The Significance and Psychosocial Burden of Refractory Chronic Cough: Interview with Two Key Opinion Leaders and a Patient

Interviewees:



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Interview Summary

Refractory chronic cough (RCC) is defined as a cough that lasts for at least 8 weeks and is unresponsive to guideline-based evaluation and treatment of underlying conditions. RCC is a disabling disease that remains a persistent clinical challenge and has few therapeutic options. Recent advances in research indicate that RCC derives

from a cough hypersensitivity involving both peripheral and central mechanisms rather than external physiological causes. For this article, EMJ conducted interviews in February 2025 with key opinion leaders Daiana Stolz from Clinic for Pneumology, Faculty of Medicine, University of Freiburg, Germany, and Jacky Smith from Division of Immunology, Immunity to Infection and Respiratory Medicine, University of Manchester and Manchester University NHS Foundation Trust, UK; as well as Mandy Beadnell, a patient with RCC from Worthing, West Sussex, UK, to raise awareness of RCC and discuss the significance and psychosocial burden of this disease. Stolz provided a pulmonologist's view of RCC, including identifying and managing patients with this disease, assessing the psychosocial burden of RCC, and raising awareness of RCC in the medical community. Smith discussed the central and peripheral mechanisms of RCC, as well as neuronal hypersensitivity and drivers of the urge to cough. In addition, Smith explored cough bouts and why they are important, including defining and measuring cough bouts, the relationship between cough bouts and the severity of disease, and measuring treatment effectiveness in patients with RCC in clinical practice. Beadnell described the patient experience of living with RCC, covering topics such as the impact of RCC on daily life, the journey to diagnosis and beyond, the level of awareness of RCC among healthcare professionals (HCP), and what the medical community can do to support and empower patients with RCC. Finally, Stolz, Smith, and Beadnell outlined potential future developments in RCC clinical practice and research, and advances in diagnosis, treatment, and patient support that they would like to see.

INTRODUCTION

Cough is one of the most common reasons for which patients seek medical attention in the outpatient setting.[1] Chronic cough in adults is defined as a cough that lasts for at least 8 weeks[2,3] and has a global prevalence of approximately 10%.[1,3] A chronic cough that is unresponsive to guideline-based evaluation and treatment of underlying conditions is defined as refractory.[1] RCC is a disabling disease that remains a persistent clinical challenge and has few therapeutic options.[4,5] Recent advances in research indicate that RCC derives from a cough hypersensitivity involving both peripheral and central mechanisms rather than external physiological causes.[1,5]

THE CURRENT LANDSCAPE OF REFRACTORY CHRONIC COUGH

Stolz and Smith explained that the global incidence of RCC is difficult to estimate, partly because the definition of RCC and the classification of the disease have only recently been established. Stolz estimated that 5–10% of patients with chronic cough have RCC.

This debilitating condition more commonly affects females than males,[6] predominantly occurs in middle age (40–65 years),[7-10] and substantially impacts quality of life.[11]

According to Stolz, the most common cause of chronic cough is chronic bronchitis caused by cigarette smoking, but this represents a different cohort to those patients with RCC. Stolz and Smith outlined the other common causes of chronic cough, including asthma, pneumonia, bronchial cancer, lung metastases, chronic infection of the upper airways (chronic sinusitis, chronic rhinitis, polyps), bacterial or viral infections, nasal disease, gastro-oesophageal reflux, and sleep apnoea. Smith suggested that about a third of patients with RCC identify a viral illness as the starting point for their cough. The experts highlighted that patients with RCC have features consistent with hyperexcitability of the nerves that control the cough reflex, but there is no obvious clinical pattern in these patients, and the cause of this debilitating disease is unknown.

Smith estimated that approximately 70% of the patients referred to the specialist cough clinic in Manchester, UK, have RCC that does not respond to treatment.

For the remaining approximately 30% of patients, the cough improves on treatment of underlying conditions such as asthma and gastro-oesophageal reflux. The patients with RCC visiting Smith's clinic describe symptoms that align with their cough reflex being overactive and hyperexcitable, including tickling and irritation in the throat. Smith explained that common triggers of cough identified by patients with RCC include changes in temperature, chemical irritants (cleaning products, perfumes, air fresheners), and food smells, as well as actions that involve moving the throat, such as eating, drinking, talking, laughing, or singing. Smith stated: "RCC is a real problem for people who enjoy singing in choirs, or who have to speak as part of their professional life, such as teachers and lecturers."

In Stolz's experience, a typical patient with chronic cough has usually been coughing for at least 10 years and has undergone hundreds of examinations before being referred to a cough specialist. Patients for whom all possible diagnostic and treatment avenues have been explored will be diagnosed with hypersensitivity and refractory cough at this stage. In patients with a less exhaustive medical history, there may be further options to explore before arriving at an RCC diagnosis. Stolz pointed out that the diagnosis of exclusion required for RCC is a different process for cough specialists versus non-cough specialist HCPs. A cough specialist will only see patients who have been referred because of cough and, therefore, will have a different overview of RCC compared with non-specialists, who will have to exclude common diseases that cause cough, as well as cancer and other serious conditions, before thinking about hypersensitivity cough.

Smith emphasised that the unmet need surrounding RCC is substantial because it is a diagnosis of exclusion, and the many tests and trials of treatment have a negative impact on the patient, as well as being a burden on the healthcare system. Furthermore, Smith disclosed: "I wonder whether the patients we see in our clinic are the tip of the iceberg. There are probably many patients out there who have given up seeking solutions and are simply 'putting up' with their RCC." Smith also highlighted a substantial unmet need for new effective treatments that have been properly developed to treat cough, and for HCPs and the public to understand how unpleasant it is to have a chronic cough.

According to Beadnell, a major unmet need in RCC management is that HCPs appear to be unwilling to listen to patients describing how they feel or what they are learning from their bodies. In Beadnell's experience, "Once serious diseases such as cancer had been ruled out, the management of my RCC felt like a factory production line. I was frequently being put back on the conveyor belt to be passed on to the next person."

A PULMONOLOGIST'S VIEW OF REFRACTORY CHRONIC COUGH

Daiana Stolz

Identifying Patients with Refractory Chronic Cough

According to Stolz, most HCPs consider cough as a symptom because this is what they were taught at medical school; however, at some point in the patient's health journey, the physician recognises that the cough is the disease itself. When this point is reached in patients with RCC is unclear and likely varies between patients.

Stolz explained that the diagnosis of exclusion approach required for RCC is complicated, time-consuming, frustrating for the patient and their physician, and dependent on the availability of the necessary expertise, funding, and resources. Moreover, Stolz noted that the necessary work-up required for a definitive diagnosis of RCC has not been clearly defined, which complicates the clinical picture.

Stolz indicated that the first step to differentiate RCC from different types of non-productive cough and other aetiologies, such as asthma and post-nasal drip, is to assess for these conditions.

There are different schools of thought on the best approach, Stolz explained, with

some physicians establishing therapy and assessing responses, and others conducting examinations to search for the condition before establishing therapy. In cases where asthma is suspected, body plethysmography is used to look for evidence of obstruction and small area disease. If the results are normal, bronchoprovocation tests are conducted, usually with methacholine. Post-nasal drip can be diagnosed clinically by asking patients if they feel there is secretion dripping behind their nose and whether they can "pull the secretion down", which only those with post-nasal drip are likely to be able to do.

Methods for exclusion of other conditions that may cause chronic cough include a CT scan of the perinasal sinus for chronic sinusitis; history taking and allergy testing for seasonal allergic rhinitis; CT scan of the lungs for interstitial lung disease, bronchiectasis, or other evidence of respiratory disease; and assessing for sleep apnoea. Further investigations may include 24-hour pH monitoring for gastro-oesophageal reflux in patients who have had a normal gastroscopy, or oesophageal manometry with impedance to check oesophageal function.

Stolz acknowledged the hard work, time, and resources involved in excluding these underlying conditions, emphasising that a thorough approach is essential to ensure any tumours or other serious conditions are identified and treated as soon as possible. Furthermore, Stolz emphasised: "Awareness of RCC as an entity is key. RCC substantially compromises the patient's quality of life and should be taken seriously. HCPs need to understand what it means to be healthy and yet have a cough that prevents normal daily activities."

Managing Patients with Refractory Chronic Cough

In Stolz's opinion, primary care physicians and other HCPs need to realise that patients whose cough continues despite a guideline-driven[12-14] work-up and treatment may require a different management approach.

Stolz explained that patients in whom underlying diseases or conditions that cause cough have been excluded, and the cough has been defined as refractory, can be prescribed off-license treatment with opioids (codeine, morphine) to reduce cough; however, these treatments are not always effective, have several side effects, including constipation and drowsiness,[15] and, in some cases, there is a risk of drug addiction and abuse.

Other therapeutic options for RCC include the anticonvulsants pregabalin and gabapentin;[15] however, in Stolz's experience, the dose required to decrease cough makes the patient very tired, which is not ideal. Further therapies for patients with RCC include speech therapy and physiotherapy to help patients suppress and control the urge to cough.[16,17] Stolz noted that these methods can be effective but require considerable dedication from the patient, and there are limited numbers of speech therapists and long waiting times for speech therapy appointments.

Drugs targeting cough receptors are a new therapeutic option in RCC that appear to have fewer side effects than current therapies and offer hope for patients with RCC.[4] A new peripherally acting oral P2X purinoceptor 3 (P2X3) receptor antagonist, gefapixant,[18] has been approved in the EU, UK, Switzerland, and Japan, but not in the USA or Canada.[1] The most common side effects reported with gefapixant are related to taste disturbance.[19] Stolz noted that patients tend to find this adverse effect much less bothersome than the RCC itself.

Assessing the Psychosocial Burden of Refractory Chronic Cough

Stolz uses a visual analogue scale from 0–10 to assess the psychosocial burden in patients with RCC. Stolz explained that the number, frequency, and intensity of coughs all contribute to how life-limiting and debilitating RCC is for patients and how much this condition impacts their quality of life. In Stolz's experience, patients with RCC are very capable of defining the burden of RCC and whether this improves under therapy using the visual analogue scale.

Stolz emphasised that patients should be informed about which therapeutic options are available and that all avenues are being explored, even though they may not be curative. Stolz mentioned: "Patients with RCC would do anything to make their cough go away, which reflects the burden of the disease. It is important for patients to know that physicians are taking RCC seriously and are trying their best to help them."

Raising Awareness of Refractory Chronic Cough in the Medical Community

In terms of raising awareness, Stolz considered that listening to patients can be "quite powerful" as this gives the physician a fundamental understanding of what the patient is experiencing. In addition, Stolz advocates for communication and education initiatives for primary care HCPs to ensure they are informed about the diagnosis and treatment of RCC. Stolz summarised: "It is important to raise awareness of RCC among HCPs to ensure they understand the huge clinical and psychosocial burden of this condition on their patients, and to inform them that there is something that can be done about it."

MECHANISMS OF REFRACTORY CHRONIC COUGH

Jacky Smith

Central and Peripheral Mechanisms of Refractory Chronic Cough

Smith indicated that there has been a substantial increase in understanding about the central and peripheral mechanisms of RCC in the last decade; however, it is unclear why drugs such as morphine and pregabalin that are currently used for RCC are effective. Smith added that there is a broad understanding that these drugs desensitise nerves, but where, how, and in which patients they will be effectual is unknown.

P2X3 receptors, a subtype of the P2 purinergic receptor family,[20] are found on the nerves that mediate cough; therefore, developing a drug that blocks these receptors was a logical next step.[21] Smith explained: "P2X3 antagonists appear to block the nerves in the airways rather than in the brain, although it feels like we're just starting to scratch the surface of this research".

A functional MRI (fMRI) study has been conducted to compare the neural activation in patients with chronic cough and control participants while inhaling capsaicin and adenosine triphosphate to evoke an urge-to-cough sensation.[22] The results showed that when urge-to-cough levels were matched, patients with chronic cough displayed significantly less neural activation in medullary regions known to integrate airway sensory inputs than control participants.[22] Neural activation in cortical brain regions known to encode cough sensations did not differ significantly between patients with chronic cough and control participants, whereas activation in a midbrain region of patients with chronic cough was significantly increased compared with that in control participants.[22] The study authors suggested that in some patients, cough hypersensitivity may involve midbrain regions that amplify ascending sensory signals or change the efficacy of central inhibitory control systems that usually filter sensory inputs.[22]

Other fMRI studies in patients with RCC versus healthy volunteers indicate that structural and functional alterations in the brain may contribute to the pathophysiology of RCC.[23,24] Smith summarised: "The increased brain activation seen in patients with RCC compared with that in healthy volunteers aligns with the concept that the neuronal pathways are overactive in patients with RCC."

Smith explained that there is a natural braking mechanism in the brain that controls cough and ensures an individual can cease coughing and start breathing again. Recent evidence from fMRI studies indicates that patients with chronic cough, including RCC, have an impaired ability to control coughing, i.e., the braking mechanism is not functioning properly.[22]

Cough Hypersensitivity and Drivers of the Urge to Cough

Smith commented that the clinical picture of RCC fits with the concept of cough hypersensitivity, where the nerves that control cough are malfunctioning and triggered too easily. Furthermore, the triggers that patients with RCC report align with the temperature, chemical, and mechanical stimuli that activate nerves.

Triggers for cough are widespread, so avoiding exposure is not a viable option. Smith suggested that further research and studies in non-clinical models and humans are needed to elucidate the mechanisms of RCC, and this may lead to the discovery of more effective treatments.

COUGH BOUTS AND WHY THEY ARE IMPORTANT

Jacky Smith

Defining and Measuring Cough Bouts

There is currently no standard definition for cough bouts.[25] Cough frequency, typically expressed as the number of explosive cough sounds per hour, is measured using cough monitors in clinical trials.[25] Investigations are being conducted into the intervals between coughs in patients with RCC, and how differences in inter-cough intervals impact bout data and patients' perceptions of disease severity.[25] Smith described that intervals of longer than 3 seconds between coughs do not appear to alter the bout data or how patients score their coughs, indicating that inter-cough intervals of ≤3 seconds could be used to define cough bouts,[25] but further research is needed to establish a standard definition.

Why Cough Bouts Are Important

Smith noted that cough bouts are important for researchers as well as for patients. Long cough bouts are described by patients as the most unpleasant aspect of cough because these bouts are impossible to hide, and "everybody notices that you've got a cough". Furthermore, cough bouts are mechanically impactful on the patient's physiology, generating high and prolonged pressure in the chest and stomach, which reduces the blood flow back to the heart and may also lead to rib fracture.[26] These physical effects cause the patient to feel dizzy and nauseous, vomit, and, rarely, pass out (cough syncope).[27] Urinary incontinence may also develop, particularly in females.[28]

Smith postulated that cough bouts might be important mechanistically, as the different cough patterns that make up these bouts may indicate what is occurring in the airways to drive cough. Smith theorised that a patient who has two bouts of 30 coughs in 24 hours (i.e., long cough bouts that are rarely triggered) might have different neurophysiological and braking mechanisms at play compared with a patient who has 30 bouts of two coughs (i.e., short cough bouts that are easily triggered) in the same time period. Smith speculated that these different patterns of cough clusters may indicate the mechanisms in the brain and airways that drive and control cough, but further research is needed.

The Relationship Between Cough Bouts and the Severity of Disease

Smith commented that patients who have long cough bouts perceive their disease to be severe, although the threshold for severity might differ between patients. With this in mind, Smith hypothesised that treatments that reduce the number of long cough bouts over a 24-hour period might help patients to feel considerably better, even if the total number of coughs does not reduce much. Therefore, RCC treatments that focus on alleviating long cough bouts may be particularly beneficial for patients.

Measuring Treatment Effectiveness in Patients with Refractory Chronic Cough in Clinical Practice

In accordance with Stolz, Smith asks patients to score their cough before, during, and after treatment using a visual analogue scale from 0–10 to assess the effectiveness of therapy. Smith describes this as a simple, quick, pragmatic, and efficient way to capture a global sense of cough severity and improvement of cough

bouts under therapy in the clinical practice setting. Smith added that cough monitoring and patient-reported outcomes have been developed for clinical trials, but whether these methods are more effective than a visual analogue scale in patient care has not been investigated.

LIVING WITH REFRACTORY CHRONIC COUGH: THE PATIENT EXPERIENCE

Mandy Beadnell

The Impact of Refractory Chronic Cough on Daily Life

It is 20 years since Beadnell developed a cough following a severe, flu-like viral infection and, since then, her life has changed immeasurably. Beadnell disclosed: "RCC affects every single thing that you do. It is often humiliating, regularly annoying, and always a nuisance."

Factors that trigger Beadnell's cough include eating or drinking anything, talking for long periods, laughing, and being stressed or busy; all of which are difficult or impossible to avoid. Beadnell emphasised that laughing is a particularly strong trigger, causing choking and retching, so comedy movies at the cinema are an impossibility. Beadnell recalled: "I broke my rule and took my children and their friends to a movie as a birthday outing. I missed chunks of the film to cough, choke, and regurgitate. Something I hadn't thought about was bladder control. I leaked on each cough as I couldn't get to the ladies' room in time. Have you any idea how this feels as a mum out with her children and their friends? I was mortified." RCC also impacted the school run, with Beadnell having to stop the car to cough, choke, and often vomit slime into tissues, then "carry on as if nothing has happened".

Any public scenario is difficult for Beadnell, from trains, planes, cinemas, and theatres to supermarkets. Beadnell described the need to "weigh up how long you've got because you can feel the cough starting to kick off, but sometimes it just comes straight out of thin air, and you can't predict it". To compound this discomfort in public situations, Beadnell has noticed a shift in the public's attitude to cough, from a supportive approach before the COVID-19 pandemic to hostility during and after this time. The difference in how Beadnell feels in public because of this change in attitude has made RCC even harder to bear.

There are a few approaches that provide Beadnell limited relief from RCC, such as drinking wine, not eating, and not talking; taking a dehydrating decongestant, amitriptyline (a tricyclic antidepressant) or fexofenadine (an antihistamine); or self-induced vomiting to "remove the offending slime".

Beadnell summarised: "My cough is exhausting. There have been times when I have wanted to pour boiling water down my throat. RCC affects daily life so much more than anybody can even begin to imagine. From the minute you wake up until the minute you go to bed, you are working around RCC."

The Journey to Diagnosis and Beyond

Between 2005–2019, Beadnell was seen by 12 different consultant specialists, often revisiting them for new ideas or pathways. These specialists investigated various potential causes of Beadnell's cough, such as gastro-oesophageal reflux, allergy, sinus disease, pharyngeal pouch, overactive salivary glands, bronchial adenoma, and impaired oesophageal sphincters. Beadnell received antibiotics, nasal sprays, and antacids, and underwent various tests, including CT scans and MRI.

Each stage of this journey took months, if not years. Beadnell conducted substantial and comprehensive research about chronic cough throughout every stage. According to Beadnell, this quest for knowledge was "driven by need much more than desire… I don't think you [can] take any credit for tenacity; it is more like desperation". Beadnell's research was a primary driver of the potential solutions explored during her journey to diagnosis. Beadnell noted: "It was a question of me doing the research.

My general practitioner didn't ever instigate anything. He would sort of head scratch. Everybody would head scratch."

Part way into the health journey, Beadnell created a set of chronological medical notes "out of sheer frustration" to simplify appointments with consultants and to address the "total disconnect" between specialists from different disciplines. Beadnell likened her health journey to a game of snakes and ladders: "I would be progressing well [up the ladder], I'd find a pathway that fitted my symptoms, then I would go straight down the snake back to square one and have to try again and keep looking for other possibilities."

As each avenue of investigation closed without a solution, Beadnell was left upset, disappointed, depressed, and feeling very alone. Comments from HCPs like "It's just a cough, live with it" and "You have a propensity to cough; I doubt you will ever get to the bottom of it" showed no depth of understanding and were enough to push Beadnell to utter despair and suicidal thoughts.

Fortunately, there was a turning point in Beadnell's health journey in 2019, when she was referred to a consultant at the Royal Brompton Hospital, London, UK, who "understands every aspect of RCC".

The Level of Awareness of Refractory Chronic Cough Among Healthcare Professionals

Beadnell currently attends a cough clinic and considers that she is "preaching to the choir" now that she is interacting with cough specialists. Prior to attending this clinic, Beadnell found that there was "absolutely no comprehension" of RCC among the HCPs that she encountered during her health journey. Beadnell explained that information flow to HCPs is slow because RCC is a life-limiting but not a life-threatening disease, clarifying, "Patients with RCC can get on with life, just not very well. It's not that HCPs don't care, it's just that they don't know about RCC. They're just not aware how much of a burden it is to patients."

What Can the Medical Community Do to Support and Empower Patients with RCC?

In Beadnell's opinion, the medical community should ensure that HCPs have access to the latest information on RCC because the landscape for this condition is changing rapidly, and many HCPs, particularly general practitioners, may not know what information is out there.

In addition, Beadnell suggested that HCPs should acknowledge patients' concerns and experiences (it is not "just a cough"); follow up with patients and continue to show interest in their condition; show empathy and make patients feel heard; provide patient education, including resources and contact details for support groups; and connect with respiratory specialists who have experience of RCC.

Suggestions for Patients with Refractory Chronic Cough

Beadnell suggested that patients with chronic cough should push to see a respiratory specialist once serious underlying conditions are ruled out, particularly as the RCC landscape has improved dramatically in the last few years. Beadnell also advocates for patients to keep an open mind and trial all the available options to try to improve their RCC and quality of life. Options such as cough syrup, apple cider vinegar, ginger shots, or avoiding dairy products are worth trying at least once, according to Beadnell.

FUTURE PROSPECTS AND CONCLUSION

Stolz would like to see the development of a test for cough hypersensitivity to help predict which patients are unlikely to respond to directed therapy for other causes of cough, and to provide HCPs with one tool to diagnose RCC rather than having to exclude many other conditions. In addition, Stolz advocates for a set of comprehensive recommendations, including the minimum work-up needed to identify RCC, to enable HCPs to recognise a cough that is not responding to treatment as early

as possible and prompt them to consider alternative strategies. Stolz highlighted that there are several therapies in development, including receptor blockers, which may broaden the therapeutic options for patients with RCC. In Stolz's opinion, the ideal medications would have minimal side effects and be inexpensive and easy to use. Stolz summarised: "We don't have a gold standard for the diagnosis of RCC; we have to use exclusion, which is complicated, expensive, and not universally reimbursed. RCC is a challenging area that few people know about, so raising awareness is vital."

In concurrence with Stolz, Smith considers that a test to directly identify patients with RCC rather than relying on a diagnosis of exclusion would be ideal. Smith hopes for a simpler and easier diagnosis of RCC that can be made by non-cough specialists, and effective treatments with fewer side effects and risks than current therapies. According to Smith, the most helpful advance in RCC would be to make it easier for primary and secondary care physicians to identify and treat patients with RCC, thus leaving the tertiary clinics for the patients with RCC who are not responding to treatment. Smith acknowledged the need to raise the profile of chronic cough and advocated for better understanding among HCPs and the public of the negative impact of RCC on quality of life, as well as to dispel the myth that RCC is related to a contagious disease. Initiatives such as 'Let's talk about cough',[29] an award-winning online resource that includes links to websites, information about living with chronic cough, and tips to control coughing, are instrumental in the quest to raise awareness of chronic cough and RCC.

Beadnell is grateful to be on a treatment pathway in which the medications are helping and appreciates the support of everyone involved in her health journey. Beadnell proposed that HCPs are the starting point for raising awareness about RCC, and patients will feel calmer if they feel they are being listened to and understood. Beadnell suggested: "Having a healthcare professional who supports you reduces your stress, gives you somebody to turn to, and you're likely to cough less because you're calmer." However, Beadnell stated: "I feel uncomfortable with the term 'refractory chronic cough'. The term 'chronic cough' doesn't actually sum up what I'm going through; it almost demeans it. I am choking rather than coughing, and I sometimes can't get any words out at all. The fact that 'refractory' is added in front of it, what is that to most people? While I'm grateful that there is an acceptance that this condition exists, I feel that 'refractory chronic cough' is not nearly a strong enough term."

References

1. Peters AT et al. Therapeutic and mechanistic advances in chronic cough. Ann Allergy Asthma Immunol. 2024:DOI:10.1016/j.anai.2024.12.021.
2. Morice A et al. Chronic cough: new insights and future prospects. Eur Respir Rev. 2021;30(162):210127.
3. Bali V et al. Patient-reported experiences with refractory or unexplained chronic cough: a qualitative analysis. Ther Adv Respir Dis. 2024;18:17534666241236025.
4. Guilleminault L et al. Drugs targeting cough receptors: new therapeutic options in refractory or unexplained chronic cough. Drugs. 2024;84(7):763-77.
5. Slovarp LJ et al. Reframing refractory chronic cough: the role of interoception. Lung. 2025;203(1):32.
6. Bai H et al. Gender difference in chronic cough: are women more likely to cough? Front Physiol. 2021;12:654797.
7. van Boemmel-Wegmann S et al. Characteristics of adults with potential refractory chronic cough identified using an algorithm designed for administrative claims databases: a descriptive study. Sci Prog. 2024;107(1):368504241238080.
8. Smith JA et al. An observational study to understand burden and cost of care in adults diagnosed with refractory chronic cough (RCC) or unexplained chronic cough (UCC). Respir Res. 2024;25(1):265.
9. Morice AH et al. Characterization of patients with refractory or unexplained chronic cough participating in a Phase 2 clinical trial of the P2X3-receptor antagonist gefapixant. Lung. 2021;199(2):121-9.
10. Kukiełka P et al. Prevalence of refractory and unexplained chronic cough in adults treated in cough centre. ERJ Open Res. 2024;10(5):00254-2024.
11. Domingo C et al. Cough severity visual analog scale scores and quality of life in patients with refractory or unexplained chronic cough. Respir Investig. 2024;62(6):987-94. Erratum in: Respir Investig. 2025;63(1):94-5.
12. Irwin RS et al; CHEST Expert Cough Panel. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153(1):196-209.
13. Morice AH et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020;55(1):1901136. Erratum in: Eur Respir J. 2020;56(5):1951136.
14. Parker SM et al. British Thoracic Society clinical statement on chronic cough in adults. Thorax. 2023;78(Suppl 6):s3-19.
15. Visca D et al. Management of chronic refractory cough in adults. Eur J Intern Med. 2020;81:15-21.

16. Balbani AP. Cough: neurophysiology, methods of research, pharmacological therapy and phonoaudiology. Int Arch Otorhinolaryngol. 2012;16(2):259-68.
17. Birring SS et al. Physiotherapy and speech and language therapy intervention for chronic cough. Pulm Pharmacol Ther. 2017;47:84-7.
18. Markham A. Gefapixant: first approval. Drugs. 2022;82(6):691-5.
19. McGarvey LP et al; COUGH-1 and COUGH-2 investigators. efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet. 2022;399(10328):909-23.
20. Spinaci A et al. P2X3 receptor ligands: structural features and potential therapeutic applications. Front Pharmacol. 2021;12:653561.
21. Garceau D, Chauret N. BLU-5937: a selective P2X3 antagonist with potent anti-tussive effect and no taste alteration. Pulm Pharmacol Ther. 2019;56:56-62.
22. Moe AAK et al. Brainstem processing of cough sensory inputs in chronic cough hypersensitivity. EBioMedicine. 2024;100:104976.
23. Wingfield Digby J et al. Central nervous system resting-state fMRI in refractory/unexplained chronic cough. Abstract P214. Thorax 2023;78(Suppl 5):A1-311.
24. Namgung E et al. Structural and functional correlates of higher cortical brain regions in chronic refractory cough. Chest. 2022;162(4):851-60.
25. Holt KJ et al. An exploration of clinically meaningful definitions of cough bouts. ERJ Open Res. 2024;10(6):00316-2024.
26. Özyurtkan MO et al. Cough-induced rib fractures: a comprehensive analysis of 90 patients in a single center. Turk Gogus Kalp Damar Cerrahisi Derg. 2024;32(1):69-74.
27. Patel K et al. Unusual etiology of chronic cough and syncope as Chiari malformation type 1. Cureus. 2023;15(6):e40598.
28. Dicpinigaitis PV. Prevalence of stress urinary incontinence in women presenting for evaluation of chronic cough. ERJ Open Res. 2021;7(1):12.
29. University of Manchester et al. Let's talk about cough. Available at: https://www.letstalkaboutcough.net/. Last accessed: 22 February 2025.

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