Chronic cough: is the end nigh?

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Chronic cough is common and hugely impactful. Cutting-edge studies have augmented our understanding and developed novel treatments. However, many challenges remain. We ask, is it possible the end of chronic cough is nigh? https://bit.ly/3NgRg7c

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Abstract

Chronic cough (lasting more than 8 weeks) is a common condition with substantial psychosocial impact. Despite huge efforts following robust guidelines, chronic cough in many patients remains refractory or unexplained (RU-CC). Recent insights support a significant role for cough hypersensitivity in RU-CC, including neuropathophysiological evidence from inhalational cough challenge testing, functional magnetic resonance imaging, and airway nerve biopsy. Along with improved approaches to measuring cough, this knowledge has developed in tandem with repurposing neuromodulator medications, including gabapentin, and evidence for non-pharmacological treatments. Most significantly, there is now a pipeline for novel classes of drugs specifically for chronic cough. The P2X3 receptor antagonist gefapixant is the first such drug to be approved in Europe. However, challenges persist. The field of chronic cough needs more robust epidemiological data, enhanced diagnostic tools, further well-designed clinical trials accounting for the effects of placebo, and treatments with minimal side-effects. Addressing these challenges are novel chronic cough registries, improved International Classification of Diseases (10th revision) coding, genetic testing options and further mechanistic studies. This Viewpoint article discusses these facets and considers how, whilst the end of chronic cough may not be imminent for all patients, the evolving landscape looks increasingly optimistic.

Introduction

Chronic cough (lasting for ⩾8 weeks) may affect 10% of the population, with a significant impact on physical, social and emotional wellbeing [1]. Management, despite an evidence-based approached, is often disappointing [2]. However, as of late 2023, the recent authorisation of the drug gefapixant in the European Union and other jurisdictions as a novel specific treatment for refractory or unexplained chronic cough (RU-CC) represents an exciting development for patient care [3, 4]. Here we discuss this important advance in the context of fresh understanding of chronic cough and consider whether a curative approach for the majority is in sight.

A (very) brief history of cough

The presumed aetiology (or aetiologies) of chronic cough has changed markedly over the years. Ancient beliefs that all disease was caused by the four humours or evil spirits eventually waned, and the focus in cough changed to inflammatory or infective causes, notably tuberculosis [5]. The 1900s heralded ageing populations and a burgeoning smoking epidemic, leading to an increased prevalence of chronic lung diseases associated with chronic cough. Towards the end of the twentieth century an "anatomical diagnostic protocol" was proposed for isolated persistent cough in the absence of easily detectable lung pathology [6]. Chronic cough was considered merely a symptom of underlying conditions, such as asthma, gastro-oesophageal reflux or rhinosinusitis, treatment of which was advocated, often empirically in the absence of typical features of those diseases [6]. Although initial success rates as high as 98% were reported [6], doubt about the pathway mounted as patients with no discernible cause of their cough often failed empirical treatments [7]. Indeed, chronic cough which is refractory or unexplained despite extensive

investigation and treatment (RU-CC) is now considered a unique entity, and essentially a disease in itself [2]. RU-CC may be the diagnosis in ∼40% of patients referred to specialist cough clinics [8]. Careful consideration must be given to factors such as asthma, rhinosinusitis and reflux, but these are now regarded as contributory treatable traits rather than the causative factors for many patients [2].

Cough hypersensitivity syndrome

In light of the above observations, expert consensus has now come to consider cough reflex hypersensitivity as the underlying driver of chronic cough in a majority of cases, particularly in the context of RU-CC. The basic concept of cough hypersensitivity syndrome (CHS), supported by clinical and experimental evidence, describes cough that is triggered by low levels of stimuli, or by no measurable stimulus at all [9]. Noting similarities to chronic pain, neuropathic pathology has been proposed, and the corresponding terms hypertussia and allotussia have been coined for these phenomena, with laryngeal paraesthesia another key feature of chronic cough (figure 1) [10].

Mechanistic studies in chronic cough help explain how heightened cough reflex sensitivity (CRS) is related to abnormal peripheral and central neural pathways, and have guided successful development of novel treatments [10]. Compared with healthy controls, subjects with chronic cough exhibit a number of physiological differences. Tussive challenge testing with capsaicin, ATP, citric acid and distilled water demonstrate increased CRS and impaired cough suppression [11–13]. Functional brain magnetic resonance imaging studies with tussive stimuli reveal increased activity in cough activation centres, and decreased activity in cough suppression centres [14]. Peripheral airway biopsies demonstrate increased epithelial nerve branching and density, indicating a role in sensory nerve plasticity [15]. Furthermore, genetic neurodegenerative conditions associated with refractory chronic cough, such as caused by biallelic repeat expansions in the *RFC1* gene [16], have provided further evidence of neuropathic aetiology, and may be prevalent in up to 16% of RU-CC [16–18].

New treatments

Understanding of the neurophysiology of cough has progressed in tandem with novel treatments. The neuromodulator medications amitriptyline, gabapentin, pregabalin and morphine have been trialled with moderate success, although side-effects are common [19]. Specialist non-pharmacological interventions have proven efficacy, largely targeting behavioural components, and therefore presumably the central pathways of cough [20]. Novel antitussives targeting airway receptors, such as P2X3, effectively reduce cough frequency, appear safe, and are currently in various stages of clinical development or regulatory review [21].

Gefapixant is the first P2X3 receptor antagonist to successfully complete phase 3 trials and as of late 2023, has been approved for use in the European Union, Switzerland and Japan [3, 4]. Efficacy of the drug is consistent across age, gender, cough frequency and severity [22]. Although antagonism of P2X2/3

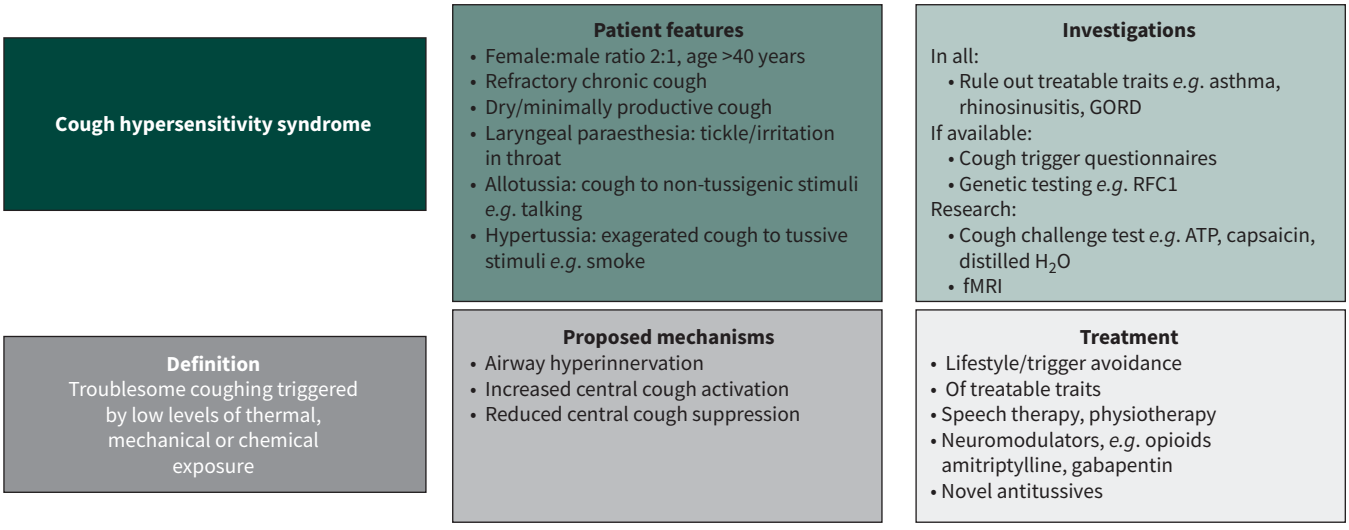

FIGURE 1 Cough hypersensitivity syndrome: definition, patient features, investigations, proposed mechanisms and treatment. GORD: gastro-oesophageal reflux disease; RFC1: replication factor C subunit 1 gene; fMRI: functional magnetic resonance imaging. Information from [2, 9, 14, 15, 33].

heterotrimer receptors also results in taste disturbance, side-effects of gefapixant are mostly mild in severity, reversible with discontinuation, and in general tolerable, leading to treatment discontinuation in 22.1%, compared with 5.7% with placebo at 52 weeks in the COUGH-2 trial [22]. In clinical practice, there will be a need for discussion about the trade-off between the benefits and side-effects of gefapixant with each patient. Meanwhile, other antagonists, currently in phase 3 trials, are more selective for the P2X3 receptor and are associated with less taste disturbance [23].

The concept of chronic cough as a neuropathic condition, treated with neuromodulators, is not new. To Thomas Willis (of circle of Willis fame) in 1667 the condition was a "convulsion" caused by "explosion of the nerves" [24]. In 1856, Edward Smith described chronic cough as a "disease in itself" due to "irritability of the nerves" which can be treated with "morphia" [25], 164 years before expert consensus in the ERS chronic cough guidelines concluded the same [2].

Looking ahead: further unmet needs

Despite recent advances, numerous challenges in chronic cough lie ahead. There is limited understanding of epidemiology, despite robust efforts [1]. Documented prevalence varies widely, from 2% in Africa to 18% in Oceania, likely relating to differences in the definition and reporting of chronic cough, but also to exposures including smoking, air pollution and obesity [1]. Observational data has provided greater understanding of patient characteristics from multiple cohorts; consistently two-thirds of those with chronic cough are female, the peak age at presentation is 60–69 years [26]. However, there are complex variations and phenotypes within chronic cough sufferers, necessitating more detailed evaluation.

Although substantial medical costs are reported from frequent healthcare visits and investigations, there is a paucity of data on the overall economic burden of chronic cough [27, 28]. Such knowledge is required to prompt provision of research funding and clinical resources. One problem for studies in this area was poor recording and classification in healthcare databases due to a lack of specific coding for chronic cough. This changed in 2022, as the World Health Organization International Classification of Diseases (10^{th} revision) introduced a code for chronic cough (R05.3), hopefully enabling chronic cough to be increasingly recognised and recorded as a discrete disease in its own right, rather than a symptom of another disorder [29].

Despite multiple objective and subjective options for measuring cough, diagnoses of chronic cough can be difficult. Tools to measure objective cough frequency, cough severity and cough-specific quality of life are used in clinical and research settings, and have been essential for progress [2, 22, 29]. However, there is currently no gold standard investigation for a diagnosis of (refractory or unexplained) chronic cough, and a limited availability of cough frequency monitoring or tussive challenge testing for general use. Moreover, these tests have uncertain utility in clinical practice with limited associations demonstrated between cough frequency and important patient-reported outcomes [29], and significant overlap between objective CRS in chronic cough and health [11]. Diagnosis of underlying causes of chronic cough, such as cough variant asthma or eosinophilic bronchitis, is often retrospective from response to treatment, rather than on objective testing. Better biomarkers that help diagnosis and predict treatment response are sorely needed [2].

The effect of placebo is a complicating factor for understanding chronic cough, frequently associated with substantial improvements in clinical end-points, including in large phase 3 trials [22]. This hampers demonstration of the efficacy of novel therapy and further dedicated investigation is required to understand this complex phenomenon and optimise clinical trial design [30].

Further exploration of the neuromechanisms of chronic cough is not simple. Despite recent advances [14, 15], the study of airway nerves and central pathways, particularly *in vivo*, is complicated and time-consuming. Novel, robust and (ideally) noninvasive techniques are needed.

Fortunately, there is plenty to look forward to in the field. NeuroCough, an ongoing European registry project in chronic cough, aims to provide sound epidemiological data, improve quality of care for patients, and guide future drug development [31]. Mechanistic studies investigating the role of central and peripheral neural pathways are ongoing. Furthermore, many novel antitussives are in development, the majority targeting refractory chronic cough and interstitial lung disease-associated cough. These include antagonists of the receptors neurokinin 1 (NK1), N-methyl-D-aspartate (NMDA), transient receptor potential vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1), sodium channel blockers, and agonists of TRP melastatin type 8 (TRPM8) and opioid receptors (Mu-antagonist/kappa-agonist) (clinicaltrials.gov) [21]. The prospect of an armoury of efficacious drugs at the clinician's disposal is exciting, as the diverse phenotypes of chronic cough may entail a tailored approach. Finally, increased awareness of chronic cough will hopefully lead to increased education, funding for research and trials, and improved patient care [28, 32].

Concluding thoughts

Is the end of chronic cough nigh? In a word, no. Our longstanding pursuit for improved diagnostics and effective treatments endures and, despite substantial advances, there is no cure foreseeable for now. However, far from succumbing to pessimism, the future looks bright. Chronic cough is rapidly gaining recognition as a unique entity, with each new study furthering understanding. Furthermore, novel, safe and effective therapies are tantalisingly close for our patients in need. Whilst the end of chronic cough is not imminent, the end is nigh to the antiquated chronic cough era, and we warmly welcome the future direction.

Key points

- Chronic cough is a common and impactful condition, now considered a disease in its own right, but currently with limited treatment options.
- Increased understanding of chronic cough neuropathophysiology coincides with the recent authorisation in the European Union of gefapixant, the first drug developed specifically for the condition.
- There remains much to learn and challenges to overcome before a cure for all chronic cough sufferers is possible.

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References

1 Song W-J, Chang Y-S, Faruqi S, *et al.* The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015; 45: 1479–1481.
2 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.
3 European Medicines Agency. Lyfnua. Date last accessed: 16 January 2024. Date last updated: 10 October 2023. www.ema.europa.eu/en/medicines/human/EPAR/lyfnua
4 Merck. Merck Provides U.S. and Japan Regulatory Update for Gefapixant. Date last accessed: 16 January 2024. Date last updated: 24 January 2022. www.merck.com/news/merck-provides-u-s-and-japan-regulatory-update-for-gefapixant/
5 Bynum H. Spitting blood: the history of tuberculosis. 1st Edn. Oxford, Oxford University Press, 2012.
6 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981; 123: 413–417.
7 Birring SS. Controversies in the evaluation and management of chronic cough. *Am J Respir Crit Care Med* 2011; 183: 708–715.
8 Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? *Chest* 2005; 127: 1710–1713.
9 Morice AH, Millqvist E, Belvisi MG, *et al.* Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014; 44: 1132–1148.
10 Chung KF, McGarvey L, Mazzone SS. Chronic cough as a neuropathic disorder. *Lancet Respir Med* 2013; 1: 414–422.
11 Koskela HO, Nurmi HM, Birring SS. Utility of cough provocation tests in chronic cough and respiratory diseases: a comprehensive review and introduction of new reference ranges for the capsaicin test. *Allergy Asthma Immunol Res* 2021; 13: 833–849.
12 Cho PSP, Fletcher HV, Turner RD, *et al.* Impaired cough suppression in chronic refractory cough. *Eur Respir J* 2019; 53: 1802203.
13 King J, Al-Sheklly B, Wingfield Digby J, *et al.* Refractory chronic cough patients are indiscriminately hyper-responsive to inhaled tussive irritants/agents. *Am J Respir Crit Care Med* 2022; 205: A2809.
14 Ando A, Smallwood D, McMahon M, *et al.* Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax* 2016; 71: 323–329.
15 Shapiro CO, Proskocil BJ, Oppegard LJ, *et al.* Airway sensory nerve density is increased in chronic cough. *Am J Respir Crit Care Med* 2021; 203: 348–355.
16 Turner RD, Hirons B, Cortese A, *et al.* Chronic cough as a genetic neurological disorder? Insights from cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). *Lung* 2023; 201: 511–519.

17 Guilleminault L, Chazelas P, Melloni B, *et al.* Repeat expansions of RFC1 in refractory chronic cough. *Chest* 2022; 163: 911–915.
18 Hirons B, Rhatigan K, Curro R, *et al.* RFC1 disorder; a genetic, neuropathic cause of chronic cough. *Thorax* 2023; 78: Suppl. 4, A241–A242.
19 Dicpinigaitis PV, Morice AH, Birring SS, *et al.* Antitussive drugs–past, present, and future. *Pharmacol Rev* 2014; 66: 468–512.
20 Birring SS, Floyd S, Reilly CC, *et al.* Physiotherapy and speech and language therapy intervention for chronic cough. *Pulm Pharmacol Ther* 2017; 47: 84–87.
21 Dicpinigaitis P. The current and emerging treatment landscape for chronic cough. *Am J Manag Care* 2022; 28: S159–S165.
22 McGarvey LP, Birring SS, Morice AH, *et al.* 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: 909–923.
23 Smith J, Mcgarvey L, Birring SS, *et al.* Safety and efficacy of BLU-5937 in the treatment of refractory chronic cough from the phase 2b soothe trial. *Am J Respir Crit Care Med* 2022; 205: A5778.
24 Eadie MJ. A pathology of the animal spirits - The clinical neurology of Thomas Willis (1621-1675) Part II - Disorders of intrinsically abnormal animal spirits. *J Clin Neurosci* 2003; 10: 146–157.
25 Smith E. On the efficacy of small doses of morphia (as opposed to the use of expectorants), in the treatment of hooping-cough, chronic bronchitis, and phthisis. *Edinb Med J* 1856; 1: 1001–1010.
26 Morice AH, Jakes AD, Faruqi S, *et al.* A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; 44: 1149–1155.
27 Cho PSP, Shearer J, Simpson A, *et al.* Healthcare utilization and costs in chronic cough. *Curr Med Res Opin* 2022; 38: 1251–1257.
28 McGarvey L, Morice AH, Martin A, *et al.* Burden of chronic cough in the UK: results from the 2018 National Health and Wellness Survey. *ERJ Open Res* 2023; 9: 00157-2023.
29 Turner RD, Birring SS. Measuring cough: what really matters? *J Thorac Dis* 2023; 15: 2288–2299.
30 Kaptchuk TJ, Hemond CC, Miller FG. Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ* 2020; 370: m1668.
31 McGarvey L, Dupont L, Birring SS, *et al.* New understanding in the treatment of cough (NEUROCOUGH) ERS Clinical Research Collaboration: improving care and treatment for patients with cough. *Eur Respir J* 2019; 53: 1900787.
32 European Lung Foundation. Chronic cough. Date last accessed: 16 January 2024. Date last updated: 16 August 2023. https://europeanlung.org/en/information-hub/lung-conditions/chronic-cough/
33 Vertigan AE, Gibson PG. Chronic refractory cough as a sensory neuropathy: evidence from a reinterpretation of cough triggers. *J Voice* 2011; 25: 596–601.