Invited Review-Symposium

Unravelling Vagal Hypersensitivity in Chronic Cough: A Distinct Disease

Mengru Zhang[1,2], Alyn H. Morice[2#]

Affiliations:

1. Department of Pulmonary and Critical Care Medicine, Tongji Hospital, School of Medicine, Tongji University, Shanghai.
2. Centre for Clinical Science, Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, UK.

#Correspondence: Alyn H. Morice, Centre for Clinical Science, Respiratory Medicine, Hull York Medical School, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire, HU16 5JQ, UK. E-mail: a.h.morice@hull.ac.uk

Running title: Vagal hypersensitivity in chronic cough

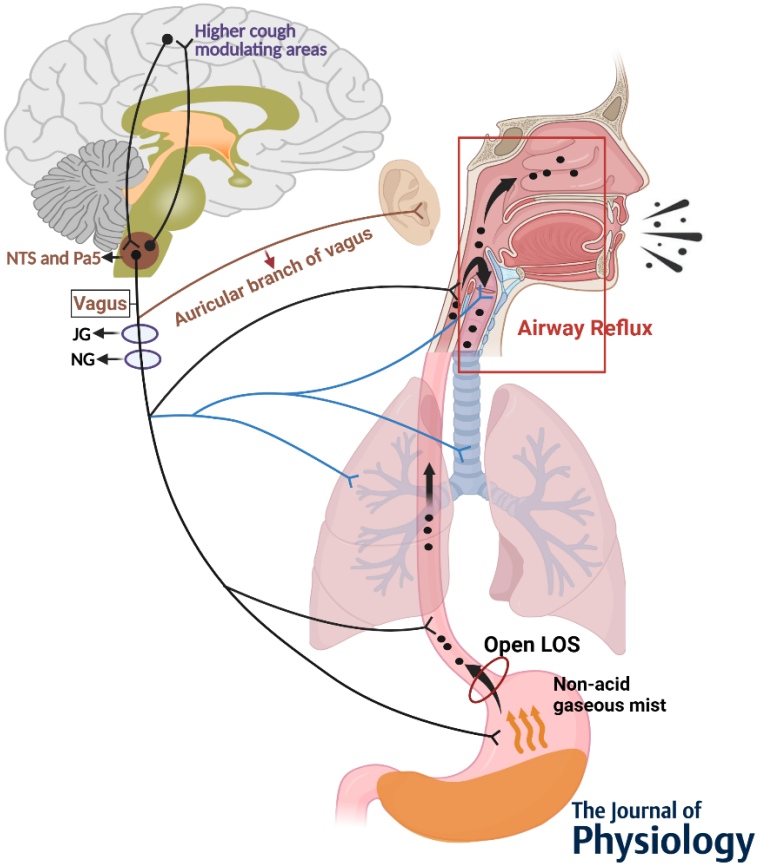
Author profile

Professor Alyn Morice (right) is the Head of Respiratory Medicine, Hull York Medical School, University of Hull in the United Kingdom. He specialises in the diagnosis and treatment of cough and runs the Hull Cough Clinic, the first UK Cough Clinic which he established in 1989 and which has become the largest centre within Europe with an international pattern of referral. He has led the European Respiratory Society and British Thoracic Society Taskforces on Cough. He also runs the Hull Respiratory Clinical Trials Unit specialising in the treatment of the airway diseases associated with cough.

Mengru Zhang (left) studied in University of Hull with Prof. Alyn Morice and have received her PhD in internal medicine at Tongji University. Her PhD thesis was focused on the underlying potential mechanisms of ATP-P2X/P2Y in cough hypersensitivity and therapeutic options in treating refractory chronic cough, which involves studies in animals, cells, and clinical trials.

Abstract

Chronic cough (CC) is a common but poorly understood disease that leaves a negative impact on quality of life. For years, clinicians were trying to find the underlying diagnosis and using the existing disease models to describe the patients' illness. This makes the picture of CC confusing. Most patients with CC presented with hypersensitivity of the cough reflex, which is characterised by laryngeal paresthesia and an increased response to the tussive stimuli or innocuous stimulus that would not trigger coughing in healthy people. Recently, it has been proposed that CC is a unique disease characterised by vagal hypersensitivity that projects to the central nervous system altering responsiveness. The evidence supports the hypothesis that CC is primarily a neurological disorder, consisting of different phenotypes.



Abstract figure legend Pattern diagram of airway reflux increasing vagal sensitivity.

Abbreviations ANR, Arnold nerve reflex; ATP, adenosine triphosphate; CC, chronic cough; CHS, cough hypersensitivity syndrome; CNS, central nervous system; GORD, gastroesophageal reflux disease; JG, jugular ganglia; LOS, lower oesophageal sphincter; NG, nodose ganglia; NK-1, neurokinin-1; NTS, nucleus tractus solitarius; Pa5, paratrigeminal nucleus; RCC, refractory chronic cough; SP, substance P; TRP, Transient Receptor Potential; UCC, unexplained chronic cough

Keywords Chronic cough; cough hypersensitivity syndrome; vagal hypersensitivity; airway reflux; oesophagus; dysmotility

1. Introduction

Since John Widdicombe first characterised Aδ-myelinated fibres mediated cough in the field of respiratory physiology in the 1950s, the science of cough has been gradually gaining traction, especially over the past two decades (Chung et al., 2013). Chronic cough (CC) in adults is generally defined as a cough lasting for at least eight weeks. It has been realized as a public health concern with high morbidity, and heavy healthcare and socioeconomic burden. The worldwide prevalence of the individuals reporting CC was found to be 10% (Song et al., 2015). Here we discuss the evidence that CC represents a unique disorder characterised by hypersensitivity of the vagus and its central projections.

Historically, CC was considered to be a symptom of other diseases and was divided into different categories such as eosinophilic bronchitis, cough variant asthma, atopic cough, upper airway cough syndrome, and gastroesophageal reflux disease (GORD/GERD). This classification was codified by international guidelines orientated to investigations and targeted therapy (Irwin et al., 2018; (Lai et al., 2018; Mukae et al., 2021). However, in a considerable proportion of patients, the cough remains unexplained after thorough assessments or lack of efficacy of aetiology targeted treatments. The terms unexplained chronic cough (UCC) and refractory chronic cough (RCC) were coined to characterise these individuals (Gibson et al., 2016; Visca et al., 2020; Chung et al., 2022).

The 2021 European Respiratory Society guidelines on CC adopted the different paradigm. CC was the disease, and the different presentations represent different phenotypes of this disease. This hypothesis arose from the observation that most patients reported cough triggered by low levels of thermal, chemical, or mechanical exposure, including cold air, perfumes, odours, and aerosols (Won et al., 2019). These external stimuli suggest hypersensitivity to otherwise innocuous provocation. Many patients also exhibited increased response to tussive stimuli (hypertussia) and laryngeal paresthesia (Sundar et al., 2021). Cough reflex hypersensitivity was seen as the root pathophysiological mechanism of CC, and termed Cough Hypersensitivity Syndrome (CHS) (Morice, Millqvist, et al., 2014). This concept is supported by the unique demographic profile of CC which predominantly occurs in postmenopausal females (Chamberlain et al., 2015). CC thus represents a disease of itself with different phenotypes depending on the type and location of the inflammation seen. The endotype of each phenotype may be different, for example, in asthmatic cough the eosinophilic inflammation is prominent and may increase hypersensitivity, but fundamentally CC is a neuropathic disorder (a structural or functional change in the vagus or its upstream pathways) with the cough hypersensitivity as its defining feature.

2. Mechanisms of CHS: vagus nerve and the brain in CC

The act of coughing involves complex neurobiological processes, including those within the peripheral nervous system, brainstem, and higher cerebral cortex, and can be under volitional and cognitive control (Mazzone, Farrell, 2019; Mazzone et al., 2022; Drake et al., 2023). There has been consensus that the excessive cough reflex sensitivity to external triggers may involve the enhanced response of the primary afferent nerves of the airways (the peripheral mechanism) coupled with abnormal associated central processing (the central mechanism) (Farrell, Mazzone, 2019).

2.1 Peripheral cough sensitization

The first demonstration of peripheral tussive stimulation was the use of citric acid to evoke the dose dependent cough response by Bickerman in 1954 (Bickerman, Barach, 1954). Subsequent inhalation studies have shown women have heightened cough reflex compared to men and that patients with CC have increased cough sensitivity (Song et al., 2014). This hypersensitivity is manifest in the whole of the distribution of the vagus nerve as has been demonstrated by the elegant study by Peter Dicpinigaitis where a positive Arnold nerve reflex (ANR) was elicited in 25% of adult patients with CC whereas only 2% of normal subjects coughed with stimulation of the external auditory meatus (Dicpinigaitis et al., 2018).

Arnold's nerve is a branch of the vagus which does not innervate any of structures commonly thought to evoke coughing, thus, indicating a pan vagal hypersensitivity. Indeed, a presumably central, global hypersensitivity, may occur as is exemplified by somatic trigger points in the peripheral nervous system (Lavorini et al., 2023).

A comprehensive review of the peripheral innervation of the vagus nerve is beyond the scope of this review (Mazzone, Farrell, 2019). Briefly, the respiratory tract is innervated by vagal afferent sensory neurons arising from the nodose and jugular ganglia which then project centrally to the brainstem. A number of polymodal nociceptors are present on the terminal projections of these neurons, including Transient Receptor Potential vanilloid 1 (TRPV1), TRP vanilloid 4 (TRPV4), and TRP ankyrin 1 (TRPA1). However, clinical trials with their antagonists have failed to relieve CC suggests a different mechanism underlies clinical CHS (European Medicines Agency, 2016; Belvisi et al., 2017; Morice, 2017; Ludbrook et al., 2019; Ludbrook et al., 2021).

A breakthrough in the understanding of CHS occurred with the demonstration in clinical studies of a dramatic reduction in CC by gefapixant, a P2X3 antagonist (Sykes, Zhang, et al., 2022). The efficacy of drugs of this class has been confirmed in other clinical studies with a variety of agents (Brister et al., 2023). The endogenous ligand for this receptor is adenosine triphosphate (ATP). Inhalation of ATP induces cough in man and is heightened in patients with CC (Fowles et al., 2017). It is suggested that epithelial damage causes the release of alarmins including ATP. Gefapixant blocks cough stimulated by inhalation of ATP and distilled water (an osmotic stimulus to ATP release), and not that evoked by capsaicin and citric acid, suggesting that peripheral hypersensitivity is largely mediated by ATP (Morice et al., 2019).

2.2 Central cough sensitization

Brain functional magnetic resonance imaging can visualise the metabolic activity and thus map the activation of the motor, sensory, and association networks in the central nervous system (CNS). Using this technique, Stuart Mazzone and his colleagues have mapped the central processing of the sensation precipitating coughing known as "urge-to-cough". They found multiple activations within the insula cortex, anterior midcingulate cortex, primary sensory cortex, orbitofrontal cortex, supplementary motor area, and cerebellum (Mazzone et al., 2007; Mazzone et al., 2009)[,]. The characteristic sex difference in the demographics of CC were shown to be associated with a greater activation of the somatosensory cortex in females (Morice, Jakes, et al., 2014). An inhibitory role in the regulation of the cough reflex; holding cough with a break on, was revealed by activation of the inferior frontal gyrus and supplementary motor cortex (Mazzone et al., 2011; Leech et al., 2013). In some patients with CHS, these areas had lower levels of activation, indicating dysfunction of a suppressive network in CC. The neural activity in the midbrain (nucleus cuneiformis and periaqueductal gray) was increased, similar to that seen in chronic pain, indicating a commonality of the two nociceptive pathways (Ando et al., 2016). The structural and functional alterations in the left frontal brain regions have been implicated in the psychological and social impact and disease duration (Namgung et al., 2022; Arinze et al., 2023).

3. The culprit of vagal hypersensitivity: the concept of airway reflux

Airway reflux is not GORD. Classical GORD, defined by the symptoms of heartburn and dyspepsia, and associated by gastroenterologists with oesophagitis is a peptic condition. It consists predominantly of reflux of acidic liquid, detected by oesophageal pH monitoring. In contrast, the non-acidic component of reflux is not detected using this technique.

Non-acid oesophageal and extraoesophageal reflux, variously termed laryngopharyngeal reflux, silent reflux and volume reflux and here referred to as "airway reflux", has proven difficult to quantify. It consists mainly of a non-acid gaseous mist, similar to a belch. This is a normal physiological phenomenon which minimises excessive gas from transiting into the lower gastrointestinal tract. The physiology of

oesophageal motility leading to airway reflux is mainly dependent on transient opening of the lower oesophageal sphincter (LOS), which may be detected by the oesophageal manometry (Sykes, Crooks, et al., 2022). We hypothesised that known precipitants of LOS opening maybe associated with coughing bouts. A validated questionnaire, the Hull airway reflux questionnaire (HARQ; available at https://www.issc.info) (Morice et al., 2011; (Zhang et al., 2020), was structured based on the physiology of LOS opening and the symptoms associated with the local deposition of airway reflux. Patients with rigorously defined CC scored on average 40/70 (upper limit of normal < 14) in the global clinical trials of gefapixant (COUGH-1 and COUGH-2) (Mcgarvey et al., 2022). Ninety percent of patients in an epidemiological study reported HARQ scores above 14, suggesting airway reflux and oesophageal dysmotility maybe major factors contributing to CHS (Van Den Berg et al., 2022).

The vagus nerve is intimately associated with the oesophagus. The vagal trunk lies on the oesophagus with the left trunk winding anteriorly and the right posteriorly to enter the oesophageal hiatus. It gives off branches to innervate the larynx (superior and recurrent laryngeal nerves) and the lungs (pulmonary plexus). Generalised vagal hypersensitivity may thus give rise to afferent sensation from a wide catchment area.

The existence of micro-aspiration in airway reflux has been successfully detected by reflux scintigraphy (*Figure 1*). In this study, 70% of patients were female and 75% had CC; 96% had demonstrable airway reflux with over half exhibiting pulmonary aspiration (Park et al., 2021). The location of the origin of vagal hypersensitivity is unknown whether it is primarily lung, larynx, or oesophagus, or more likely a combination is at present unclear and likely to differ in emphasis between individual patients.

Indeed, whether the primary stimulus for peripheral sensation is cellular damage, mechanical stress, or nociceptor stimulation is unclear since all three have been shown to release ATP and thus have potential for activating the P2X3 receptor. Although airway reflux may be a major contributor to this stimulus, it is unlikely to be the sole mechanism. Recently, we have undertaken a retrospective review of high-resolution manometry in 441 patients with unexplained respiratory symptoms (Sykes, Crooks, et al., 2022). Abnormal oesophageal motility was observed in two-thirds of patients with CC, and it is possible that dysmotility itself may be an additional direct cause of the urge to cough.

4. The clinical pharmacology of CC

When reflux was recognised as a potential cause for vagal hypersensitivity, proton pump inhibitors (PPIs) were trialled because of their beneficial effect in GORD. However, randomised controlled trials demonstrated no significant effect above placebo (Faruqi et al., 2011; Blake, Teague, 2013; Wang et al., 2020). Peptic symptoms were improved suggesting that acid does not play a significant role in CHS.

4.1 Centrally acting agents

4.1.1 Opiates

The first report of the beneficial effect of opiates in cough was by John Mudge in 1778 (Mudge, 1778). However, it was not until 2007 that a randomised placebo-controlled study demonstrated significant improvement in patients reported outcomes (Morice et al., 2007). Subsequent clinical experience has shown that whilst a third to a half of patients responded to low-dose slow-release morphine (5mg twice daily), the remainder had no discernible benefit. Unlike pain, there was no greater dose response above 10mg twice daily. The antitussive efficacy of opiates was further evidenced in a randomised placebo-controlled crossover study of patients who were previous found to be morphine responders. Five to 10mg of slow-release morphine taken twice daily reduced cough frequency by 71.8% over placebo (Al-Sheklly et al., 2017). We suggest that those patients who respond may do so through opiate receptors within the inhibitory cortical descending pathways.

Other opiates have been used in the treatment of CC and codeine is a frequently use because its regulatory status. However, codeine is 3-methylmorphine, and its metabolism by cytochrome P450 2D6 is polymorphic, producing variable morphine pharmacokinetics. Recently, the differentiation between opiate receptors mu and kappa in the antitussive efficacy has been shown in cough in CC in idiopathic pulmonary fibrosis. The selective kappa opioid agonist and mu opioid antagonist, nalbuphine, demonstrated an over 50% placebo adjusted efficacy in 24-hour cough counts suggesting a receptor specific antitussive activity (Molyneaux et al., 2022; Maher et al., 2023).

4.1.2 Neuromodulators

"Neuromodulators" such as gabapentin (a γ-aminobutyric acid analogue), pregabalin, amitriptyline, and baclofen (a γ-aminobutyric acid type B receptor agonist) are widely prescribed, particularly in the Americas, for the treatment of CC. There is however limited clinical trial evidence to support their use. A single parallel group randomised controlled trial in 62 patients demonstrated a change in cough counts and cough quality of life, but no change in cough sensitivity as demonstrated by capsaicin challenge (Ryan et al., 2012). Whether these findings translate into meaningful long term therapeutic response is unclear. Adverse events are common. Real-world evidence suggests a response rate of 55%, similar to that seen in the placebo arm of P2X3 antagonist studies (Mcgarvey et al., 2023; Zhang et al., 2023).

4.1.3 Neurokinin-1 (NK-1) receptor antagonists

In the first study demonstrating vagal hypersensitivity due to angiotensin-converting enzyme inhibitor therapy, it was hypothesised that the hypersensitivity was due to increase in the substance P (SP) through inhibition of its metabolism (Morice et al., 1987). Recently, orvepitant, a brain-penetrant neurokinin-1 (NK-1) antagonist, has been investigated in CC in an open-label phase 2 study (Smith et al., 2020). A 26% cough reduction with improved quality of life was seen. A subsequent multi-centre study confirmed significant quality of life improvement but failed to demonstrate reduction in cough counts possibly due to the insensitivity of the cough counting methodology (Smith et al., 2019). Another NK1 antagonist, aprepitant, also demonstrated antitussive activity (22.2% cough reduction over placebo) in patients with lung cancer in a small randomized controlled trial (Smith et al., 2021).

These studies suggest that SP may be an important neurotransmitter in vagal hypersensitivity although larger trials are required to define the clinical efficacy and the mechanism action.

4.2 Peripheral acting agents: P2X3 antagonists

P2X3 antagonists have demonstrated efficacy in patients with CC in large randomised controlled clinical trials. The archetypal compound, gefapixant (formerly called AF-219/MK-7264) 45mg twice daily reduced cough counts and improved quality of life in over two thirds of patients in COUGH-1 and COUGH-2 (Mcgarvey et al., 2022). P2X3 receptors have been demonstrated to be present on the afferent nerve terminals of several vagally innervated organ (Marucci et al., 2019) and has been suggested the primary action is to block binding of ATP released in the local milieu. Other P2X3 antagonist including camlipixant (BLU-5397) (Birring et al., 2022), filapixant (BAY-1902607) (Friedrich et al., 2023), sivopixant (S-600918) (Mcgarvey et al., 2023), and eliapixant (BAY-1817080) (Francke et al., 2023) have demonstrated a similar efficacy, suggesting that the ATP/P2X3 axis is an important mechanism in hypersensitivity, but it does not reveal the mechanism producing the generalized vagal hypersensitivity. Cough challenge agents such as capsaicin mediated though nociceptors rather than this axis are also hypersensitive in CC.

5. Conclusions

CC is a common but poorly recognised disease characterised by hypersensitivity of the vagus and its CNS projections. It has a unique demographic profile and a very characteristic clinical history, distinct from other respiratory disease. The history points to the oesophagus as a major source of the irritation causing

this hypersensitivity and a majority of patients suffering from CC have abnormalities in oesophageal motility. Therapeutic advances have shown that the ATP/P2X3 axis may regulate peripheral sensitivity in approximately two thirds of patients whereas opiate response is seen in approximately a third pointing to central modulation.

Competing interests

The authors declare no conflict of interest.

Author contributions

Mengru Zhang and Alyn Morice drafted the work and revised it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding Sources: None.

Acknowledgements

The authors thank Samuel James Morice for some language supports.

References

European Medicines Agency. (2016. Date last accessed: April 15, 2019). Clinical Trial Results: A Phase 2a, Multi-Centre, Randomised, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate Efficacy, Safety and Tolerability of Inhaled GRC 17536, Administered for 4 Weeks, in Patients with Refractory Chronic Cough. *EU Clinical Trials Registry* www.clinicaltrialsregister.eu/ctr-search/trial/2013-002728-17/results

Al-Sheklly, B., Mitchell, J., Issa, B., Badri, H., Satia, I., Collier, T., Sen, S., Webber Ford, J., Corfield, D., Smith, J. (2017). S35 Randomised control trial quantifying the efficacy of low dose morphine in a responder group of patients with refractory chronic cough. *Thorax* **72**, A24-A25. https://doi:10.1136/thoraxjnl-2017-210983.41

Ando, A., Smallwood, D., Mcmahon, M., Irving, L., Mazzone, S. B., Farrell, M. J. (2016). Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax* **71**, 323-329. https://doi:10.1136/thoraxjnl-2015-207425

Arinze, J., Vinke, E., Verhamme, K., De Ridder, M., Stricker, B., Ikram, M., Brusselle, G., Vernooij, M. (2023). Chronic Cough-Related Differences in Brain Morphometry in Adults: A Population-Based Study. *Chest* https://doi:10.1016/j.chest.2023.02.007

Belvisi, M. G., Birrell, M. A., Wortley, M. A., Maher, S. A., Satia, I., Badri, H., Holt, K., Round, P., Mcgarvey, L., Ford, J., Smith, J. A. (2017). XEN-D0501, a Novel Transient Receptor Potential Vanilloid 1 Antagonist, Does Not Reduce Cough in Patients with Refractory Cough. *Am J Respir Crit Care Med* **196**, 1255-1263. https://doi.org/10.1164/rccm.201704-0769OC

Bickerman, H. A. and Barach, A. L. (1954). The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents. *Am J Med Sci* **228**, 156-163. https://doi:10.1097/00000441-195408000-00005

Birring, S. S., Smith, J. A., Mcgarvey, L., Morice, A. H., Goldsobel, A., Lanouette, S., Yang, R., Levengood, A., Garin, M., Bonuccelli, C. M. (2022). Efficacy in SOOTHE, A Phase 2b Trial of BLU-5937 In Refractory Chronic Cough, Was Not Dependant of Taste Disturbance Adverse Events. *Eur Respir J* **60**, 807. https://doi:10.1183/13993003.congress-2022.807

Blake, K. and Teague, W. G. (2013). Gastroesophageal reflux disease and childhood asthma. *Curr Opin Pulm Med* **19**, 24-29. https://doi:10.1097/MCP.0b013e32835b582b

Brister, D., Wahab, M., Rashad, M., Diab, N., Kolb, M., Satia, I. (2023). Emerging drugs in the treatment of chronic cough. *Expert Opin Emerg Drugs* **28**, 67-77. https://doi:10.1080/14728214.2023.2203912

Chamberlain, S. A., Garrod, R., Douiri, A., Masefield, S., Powell, P., Bücher, C., Pandyan, A., Morice, A. H., Birring, S. S. (2015). The impact of chronic cough: a cross-sectional European survey. *Lung* **193**, 401-408. https://doi:10.1007/s00408-015-9701-2

Chung, K. F., Mcgarvey, L., Song, W. J., Chang, A. B., Lai, K., Canning, B. J., Birring, S. S., Smith, J. A., Mazzone, S. B. (2022). Cough hypersensitivity and chronic cough. *Nat Rev Dis Primers* **8**, 45. https://doi:10.1038/s41572-022-00370-w

Chung, K. F., Nadel, J. A. and Fontana, G. (2013). John Widdicombe's contribution to respiratory physiology and cough: reminiscences. *Cough* **9**, 6. https://doi:10.1186/1745-9974-9-6

Dicpinigaitis, P. V., Kantar, A., Enilari, O., Paravati, F. (2018). Prevalence of Arnold Nerve Reflex in Adults and Children With Chronic Cough. *Chest* **153**, 675-679. https://doi:10.1016/j.chest.2017.11.019

Drake, M. G., Mcgarvey, L. P. and Morice, A. H. (2023). From bench to bedside: The role of cough hypersensitivity in chronic cough. *Clin Transl Med* **13**, e1343. https://doi:10.1002/ctm2.1343

Farrell, M. J. and Mazzone, S. B. (2019). Are neural pathways processing airway inputs sensitized in patients with cough hypersensitivity? *Pulm Pharmacol Ther* **57**, 101806. https://doi.org/10.1016/j.pupt.2019.101806

Faruqi, S., Molyneux, I., Fathi, H., Wright, C., Thompson, R., Morice, A. (2011). Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. *Respirology (Carlton, Vic)* **16**, 1150-1156. http://doi.org/10.1111/j.1440-1843.2011.02014.x

Fowles, H. E., Rowland, T., Wright, C., Morice, A. (2017). Tussive challenge with ATP and AMP: does it reveal cough hypersensitivity? *Eur Respir J* **49**, 1601452. https://doi.org/10.1183/13993003.01452-2016

Francke, K., Chattopadhyay, N., Klein, S., Rottmann, A., Krickau, D., Van De Wetering, J., Friedrich, C. (2023). Preclinical and Clinical Pharmacokinetics and Bioavailability in Healthy Volunteers of a Novel Formulation of the Selective P2X3 Receptor Antagonist Eliapixant. *Eur J Drug Metab Pharmacokinet* **48**, 75-87. https://doi:10.1007/s13318-022-00805-5

Friedrich, C., Francke, K., Birring, S. S., Van Den Berg, J. W. K., Marsden, P. A., Mcgarvey, L., Turner, A. M., Wielders, P., Gashaw, I., Klein, S., Morice, A. H. (2023). The P2X3 receptor antagonist filapixant in patients with refractory chronic cough: a randomized controlled trial. *Respir Res* **24**, 109. https://doi:10.1186/s12931-023-02384-8

Gibson, P., Wang, G., Mcgarvey, L., Vertigan, A. E., Altman, K. W., Birring, S. S., Panel, C. E. C. (2016). Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. *Chest* **149**, 27-44. https://doi.org/10.1378/chest.15-1496
Irwin, R. S., French, C. L., Chang, A. B., Altman, K. W., Panel, C. E. C. (2018). Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. *Chest* **153**, 196-209. https://doi:10.1016/j.chest.2017.10.016
Lai, K., Shen, H., Zhou, X., Qiu, Z., Cai, S., Huang, K., Wang, Q., Wang, C., Lin, J., Hao, C., Kong, L., Zhang, S., Chen, Y., Luo, W., Jiang, M., Xie, J., Zhong, N. (2018). Clinical Practice Guidelines for Diagnosis and Management of Cough-Chinese Thoracic Society (CTS) Asthma Consortium. *J Thorac Dis* **10**, 6314-6351. https://doi:10.21037/jtd.2018.09.153
Lavorini, F., Bernacchi, G., Fumagalli, C., Noale, M., Maggi, S., Mutolo, D., Cinelli, E., Fontana, G. A. (2023). Somatically evoked cough responses help to identify patients with difficult-to-treat chronic cough: a six-month observational cohort study. *EClinicalMedicine* **57**, 101869. https://doi:10.1016/j.eclinm.2023.101869
Leech, J., Mazzone, S. B. and Farrell, M. J. (2013). Brain activity associated with placebo suppression of the urge-to-cough in humans. *Am J Respir Crit Care Med* **188**, 1069-1075. https://doi:10.1164/rccm.201306-1079OC
Ludbrook, V. J., Hanrott, K. E., Kreindler, J. L., Marks-Konczalik, J. E., Bird, N. P., Hewens, D. A., Beerahee, M., Behm, D. J., Morice, A., Mcgarvey, L., Parker, S. M., Birring, S. S., Smith, J. (2021). Adaptive study design to assess effect of TRPV4 inhibition in patients with chronic cough. *ERJ Open Res* **7**, 00269-02021. https://doi.org/10.1183/23120541.00269-2021
Ludbrook, V. J., Hanrott, K. E., Marks-Konczalik, J., Kreindler, J. L., Bird, N. P., Hewens, D., Beerahee, M., Behm, D. J., Morice, A., Mcgarvey, L., Et Al. (2019). A placebo-controlled, double-blind, randomised, crossover study to assess the efficacy, safety and tolerability of TRPV4 inhibitor GSK2798745 in participants with chronic cough. *Thorax* **74**, A18-. https://doi:10.1136/thorax-2019-BTSabstracts2019.33
Maher, T. M., Avram, C., Bortey, E., Hart, S. P., Hirani, N., Molyneux, P. L., Porter, J. C., Smith, J. A., Sciascia, T. (2023). Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis. *NEJM Evidence* **2**, EVIDoa2300083. https://doi:10.1056/EVIDoa2300083
Marucci, G., Dal Ben, D., Buccioni, M., Marti Navia, A., Spinaci, A., Volpini, R., Lambertucci, C. (2019). Update on novel purinergic P2X3 and P2X2/3 receptor antagonists and their potential therapeutic applications. *Expert Opin Ther Pat* **29**, 943-963. https://doi:10.1080/13543776.2019.1693542
Mazzone, S., Satia, I., Mcgarvey, L., Song, W., Chung, K. (2022). Chronic cough and cough hypersensitivity: from mechanistic insights to novel antitussives. *The Lancet Respiratory medicine* **10**, 1113-1115. https://doi:10.1016/s2213-2600(22)00404-0
Mazzone, S. B., Cole, L. J., Ando, A., Egan, G. F., Farrell, M. J. (2011). Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci* **31**, 2948-2958. https://doi:10.1523/JNEUROSCI.4597-10.2011
Mazzone, S. B. and Farrell, M. J. (2019). Heterogeneity of cough neurobiology: Clinical implications. *Pulm Pharmacol Ther* **55**, 62-66. https://doi.org/10.1016/j.pupt.2019.02.002
Mazzone, S. B., Mcgovern, A. E., Koo, K., Farrell, M. J. (2009). Mapping supramedullary pathways involved in cough using functional brain imaging: Comparison with pain. *Pulm Pharmacol Ther* **22**, 90-96. https://doi:10.1016/j.pupt.2008.08.003
Mazzone, S. B., Mclennan, L., Mcgovern, A. E., Egan, G. F., Farrell, M. J. (2007). Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med* **176**, 327-332. https://doi:10.1164/rccm.200612-1856OC
Mcgarvey, L., Smith, J. A., Morice, A., Birring, S. S., Chung, K. F., Dicpinigaitis, P. V., Niimi, A., Benninger, M. S., Sher, M., Matsunaga, Y., Miyazaki, S., Machida, M., Ishihara, H., Mahmood, A., Gomez, J. C. (2023). A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 2b Trial of P2X3 Receptor Antagonist Sivopixant for Refractory or Unexplained Chronic Cough. *Lung* **201**, 25-35. https://doi:10.1007/s00408-022-00592-5
Mcgarvey, L. P., Birring, S. S., Morice, A. H., Dicpinigaitis, P. V., Pavord, I. D., Schelfhout, J., Nguyen, A. M., Li, Q., Tzontcheva, A., Iskold, B., Green, S. A., Rosa, C. L., Muccino, D. R., Smith, J. A. (2022). 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. *The Lancet* **399**, 909-923. https://doi.org/10.1016/S0140-6736(21)02348-5
Molyneaux, P., Forbes, W., Bortey, E., Sciascia, T., Maher, T. (2022). S15 Efficacy of oral nalbuphine extended release for the treatment of chronic cough in idiopathic pulmonary fibrosis: analysis of a phase 2 study. *Thorax* **77**, A13-A14. https://doi:10.1136/thorax-2022-BTSabstracts.21
Morice, A., Jakes, A., Faruqi, S., Birring, S., Mcgarvey, L., Canning, B., Smith, J., Parker, S., Chung, K., Lai, K., Pavord, I., Van Den Berg, J., Song, W., Millqvist, E., Farrell, M., Mazzone, S., Dicpinigaitis, P. (2014). A worldwide survey of

chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* **44**, 1149-1155. https://doi:10.1183/09031936.00217813
Morice, A., Millqvist, E., Belvisi, M., Bieksiene, K., Birring, S., Chung, K., Dal Negro, R., Dicpinigaitis, P., Kantar, A., Mcgarvey, L., Pacheco, A., Sakalauskas, R., Smith, J. (2014). Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* **44**, 1132-1148. https://doi:10.1183/09031936.00218613
Morice, A. H. (2017). TRPA1 receptors in chronic cough. *Pulm Pharmacol Ther* **47**, 42-44. https://doi.org/10.1016/j.pupt.2017.05.004
Morice, A. H., Faruqi, S., Wright, C. E., Thompson, R., Bland, J. M. (2011). Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* **189**, 73-79. https://doi.org/10.1007/s00408-010-9272-1
Morice, A. H., Kitt, M. M., Ford, A. P., Tershakovec, A. M., Wu, W. C., Brindle, K., Thompson, R., Thackray-Nocera, S., Wright, C. (2019). The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. *Eur Respir J* **54**, https://doi.org/10.1183/13993003.00439-2019
Morice, A. H., Lowry, R., Brown, M. J., Higenbottam, T. (1987). Angiotensin-converting enzyme and the cough reflex. *Lancet* **2**, 1116-1118. https://doi:10.1016/s0140-6736(87)91547-9
Morice, A. H., Menon, M. S., Mulrennan, S. A., Everett, C. F., Wright, C., Jackson, J., Thompson, R. (2007). Opiate therapy in chronic cough. *Am J Respir Crit Care Med* **175**, 312-315. https://doi.org/10.1164/rccm.200607-892OC
Mudge, J. *A radical and expeditious cure for a recent catarrhous cough*. London: printed by E. Allen; and sold by J. Walter; B. Thorn, at Exeter; and M. Haydon, at Plymouth, 1778.
Mukae, H., Kaneko, T., Obase, Y., Shinkai, M., Katsunuma, T., Takeyama, K., Terada, J., Niimi, A., Matsuse, H., Yatera, K., Yamamoto, Y., Azuma, A., Arakawa, H., Iwanaga, T., Ogawa, H., Kurahashi, K., Gon, Y., Sakamoto, H., Shibata, Y., Tamada, T., Nishioka, Y., Haranaga, S., Fujieda, S., Miyashita, N., Mochizuki, H., Yokoyama, A., Yoshihara, S., Tamaoki, J. (2021). The Japanese respiratory society guidelines for the management of cough and sputum (digest edition). *Respir Investig* https://doi:10.1016/j.resinv.2021.01.007
Namgung, E., Song, W., Kim, Y., An, J., Cho, Y., Kang, D. (2022). Structural and Functional Correlates of Higher Cortical Brain Regions in Chronic Refractory Cough. *Chest* **162**, 851-860. https://doi:10.1016/j.chest.2022.04.141
Park, J. S., Burton, L., Van Der Wall, H., Falk, G. L. (2021). Modified Reflux Scintigraphy Detects Pulmonary Microaspiration in Severe Gastro-Esophageal and Laryngopharyngeal Reflux Disease. *Lung* **199**, 139-145. https://doi:10.1007/s00408-021-00432-y
Ryan, N. M., Birring, S. S. and Gibson, P. G. (2012). Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *The Lancet* **380**, 1583-1589. https://doi:10.1016/s0140-6736(12)60776-4
Smith, J., Allman, D., Badri, H., Miller, R., Morris, J., Satia, I., Wood, A., M, K. T. (2020). The Neurokinin-1 Receptor Antagonist Orvepitant Is a Novel Antitussive Therapy for Chronic Refractory Cough: Results From a Phase 2 Pilot Study (VOLCANO-1). *Chest* **157**, 111-118. https://doi:10.1016/j.chest.2019.08.001
Smith, J., S, Ballantyne, E., Kerr, M., Mcgarvey, L., Morice, A., Sher, M., Trower, M., Pawsey, S. (2019). Late Breaking Abstract - The neurokinin-1 receptor antagonist orvepitant improves chronic cough symptoms: results from a Phase 2b trial. *Eur Respir J* **54**, PA600. https://doi:10.1183/13993003.congress-2019.PA600
Smith, J. A., Harle, A., Dockry, R., Holt, K., Russell, P., Molassiotis, A., Yorke, J., Robinson, R., Birrell, M. A., Belvisi, M. G., Blackhall, F. (2021). Aprepitant for Cough in Lung Cancer. A Randomized Placebo-controlled Trial and Mechanistic Insights. *Am J Respir Crit Care Med* **203**, 737-745. https://doi:10.1164/rccm.202006-2359OC
Song, W., Chang, Y., Faruqi, S., Kim, J., Kang, M., Kim, S., Jo, E., Kim, M., Plevkova, J., Park, H., Cho, S., Morice, A. (2015). The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* **45**, 1479-1481. https://doi.org/10.1183/09031936.00218714
Song, W. J., Kim, J. Y., Jo, E. J., Lee, S. E., Kim, M. H., Yang, M. S., Kang, H. R., Park, H. W., Chang, Y. S., Min, K. U., Cho, S. H. (2014). Capsaicin cough sensitivity is related to the older female predominant feature in chronic cough patients. *Allergy Asthma Immunol Res* **6**, 401-408. https://doi:10.4168/aair.2014.6.5.401
Sundar, K. M., Stark, A. C., Hu, N., Barkmeier-Kraemer, J. (2021). Is laryngeal hypersensitivity the basis of unexplained or refractory chronic cough? *ERJ Open Res* **7**, 00793-2020. https://doi:10.1183/23120541.00793-2020
Sykes, D. L., Crooks, M. G., Hart, S. P., Jackson, W., Gallagher, J., Morice, A. H. (2022). Investigating the diagnostic utility of high-resolution oesophageal manometry in patients with refractory respiratory symptoms. *Respir Med* **202**, 106985. http://doi.org/10.1016/j.rmed.2022.106985
Sykes, D. L., Zhang, M. and Morice, A. H. (2022). Treatment of chronic cough: P2X3 receptor antagonists and beyond. *Pharmacol Ther* **237**, 108166. https://doi.org/10.1016/j.pharmthera.2022.108166
Van Den Berg, J. W. K., Baxter, C. A., Edens, M. A., Patberg, K. W., Van Der Velden, H., Weijerse, A., Salomonsson, S. (2022). The demographics, clinical characteristics and quality of life of patients with chronic cough from the Isala Cough Clinic in the Netherlands. *ERJ Open Res* **8**, https://doi:10.1183/23120541.00232-2022
Visca, D., Beghè, B., Fabbri, L. M., Papi, A., Spanevello, A. (2020). Management of chronic refractory cough in adults. *Eur J Intern Med* https://doi.org/10.1016/j.ejim.2020.09.008

Wang, Y. T., Tsai, M. C., Wang, Y. H., Wei, J. C. (2020). Association Between Proton Pump Inhibitors and Asthma: A Population-Based Cohort Study. *Front Pharmacol* **11**, 607. https://doi:10.3389/fphar.2020.00607
Won, H. K., Kang, S. Y., Kang, Y., An, J., Lee, J. H., Lee, S. M., Kwon, J. W., Kim, M. H., Jo, E. J., Lee, S. E., Kim, S. H., Kim, S. H., Chang, Y. S., Kim, S. H., Lee, B. J., Cho, S. H., Birring, S. S., Song, W. J. (2019). Cough-Related Laryngeal Sensations and Triggers in Adults With Chronic Cough: Symptom Profile and Impact. *Allergy Asthma Immunol Res* **11**, 622-631. https://doi:10.4168/aair.2019.11.5.622
Zhang, M., Chen, Q., Dong, R., Yu, L., Ai, Z., Xu, X., Qiu, Z. (2020). Prediction of therapeutic efficacy of gabapentin by Hull Airway Reflux Questionnaire in chronic refractory cough. *Ther Adv Chronic Dis* **11**, 2040622320982463. https://doi.org/10.1177/2040622320982463
Zhang, M., Morice, A. H., Si, F., Zhang, L., Chen, Q., Wang, S., Zhu, Y., Xu, X., Yu, L., Qiu, Z. (2023). Antitussive efficacy of the current treatment protocol for refractory chronic cough: our real-world experience in a retrospective cohort study. *Ther Adv Respir Dis* **17**, 17534666231167716. https://doi:10.1177/17534666231167716

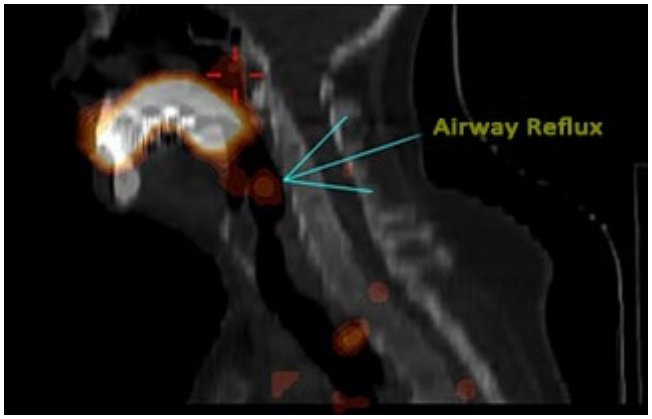


Figure 1. Sagittal view of combined SPECT-CT demonstrating contamination of pharynx with radioactive colloid two hours after ingestion. Modified from Figure 1 in reference (Park et al., 2021).