28] As summarized by Smith,[29] the therapeutic landscape in chronic cough has evolved rapidly.

Successful management begins with systematic evaluation and treatment of common underlying disorders such as upper airway cough syndrome, asthma, non-asthmatic eosinophilic bronchitis, GERD, and interstitial lung disease.[3] Real-world data suggest that, after adjusting for confounding factors, higher cough VAS [odds ratio 1.44; 95% confidence interval: 1.06–1.97; $p = 0.02$] and diagnosis of postnasal drip (odds ratio 1.76; 95% confidence interval: 1.02–3.02; $p = 0.04$) are significantly associated with early response.[30] Other study, highlighted that GERD is particularly challenging to manage, as acid suppression alone is often insufficient and strict adherence to dietary and lifestyle modifications is difficult to sustain.[3]

Once refractory or unexplained CC is established, management should focus on treatment options with evidence of efficacy in randomized, placebo-controlled trials.[3]

Non-pharmacological strategies include speech pathology and language therapy, continuous positive airway pressure, pulmonary rehabilitation, breathing training, chest band, radiofrequency neurolysis, and transcranial magnetic stimulation have shown benefits.[9] Mindfulness-based interventions have also demonstrated effectiveness in improving cough control.

CC shares neurophysiological characteristics with overactive bladder and urinary urge incontinence, conditions that respond well to behavioral interventions.[7] This analogy has guided the development of multimodal speech therapy—or cough control therapy—usually delivered by a speech and language pathologist over two to four sessions. The program combines education, cough suppression strategies, breathing and laryngeal deconstriction exercises, and psychoeducational counseling. Its goal is to strengthen interoceptive awareness and inhibitory control through neuroplastic adaptations.[7] Patients are trained both to anticipate and manage the urge to cough using competing strategies (e.g., modified swallow, breathing technique) while reducing exposure to peripheral triggers such as vocal strain and irritants (caffeine, alcohol, smoking).[9] Cortical activations that modulate subcortical and brain-stem responses to cough stimuli may explain the success of this approach, although the precise mechanism remains uncertain.[3] Virtual, group-based cough suppression therapy programs have also been shown to be effective.[31] Evidence supports this approach. A randomize control trial show statistically significant improvement, though modest improvements.[32] A systematic review and meta-analysis confirmed that cough therapy reduces cough frequency more effectively than control interventions despite study heterogeneity.[9] Unfortunately, patients frequency face long delays before referral, often waiting up to two years and undergoing medical consultations and drug trials prior to referral.[9] Early referral could therefore represent a more cost-effective strategy, improving clinical outcomes, patient satisfaction, and quality of life.[9]

Recent evidence underscores the central role of the nervous system in CC, providing a rationale for the limited efficacy of purely peripherally targeted treatments.[7] Functional magnetic resonance imaging studies demonstrate cortical changes in affected patients, including reduced activity in motor inhibitory pathways, which are crucial for suppressing cough. Centrally acting neuromodulators such as amitriptyline, gabapentin, low-dose release morphine (5–10 mg), baclofen and nalbuphine have shown clinical benefit in reducing cough frequency and severity.[3,4,6] A placebo-controlled trial further demonstrated that combining multimodal speech therapy with pregabalin yields superior outcomes compared with either intervention alone.[3] Despite support from the European Respiratory Society, these agents remain off-label and are limited by frequent adverse effects,[5] making shared decision-making and regular reassessment essential.[3] The comparative effectiveness of neuromodulators remains uncertain. A systematic review published by Cohen and Misono in 2013 did not identify a clearly superior drug, optimal treatment duration, or follow-up.[33] In real-world practice in the United States, a survey of laryngologists found that gabapentin (45.1%), amitriptyline (39.0%), and tramadol (11.0%) as the most common first-line options. When effective, neuromodulators were typically continued for 3–6 months before tapering to the lowest effective dose (68.3%) or discontinuing completely (24.4%). If ineffective, clinicians often switched to an alternative neuromodulator (43.9%), or pursued superior laryngeal nerve block (24.4%).[34]

Other pharmacological options that have been investigated include first-generation antihistamines, dextromethorphan, and guaifenesin,[35] as well as azithromycin, although a clinical trial found no significant difference with placebo.[36]

Historically, research on cough hypersensitivity has focused more on peripheral mechanisms than central neural processes.[7] For patients with unexplained or refractory CC, the development of safe and effective drugs that antagonists vagal signaling pathways would represent a major therapeutic advance.[3] Supporting this rationale, bronchial biopsies from CC patients show increased airway nerve density, and novel agent targeting peripheral sensory receptors have demonstrated efficacy in CC, particularly antagonists of ATP-gated P2X3 ion channels.[4] The first and best studied drug in this case is the purinergic antagonist, gefapixant, evaluated in the pivotal COUGH-1 and COUGH-2 phase III trials.[28] Only the 45-mg dose showed significant reductions in cough frequency, while the 15-mg dose failed to separate from placebo.[28,37] Despite, multi-billion-dollar development, the US Food and Drug Administration rejected approval, citing a modest effect size over a strong placebo

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

Table 2
Therapeutic options for refractory or unexplained chronic cough.

Refractory chronic cough or unexplained chronic cough treatment						
Non pharmacological						
Cough control therapy (speech and language pathologists)						
Pharmacological						
Drug	Starting dose	Maximum dose	Expected effect	Time to effect	Adverse effects	Evidence
Modified release morphine	5 mg BID	10 mg BID (SID if symptoms are mainly during waking/overnight hours)	↓ **Cough severity** −1.96 (95% CI −1.09– − 2.11) ↑ **LCQ** + 2 (95% CI 0.93–3.07)	3–7 days	Constipation and drowsiness * Codeine not recommended (except if sole opioid) due to CYP2D6 variability (unpredictable efficacy and adverse effects).	Morice et al., ERJ 2020[1] Parker et al., Thorax 2023[38] Satia et al., JIACI 2025[6]
Gabapentin	100 mg TID	600 mg TID	↓ **Cough frequency** −27.31 (95% CI −2.87 to −51.75) ↑ **LCQ** +1.80 (95% CI 0.56–3.04; $p = 0.004$) NNT ≈ 3.6	After titration	Blurred vision, disorientation, dizziness, dry mouth, fatigue and nausea.	
Pregabalin	25 mg BID	75 mg BID	*Combined with speech therapy*: ↑ **LCQ** +3.5 (95% CI 1.1–5.8; $p = 0.024$) **No changes in cough frequency**	After titration		
Gefapixant	45 mg BID	X	↓ **Cough severity** −6.2 (IC 95%, −4.1 to −8.4) = **LCQ**: 1 (IC 95%, 0.7–1.4)	12 weeks	Ageusia, dysgeusia, hypogeusia. 25% improve on treatment; resolve in mots patients shortly after stopping	Kum et al., JAMA 2024[37]

BID: twice daily; LCQ: Leicester Cough Questionnaire; NNT: number needed to treat; SID: once daily; TID: three times daily.

response, as measured by 24 hour objective cough counts.[3,28] In contrast, regulatory agencies in Europe, United Kingdom and Japan have granted approval.[6,38] Real-world data of a large Japanese study by Matsumoto et al.,[39] report more than half of the patients treated with gefapixant achieved clinically meaningful improvement, and a subset identified as "super-responders". Interestingly, response rates appeared higher among patients with asthmatic cough and those with prominent laryngeal symptoms, suggesting that specific clinical subgroups may derive greater benefit.

The therapeutic pipeline for CC is expanding rapidly. Among next-generation, more selective P2X3 antagonists, gefapixant appears to be the most significant therapeutic benefit but also highest incidence of adverse effects.[40] Camiplixant has demonstrated a more balanced efficacy-tolerability profile, with a marked incidence of dysgeusia (6.5%) compared with the 48% reported in the phase II SOOTHE trial of gefapixant.[40,41] Eliapixant and filapixant both showed efficacy compared with placebo, although with adverse effects.[40] The efficacy of sivopixant remains uncertain.[40]

In parallel, agents targeting alternative neural pathways, including TRPV1 and TRPA1 ion channels and neurokinin-1 receptor antagonists, are emerging as promising candidates. Collectively, these developments signal a transition toward mechanism-based therapies, moving beyond the traditional reliance on nonspecific neuromodulators or purely behavioral interventions.[3]

Key therapeutic options, including non-pharmacological interventions and both off-label and emerging pharmacological treatments, are outlined in Table 2.

Conclusions

CC should be recognized as a distinct disease entity rather than merely a symptom of other conditions. Growing insight into cough hypersensitivity underscores the urgent need for standardized biomarkers and robust patient-reported outcomes to refine both diagnosis and therapeutic evaluation. Looking forward, optimal management will depend on an integrated, mechanism-based strategy that combines novel pharmacological agents with non-pharmacological interventions such as speech therapy and behavioral retraining. Such an approach has the potential to bridge the persistent gap between patient suffering and therapeutic progress, ultimately improving quality of life and advancing truly patient-centered care.

Ethical considerations

Not applied.

Funding source

I declare that this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

I declare having no conflicts of interest related to this publication.

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.

References

1. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*. 2020;55:1901136.
2. Morice A. A survey of UK respiratory specialists' opinion on the management of chronic cough. *ERJ Open Res*. 2024;10:00021–2024.
3. Irwin RS, Madison JM. Unexplained or refractory chronic cough in adults. *N Engl J Med*. 2025;392:1203–1214.
4. Turner RD, Birring SS. Chronic cough as a disease. *ERJ Open Res*. 2024;10:00459–2024.
5. Domínguez-Ortega J, Virchow JC, Guilleminault L, et al. Prevalence and burden of possible refractory chronic cough in four European countries. *ERJ Open Res*. 2025;11:00888–2024.
6. Satia I, Hassan W, McGarvey L, Birring SS. The clinical approach to chronic cough. *J Allergy Clin Immunol Pract*. 2025;13:454–466.
7. Slovarp LJ, Reynolds JE, Gillespie AI, Jetté ME. Reframing refractory chronic cough: the role of interoception. *Lung*. 2025;203:32.
8. Morice A. Chronic cough: symptom, sign or disease? *ERJ Open Res*. 2024;10:00449–2024.
9. Vertigan AE, Haines J. Nonpharmacological approaches to chronic cough. *J Allergy Clin Immunol Pract*. 2025;13:480–488.
10. Chung KF, Mazzone SB, McGarvey L, Song W-J. Chronic cough as a disease: implications for practice, research, and health care. *Lancet Respir Med*. 2025;13:110–112.
11. Guilleminault L, Demoulin-Alexikova S, de Gabory L, et al. Guidelines for the management of chronic cough in adults. Endorsed by the French speaking society of respiratory diseases (Société de Pneumologie de Langue Française, SPLF), the Société Française d'Oto-Rhino-Laryngologie et de Chirurgie de la Face et du Cou (SFORL), the Société Française de Phoniatrie et de Laryngologie (SFPL), the Société Nationale Française de Gastro-entérologie (SNFGE). *Respir Med Res*. 2023;83:101011.
12. Puente-Maestu L, Molina-París J, Trigueros JA, et al. A survey of physicians' perception of the use and effectiveness of diagnostic and therapeutic procedures in chronic cough patients. *Lung*. 2021;199:507–515.
13. Khan S, Brister D, Abraham T, et al. Patient satisfaction with the management of refractory and unexplained chronic cough in Canada: results from a national survey. *PLoS ONE*. 2024;19.
14. Chamberlain SAF, Garrod R, Douiri A, et al. The impact of chronic cough: a cross-sectional European survey. *Lung*. 2015;193:401–408.
15. Kim Y, Song W-J. Disease finds its identity with treatment in the real world: the use of gefapixant in chronic cough. *ERJ Open Res*. 2025;11:00096–2025.
16. Lee B, Song W-J. Redefining chronic cough as a disease: why patient registries matter. *ERJ Open Res*. 2025;11:00608–2025.
17. Sykes DL, Zhang M, Morice AH. Treatment of chronic cough: P2X3 receptor antagonists and beyond. *Pharmacol Ther*. 2022;237:108166.
18. Kim M-Y, Lee HY, Oh J-Y, et al. Longitudinal evaluation of the Cough Hypersensitivity Questionnaire in a cohort of chronic cough. *J Allergy Clin Immunol Pract*. 2025;13:1471–1473.e1.
19. King J, Galgani S, Digby JW, et al. Clustering chronic cough patients using reported sensations and triggers, results from the topic questionnaire. *CHEST*. 2025. S0012369225008359.
20. Hirons B, Cho PSP, Krägeloh C, et al. The development of the Cough Hypersensitivity Questionnaire for chronic cough. *ERJ Open Res*. 2024;10:00468–2024.
21. Kim M-Y, Won H-K, Oh J-Y, et al. Could cough hypersensitivity symptom profile differentiate phenotypes of chronic cough? *ERJ Open Res*. 2024;10:00260–2024.
22. Kim Y, Lee S-E, Jo E-J, et al. Treatable traits in chronic cough: a prospective evaluation for predicting cough persistence. *ERJ Open Res*. 2025;11:01357–2024.
23. Turner RD, Birring SS. How bad is your cough? The McMaster Cough Severity Questionnaire as a new tool to measure chronic cough. *Eur Respir J*. 2025;65:2402289.
24. Palones E, Arismendi E, Macías A, et al. Design of a tool to classify chronic cough according to its severity: Cough Severity Questionnaire (CSQ). *Open Respir Arch*. 2025;7:100464.
25. Kum E, Guyatt GH, Abdulqawi R, et al. The McMaster Cough Severity Questionnaire (MCSQ): a cough severity instrument for patients with refractory chronic cough. *Eur Respir J*. 2025;65:2401565.
26. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58:339–343.
27. Koskela HO, Kaulamo JT, Lätti AM. Severity grading of the Leicester Cough Questionnaire in chronic cough. *ERJ Open Res*. 2024;10:00142–2024.
28. Zhang M, Zhang B, Morice AH. Decoding the impact of the placebo response in clinical trials for chronic cough. *ERJ Open Res*. 2024;10:00335–2024.
29. Smith JA. The therapeutic landscape in chronic cough. *Lung*. 2024;202:5–16.
30. An TJ, Shin JH, Kim S, et al. Clinical characteristics of the early responders in the treatment of chronic cough. *J Thorac Dis*. 2025;17:1278–1288.
31. Kear EC, Williams ZJ, Selby J, et al. Effectiveness of virtual, group cough modulation therapy for chronic refractory cough. *ERJ Open Res*. 2025;11:01151–2024.
32. Weinberger M, Anbar RD, Buettner D. Another nonpharmacologic procedure for cessation of refractory chronic cough. *J Allergy Clin Immunol Pract*. 2025;13:1875–1876.
33. Cohen SM, Misono S. Use of specific neuromodulators in the treatment of chronic, idiopathic cough: a systematic review. *Otolaryngol Head Neck Surg*. 2013;148:374–382.
34. Dwyer CD, Johns MM, Shin JJ, Carroll TL. Practice trends in laryngology: neuromodulators for treatment of chronic cough. *Laryngoscope*. 2025;135:2454–2462.
35. Dicpinigaitis P. The current and emerging treatment landscape for chronic cough. *Am J Manag Care*. 2022;28:S159–S165.
36. Hodgson D, Anderson J, Reynolds C, et al. The effects of azithromycin in treatment-resistant cough. *Chest*. 2016;149:1052–1060.
37. Kum E, Patel M, Diab N, et al. Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose–response meta-analysis. *JAMA*. 2023;330:1359–1369.
38. Parker SM, Smith JA, Birring SS, et al. British Thoracic Society Clinical Statement on chronic cough in adults. *Thorax*. 2023;78:s3–s19.
39. Matsumoto H, Kanemitsu Y, Ohe M, et al. Real-world usage and response to gefapixant in refractory chronic cough. *ERJ Open Res*. 2025;11:01037–2024.
40. Yamamoto S, Horita N, Hara J, et al. Benefit–risk profile of P2X3 receptor antagonists for treatment of chronic cough: dose–response model-based network meta-analysis. *CHEST*. 2024;166:1124–1140.
41. Smith JA, Birring SS, Blaiss MS, et al. Camlipixant in refractory chronic cough: a phase 2b, randomized, placebo-controlled trial (SOOTHE). *Am J Respir Crit Care Med*. 2025;211:1038–1048.

Descargado para Anonymous User (n/a) en Andrés Bello University de ClinicalKey.es por Elsevier en enero 25, 2026. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2026. Elsevier Inc. Todos los derechos reservados.