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Cough Hypersensitivity and Chronic Cough

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Abstract

Chronic cough is globally prevalent across all age groups. It is challenging to treat because many pulmonary and extrapulmonary conditions can present with chronic cough, and cough can also be present without any identifiable underlying cause or be refractory to therapies that improve associated conditions. Most patients with chronic cough display cough hypersensitivity, characterized by a state of increased neural responsivity to a range of stimuli impacting the airways and lungs and extending to other tissues innervated by common nerve supplies. Cough hypersensitivity presents clinically as excessive coughing often in response to relatively innocuous stimuli, causing significant psychophysical morbidities and impacting on patient quality of life. The understanding of the mechanisms that contribute to cough hypersensitivity and excessive coughing in different patient populations and across the lifespan is rapidly advancing. This has contributed to the development of new therapeutic approaches in the clinic and in clinical trials of chronic cough in adults. Due to the differences in the pathological processes leading to development and maintenance of chronic cough, the organs involved and potential individual patient factors, chronic cough management is progressing towards a personalized approach and in the future, novel ways to endotype cough patients may prove valuable in management.

[H1] Introduction

Cough is among the most common symptoms presenting to primary care and a chief complaint for patients seeking medical attention in respiratory or allergy specialist clinics[7,8]. Widely accepted clinical guidelines have adopted the definition of chronic cough as a cough persisting for >8 weeks in adults and >4 weeks in children[2,4,9]. However, many epidemiological studies define chronic cough as lasting >3 months[10]. In each instance the definition is guided by expert opinion as definitive clinical criteria to distinguish acute cough from chronic cough are lacking. In practice, chronic cough is often a long lasting and burdensome condition, persisting for several years and sometimes decades for a significant number of patients, despite exhaustive medical intervention[11-13]. Many pulmonary and some extrapulmonary diseases and disorders can present with chronic cough, making diagnosis and treatment challenging. In up to 40% of adults with chronic cough referred for specialist evaluation, either no cause is identified ('unexplained chronic cough') or cough persists despite optimal treatment for conditions associated with chronic cough ('refractory chronic cough')[5].

There is broad consensus that chronic cough in adults, regardless of the etiology, reflects a hypersensitivity condition, which is characterised by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure[14]. The considerable patient burden often associated with a chronic cough that persists has led to an appreciation of *Cough Hypersensitivity* as a distinct clinical entity in adults. In addition, the recent efforts that have been dedicated to understanding the associated and underlying processes that might lead to this hypersensitivity have revealed distinct mechanisms involving both peripheral and central neural pathways. Such distinctive mechanisms have motivated recent advances in cough suppressant (anti-tussive) drug discovery[15]. The etiology of chronic cough and its management in children differ from those in adults and the relevance of cough hypersensitivity as an underpinning mechanism in children remains unclear, with the need for further exploration.

This primer discusses the global prevalence and mechanisms of cough, with a focus on the most common causes of cough hypersensitivity. It will overview the current state-of-the-art recommendations for cough diagnosis and management and present a viewpoint of recent advances in cough hypersensitivity and chronic cough which may soon have an impact on treatment.

[H1] Epidemiology

Chronic cough is a significant global problem, affecting about 10% of adults in various general populations[16]. Its published prevalence is higher in Europe, America, and Australia (10-20%) than Asia (<5%). The regional difference in prevalence has been emphasised in a meta-analysis of 29 cross-sectional studies conducted between 2000 and 2020 using specific disease definitions and random sampling methodology (Figure 1 and Supplementary Table 1). In a Copenhagen general population, the prevalence of chronic cough was 4% overall and 3% in never smokers, 4% in former smokers, and 8% in current smokers[17], while a meta-analysis showed that the prevalence of chronic cough was 6.22% (95% CI 5.03-7.41%) in adults in China[18]. The incidence of chronic cough range between 1.16 to 5.70 per 100 person-years in population-based studies of adults aged ≥45 years in Belgium and Canada[19,20]. However, there are no data estimated on a global or continental scale. Longitudinal epidemiology of chronic cough and cough hypersensitivity remains largely unknown, but cough may persist despite treatments for longer than 5 to 15 years in adult patients with chronic cough[12,13,21]. Certain patient traits, such as comorbid obesity, reflux disease, or genetic background, were associated with longer disease duration, but warrant further investigation[13,21].

The prevalence of chronic cough in children is not as clearly defined as in adults, and dependent on the method of data collection, the definition of chronic cough, the setting (e.g., high vs low-income country) and the age of children (Table 1). Overall, the prevalence ranges from 1.1% to 21.9%[22,23]. This wide variation in prevalence likely relates to the factors above. There is little data on the incidence of chronic cough following an acute respiratory infection; one study[24] reported that 171 of the 839 children (20.4%, 95% CI 17.7 to 23.1) recruited from the emergency department of a specialist children's hospital had chronic cough (>4 weeks) but 63 of these children already had chronic cough at presentation. Thus, the incidence is likely 108/839 (12.9%). Of the children with chronic cough who were reviewed by paediatric pulmonologists (n=117), a new and serious chronic lung disease was diagnosed in 30.8% and a further 47.0% had protracted bacterial bronchitis[24].

[H2] Risk factors

In individuals, a wide variety of environmental and host factors, such as respiratory infection, air pollutant, occupational irritants, allergens, eosinophils, or refluxate, can sensitize and trigger cough and are potential risk factors of chronic cough[25,26]. Biological traits, such as age or sex hormonal status, also interact with these triggers in developing chronic cough. At population level, a

systematic review of population-based studies found that persistent smoking, asthma, allergic rhinitis, and lower socioeconomic status were consistently associated with chronic cough[27]. Neurobiological susceptibility or risk factors such as chronic pain and pruritus were suggested in individual studies[28,29]. However, current definition of chronic cough used in population-based studies is simply based on cough duration and does not well differentiate protective cough responses from hypersensitivity and does not represent the key nature defining cough as the disease, such as the impact, severity, and hypersensitivity, and thus the epidemiological research definition should be refined for elucidating the risk factors[10].

[H3] Patient factors

Age and sex are two major factors that underlie the burden and prevalence of chronic cough, although we are yet to understand how cough hypersensitivity relates to this epidemiology. In a survey of 10,032 patients presenting with chronic cough to specialist clinics in 6 countries, two-thirds of the patients were females and the most common decade for presentation was 60-69 years[30], a relationship that is also seen in general adult population studies of chronic cough prevalence[17,31,32] (but not in children[33]). Greater impact of chronic cough in older females may explain the distinct profile, as they have more frequent complications such as stress urinary incontinence[34]. Another possible explanation for the increased prevalence of chronic cough in females is the observation that the cough reflex in adult females is more sensitive than in adult males, as reported in inhalation capsaicin cough reflex sensitivity tests[35]. Similarly, there is a greater activation of the somatosensory brain cortex in adult females in response to capsaicin inhalation than in males[30]. Notably, however, sex differences in capsaicin cough reflex sensitivity are not observed during prepubertal ages but are observed after puberty and persist throughout adulthood[36,37], perhaps suggesting that mechanisms predisposing to a hypersensitive state are not fully at play in children. In support of this, the prevalence of Arnold's nerve cough reflex (evoked by mechanical stimulation of vagal fibres innervating the external auditory canal) is 11-fold higher in adults with chronic cough compared to healthy adults and adults with respiratory disease without cough, indicative of a vagal hypersensitive state, whereas in children with chronic cough, the prevalence of this reflex is similar to that in healthy children[38]. Other patient populations can similarly display unique cough epidemiology. In China, most chronic cough patients are younger adults aged around 40 years, with an equal gender proportion, despite the enhanced cough sensitivity in female patients[30,39]. Relatively few studies

have identified specific genetic risk factors related to chronic cough, but include mutations in the gene encoding transient receptor potential 1 (TRPV1)[40] , the neurokinin 2 (NK2) receptor[41] , and a replication factor complex subunit 1 (*RFC1*) gene expansion associated with sensory neuropathy[42,43].

[H3] Clinical factors

Up to 40% of adults with chronic cough have unexplained chronic cough or refractory chronic cough, which can make clinical diagnosis challenging[5]. Cigarette smokers are three times more likely to report chronic cough than never-smokers and ex-smokers and the cough is usually due to chronic bronchitis[44]. However, most patients in cough specialist clinic are non-smokers. Infection with respiratory viruses (e.g., rhinovirus, SARS-CoV-2) are common causes of acute cough and usually self-limiting, but post-infectious cough may persist for months in some individuals, as observed in 10-20% of post-COVID cases[45] or 8.5-43% of post-H1N1 influenza cases[46,47], and may be related with cough reflex hypersensitivity. It is not clear what kind of viruses are more likely to induce post-infectious cough. Infection with *Bordetella pertussis* may be associated with a prolonged and debilitating cough, associated with a characteristic 'whoop', which can be difficult to treat[48,49]. In a non-smoker with a normal chest x-ray and spirometry, common pulmonary causes associated with chronic cough are corticosteroid-responsive cough/eosinophilic conditions, including cough variant asthma, non-asthmatic eosinophilic bronchitis and atopic cough[50,51]. Extra-pulmonary conditions are also commonly associated with cough, including GERD and upper airway cough syndrome (previously called 'post-nasal drip syndrome') due to a rhinitis or rhinosinusitis, while the proportion of GERD in East Asia is not as high as that in European and US patients with chronic cough. Indeed, cough variant asthma, eosinophilic bronchitis, upper-airway cough syndrome, and GERD, account for 51% to 92% of cases of adult chronic cough[3,51]. However, the existence of upper airway cough syndrome as a distinct clinical entity has been debated and proposed to reflect generalized airway inflammation resulting from asthma or airway reflux[4], potentially underestimating the true incidence of cough in these conditions. Chronic obstructive pulmonary disease (COPD), bronchiectasis, lung cancer, interstitial lung disease and obstructive sleep apnoea are associated with chronic cough but chest radiology and/or lung physiology measurements are usually abnormal[52-57]. Chronic cough is widely recognised as a side-effect of angiotensin-converting enzyme inhibitors (taken as anti-hypertensives or for heart failure)[58]. Rare causes of chronic cough in adults account for less than 15% of cases and commonly include protracted bacterial bronchitis, somatic cough syndrome (more common in children), diffuse

panbronchiolitis, and obstructive sleep apnea syndrome[59]. However, there is limited high quality evidence on their prevalence and clinical implications in adults with chronic cough. Less common extra-pulmonary conditions include atypical cardiac failure and cardiac arrhythmias, obstructive sleep apnea and tracheobronchomalacia (Table 2).

[H3] Environmental factors

Air pollution is recognised as an important risk factor for chronic cough particularly in East Asia where there are high levels of air pollution[18,60,61]. Occupational irritants may also cause cough, either by triggering cough reflex or inducing oxidative stress and eosinophilic inflammation[62-64]. However, the precise impact of environmental factors on chronic cough remains elusive. At population level, the annual level of fine particulate matter with a diameter of 2.5 $\mu g/m^3$ or less (PM2.5) is higher in Asian countries than in European or North American countries, but the prevalence of chronic cough is lower. Data from within-population studies, suggest the degree of air pollution is associated with the incidence of chronic cough or bronchitis[65,66] highlighting potential host-environmental interactions in developing chronic cough. However, the duration-based definition of chronic cough used in population-based studies does not differentiate protective cough responses from hypersensitive cough, and thus improved methodology for data collection is warranted to further understand the role of environmental factors in patients with chronic cough.

[H1] Mechanisms/ pathophysiology

The sensorimotor phenomenology of cough (Box 1) is indicative of a complex suite of neurobiological processes involving the peripheral nervous system, brainstem and higher brain. Cough can be a reflex, initiated by irritant stimuli activating airway mucosal sensory nerve fibers which convey this information to brainstem circuitry involved in altering the normal breathing cycle to a cough motor pattern. Cough can also be under volitional and cognitive control and is often accompanied by an irritant sensation known as the urge-to-cough. These aspects of cough involve neural processing in subcortical and cortical brain sites. An appreciation of this neurobiology is important for understanding cough, including in clinical settings.

[H2] Studying cough and cough hypersensitivity

Human neurophysiological studies have contributed immensely to our understanding of processes involved in cough and cough hypersensitivity, but they are limited by the types of measurements and interventions possible. Detailed mechanistic studies into basic cough neurophysiology have therefore relied heavily on laboratory animals, especially guinea pigs and cats. Cough in these species can be reliably induced with stimuli that also evoke cough in humans[67] and as such animal studies have been invaluable in identifying the mechanisms leading to sensory nerve activation, normal cough induction and the fundamental neural pathways mediating reflex coughing[68]. However, the utility of animals for modeling processes involved in the development and maintenance of cough hypersensitivity in humans has been debated[67]. Unlike humans, current animal models used to study pathological cough are largely devoid of any spontaneous coughing, requiring cough induction with an inhaled stimulus to assess the hypersensitive state. Consequently, although reflex cough hypersensitivity can be demonstrated in animals during pathological conditions, therapeutics that reliably reverse this reflex hypersensitivity have mostly not proven to be clinically effective in humans[15].

[H2] Peripheral neurophysiology

In guinea pigs, two peripheral sensory fiber subtypes originating in the vagus nerves can initiate cough when stimulated: a thinly myelinated Aδ-fiber subtype and a nociceptive unmyelinated C-fiber subtype (Figure 2)[68-71]. The cell bodies of cough Aδ-fibers and C-fibers arise from anatomically and embryologically distinct vagal ganglia[68,69] and their peripheral terminations are thought to reside predominately in the major airways (larynx, trachea and large bronchi)[68], although terminations in the lung parenchyma cannot be discounted as several parenchymal lung diseases present with chronic cough. Molecular analyses show differing patterns of gene expression and novel mechanisms for regulation[72,73]. Aδ-fibers respond to aspirated particulates, accumulated secretions, and mucosal acidification[69] as might happen following aspiration of gastric contents. Conversely, C-fiber cough is triggered by a range of irritant environmental chemicals and mediators of inflammation or tissue damage[68]. Cough challenge studies and histochemical staining of airway biopsies suggest that these two cough pathways similarly exist in humans[67,71,74]. A combination of animal and human studies have provided a comprehensive understanding of the ion channels and receptors responsible for excitation of cough sensory fibers, the channels, pumps and exchangers that contribute to action potential formation, patterning and axonal conduction, and the neurotransmitters and receptors

encoding cough at the central terminations, and many of these represent potential targets for antitussive therapies (Figure 2)[15].

[H2] Central neurophysiology

In mammals, many vagal sensory neurons terminate in the nucleus of the solitary tract, an important sensory processing nucleus in the medulla oblongata (Figure 2)[68]. Guinea pig studies suggest that the regions involved in integrating signals from cough sensory neurons share little overlap with other vagal fiber subtypes innervating the airways and lungs[68,75]. More recently, the paratrigeminal nucleus has been shown to also receive vagal cough sensory neuron inputs[76]. The nucleus of the solitary tract and the paratrigeminal nucleus differ with respect to the type of vagal sensory neurons that terminate in these locations (Aδ versus C-fibres) and in the output connectivity of their neurons involved in cough[68,75,77,78]. In guinea pigs, cough mediated by jugular C-fiber stimuli is reduced by targeted lesioning of neurons in the paratrigeminal nucleus, while Aδ fiber cough is unaffected[78]. Although precision mapping of sensory terminations in the human brainstem is not feasible, functional brain imaging studies employing stimuli differentially activating nodose and jugular neural pathways support the conservation of this wiring in humans[74].

Electrophysiological and pharmacological studies in guinea pigs suggest that Aδ-fibers and C-fibers both utilize glutamate to encode coughing at their central terminations, with post-synaptic N-Methyl-D-Aspartate (NMDA) receptors playing of role[79,80]. C-fibers may also encode coughing through neurokinin (NK) receptors[70,78,81]. Studies in animals and humans have demonstrated anti-tussive actions of NMDA and NK1 receptor blockade[82,83]. In rodent circuit mapping studies, brainstem neurons receiving cough sensory inputs contribute to neural circuits important for autonomic, limbic and somatosensory processing (Figure 2)[76]. Functional brain imaging studies in humans demonstrate widely distributed brain activity accompanying inhalation of cough-evoking stimuli, encompassing primary and secondary sensory cortical areas, and the cingulate, insula and orbitofrontal cortices. This pattern of activity likely reflects the diverse autonomic responses, and the affective, hedonic and discriminative sensory experiences accompanying cough[84].

[H2] Peripheral mechanisms regulating cough sensitivity

Experimental induction of pathophysiological processes in animals and a range of naturally occurring airway diseases in humans are accompanied by alterations in the excitability of the peripheral terminals of vagal sensory fibers regulating cough (Figure 3)[68]. For example, impaired bradykinin metabolism is linked to coughing in patients using ACE inhibitor antihypertensive therapy[85]. Excess release and/ or impaired metabolism may also explain ATP-dependent coughing associated with refractory chronic cough[15]. Inflammation may additionally cause plasticity of airway mucosal innervation, including changes in receptors, ion channels, neurochemistry, fiber densities or the cells contributing to fiber excitation[68,86,87]. For example, chronic cough patients showed a ~30-fold increase in cough responsiveness to inhaled capsaicin accompanied by an increased density of TRPV1-expressing fibers in bronchial biopsies[88]. Indeed, in animal studies, upregulated TRP channel expression or activity, including TRPV1, TRPA1 and TRPM8, has been shown to play a central role in the development of hypersensitivity to inhaled cough challenges[89,90]. However, clinical trials employing antagonists acting at each of these channels have so far failed to demonstrate any benefit against natural cough in human patient populations[15,90], suggesting animal studies of reflex cough hypersensitivity may not adequately reflect cough hypersensitivity leading to chronic cough in humans. Animal studies also suggest that neural plasticity during pulmonary pathologies may relate to a neuroinflammatory state (neuropathy) within the vagus nerve or ganglia characterized by increased inflammatory cell influx, upregulated inflammatory gene transcription and the release of inflammatory molecules from sensory neurons and resident or infiltrating immune cells[91-93]. The cause of this vagal neuropathy is unclear, but likely relates to both peripheral vagal detection of tissue inflammation and adverse effects associated with inflammation-induced persistent firing of action potentials in sensory neurons[91,94]. Whether this occurs in humans is not proven, but hypothesised as a cause of cough in some patients[95].

Functional interactions between sensory fiber subtypes in the brainstem can also impact cough. In humans, mechanical stimulation of the external ear can evoke coughing (Arnold's reflex)[38] attributable to activation of the vagal auricular nerves which have been shown to project to the paratrigeminal nucleus[77,96]. Co-activation of cough Aδ-fibers and C-fibers may induce cough hypersensitivity[97], while coughing is inhibited activation of nasal menthol-sensitive sensory fibers, lung stretch receptors and a subtype of C-fibers innervating the lungs[79,98,99].

[H2] Central mechanisms regulating cough sensitivity

Airway inflammation in animal models is accompanied by altered synaptic transmission, glial cell mobilization and activation and inflammatory gene transcription within the nucleus of the solitary tract[100-103]. These processes are expected to amplify the inputs from cough sensory fibres and contribute to the development of cough hypersensitivity. Consistent with this, upregulated cough network activity in the mid-brain has been demonstrated in patients with cough hypersensitivity[104], in regions reportedly involved in the development of other sensory hypersensitivities[105,106].

In humans, cough and the urge-to-cough are highly responsive to placebo. In controlled clinical trials, patients assigned to placebo often demonstrate large, clinically significant improvements in cough severity measures. In laboratory studies in healthy humans, placebo conditioning reduces the urge-to-cough during capsaicin inhalation by as much as 40 percent, which is accompanied by a significant reduction in inhaled capsaicin-evoked brain activity[107,108]. The mechanism by which placebo is active in cough is comparable to placebo analgesia, involving recruitment of a descending neural pathway enacting opioid-dependent suppression of sensory processing in the brainstem[108,109].

Cough in humans can be voluntarily induced (or enhanced) and suppressed through higher brain motor control pathways[110,111]. In some patients, especially children, behavioral coughing (somatic cough syndrome) may be the primary cause for chronic cough[112]. Volitional cough suppression involves a brain network important for general motor response inhibition[110,113,114]. Patients with refractory chronic cough display attenuated volitional cough suppression[115,116], and impaired engagement of this cough inhibition network[104]. Cough and the related brain activity are also modulated by acute painful stimuli applied to the skin[89,117], via an extension of the *Conditioned Pain Modulation (CPM)* phenomenon whereby noxious stimuli applied to one part of the body inhibits the processing of noxious stimuli applied elsewhere. CPM modulation of cough is also reduced in patients with refractory chronic cough[117]. These observations suggest the pathophysiology of refractory chronic cough involves altered efficacy of multiple central cough suppression processes. Components of these inhibitory systems regulating cough utilize the inhibitory neurotransmitter GABA, and GABA receptor agonists modify evoked coughing in animals and in humans[118,119]. Patients with COPD do not display altered volitional cough suppression[115], suggesting that distinct neural endotypes contribute to chronic cough[84].

[H2] Mechanisms of cough in commonly-associated diseases

Chronic cough in adults is commonly associated with asthma, non-asthmatic eosinophilic bronchitis, GERD, upper airway conditions (including nasal and sinus disease) and laryngeal dysfunction[3]. However, chronic cough is not a problem in all patients with these diseases, suggesting additional pathophysiological processes must account for this distinct presentation. The specific etiology of cough hypersensitivity and chronic cough likely differs both between and within patient groups, indicating that unique cough endotypes exist[84]. However, several general processes are thought to be important (Figure 3).

[H3] Direct sensitization or activation of cough

In asthma, the mediators of bronchopulmonary inflammation might directly impact airway nerve fiber activity (Figure 3). Notably in some asthmatics chronic cough is the sole presenting symptom, a condition referred to as *Cough Variant Asthma*, while other patients with chronic cough have eosinophilic disease but not asthma, including nonasthmatic eosinophilic bronchitis and the hypereosinophilic syndrome[120,121]. Whether different inflammatory processes contribute to cough across this spectrum of patients is unclear (Box 2). In GERD, chronic cough could occur directly through refluxate stimulating vagal sensory fibers in the larynx and airways. Although esophageal pH and impedance monitoring is routine, the detection of laryngopharyngeal reflux is technically challenging and symptomatology is proposed as evidence of laryngopharyngeal reflux, but with no objective measures for validation[122,123]. Similarly, detection of microaspiration through pepsin or bile acids in saliva, sputum or airway samples may not be reliable[124] and pepsin levels in chronic cough patients versus healthy controls are not different[125-127]. Gaseous reflux might also be important in chronic cough, but supportive evidence is lacking. In upper airway cough syndrome, inflammation or mucous from the nose or sinuses may extend or drip down the pharyngeal wall to the larynx and trigger activate cough sensory fibers. Although many patients with chronic cough complain of a sensation of post-nasal drip, there is a paucity of research exploring the relevance of these processes[128].

[H3] Indirect facilitation of cough

Direct stimulation of the esophagus or nose rarely evokes coughing. However, activating extrapulmonary sensory fibers can act synergistically with cough sensory fibers to produce cough hypersensitivity (Figure 3)[129,68,130,131]. Esophageal acid instillation sensitizes cough evoked by inhaled capsaicin in healthy volunteers and causes coughing in patients with chronic cough[132,133], while application of capsaicin to the nose of healthy volunteers sensitises cough and nasal menthol inhibits coughing[98,134]. Coughing follows reflux events in chronic cough patients more often than would be expected by chance alone[135-137], and both acid (pH<4) and non-acid (pH>4) events are equally likely to precede coughing while reflux events extending to the proximal esophagus are no more likely to precede coughing than distal events. These observations suggest that reflux, mucus or inflammatory mediators need not reach the airways to modulate coughing.

[H1] Diagnosis, screening and prevention

Initial evaluation of patients generally occurs in primary care, where treatment is commenced in patients with symptoms, clinical signs and/or investigations that point to one, or more potential underlying causes. In patients for whom the cause of cough is elusive and those whose cough does not respond to treatment in primary care, referral to secondary care specialists often occurs for more detailed investigation. Typically, referrals are to pulmonary specialists, but may also be to allergists, ear nose and throat specialist, or gastroenterologists depending on the clinical presentation. It is not unusual for adult patients with multiple co-morbid conditions to be referred to multiple specialities making the patient journey long. For those in whom cough remains problematic despite detailed evaluation and further trials of treatment in secondary care, specialist cough clinics have been developed. These services review the patients work up to ensure optimal treatment of co-morbid conditions that might be driving cough. In adults, they are often required to confirm a diagnosis of refractory cough (where an associated condition has been adequately treated but cough persists) or unexplained chronic cough (where no causes or conditions are associated with chronic cough can be diagnosed), utilise therapies shown to be of benefit in this patient group and often provide opportunities for patients to participate in clinical research including trials of novel therapies. However, the provision of such services varies significantly between countries.

[H2] Clinical characteristics of chronic cough

Cough is an explosive effort associated with a characteristic sound (Box 1). The distinct quality of the sound can be characterised, for example wet cough (moist, loose, productive, rattling) or dry (barking, hoarse). Wet chronic cough is thought to associated with diagnoses characterised by mucus production such as chronic bronchitis, COPD, and bronchiectasis. Whilst clinicians can distinguish reliably wet from dry cough, their ability to diagnose the cause of cough from the quality of sound is poor, only 34% of cases in one case series[138]. In some patients, two or more distinct types of coughs can coexist, for example a wet and dry cough. The frequency of cough sounds can be counted, and the intensity assessed[139]. Patients seldom describe the frequency of cough. They are more likely to describe clusters of cough or bouts, cough intensity and cough triggers, typically providing subjective accounts of when they occur and how much it bothers them. The pattern of chronic cough may show waxing and waning over periods of weeks or months, with patients indicating good periods and bad periods of cough.

Adults with chronic cough also frequently report throat clearing. Throat clearing, like cough, is thought to be an action to clear an unpleasant sensation or irritation and may represent an aspect of laryngeal dysfunction in chronic cough. This may also result from the feeling of mucus stuck at the back of the throat that needs to be cleared with the throat clearing process leading to mucus being swallowed. Throat clearing may be part of the spectrum of cough events but whether its presence is associated with specific diagnoses is not known. It is also unknown if patients distinguish throat clearing from cough and what the impact of this may be on a patient's perception of their morbidity.

Adult patients with chronic cough often display characteristic signs of cough hypersensitivity. Clinically this presents as *allotussia* with patients reporting cough triggered by innocuous stimuli such as talking, eating, and perfumes and/ or *hypertussia*, a heightened cough sensitivity to known tussive stimuli such as smoke, fumes and bleach[14,123]. Another common symptom of cough hypersensitivity is the presence of an uncontrollable urge-to-cough. Sensations in the larynx (laryngeal paraesthesia) or chest such as tickle, itch, or irritation can trigger coughing and can be more bothersome than the cough itself[140]. The presence of triggers and sensory symptoms may be the only feature suggesting the diagnosis of cough hypersensitivity. Whilst sensory symptoms are present in most adult patients, a small proportion (<5%) report no triggers or urge to cough[141]. Many patients with chronic cough, in addition to showing signs of cough hypersensitivity, also display laryngeal hypersensitivity[142].

Laryngeal hypersensitivity and dysfunction very often present with chronic cough, associated with vocal cord dysfunction, muscle tension dysphonia and globus (Box 3).

[H2] Evaluation of a patient with chronic cough

Recommendations for the evaluation of adult patients with chronic cough (Figure 4) are based on the anatomic diagnostic protocol first proposed more than 40 years ago[128] and founded on the principle that organs and anatomical structures innervated by vagal sensory fibers represent potential sites for generation of chronic cough[2,143]. This remains a useful approach as it can assist with identifying possible treatable traits in some patients. Any 'associated conditions' are initially the presumed 'cause' of cough, recognizing that treatment of the presumed cause does not always improve the cough. Consequently, initial clinical assessment, investigations and trials of therapy tend to be focused on asthma, gastro-oesophageal reflux disease and upper airway conditions (notably rhinitis, rhinosinusitis). A clinical history, focused on cough characteristics, associated sensations (e.g., urge-to-cough, need to clear throat) and common triggers, concomitant symptoms, combined with physical examination represent the first important steps in evaluation of a patient with chronic cough[2,143]. Concomitant symptoms associated with gastroesophageal reflux, and rhino-sinusitis may indicate the causes of chronic cough, but a reliance solely on symptoms to guide management may be misleading. For example, the presence of upper airway symptoms may reflect only co-existent rhinitis or rhinosinusitis and the absence of heartburn does not exclude reflux as the cause for the cough[2,144]. Clinical findings are frequently unremarkable in patients referred with chronic cough but finger clubbing, evidence of inflamed and/or obstructed nasal passages or the presence of wheeze or crackles on chest auscultation should inform consequent investigations and treatment. A chest radiograph and spirometry are both considered mandatory investigations for patients undergoing assessment for chronic cough[2]. Measurement of inflammatory markers representing Type 2 inflammation, such as fractional exhaled nitric oxide or sputum eosinophil count, may be useful in the early stage of workups. Additional tests such as chest computerized tomography, polysomnography and bronchoscopy should be requested depending on the physician's review of the case as set out in Supplementary Table 2.

To help identify the underlying cause of cough in children, paediatricians use the basic constructs of cough characterisation, pointers (like traits) and red flags (Figure 5). These concepts have been shown to be useful in current clinical practice, evidenced by calculation of likelihood

ratios[145] and incorporation of these facets in pediatric cough algorithms[1,146]. Using cough algorithms to manage pediatric chronic cough is efficacious in improving clinical outcomes. This has been demonstrated in cohort studies[147] as well as RCTs, based in specialist clinics[147] and in children enrolled in the community from primary care[146]. The later randomized control trial[146] was undertaken in the early phases of chronic cough where children who presented with an acute cough were randomised to use (vs non-use) of the pediatric chronic cough CHEST algorithm[147] at the 4-week timepoint post randomization. Further details of the pediatric diagnostic protocols are contained in the current guidelines[1,2].

[H2] Cough assessment tools

There are several validated tools available to assess cough in adults and children in clinical practice (Supplementary Box 1). Cough can be assessed subjectively to evaluate the patient's perspective. This includes cough severity, intensity, impact on health-related quality of life and triggers and symptoms suggestive of cough hypersensitivity. Cough can be assessed objectively by measuring frequency with sound or physiological measures (EMG, airflow or chest wall movement), intensity and the sensitivity of the cough reflex. The relationship between objective and subjective measures of cough is moderate at best[148]. This suggest they assess unique aspects of cough and that they should be viewed as complementary and equally valuable tools in evaluation of patients.

There are numerous validated tools available to assess cough subjectively. They are important because they assess the patient perspective, and this is what matters most. However, it is important to be able to assess a disorder objectively and be confident that measurements are specific to the disease and not influenced by co-morbid conditions or traits such as anxiety and depression. The objective assessment of cough is largely confined to research and clinical trial use because the tools involve time consuming analysis, are expensive and their clinical usefulness has not been established. The evaluation of the efficacy of cough medicines has benefited from the development of cough monitoring tools because of the smaller sample size required for studies compared to subjective tools and they address the preference of some medicines regulatory agencies to include objective endpoints in clinical trials[149].

Cough reflex sensitivity tests are used extensively in preclinical mechanistic studies, antitussive drug development to demonstrate engagement of therapies with the intended target receptor and for identifying optimal dosing strategies[150]. They are often not useful for assessing the efficacy of

504 treatment as they are not predictive of a reduction in coughing in patients[151]. Whilst patients with
505 cough have significantly lower thresholds for coughing during challenge tests compared to healthy
506 subjects, the ranges can overlap, limiting its diagnostic potential[152]. It may be possible to improve the
507 sensitivity and specificity of cough challenge tests for discriminating patients with cough from healthy
508 subjects with the standardization of equipment, protocols and analysis methods, which should be
509 explored further[153]. The selection of tussive agent for each study matters and depends on the research
510 question being asked. Further work is needed to broaden the choice of antitussive agents for challenge
511 studies and simplify methodology to facilitate wide-spread testing and evaluation.

512

513 ***[H2] Screening and prevention***

514 Screening for chronic cough is not carried out in clinical practice and there have been no studies
515 investigating this. It is not clear how screening should be done and whether it leads to clinical benefit.
516 There may be some potential benefit to screen patients with chronic respiratory disease as cough is
517 often overlooked during evaluation. Early identification may improve the quality of life of patients and
518 possibly avoid over treatment by specifically targeting cough. A simple method to screen patients is to
519 use a numeric rating scale to assess cough severity and ascertain the duration of cough. There may be
520 benefits to screening the general population. This may identify patients with respiratory disorders such
521 as COPD, asthma, lung cancer and smoking related chronic bronchitis at an earlier stage. The most
522 important diagnosis is that of lung cancer where development of a cough may be the first symptom
523 particularly in a smoker.

524 It is not known if chronic cough (non-smoking related) is preventable. A greater understanding
525 of the mechanism of cough, in particular cough hypersensitivity, is needed.

526

527 **[H1] Management**

528 The management of patients with chronic cough can be prolonged and complex, especially in
529 those found to have multiple co-morbidities requiring treatment and when the cough may ultimately
530 be refractory to such interventions. This section describes the management of comorbid conditions
531 potentially driving chronic cough and also therapies directed at cough hypersensitivity in patients
532 whose cough is refractory or unexplained.

[H2] Disease specific therapy in chronic cough

For many adult patients presenting with chronic cough, treatment of comorbid asthma, GERD or nasal disease (upper airway cough syndrome) improves their cough. However, few randomized controlled trials have assessed the efficacy treatments compared with placebo specifically against cough in these conditions.

[H3] Asthma

Several randomised controlled trials have assessed the efficacy of asthma therapies in patients with asthma and chronic cough, but as few trials have been performed in the last decade, current inhaled therapies are poorly represented[50]. Guidelines suggest increasing inhaled corticosteroid dose and considering trials of leukotriene inhibitor and beta-agonists in those for who the treatment response is incomplete, based on evidence in classical asthma[50]. The use of inhaled corticosteroid is considered the first line treatment in adults with cough variant asthma. Of note, the efficacy of inhaled therapies for asthma in patients with chronic cough can be subverted if the inhaled treatment evokes coughing. In this situation, a short course of oral prednisolone can be the simplest means of assessing the response of chronic coughing to asthma therapy. In children, chronic cough should not be attributed to asthma unless other symptoms/signs are present[154], and cough in pediatric asthma should not be regarded as a marker of severity.

[H3] GERD

Proton pump inhibitors (PPIs) act by reducing the acidity of refluxate. Histamine (H2) receptor blockers are sometimes used and have a similar, but more prolonged, effect. Lifestyle measures such as weight loss, elevating the head of the bed and avoidance of eating before bedtime may provide benefit. Small randomised controlled trials of acid suppressing therapy in patients with chronic cough have been performed but none reported positive results. A pooled analysis of these data suggests that adults with acid reflux on 24h pH monitoring or symptoms of heartburn are most likely to experience benefit, which is now reflected in clinical guidelines[4,144,155]. Observational data supports this approach, but response rates were low (28%) even in chronic cough patients complaining of heartburn[156]. Treatments for non-acid reflux are limited. Promotility agents (e.g., the

dopamine antagonists, metoclopramide and domperidone) can be only prescribed for short term use due to their adverse effects and lack evidence of efficacy in reflux-related chronic cough. Macrolide antibiotics promote gastric emptying but small studies in refractory chronic cough patients have failed to show benefit [157,158]. The GABAb agonist baclofen blocks relaxations of the lower esophageal sphincter, and therefore all types of reflux, but has unacceptable adverse effects for long term use. while a peripherally acting GABAb agonist, lesogaberan, with far fewer adverse effects, did not reduce cough frequency in refractory chronic cough patients in a randomised controlled trial. Laparoscopic fundoplication in patients with GERD and chronic cough is rarely indicated due to limited evidence for efficacy and significant risk of long-term complications.

The management of children with GERD is different to that of adults. Treatment is dependent on age and disease severity, and acid suppressive therapy should not be used solely for their chronic cough but are managed in accordance to their GERD severity[162]. Also, "trial of treatment" approach is dependent on the child's age, feeding regimen, and symptoms. PPIs and H_2 receptor antagonists should not be used for longer than 4 to 8 weeks without further evaluation[162].

[H3] Upper airway cough syndrome

A collection of nasal diseases, including allergic rhinitis, non-allergic rhinitis and chronic rhinosinusitis, are frequently found in adults presenting with chronic cough. The treatment of patients presenting with chronic cough and concurrent symptoms of nasal disease is standard care for the nasal condition diagnosed. Clinical trials evaluating the effectiveness of treating nasal diseases in patients with chronic cough are lacking and therefore predictors of improvement in chronic cough uncertain[163]. Many patients are thought to have allergic or nonallergic rhinitis which are treated by nasal corticosteroids, first or second generation and intranasal antihistamines, decongestants and if sinusitis is present antibiotics. The potential role of nasal surgery in patients with chronic cough is unclear[164,165].

[H3] COPD, Bronchiectasis and Interstitial lung disease

Cough, typically productive, is a common first symptom of COPD and usually attributed to cigarette smoking and/or exposure to environmental pollutants. Chronic bronchitis is recognised as a distinct phenotype of COPD and defined as chronic cough productive of sputum for 3 months over

the course of a year for 2 consecutive years[166]. In established disease, cough is reported in 70% of patients[52] and many consider it to be extremely severe. It is a prominent feature of disease exacerbations and associated with adverse clinical outcomes[53,167,168]. Measuring the severity and burden of cough using symptom based questionnaires is now recommended in the routine clinical evaluation of patients with COPD[169]. Chronic cough accompanied by the expectoration of large quantities of mucopurulent sputum is a central clinical feature of bronchiectasis. Typically coughing is much worse during exacerbations and contributes to impaired health status[170]. Impaired airway clearance, mucus retention and bacterial colonisation cause inflammation and lung damage which contribute to cough severity but are independent of cough reflex sensitivity[171]. Cough is a common and disabling symptom in idiopathic pulmonary fibrosis and may be due to inflammatory consequences of the fibrosis itself or to comorbid reflux disease. Currently there are no medicines approved to treat cough in these patients and current consensus is based on limited evidence[56].

[H2] Non-specific pharmacological therapies in adults with chronic cough

When the treatment of comorbid disease associated with cough is unsuccessful at relieving coughing, or in situations where there is no obvious cause for a chronic cough, pharmacological therapies directed at eliminating cough are required. These are restricted to use in adults as, for cough management purposes, the age cut-off used in children is usually 14 years. As most studies assess patients with refractory or unexplained chronic cough, whether other specific patient groups would benefit from adjunct non-specific cough therapy is unclear, and controlled trials are needed.

[H3] Opiates

Codeine and morphine are the most used antitussives in adult-based clinical practice and have anti-tussive effects via central opioid receptors[172]. Accordingly, effective antitussive doses of opiates are likely to cause sedation. Opioid receptor activation leads to reduced neuronal activity, although the receptor subtype by which opiates inhibit cough remains debatable as μ-, κ- or δ-opioid receptor agonists have all been shown to be antitussive[173]. Opioid receptors are also localized to vagal sensory neurons and their activation can suppress sensory fiber activity. However, inhaled morphine or codeine does not inhibit inhaled capsaicin-induced cough, unlike oral codeine or intravenous

morphine, arguing against a peripheral antitussive effect of opiates[174]. Opiates has no role in the management of children with chronic cough as they can cause death[1].

. Codeine has a rapid onset of action, facilitating differentiation of responders from non-responders. Although widely used, codeine's efficacy is not supported by clinical studies. Notably, less than 50% of patients with chronic refractory cough benefit from codeine, and treatment responses cannot be predicted. Several randomized placebo-controlled trials for cough in patients have been published, without objective cough measurements[175,176], and others did not report significant benefits of codeine over placebo[177,178]. Thus, 60 mg of codeine phosphate per day was no more effective than the placebo in reducing either objective cough frequency or subjective cough severity among patients with stable COPD and cough[178]. There concerns around safety, inter-individual variability in codeine metabolism, and dependence[179], although this may be low in those without vulnerability to dependence[180]. Adverse reactions, such as nausea, constipation, dyspepsia, dizziness or somnolence occur in up to 50% of patients and are mostly non-critical in adults[181].

Morphine is approximately 10 times more potent than codeine and mostly considered in patients with severe intractable cough. The antitussive effects and tolerability of a low-dose slow-release morphine therapy (5–10 mg b.i.d.) in patients with refractory chronic cough has been reported in a 4-week randomized placebo-controlled crossover trial. Morphine treatment was associated with significant improvements in subjective cough measures[182]. There was a significant improvement in the Leicester Cough Questionnaire scores of 3.2 points above baseline ($p<0.01$) and a reduction in daily cough severity scores of 40% ($p<0.01$). Eight out of 27 participants showed no or little difference in the cough severity scores between placebo and morphine treatment. The most common side-effects were constipation (40%) and drowsiness (25%), and none of the patients withdrew because of adverse events. Like codeine, the effects of morphine were mostly observed within a week, but less than 50% of patients benefitted. There are several safety concerns with its use, including respiratory depression, drowsiness, and addiction, depending on the dose[183].

[H3] Gabapentinoids

Gabapentin and pregabalin are derivatives of the inhibitory neurotransmitter GABA, devoid of activity at GABA receptors but inhibitors of α2δ subunit-containing voltage-dependent calcium channels and possibly NMDA receptors[184,185]. Gabapentinoids freely pass the blood-brain barrier and

are commonly used for treatment of seizures and neuropathic pain, although the sites of central action are poorly understood. In a 10-week randomized controlled trial on 62 patients with chronic refractory cough[186], gabapentin significantly improved subjective cough measures and objective cough frequency. However, clinical benefits were not sustained after cessation of treatment. There was no improvement in the capsaicin cough reflex sensitivity, suggesting a lack of effect on cough hypersensitivity. Some patients do not experience any improvement in cough. Pregabalin, as an add-on to speech therapy, significantly improved subjective cough measures compared with speech therapy alone at week 14[187]. However, its effects on objective cough frequency were not significant**.** Gabapentinoids cause common, and sometimes intolerable, adverse reactions, including dizziness, disorientation, confusion, fatigue, and blurred vision. The benefit of long-term use of gabapentinoids is difficult to predict given these adverse events.

[H3] Tricyclic antidepressants

Amitriptyline increases noradrenergic or serotonergic neurotransmission by blocking presynaptic norepinephrine or serotonin transporters, and has strong binding affinities for alpha-adrenergic, histamine (H1), and muscarinic (M1) receptors. [188]. In a randomized trial involving 28 patients with a post-viral cough hypersensitivity and cough lasting greater than 6 months, treatment with low-dose amitriptyline (10 mg) at bedtime was significantly more effective than a codeine/guaifenesin combination treatment in improvement of subjective measures of cough after 10 days of treatment[189]. . In a small observational study of 48 patients with idiopathic (refractory or unexplained) cough, up to 67% reported an improvement of greater than 50% at 2-3 months of starting treatment, but by 2-3 years only one third were still on the treatment with only 53% reporting an improvement of greater than 50%[190]. A controlled, double-blind study of amitriptyline in chronic cough is needed. The most common side effects of amitriptyline include dry mouth, dizziness, headache, and somnolence.

[H3] Non-specific cough suppression and the risk of dystussia

Cough has an important protective function in the respiratory tract in both healthy individuals and patients as it is needed to expel excessive airway secretions, prevent aspiration and protect against inhaled irritant stimuli, such as smoke. An ideal cough suppressant therefore would reduce

682 unwanted, excessive coughing without suppression of protective cough, essentially targeting the
683 hypersensitive state. Studies in laboratory animals and humans demonstrate the potential of opiates
684 and other centrally acting neuromodulators (gabapentin, baclofen) to inhibit cough evoked by a
685 broad range of chemical and mechanical stimuli[161,191-193]. This action reflects a dose-dependent
686 generalized suppression of the nervous system (sedation), an inhibition of the brainstem neurons
687 involved in generating respiratory rhythm and/ or a direct suppression of cough sensory nerve
688 activity[172,194,195]. Consequently, there is a risk that some non-specific cough suppressants could cause
689 dystussia, although the prevalence of this in practice is not well documented. A post-hoc analysis of
690 patients receiving morphine and codeine for cough suppression suggests that sedation is unlikely to
691 contribute to their cough suppressing properties[196], while gabapentin improved cough-specific
692 quality of life in refractory cough patients without suppressing capsaicin cough reflex sensitivity[186]. It
693 seems likely that the risk of dystussia and aspiration is related to dosing[197,198] and some patient
694 groups who are more prone to dystussia (such as the elderly and patients with spinal trauma or
695 neurological disease) may be more susceptible to generalized cough suppression by centrally acting
696 non-specific cough therapies[199,200]. At least one new peripherally acting non-specific cough therapy
697 in clinical trial (the P2X3 antagonist, Gefapixant) has been shown not to produce generalized cough
698 suppression at therapeutic doses[150].

699

700 ***[H2] Speech and language therapy in chronic cough***

701 Speech and language therapy consists of education, cough control/ suppression techniques,
702 breathing exercises, vocal hygiene, hydration strategies and counselling[201] (Box 4). Two randomized
703 control studies have evaluated the effectiveness of speech and language therapy for treatment of
704 adults with unexplained/ refractory chronic cough. The duration of treatment and length of sessions
705 varied between studies from four sessions delivered weekly, to four sessions over two months. In one
706 study[202], 88% of participants in the treatment group compared with 14% in the placebo group, showed
707 improvement in symptom frequency and severity scores for breathing, cough, voice and upper airway
708 symptoms. In a multicenter randomized control trial[203], therapy led to an improvement in cough-
709 specific quality of life and a reduction in cough frequency in the treatment group over the control
710 group. The Leicester Cough Questionnaire scores improved by a mean of 1.53 points in the
711 physiotherapy and speech and language therapy group compared to the control group (p=0.024), with
712 a reduction in cough frequency of 41% in treated versus controls (p=0.030). There was no significant

difference between therapy and control regarding subjective measures of cough and cough reflex sensitivity.

The antitussive mechanisms of action of speech and language therapy remains unclear. One hypothesis is that improved understanding of the condition through education and counselling, along with training in suppression strategies, may impact the decreased inhibitory control of cough that is present in such patients[68,95,104]. However, empirical studies to address this have not been conducted. An improvement in paradoxical vocal fold movement and dysfunctional breathing may also contribute to control of cough[204].

[H2] Managing chronic cough in children

Successfully managing a child with chronic cough (i.e., leading to cough resolution) is dependent on identifying the aetiology of the cough and treating it (see current clinical guidelines[1,2]). Thus, the suggested approach for managing children with chronic cough is aimed at identifying the underlying cause (i.e., obtaining the diagnosis which represents a treatable trait), in addition to attention to contributing factors (e.g., tobacco smoke exposure) and understanding the effect of the cough on the child and parents/guardians[1,2,147]. Older children are usually managed in accordance with adult pathways.

[H1] Quality of life

Cough has a significant impact on physical and mental health and quality of life is one of the key endpoints in clinical trials with novel anti-tussives and clinical practice guideline decision making[2]. Impacts in adults include urinary incontinence, pain, sleep disturbance, interference with speech, anxiety and depression, avoidance of social situations and inability to work[205]. Less common but extreme complications include syncope and head injury, hernia, suicidal ideation and rib fracture[205]. Stress urinary incontinence is under recognised in adults with cough. Approximately 65% of patients with chronic cough are female and 65% will experience cough induced urinary incontinence[206]. Patients are often too embarrassed to mention this to their physician. In some patients, the inability to control the urge to cough or throat tickle sensation can be worse than the cough itself[141]. In children, the key impacts are annoyance, frustration, impact on activities and tiredness[207] whilst that of parents of children with chronic cough are worries on etiology of cough, helplessness and sleep disturbance[208]. Data on the economic burden due to chronic cough are lacking.

744 Quality-of-life can be assessed informally in the clinic by simply asking patients about the range
745 of impacts known to be associated with cough. Health related quality of life (HRQOL) questionnaires
746 can be used to quantify quality of life in a validated and standardised manner. Quality of life tools
747 have broad applicability, even in conditions with considerable heterogeneity that can limit the
748 usefulness of objective tools. They capture aspects of disease severity not possible with objective
749 tools such as general health effects, for example fatigue and sleep disturbance. In patients with
750 cough, they have the potential to assess intensity, urge to cough, impacts that are not possible with
751 cough frequency monitors[209]. This is particularly important for patients who cough infrequently but
752 are greatly bothered by it. In studies that have investigated quality of life of patients with chronic
753 cough using validated tools, women have significantly worse quality of life compared to men
754 ($p=0.002$)[34]. Women were specifically worse off due to physical complaints, psychosocial issues and
755 extreme physical complaints. The great greatest disparity between gender was due to stress urinary
756 incontinence in women ($p<0.001$). Patients with a longer duration of cough, ($p<0.002$), depression
757 ($p=0\ 0014$), younger age ($p=0.001$) and interference with speech due to cough ($p=0.002$) have also
758 been reported to have worse quality of life[210]. The presence of urge to cough it's also highly
759 correlated with impairment in quality of life (Spearman correlation coefficient 0.64)[210]. In a
760 longitudinal study of patients undergoing treatment for chronic cough, improvement in cough was
761 associated with a significant improvement in quality of life at three months and continued
762 improvement at six months[210-212]. The improvement in quality of life was associated with
763 improvements in urinary incontinence, urge to cough and anxiety symptoms[210]. Future studies to
764 address gaps in knowledge should establish the frequency and characteristics of complications of
765 cough to improve management and understand the direction of relationship between cough, anxiety
766 and depression. The economic impact of cough to individual also needs investigation.

767 The Leicester Cough Questionnaire is the most widely used HRQOL tool in adult patients. It
768 comprises of 19 items, addressing physical, psychological and social domains[213], has good
769 repeatability and responsiveness and the minimal important clinical difference has been
770 established[214]. The Leicester Cough Questionnaire was used to demonstrate improvement in HRQOL
771 in a randomised, placebo-controlled and double-blind phase 3 trial assessing antitussive activity of
772 the P2X3 receptor antagonist, Gefapixant[215]. The 50 mg twice daily dosing of Gefapixant led to a
773 37% reduction in awake cough count and an improvement of 1.9 units of the LCQ score from placebo
774 treatment. The Cough Quality of Life (CQLQ) is another validated tool for adult patients with chronic

cough[212]. It comprises of 28 items, good repeatability and responsiveness and the minimal important clinical difference has been established[216]. HRQOL assessments are also valuable in the pediatric setting and are performed using acute cough[217] or child-specific chronic cough[207] HRQOL tools. Furthermore, as child's illness and management impacts on the child's family quality of life, 27-item and 8-item generic parent-proxy HRQOL tools are available for use in conjunction with cough-specific HRQOL assessments[208,218].

Little is known about the long-term outcomes of patients with chronic cough. In a study following patients for seven years, only 14% of patients experience resolution of their cough while 26% reported a reduction in cough severity. No predictors of improvement in cough were found in this study[12]. There may be long-term health risks related to having chronic cough, such as risks of mortality, morbidity, or drug side effects, although these have not been elucidated in patients with chronic cough.

[H1] Outlook

[H2] Linking cough hypersensitivity, chronic cough and patient perceptions

Cough hypersensitivity has become an important conceptual framework for understanding and managing adult chronic cough. The notion that many cough patients display a common phenotypic trait, despite the diverse pathologies that may underpin their chronic cough, has helped focus attention towards understanding the mechanisms that are central to the development of the hypersensitivity. With this has come significant advancement in therapeutic development, including successes treating adult chronic cough with drugs such as gabapentin commonly used for other sensory hypersensitivities and the discovery of a purinergic signalling axis involved in cough sensitization[187,219]. However, our understanding of the relationship between cough hypersensitivity and chronic cough is incomplete. For example, even though some therapeutic benefit has been shown using treatments that target mechanisms putatively involved in establishing or maintaining the state of hypersensitivity, these treatments invariably do not work for all patients, nor do they provide complete resolution of cough in most patients who do show responsivity[15]. Whether this reflects the existence of multiple concurrent processes involved in cough hypersensitivity, or yet to be discovered 'lynch pin' processes, is unclear. Alternatively, it may argue that the cough hypersensitivity phenotype does not adequately explain chronic cough for all patients. This is notable in children

where evidence for cough hypersensitivity is lacking and targeting specific clinical conditions results is effective cough resolution.

We do not understand the relationship between the presentation of chronic cough across the lifespan and a key question to answer is whether cough hypersensitivity evolves in some patients because of having troublesome cough at an in earlier time in their life. For example, whether children with chronic cough are more at risk of developing cough hypersensitivity as adults is not known. Indeed, there may even be important genetic determinants that impact the risk of developing cough hypersensitivity, an area of research that has remained understudied. One challenge in investigating future health impacts of chronic cough lies in the lack of a distinct diagnostic code for chronic cough in the International Classification of Diseases (ICD) systems[220]. Establishment of a proper code will facilitate large-scale routinely collected health data to further understand the burden and epidemiology of chronic cough.

The answers to many of the lingering questions will be dependent on an improved understanding of the multiple clinical dimensions of cough. Highlighted in recent clinical trials, patient reports of their disease severity and its impact on their quality of life do not always track linearly with objective measures of cough frequency. We have only a limited understanding of what aspects of chronic cough have the greatest impact on patient's lives. This proves problematic in trials of therapies that rely on only one output as the primary endpoint measure. For example, only short-term (24 hours or less) objective cough frequency is used by drug regulators in clinical trials of new anti-tussive therapies, meaning that drugs that bring about clinically important improvements in patient reported outcomes, but not cough frequency, are unlikely to advance. Yet in other clinical hypersensitivities, for example chronic pain, subjective measures of pain severity and quality of life are accepted as gold standard endpoint measures. Newer, less invasive, devices for counting coughs over longer periods of time in natural settings, potentially assessing other aspects of cough including the variability of cough, and the analysis of the sound, intensity, cough bout duration and the time of day[221] may disentangle the relationships between objective and subjective measures, but ultimately an acceptance of the clinical importance of the subjective dimensions of cough is needed.

[H2] Cough endotypes and personalized medicine

The existence of a common disease phenotype, cough hypersensitivity, does not negate the existence of multiple disease pathways that lead to this phenotype. Indeed, significant heterogeneity

between pathological processes defines the many varied conditions via which chronic cough can develop and recent suggestions of cough endotypes may help clinical management of cough. Conventionally, these endotypes have been considered in terms of the underlying clinical condition (e.g., asthma, gastroesophageal reflux, upper airway cough syndrome etc)[84] but conceivably there may be other ways for endotyping cough patients that need to be explored. Recent clinical trials with P2X3 antagonists suggest a subset of refractory chronic cough patients respond well to purinergic inhibition, perhaps reflecting a currently unrecognised endotype[215]. Trials of other antitussives have similarly shown heterogeneity in responsivity which may reflect differing pathological processes driving cough in different patients. A more careful assessment of this heterogeneity may identify clear endotypes that then allows for more personalized approaches to cough management. In the absence of discovering a 'magic bullet' that treats all chronic cough, personalized cough management will be needed and improved endotyping of cough patients will facilitate this.

[H3] Emerging therapies for treating cough hypersensitivity

Our improved understanding of cough neurophysiology has advanced the development of new antitussive therapies, several of which are progressing through clinical trial pipelines (Supplementary Table 3). Molecules targeting P2X3 and P2X2/3 ATP receptors are generating much excitement and at least four companies have molecules in advanced clinical trials. The front runner of these, gefapixant, has recently completed phase III trials showing efficacy in refractory chronic cough adult patients[215]. Trials have also been conducted with centrally acting neurokinin 1 receptor antagonists, demonstrating some clinical benefit, notably in lung cancer patients presenting with chronic cough[83]. In earlier phases of clinical development are drugs targeting the sodium channels involved in cough sensory neuron action potential conduction[222]. Whether these will show efficacy in patients is currently not known. To date, trials with various TRP channel agents have been disappointingly negative (Supplementary Table 3) and enthusiasm for these as therapeutic targets has waned. A challenge for these antitussive studies has been overcoming a large placebo effect that accompanies current trial designs. The development of improved animal models that better recapitulate the processes underpinning chronic cough and cough hypersensitivity in disease, along with reimagined clinical trial designs and/ or improved end-point measures may be required to tease out true therapeutic efficacies. Furthermore, clinical trials for new compounds have only assessed adults,

mostly with refractory chronic cough, and it will be important to ascertain the clinical utility of these new antitussives, if any, other patient groups as well as in children.

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1513 **Table 1:** Prevalence of chronic cough in children.

Author, Year	Age; N	Prevalence	Chronic Cough Definition	Setting
Carter, 2006[223]	11-15 years, n=2397	7.2% (all) 3.4% (excluding "asthma")	Chronic productive cough - "daily cough productive of phlegm for at least 3 months out of the year"	Cross sectional survey of Seattle middle school students using written and video respiratory-symptom questionnaires
Faniran, 1999[224]	5-7 years, n=511 8-11 years, n=654 8-11 years: n=566	10.4% 9.6% 5.1%	"In the last 12 months has your child had a cough that lasted more than 3 weeks and was not associated with a cold or flu?"	Enrolled from public schools within a 10-km radius of Royal Prince Alfred Hospital, Sydney, Australia. Questionnaire-based Enrolled from 6 schools in Nigeria. Questionnaire based
Flynn, 1994[23]	Mean, 9.6 years, n=2,173	21.9%	"Has this child coughed mucus on most mornings in the last 12 months"	Suva City school children, Fiji. Questionnaire-based
Migliore, 2005[225]	6–7 years, n=20,016 13–14 years, n=13,616	6.8%	Cough or phlegm for ≥4 days a week (in the absence of a cold) for ≥1 month/year	12 centres in northern, central and southern Italy. Self-administered questionnaires completed by parents
Laird, 2019[226]	Median,3.5 years, n=203	13%	Parent-reported daily wet cough for ≥4 weeks with clinician researcher confirmed (with physiotherapist using non-invasive techniques to elicit a cough if necessary)	Whole-population prospective study undertaken in 4 remote communities in north Western Australia
Pan, 2010[61]	3-12 years, n=11,860	Persistent cough=9.5% Persistent phlegm=4.6%	Cough on most days (>4 days/week) for as long as 3 months/year, either together with or separately from colds. Seemed congested or brought up phlegm or mucus from the chest on most days (>4 days/week) for as long as 3 months/year, either together with or separately from colds	18 districts of 6 cities in Liaoning province, China. Chinese language translation of the Epidemiologic Standardization Project Questionnaire of American Thoracic Society. Self-completed by parents
Rylance, 2019[227]	Mean, 7.1 years, n=804	8%	"Does your child usually have a cough when they don't have a cold?" and "Are there months in which they cough on most days?"	Children who participated in CAPS and BOLD-Chikhwawa studies, Chikhwawa District, rural Malawi. Electronic questionnaire in Chichewa, the local language
Singh, 2002[22]	1-15 years, n=2275	1.1%	Cough lasting for >3 weeks	5 villages in Dehlon Block of Ludhiana, Punjab, India
Stein, 1999[228]	Mean, 1.1 years, n=1064 Mean, 2.1 years, n=945 Mean, 5.8 years, n=1024 Mean, 8.1 years, n=841	6.7% 4.5% 12.2% 12.1% 12.4%	Score of ≥3 to question "How often has this child been bothered by cough" at least 2-3 episodes in the past year	Follow-up of a birth cohort where parents completed questionnaires or survey at different years

	Mean, 10.4 years, n=956			

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1516 **Table 2:** Additional conditions associated with chronic cough in adults and children

Condition	Possible mechanism(s)	Clinical picture
Obstructive sleep apnea	Airway inflammation associated with excess snoring, GERD reflux disease, increased cough reflex sensitivity (cough hypersensitivity) and tracheobronchomalacia	Presence of nocturnal cough, snoring; nocturnal heartburn; in older children/adults: raised body mass index, excessive daytime somnolence and in young children: behaviorial issues, tonsillar-adenohypertrophy, facial abnormality. Prevalence reportedly ranges from 33-68% in patients with confirmed OSA[57]. Continuous positive airway pressure (CPAP) therapy may be effective in alleviating cough[57]
Ear diseases or obstructions, including excessive wax or foreign body	Activation of Arnold's nerve cough reflex, vagal neuropathy	Cough is triggered by mechanical stimulation of the external auditory meatus. This occurs in 2% of the adult population but in 25% of people with chronic cough[38]. It can be a cause of chronic cough, when the mechanical stimulation of the external auditory meatus is accompanied by features of cough hypersensitivity such as throat irritation and allotussia[229]
'Cardiac cough': Premature ventricular contractions, cardiac arrhythmias, heart failure	Haemodynamic changes in the pulmonary circulation, activation of cardiopulmonary C-fibers; pulmonary edema	Ventricular arrythmia-induced cough and of cough syncope may be present in 5% of cases[230]. Nocturnal cough can be a symptom of patients with cardiac failure and could represent the effect of airway oedema on cough receptors in large airways or the pressure of enlarged left atrium on cough receptors in airways
Peripheral sensory neuropathy ±- ataxia	Genetic mutations and/ or nerve pathology leading to altered sensory neuron function	A rare autosomal dominant hereditary sensory neuropathy associated with chronic cough, cough hypersensitivity and gastrooesophageal reflux[231]
Tracheobronchomalacia or Expiratory central airway collapse	Possible problems clearing airway secretions/ changes in mechanical properties of the trachea during breathing	An excessive dynamic airway collapse of the posterior membrane presenting with a Seal-like barking cough caused by excessive vibration of posterior tracheal wall. This condition can mimic or co-exist with asthma, COPD and bronchiectasis. It is often associated with poor airway clearance of secretions.
Diffuse panbronchiolitis	Airway and lung inflammation	Chronic cough may be the sole or predominate symptom; normal respiratory function or mild airflow limitation; normal chest X-ray findings and mild dilation of the bronchiolar passages and a "tree-in-bud" pattern on chest high resolution CT; potential improvement in cough with long-term macrolide antibiotic therapy
Tumors (lung and airway)	Airway and lung inflammation, mechanical distortion of the airways	A change in cough pattern in a smoker can herald the presence of lung cancer. Lung cancer causes of cough include the direct effect of tumor mass leading to obstruction, collapse of lung or pleural or pericardial

		effusion, treatment of cancer with thoracic irradiation and chemo and/or immunotherapy[232]
Interstitial lung diseases (ILD) including interstitial pulmonary fibrosis and systemic sclerosis-associated ILD	Airway and lung inflammation, activation of cough receptors in fibrosis with neuroinflammatory factors	Cough and dyspnea are the main presenting features with often, chronic cough being the main distressing symptom. Other causes of chronic cough need to be excluded such as GERD, obstructive sleep apnea, emphysema, lung cancer, asthma etc. Often accompanied by features of cough hypersensitivity with an increase in capsaicin cough sensitivity
Somatic cough syndrome (psychogenic cough) and tic cough (habit cough)	Tic/habit cough in children, rare in adults: possibly anxiety related Somatic cough syndrome: Psychological-functional disorder i.e. transfer of psychological distress into a physical symptom	Tic cough Single repetitive cough, maybe barking/honking character and usually absent in sleep. Somatic cough syndrome: DSM-5 criteria must be present: "disruption of daily life; excessive thoughts about the seriousness of the symptoms, persistent anxiety about health or symptoms, or excessive time and energy devoted to symptoms or health concerns; and persistence of symptoms (typically more than six months)"[112]
Parasitosis	Airway and lung eosinophilic inflammation and mechanical stimulation	Parasitosis such as paragonimiasis or mammomonogamosis is a rare but relevant cause in some tropical regions or travellers. It can often present as a dry persistent cough with normal chest X-rays. Blood eosinophilia is frequent.[233]
Hypereosinophilic syndrome	Airway eosinophilic inflammation with or without FIP1L1-PDGFRA fusion gene and aberrant tyrosine kinase activity	Presenting with chronic cough as the sole or predominate symptom, hypereosinophilia in blood and sputum, and respond well to imatinib.[121]

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Figure legends

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Box 1 | **Sensorimotor phenomenology**

- Cough is an observable respiratory event in which the pattern of normal eupneic breathing is temporarily altered to allow for a forceful expiration, the normal purpose of which is to clear the airways of foreign materials, chemicals or secretions.
- A typical cough consists of three respiratory phases: (1) a brief *inspiratory phase* to prime the lungs with a volume of air; (2) a *compression phase* characterized by expiratory muscle contraction against a closed glottis, needed to ramp up intrapulmonary pressure; and finally (3) the *expiratory phase* during which the glottis opens, and high velocity expiratory airflow occurs[234].
- Variants of cough may see the inspiratory phase skipped, especially during bouts of repetitive coughing. Where there is glottic closure and expiratory effort but without the preceding inspiration, the event is termed an expiration reflex. In the clinic, expiration reflexes cannot be distinguished from cough since they both produce similar sounds. The identification of an expiration reflex requires assessment of airflow with a pneumotachograph in the laboratory. The clinical relevance of the expiration reflex has therefore been difficult to study[234].
- The induction of cough motor patterning is often linked to a reflex action, initiated by sensory detection of irritant stimuli in the airways leading to a brainstem mediated activation of cough motor pathways[235], in much the same way that painful stimuli initiate spinal withdrawal reflexes. However, cough can also be a purely volitional act, initiated at will in the absence of any peripheral sensory stimuli. Similarly, voluntary control can be exerted to behaviorally change the intensity of an evoked cough effort, or to suppress coughing entirely[110,236,237].
- Airway irritation can also give rise to perceivable sensations (e.g., an itchy or scratchy throat) referred clinically as the urge-to-cough. These sensations are thought to provide an awareness of the presence of irritating airway stimuli, and often contribute as much to patient morbidity as does cough itself. The urge-to-cough may be an important determinant of behavioral cough induction or regulation[84,238].

Box 2 | **Cough in asthma and related disorders**

- Cough is a common symptom of asthma. Patients with less well-controlled asthma cough more frequently[239], and bronchoconstriction and allergen exposure are known to sensitize and/ or provoke coughing in asthmatics[240,241]. However, in the laboratory, bronchoconstriction and cough pathways can be separately inhibited[242,243] and the severity of cough does not always reflect asthma severity. Chronic cough is the primary presenting symptom in patients with *cough variant asthma*[239] , while in the pediatric literature isolated cough is rarely asthma[1].
- Patients with classical asthma exhibit heightened responses to inhaled irritants such as capsaicin compared with healthy controls, although not to the same degree as those presenting with chronic cough[241,244]. The mechanisms leading to this remain elusive. Airway nerve density and neuronal branching is increased in bronchoscopy samples obtained from patients with classical asthma, like that seen in non-asthmatic patients with chronic cough[87,245].
- The precise mechanisms underlying why some patients develop cough-variant asthma as opposed to other asthma phenotypes is unclear and few studies have compared cough variant asthma with other phenotypes. Sputum eosinophilia might be less in cough variant asthma compared with typical asthma, and cough variant asthma patients have normal ventilation function or less severe impairment of lung function[246,247]. However, patients with non-asthmatic eosinophilic bronchitis, without variable airway obstruction or hyperresponsiveness characteristic of asthma, also present with chronic cough[248].
- The localization of mast cells within airway smooth muscle in asthma but not non-asthmatic eosinophilic bronchitis patients has been proposed as an explanation for the lack of bronchial hyper-responsiveness in non-asthmatic eosinophilic bronchitis. However, as other histological features are similar, it is unclear why non-asthmatic eosinophilic bronchitis patients present with chronic cough without airway obstruction and hyper-responsiveness[249]. The difference in airway function observed in subjects with eosinophilic bronchitis and asthma could be due to differences in mediator (e.g., prostaglandin E2[250]) production in the airways. Eosinophils may interact with airway sensory nerve fibers in asthmatics and promote increased airway sensory fiber density, nerve remodeling and airways hyperreactivity[245], while no relationship between eosinophils and the increased nerve fiber density was noted in patients with chronic cough without asthma[87].

Box 3 | **Laryngeal hypersensitivity and dysfunction in chronic cough**

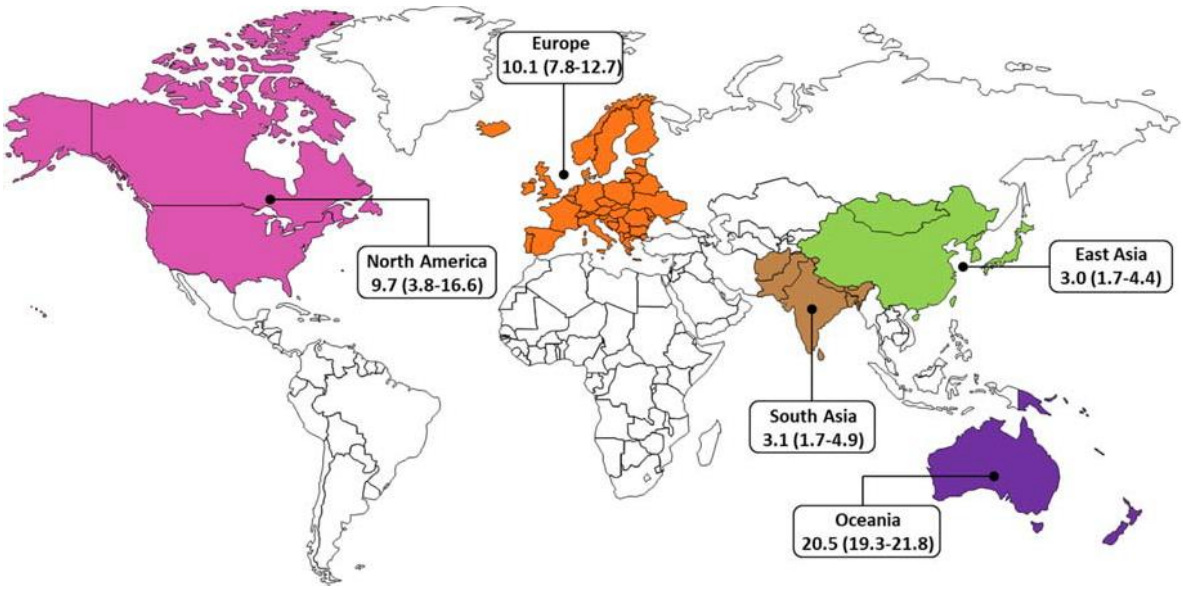
- Laryngeal hypersensitivity refers to the excessive abnormal laryngeal adduction of the vocal cords during breathing or exercise, resulting in laryngeal dysfunction[251]. Laryngeal hypersensitivity and dysfunction represent an increased responsiveness of laryngeal protective reflexes triggered by mechanical or chemical stimuli, and is considered to be part of the cough hypersensitivity syndrome.
- Laryngeal hypersensitivity and dysfunction are present in many patients with chronic cough and cough hypersensitivity[142,252]. It is often associated with co-morbid postnasal drip, rhinosinusitis, GERD and asthma [253].
- Symptoms are usually localized to the laryngeal area e.g., 'scratchy' or 'tickly' feeling of an urge-to-cough, or sometimes inspiratory stridor of airflow or feeling of suffocation or difficulty in breathing.
- Laryngeal dysfunction in patients with refractory chronic cough has been associated with paradoxical vocal fold movement manifesting as vocal cord dysfunction with episodes of suffocation or difficulty in breathing or laryngospasm [254]. Other aspects of laryngeal dysfunction include muscle tension dysphonia that can be revealed during vocalization[251].
- Investigations include direct laryngoscopic examination of vocal fold motion during challenge (using external triggers such as exercise or scents), laryngeal electromyogram and voice assessment [255].
- Laryngeal hypersensitivity and dysfunction in patients with chronic refractory cough may respond to speech pathology intervention and behavioural management of cough, with the use of voice therapy techniques and breathing exercises [256]. Cough neuromodulators such as amitriptyline and gabapentin might also be beneficial.

Box 4 | **Speech and language therapy management of chronic cough**

The approach to cough-specific speech and language therapy involves 4 steps:

- *Education.* Patients are provided education on the biology of coughing, chronic cough and cough hypersensitivity, while explaining the negative effects of repeated coughing and throat clearing.
- *Vocal hygiene.* Vocal and laryngeal hygiene and hydration is advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation.
- *Cough control/ suppression training.* Following identification of patient cough triggers, patients are taught a range of suppression strategies including forced/dry swallow, sipping water, chewing gum or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing whilst inhaling through the nose.
- *Psycho-educational counselling.* Behavior modification is used to reduce over-awareness of the need to cough and facilitate individuals' internalization of control over their cough and to help manage stress and anxiety.

[Note for reviewers: Please note that, should you recommend publication, all figures will be redrawn to our style by our in house art editors. In your review, please focus on the content (correctness, completeness, accuracy) of the figures, rather than their appearance. Thank you.]



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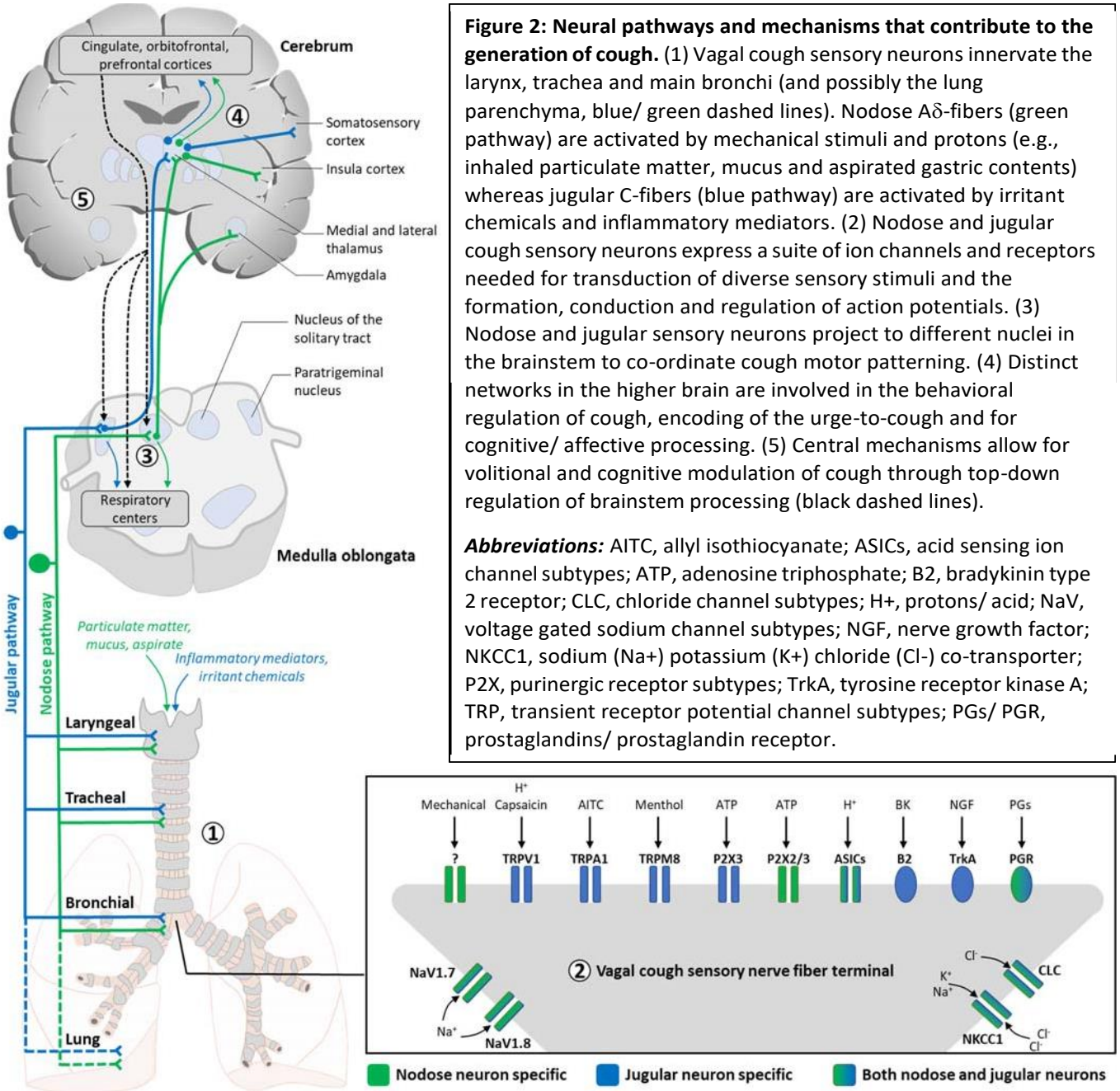

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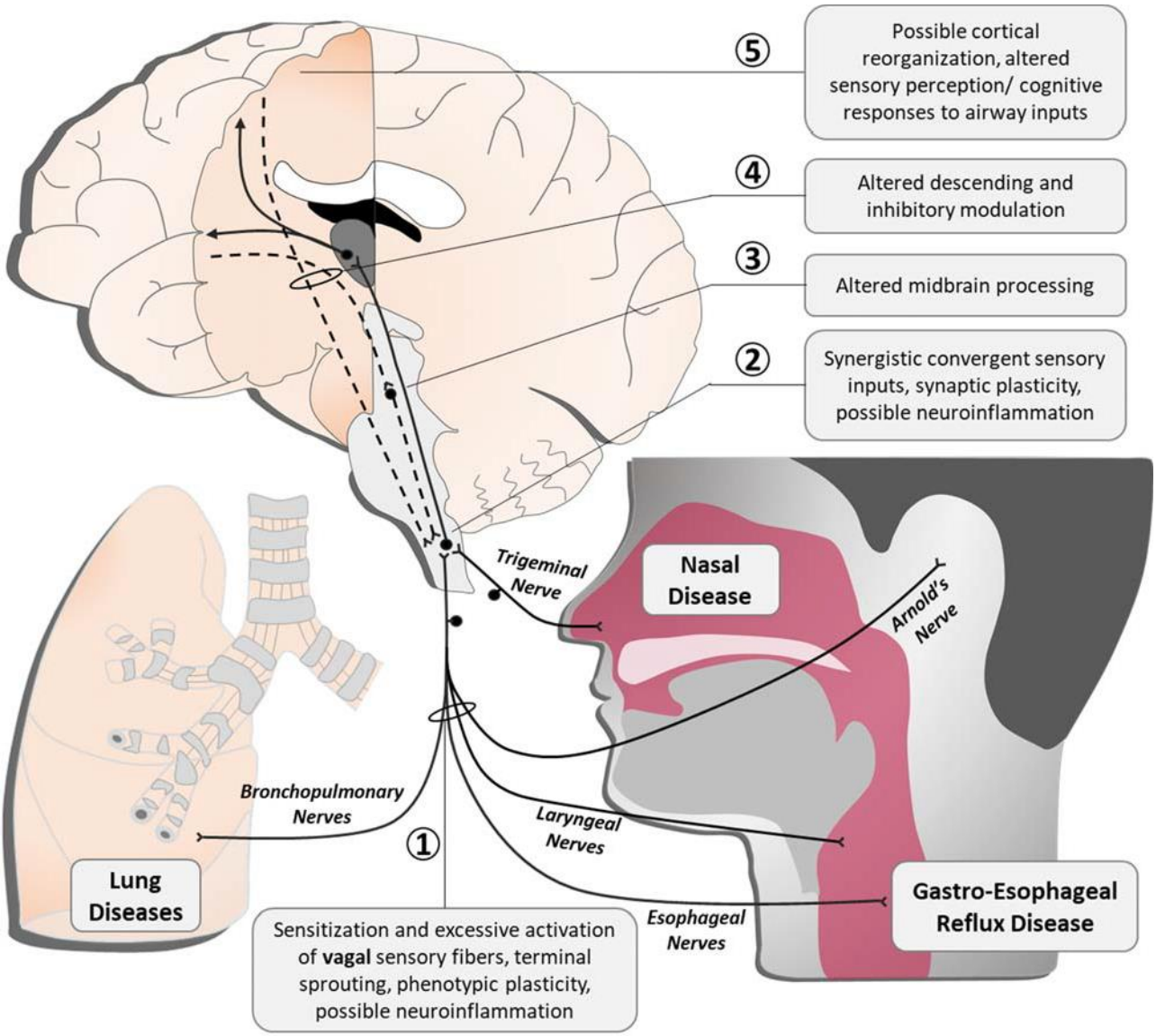

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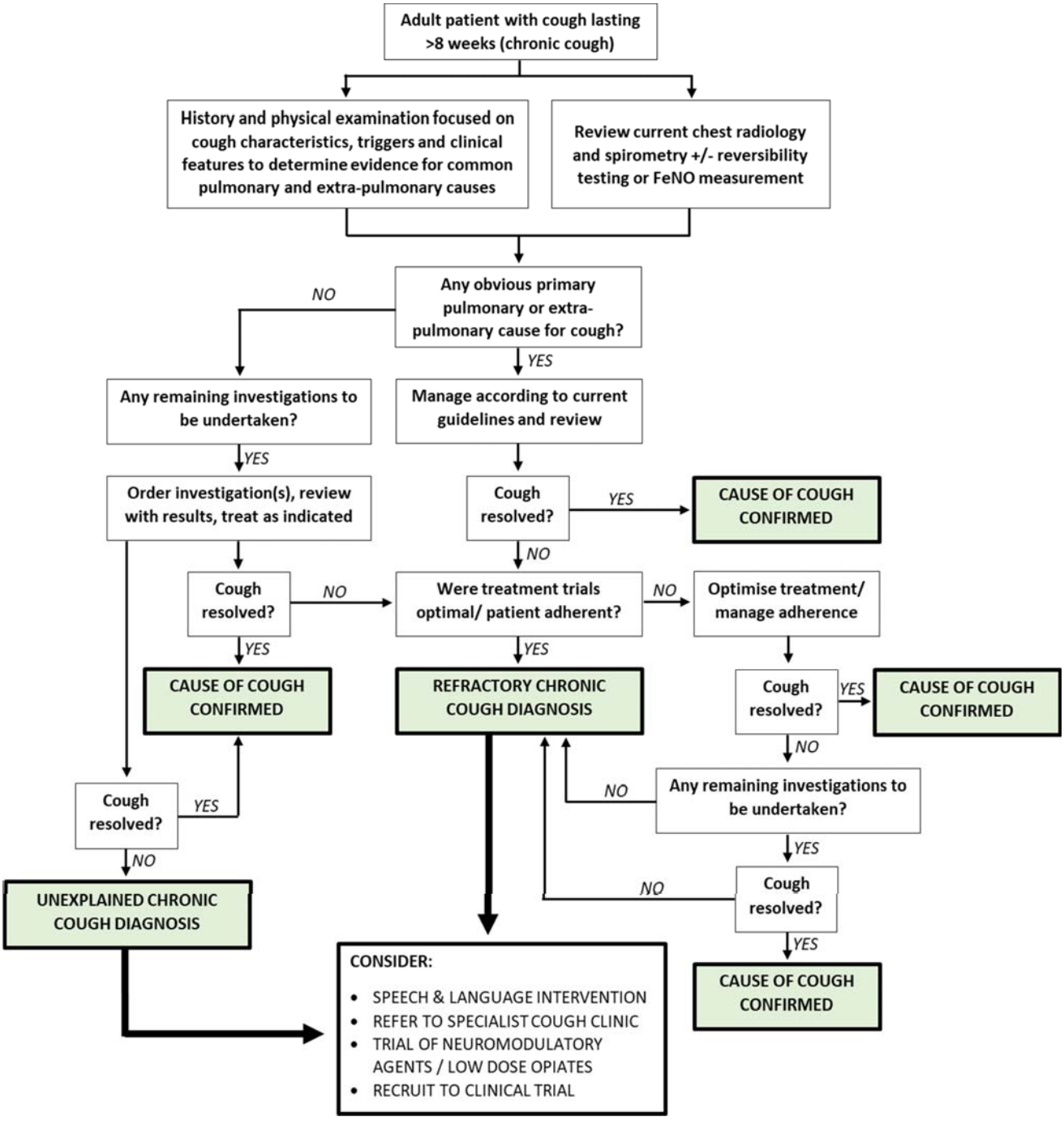

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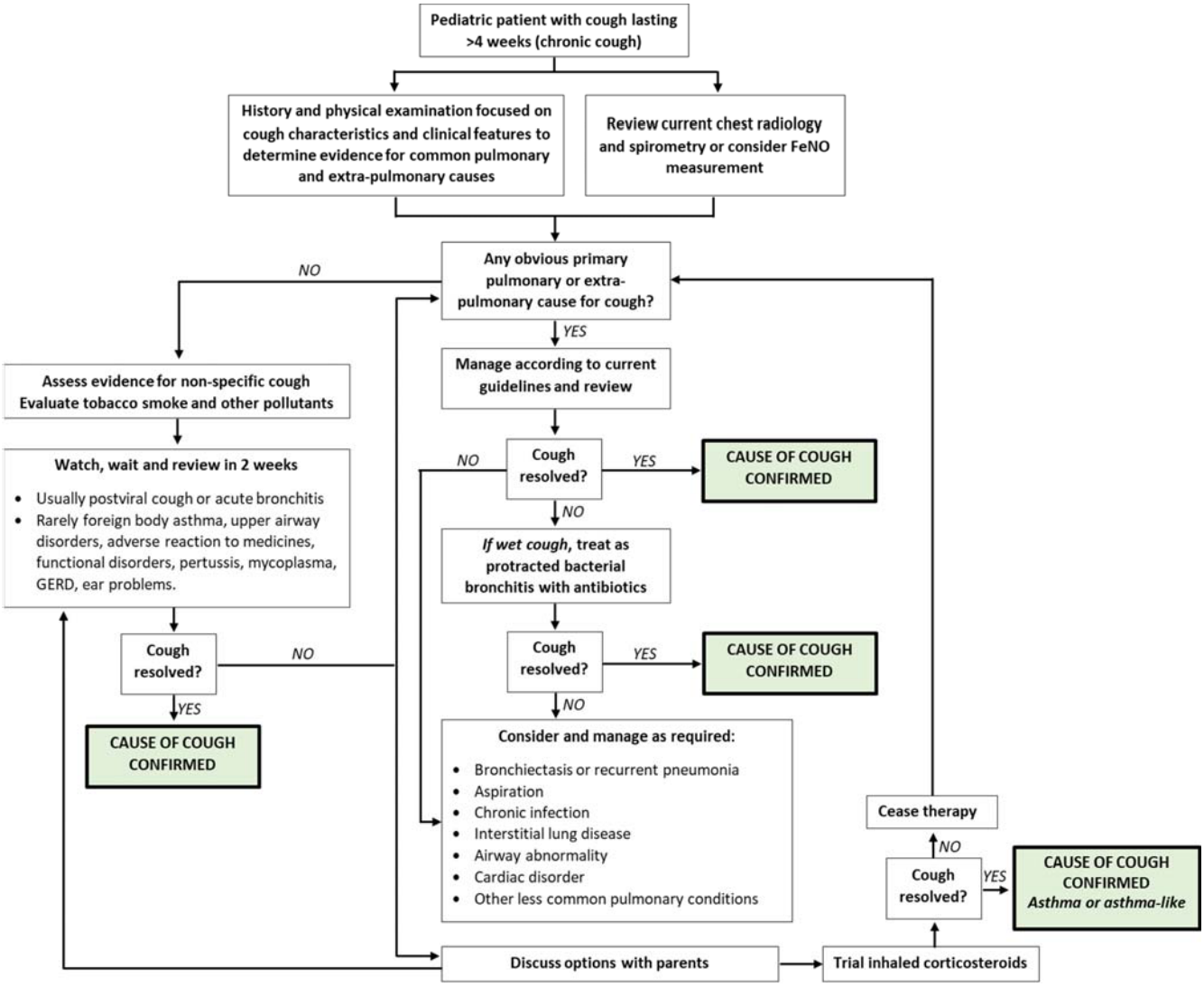

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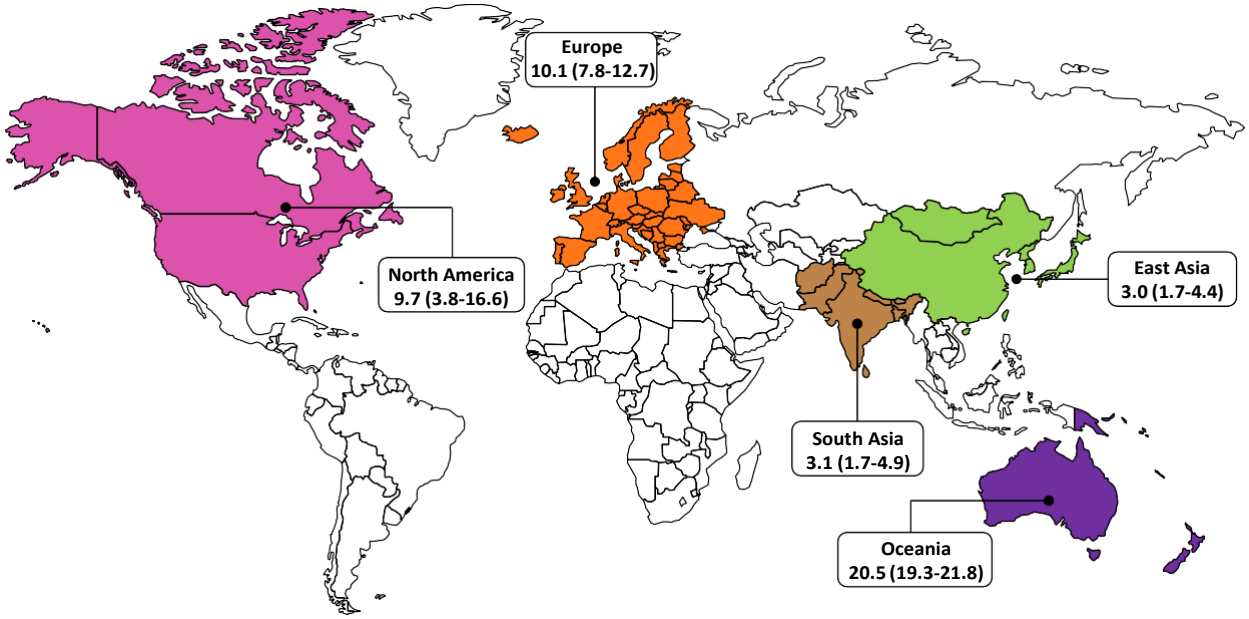

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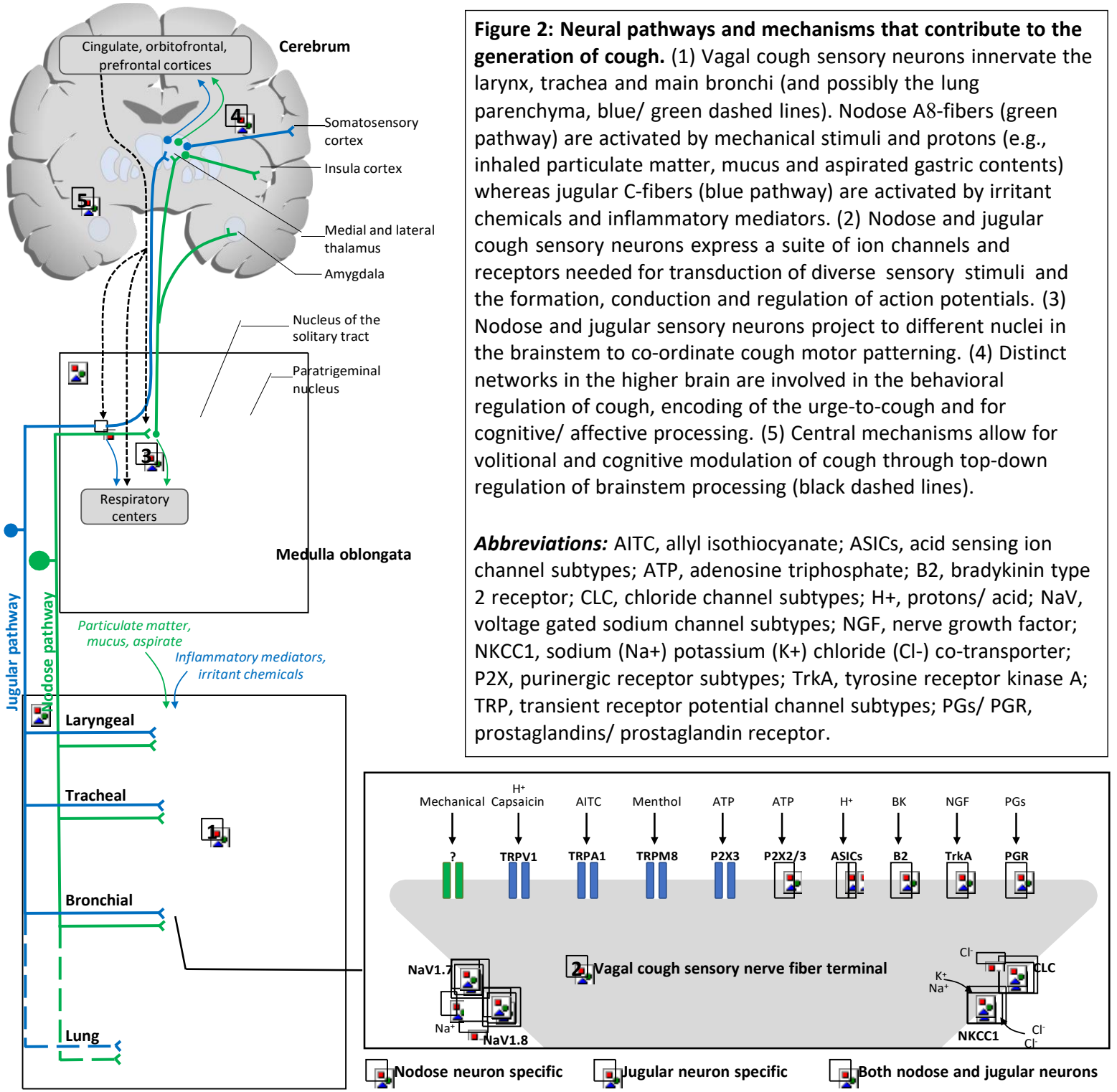

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Abbreviations: AITC, allyl isothiocyanate; ASICs, acid sensing ion channel subtypes; ATP, adenosine triphosphate; B2, bradykinin type 2 receptor; CLC, chloride channel subtypes; H+, protons/ acid; NaV, voltage gated sodium channel subtypes; NGF, nerve growth factor; NKCC1, sodium (Na+) potassium (K+) chloride (Cl-) co-transporter; P2X, purinergic receptor subtypes; TrkA, tyrosine receptor kinase A; TRP, transient receptor potential channel subtypes; PGs/ PGR, prostaglandins/ prostaglandin receptor.

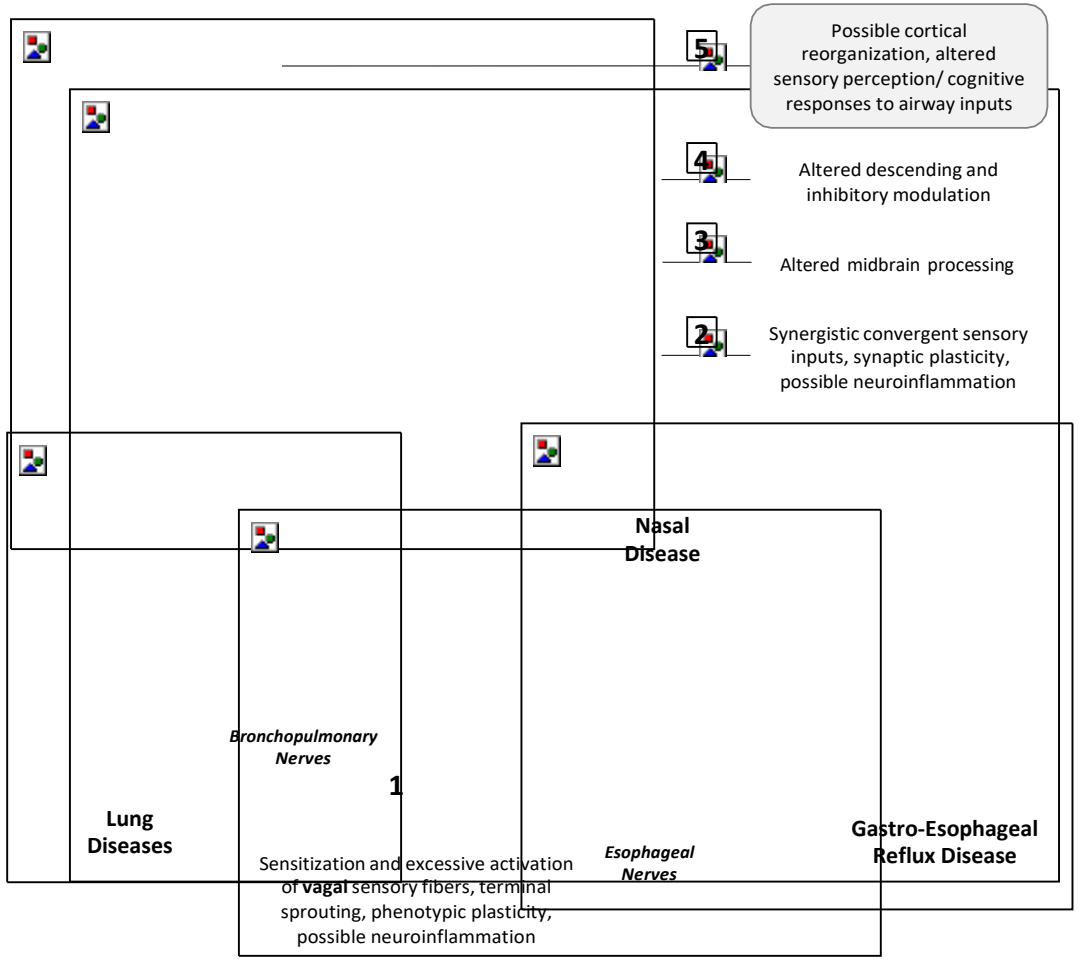

Figure 3. Peripheral and central processes contributing to cough hypersensitivity. (1) Preclinical studies have described potential mechanisms that impact vagal sensory nerve fibers, driven by the inflammatory pathology of the underlying diseases and potentially reversed by disease specific therapy. (2) Functional synergy may also exist between sensory neurons innervating the different tissues shown. These interactions likely occur at the level of the brainstem, where convergence of vagal and/ or trigeminal inputs leads to enhanced cough sensitivity. Peripheral organ pathologies have also been shown to alter synaptic efficacy in the brainstem, indicative of state of central sensitization. Human patients with cough hypersensitivity have (3) increased activity in midbrain areas, and (4) a reduced ability to suppress coughing due to a failure to recruit descending brain networks that subserve cough suppression. (5) Patients with chronic cough have a range of impacts in the cognitive domain, suggestive of altered cortical processing of airway sensory information. Drugs that target vagal sensory neurons and inhibit their activity, neuromodulatory drugs that target brain processes involved in maintaining hypersensitive states, and speech and language therapy aimed at improving the cough control, are all clinically useful antitussive options for patients with troublesome cough.

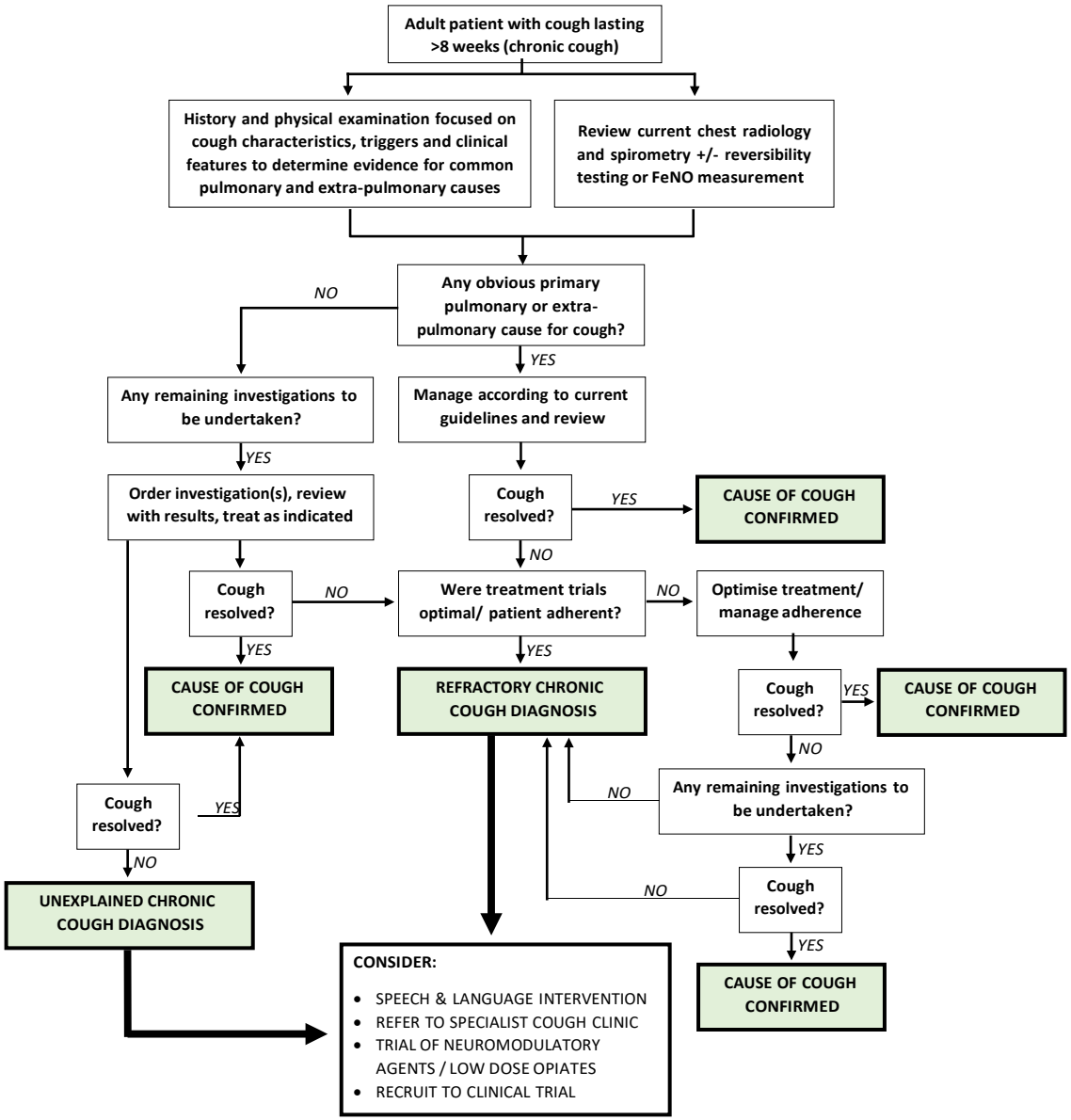

Figure 4: Evaluation and management of chronic cough in adults. A proposed algorithm for the clinical management of patients with chronic cough, including recommendations for managing difficult to treat cough. The algorithm was devised using recommendations contained in existing clinical guidelines and other reference material[2-6].

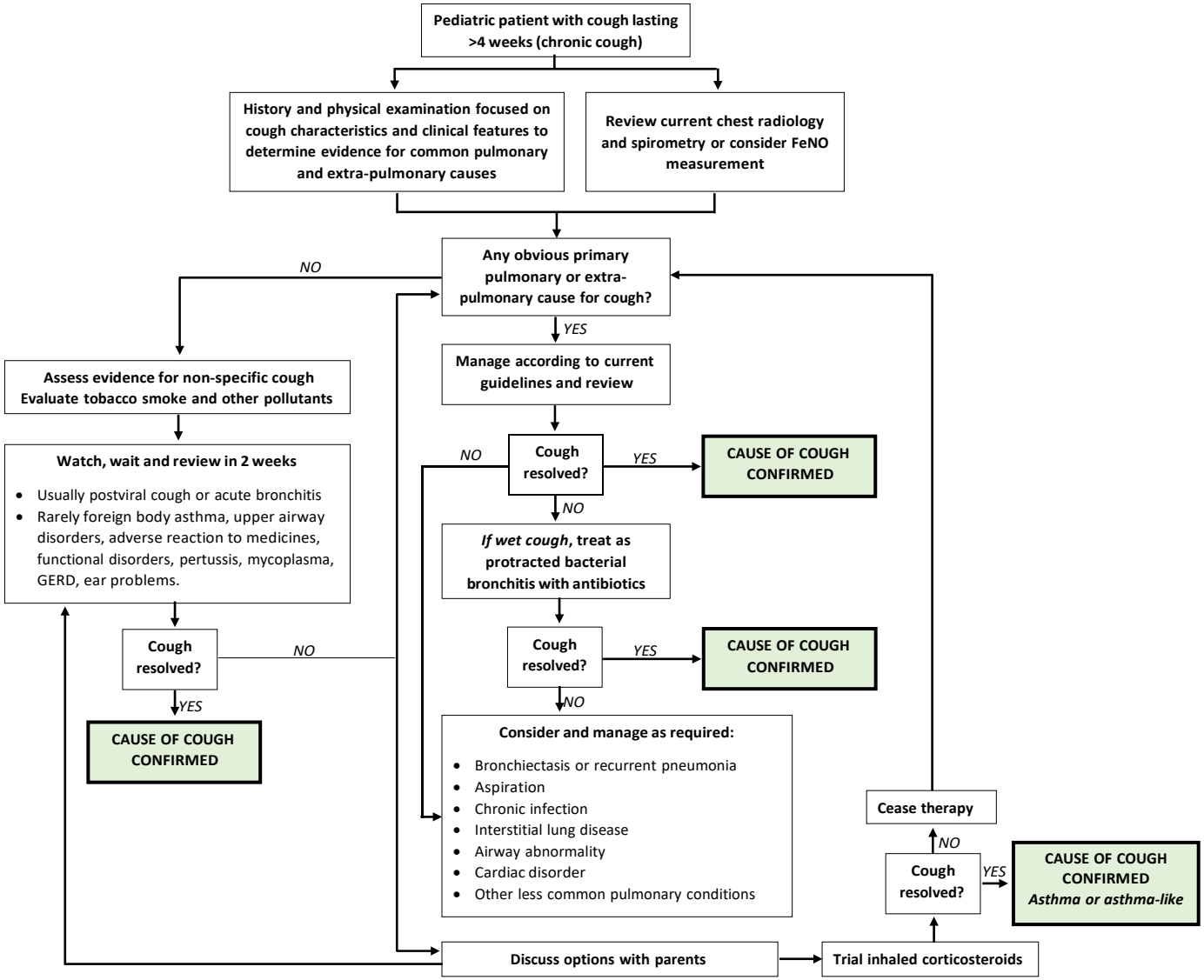

Figure 5: Evaluation and management of chronic cough in children. A proposed algorithm for the clinical management of pediatric patients with chronic cough. The algorithm was devised using recommendations contained in existing clinical guidelines[1,2].