Chronic cough as a disease

Richard D. Turner [1,2] and Surinder S. Birring [3,4]

[1]Princess Alexandra Hospital, Brisbane, Australia. [2]School of Medicine and Dentistry, Griffith University, Southport, Australia. [3]King's College Hospital, London, UK. [4]Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK.

Corresponding author: Richard Turner (richard.turner@health.qld.gov.au)

Shareable abstract (@ERSpublications)
Chronic cough should be considered a disease. The condition has distinct characteristics and is more than a symptom of other disorders. Approaching chronic cough as a disease should sharpen focus, increase understanding and improve patient outcomes. https://bit.ly/4chgfl3

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Abstract

Chronic cough is a frequent reason for medical consultation and has significant impact on quality of life. Due to the limited effectiveness of currently available treatments, and delays in accessing care, patients are often inadequately managed. There remains an overreliance by clinicians on outdated management algorithms, addressing chronic cough only as symptom of other medical conditions, and advocating investigation and trials of treatment of diseases which are often not present. This may lead to unnecessary cost, frustration and potential harm. Newer clinical guidelines in essence consider chronic cough as a disease in itself, resulting from afferent neuronal hypersensitivity and central nervous system dysfunction. Secondary factors which aggravate chronic cough (smoking, asthma, gastro-oesophageal reflux, *etc.*) are better considered as treatable traits associated with the primary disease process rather than direct "causes" of cough.

Explicitly approaching chronic cough as a discrete entity is consistent with the way in which "diseases" are generally characterised, and has advantages. The patient should be better able to understand their condition, and may have better confidence in attempts at management. The clinician should have better focus and avoid unfruitful treatments and investigation. In general, considering chronic cough as a disease should help to raise the profile of the condition, improve organisation of health service pathways, increase attention for research, and further the development of new treatments.

Introduction

Chronic cough is common and detrimental to quality of life. The global prevalence of cough of >8 weeks' duration is estimated at up to one in 10 people [1], and in many individuals troublesome frequent coughing may persist >15 years or a lot longer, despite attempts at treatment [2]. Adverse impacts on daily activities, wellbeing and psychological health are common [3].

Cough can clearly be associated with many diseases. This includes those which are significantly life-limiting, such as cancer. However, once easily diagnosable conditions associated with cough have been excluded or treated, patients can be left bereft of management options for cough which nevertheless persists. Part of this might be due to trivialisation or lack of interest from health practitioners who may see chronic cough as unimportant, thought of as merely a symptom of other conditions. In a large pan-European community survey, only 30% of >1100 people with chronic cough reported that their doctor had "dealt with their cough thoroughly" [3]. In public health systems, referrals for chronic cough to respiratory clinics are often given the lowest priority behind other conditions [4], and many health practitioners have limited knowledge of evidence-based approaches to chronic cough [5, 6]. The wider population may also underappreciate the significant physical, psychological and social morbidity associated with chronic cough [7, 8].

Much of the current clinical approach to chronic cough remains heavily influenced by an "anatomic diagnostic" paradigm. First proposed in the early 1980s, this idea posits that the large majority of chronic cough of no immediately obvious cause can be explained and successfully managed as one of three

disease processes affecting the main sites involved in cough reflex pathways: rhinosinusitis (of the nasopharynx), asthma (lower airways) and reflux disease (oesophagus) [9]. "Trials of treatment" were advocated for chronic cough on the basis of a rigid protocol [10], involving medications for this trio of conditions, potentially sequentially. Such practice has become widespread [11], even in the absence of specific evidence for those conditions, which are overdiagnosed as "causes" of cough [12]. A belief that chronic cough must be caused by overlooked diseases also led to recommendations for extensive investigation [13], in practice often a long, costly and frustrating process, especially for the patient [14], and potentially involving a number of different medical specialists [15].

Although very attractive and popular, initial data in support of anatomic diagnostic protocols were only from single-centre case series [16]. A big problem in assessing responses to treatments in chronic cough is a substantial placebo effect, even when measuring cough objectively [17]. Further issues are regression to the mean, and natural resolution of cough with time [18].

The accumulation of clinical experience over the past four decades, especially from specialist cough clinics, has made it very clear that many patients (>40% in some series) suffer with persistent chronic cough despite excluding or effectively addressing potential associated medical conditions [19]. Furthermore, compared to the effects of placebo on nonspecific chronic cough, carefully conducted prospective randomised clinical trials have not shown clear benefits of frequently used "anatomically directed" treatments such as proton pump inhibitor medication [20] and inhaled corticosteroids [21]. Consequently, "empirical trials" of treatment are not advocated for chronic cough in newer evidence-based guidelines [22, 23], and nor is extensive investigation if clinical features pointing to specific coexisting medical conditions are lacking [22].

Therefore, it is increasingly apparent that chronic cough is very often not merely a symptom of other disease. Rather, chronic cough may in many respects be better considered a disease in its own right. What follows is an examination of how approaching chronic cough as disease might be both justified and helpful.

Current concepts of chronic cough

Although chronic cough is associated with many diagnoses, cough is by no means universal in patients with diseases commonly stated to be "causes" of cough. For example, chronic cough may affect only two-thirds of patients with uncontrolled asthma [24], and <10% of those with chronic rhinosinusitis may have cough not attributable to other factors [25]. An association with gastro-oesophageal reflux events and cough exists, but is inconsistent and complex [26]. Chronic cough is more common in middle-aged women than other groups [27], an observation difficult to explain if cough was only a manifestation of other disease such as these. Furthermore, as described, chronic cough frequently exists in the absence of any other discernible pathology.

The current paradigm for chronic cough, among researchers and clinicians with a specialist interest, is that of a hypersensitivity disorder with features of vagal nerve neuropathy and central nervous system dysfunction [28, 29] (figure 1). There is much supportive evidence for this idea, from pre-clinical, physiological, neurobiological and clinical data, and from therapeutic trial outcomes [29]. The proposed

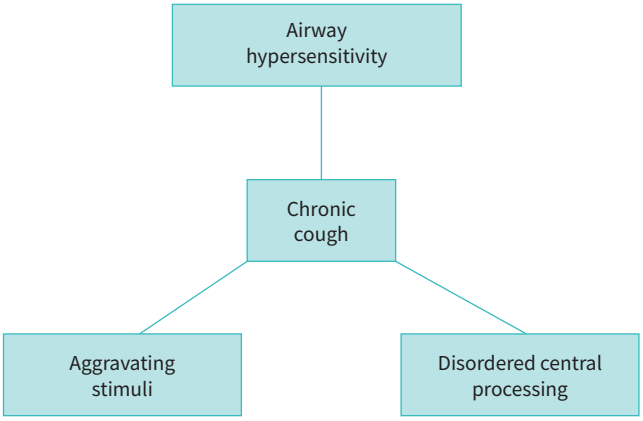

FIGURE 1 A model of chronic cough: three main components.

neuropathology has many similarities to chronic pain [30]. Clinically, patients often report features of hypersensitivity: coughing in response to low levels or no irritant exposure [31]. This can be demonstrated by measuring tussive responses to aerosolised solutions of diluted capsaicin and other compounds [32], during which a reduced ability to voluntarily supress cough may also be observed compared to healthy volunteers [33]. Increased airway nerve density changes have been documented in bronchial biopsy samples from individuals with chronic cough [34], and novel treatments targeting peripheral airway sensory receptors have proven efficacy in chronic cough, particularly antagonists of ATP-gated P2X3 ion channels [35, 36]. Functional magnetic resonance imaging has revealed cortical changes in those with chronic cough, including reduced activity in motor inhibitory pathways [37]. Chronic cough responds to centrally acting neuromodulator medications such as amitriptyline and gabapentin [38, 39].

A pathoneurophysiological basis for chronic cough is therefore beginning to emerge. In some cases, this may be underpinned by genetic variation, the best-studied example being cough associated with bi-allelic AAGGG repeat expansion sequences within the DNA polymerase-regulating gene *RFC1* [40]. This genetic variant is the cause of the neurological condition CANVAS (cerebellar ataxia with neuropathy and vestibular areflexia syndrome), although through mechanisms that are not yet clear [41]. Chronic cough is commonly associated with CANVAS, in the absence of other cough-provoking conditions, typically emerging years or decades before the classical neurological features of the disease [42, 43], and with clinical features of hypersensitivity as seen in chronic cough in other contexts [44].

Recent clinical guidelines for the management of chronic cough are very much more consistent with the idea of chronic cough as a disease rather than as a symptom of something else [22, 45]. In the absence of other symptoms, signs and risk factors for particular conditions associated with cough, investigation to seek evidence of other pathology should not be extensive but kept to a minimum; only chest radiography, spirometry, and measurement of fractional exhaled nitric oxide are probably essential in all, with further tests dependent on context [22]. An approach of seeking and managing treatable traits is now strongly advocated [46], in which relevant patient features and associated diagnoses (including smoking, angiotensin-converting enzyme (ACE) inhibitor medication, airways disease, gastro-oesophageal reflux, *etc*.) are generally considered aggravating factors for cough rather than “causes” in themselves [22, 45]. Treatments are then advocated and are of proven value directed at the putative disordered neuropathophysiological processes underlying cough hypersensitivity. Behavioural training and centrally acting neuromodulator medications target the cortical and subcortical pathways of chronic cough [39, 47–49], while novel medications are in various stages of development against afferent airway components of the cough reflex [36, 50, 51] (figure 1).

Cough as a disease

There is no generally agreed definition of disease: what may seem superficially a simple concept is difficult to pin down [52]. Disease may refer to a specific combination of signs and symptoms, a set of features associated with a disorder of organ function, or poor health associated with a specific cause [53]. The concept of disease also varies between health professionals, members of the public and health system funders or legislators [54]. Areas of difficulty and debate include where the line should be drawn between different “disease” entities, and what should be classed as more than “normal” population variation [55, 56].

Although the World Health Organization (WHO) publishes an International Classification of Diseases (ICD) [57], what actually constitutes disease is not explicitly stated. Furthermore, the document includes classification codes for other medical conditions, disorders, and clinical findings which most would not consider as “diseases”, such as instrumentally assisted childbirth, or gunshot injuries. In this context chronic cough has its own entry in the ICD-10 in the USA and some other jurisdictions, code R05.3, under the category “symptoms and signs involving the circulatory and respiratory systems” [58]. While this is useful for billing purposes and to give the condition some recognition as a discrete entity, chronic cough has not yet reached the official status of “disease”.

As described earlier, chronic cough is much more than a symptom. There is an understanding of underpinning pathophysiological processes, guidelines for chronic cough [22, 23, 45], specific treatments for the condition available and in development [51, 59], patient support information [60], groups for chronic cough (*e.g.* www.facebook.com/groups/ChronicCough/), and distinct referral pathways for patients within public health systems [4]. Cough can also be measured subjectively and objectively using methods which are now well established [61].

Approaching chronic cough as a discrete disease entity has many potential benefits. It should improve understanding for patients and their families, also helping patients in explaining the reason for coughing to

BOX 1 Chronic cough as a disease

Characteristics of chronic cough consistent with distinct disease status	Potential advantages of considering chronic cough as a disease
Definable (cough lasting >8 weeks)	Improved understanding for patients, and validation of their concerns
Existing model of pathophysiological basis (combination of aggravating stimuli, afferent hypersensitivity and central nervous system dysfunction)	Increased focus for clinicians, with improved awareness of chronic cough management guidelines
Measurable (patient-rated and objective, *e.g.* cough frequency monitoring, cough reflex testing)	Better organisation of clinical services for chronic cough
Treatable, with specific interventions of proven efficacy (*e.g.* gabapentin, gefapixant, cough suppression training)	Increased funding and efforts for research
	Increased general profile of chronic cough in the medical community

concerned onlookers [8]. A specific disease label for a condition can help patients validate their chronic illness and increase confidence in treatment [62]. Treating chronic cough as a disease should also improve focus for clinicians, and help avoid unhelpful, costly, time-consuming, and even potentially harmful investigations and treatment trials. In turn, the profile of chronic cough generally should be increased, helping in the organisation of health services for patients with the condition, and in directing funding for research (box 1).

There is an argument that new diseases may be often defined under the influence of those with vested interests, particularly where states which were previously considered healthy are now considered not so, and where treatments might now be used where they were not previously considered necessary [55]. This does not hold for chronic cough, in which patients clearly do not meet the WHO definition of health ("a state of complete physical, mental and social well-being…" [63]), and who are already often being treated, but with medications which have limited efficacy for their underlying condition [11]. New pharmacological treatments for chronic cough are also likely to be highly regulated, and funded by public health budgets only according to certain criteria [59]. For the reasons outlined above, the reasons for considering chronic cough as a discrete disease outweigh any disadvantages of not doing so.

Nomenclature of chronic cough

One reason in which the idea of chronic cough as a disease has been slow to catch on may be terminology. This is a difficult area, in which there is debate and where consensus is sometimes lacking. Chronic cough is that which lasts >8 weeks [10]. Chronic cough of no discernible cause is termed unexplained or idiopathic [13, 19]. Refractory chronic cough is then that which may or may not be associated with another condition (such as asthma), but which persists despite adequately addressing associated pathology [64]. Cough hypersensitivity syndrome applies to the pathophysiological processes which are thought to underlie chronic cough in a large proportion of cases [28], referred to by some as a neuropathic cough [64]. These terms are sometimes used interchangeably, but may convey slightly different meanings, and lead to confusion [65].

The authors of the recent British Thoracic Society clinical statement on chronic cough suggest a clear workable solution to this semantic problem. They suggest using the general term refractory chronic cough to apply to all those patients in which cough has persisted >8 weeks and treatable traits have been adequately addressed [22]. Following clinical assessment the term (refractory) chronic cough can then be followed by "associated with" or "with features of" ACE inhibitor use, asthma, obstructive sleep apnoea, *etc.*, or refractory chronic cough with no treatable traits [22].

In our opinion, the term chronic cough is already familiar, and would apply to the overarching "disease", within which cough hypersensivity, refractory chronic cough and other terms have more specific meanings, some applying to particular cough phenotypes [66].

Conclusion

Thanks to increased clinical and research interest, much has changed in the understanding of and the approach to chronic cough over the past 20 years, culminating not least in the first novel drugs developed

and approved specifically for chronic cough, and clinical guidelines for management which are based on more evidence than ever before [67]. Despite this, many patients remain without effective treatment, even if recommended management approaches have been followed (which often is not the case). One simple step towards further advances for patients with chronic cough is the wider recognition of the condition as a discrete disease entity.

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