Cough is one of the most common symptoms for which people present to primary care and is a chief complaint for patients seeking medical attention in respiratory or allergy specialist clinics. The definition of chronic cough in clinical guidelines is cough persisting for >8 weeks in adults and >4 weeks in children; however, in many epidemiological studies, chronic cough is defined as cough that lasts >3 months. The definition of chronic cough 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 substantial number of patients, despite exhaustive medical intervention. Many pulmonary and some extrapulmonary diseases and disorders can present with chronic cough, making diagnosis and treatment challenging. Moreover, 40% of adults with chronic cough referred for specialist evaluation have no identified cause (known as unexplained chronic cough) or have persistent cough despite optimal treatment of conditions associated with chronic cough (known as refractory chronic cough).

Chronic cough of any aetiology in adults is widely believed to reflect a hypersensitivity condition, characterized by coughing that is often triggered by low levels of thermal, mechanical or chemical exposure. The considerable burden of persistent chronic cough has led to an appreciation of cough hypersensitivity as a distinct clinical entity in adults. Distinct mechanisms that involve both peripheral and central neural pathways have a role in this hypersensitivity, and have motivated advances in cough suppressant (antitussive) drug discovery. The aetiology and management of chronic cough differs in children from that in adults, and the relevance of cough hypersensitivity as an underpinning mechanism in children remains unclear.

This Primer discusses the global prevalence and mechanisms of cough, with a focus on the most common causes of cough hypersensitivity. This Primer provides an overview of the current state-of-the-art recommendations for cough diagnosis and management, and presents a viewpoint of recent advances in cough hypersensitivity and chronic cough that may have a future effect on treatment.

**Epidemiology**

Chronic cough affects ~10% of adults in various general populations. The prevalence of chronic cough is higher in Europe, America and Australia (10–20%) than in Asia (<5%) (Fig. 1). In the general population of Copenhagen, Denmark, the prevalence of chronic...
Author addresses
1Experimental Studies Unit, National Heart & Lung Institute, Imperial College London, London, UK.  
2Department of Respiratory Medicine, Royal Brompton and Harefield Hospital, London, UK.  
3Welcomes–Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University Belfast, Belfast, UK.  
4Department of Allergy and Clinical Immunology, University of Ulster College of Medicine, Asan Medical Center, Seoul, Korea.  
5Australian Centre for Health Services Innovation, Queensland’s University of Technology and Department of Respiratory and Sleep Medicine, Queensland Children’s Hospital, Brisbane, Queensland, Australia.  
6Division of Child Health, Menzies School of Health Research, Darwin, Northern Territory, Australia.  
7The First Affiliated Hospital of Guangzhou Medical University, National Center of Respiratory Medicine, National Clinical Research Center for Respiratory Disease, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou, China.  
8Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA.  
9Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King’s College London, London, UK.  
10Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester, UK.  
11Department of Anatomy and Physiology, University of Melbourne, Victoria, Australia.

Cough was 4% overall, with a prevalence of 3% in never-smokers, 4% in former smokers and 8% in current smokers. Moreover, the prevalence of chronic cough in a meta-analysis was 6.2% in adults in China. The incidence of chronic cough ranges from 1.2 to 5.7 per 100 person-years in population-based studies of adults ≥45 years of age in Belgium and Canada19. However, no global or continental-level data are available. The longitudinal epidemiology of chronic cough and cough hypersensitivity is largely unknown, but cough may persist for longer than 5 years despite treatment in adults with chronic cough20. Certain patient traits, such as comorbid obesity, gastro-oesophageal reflux disease (GERD) and genetic background are associated with longer disease duration but warrant further investigation.

The prevalence of chronic cough in children is not as clearly defined as in adults. Overall, prevalence of chronic cough in children ranges from 1.1% to 21.9%19,20; the difference in these estimates is likely due to differences in the method of data collection, definition of chronic cough used, setting studied (such as high-income versus low-income country) and age of children studied (Table 1). Few data are available on the incidence of chronic cough following an acute respiratory infection; one study reported that 171 of the 839 children (20.4%, 95% CI 17.7–23.1) recruited from the emergency department of a specialist children’s hospital had chronic cough (defined as cough for >4 weeks) but 63 of these children already had chronic cough at presentation. Thus, the incidence is likely 108 of 839 (12.9%). Of the children with chronic cough who were reviewed by paediatric pulmonologists, 30.8% had a new and serious chronic lung disease and 47.0% had protracted bacterial bronchitis.

Risk factors
Various environmental and host factors, such as respiratory infection, air pollutants, occupational irritants, allergens, eosinophils or refluxate, can sensitize and trigger cough and are potential risk factors for chronic cough22,23. Biological traits, such as age or sex hormonal status, also interact with these triggers in developing chronic cough24-26. However, the definition of chronic cough used in population-based studies is based on cough duration, does not differentiate protective cough responses from hypersensitivity and does not represent the key nature that defines 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.

Patient factors. Age and sex underlie the burden and prevalence of chronic cough, although the mechanisms that underlie this association are unknown. In one survey, two-thirds of the patients presenting with chronic cough to specialist clinics were female, and the most common decade for presentation was 60–69 years. The high proportion of women in specialist clinics may be due to greater efforts of cough in older women, as they have more frequent complications such as stress urinary incontinence. Another possible explanation for the increased prevalence of chronic cough in female adults is that women have a more sensitive cough reflex than men, as demonstrated by inhalation capsaicin cough reflex sensitivity tests or that women have greater activation of the somatosensory brain cortex in response to capsaicin inhalation than men.

Notably, sex differences in capsaicin cough reflex sensitivity are not observed during prepubertal ages, suggesting that mechanisms that predispose to hypersensitivity do not occur 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 than in healthy adults and those with respiratory disease without cough, indicative of vagal hypersensitivity, whereas prevalence of this reflex is similar in children with chronic cough and in healthy children.

Other populations can have unique cough epidemiology. For example, in China, most patients with chronic cough are ~40 years of age, with an equal sex proportion, despite the enhanced cough sensitivity in women.

Relatively few studies have identified specific genetic risk factors for chronic cough. Identified genetic risk factors include mutations in TRPV1 (encodes transient receptor potential cation channel subfamily V member 1) and TAC2R (encodes neurokinin 2 receptor) and a RFC1 (encodes replication factor complex subunit 1) expansion associated with sensory neuropathy.

Clinical factors. 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. However, most patients in cough specialist clinic are non-smokers.

Infection with respiratory viruses (such as rhinovirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) is a common cause of acute cough and is usually self-limiting, but post-infectious cough may persist for months in some individuals. For example, 10–20% of patients after SARS-CoV-2 infection and
8.5–43% of patients after H1N1 influenza have persistent cough, which may be related to cough hypersensitivity. The viruses that are likely to induce post-infectious cough are unclear. Infection with *Bordetella pertussis* may also be associated with a prolonged and debilitating cough (whooping cough), which can be difficult to treat.

Common pulmonary causes of chronic cough in non-smokers with normal chest X-rays and spirometry are corticosteroid-responsive cough such as eosinophilic conditions, including cough variant asthma, non-asthmatic eosinophilic bronchitis and atopic cough. Extrapulmonary conditions are also commonly associated with cough, including GERD and upper airway cough syndrome (previously called 'post-nasal drip syndrome') due to rhinitis or rhinosinusitis. Indeed, cough variant asthma, eosinophilic bronchitis, upper airway cough syndrome and GERD account for 51–92% of cases of adult chronic cough globally. However, the existence of upper airway cough syndrome as a distinct clinical entity has been debated and is proposed to reflect generalized airway inflammation resulting from asthma or airway reflux, potentially underestimating the true incidence of cough in these conditions. Of note, the proportion of patients with chronic cough with GERD is lower in East Asia than in Europe and the USA. Chronic obstructive pulmonary disease (COPD), bronchiectasis, lung cancer, interstitial lung disease and obstructive sleep apnoea are also associated with chronic cough and cough hypersensitivity but chest radiology and/or lung physiology measurements are usually abnormal.

Chronic cough is widely recognized as an adverse effect of angiotensin-converting enzyme (ACE) inhibitors, which are prescribed as anti-hypertensives or for heart failure.

Rare causes of chronic cough in adults account for <15% of cases and commonly include protracted bacterial bronchitis, somatic cough syndrome (which is more common in children), diffuse panbronchiolitis and obstructive sleep apnoea syndrome. However, only limited high-quality evidence is available regarding their prevalence and clinical implications in adults with chronic cough. Less common extrapulmonary conditions include atypical cardiac failure and cardiac arrhythmias and tracheobronchomalacia (Table 2).

**Environmental factors.** Occupational irritants such as fumes, gases, cleaning products or dust may cause cough, either by triggering cough reflex or by inducing oxidative stress and eosinophilic inflammation. However, the precise effect of environmental factors on chronic cough remains elusive. Air pollution is an important risk factor for chronic cough particularly in East Asia where air pollution levels are high. At the population level, the annual level of fine particulate matter with a diameter of ≤2.5 μm (known as 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 that the degree of air pollution is associated with the incidence of chronic cough or bronchitis, highlighting potential host–environmental interactions in developing chronic cough.

### Table 2

| Environmental factor | Prevalence of chronic cough in adult populations (%) |
|----------------------|-----------------------------------------------------|
| GERD                 | 5–10                                                |
| Upper airway cough syndrome | 10–15                                    |
| Chronic obstructive pulmonary disease | 15–20                                          |
| Bronchiectasis       | >20                                                 |
| Lung cancer          | Data not available                                 |

Fig. 1 | Global prevalence of chronic cough. Map showing the results of a meta-analysis of 90 published studies assessing the regional pooled prevalence of chronic cough in adult populations. Reprinted with permission from REF13, ERS.
Mechanisms/pathophysiology

The sensorimotor phenomenology of cough (BOX 1) suggests the involvement of a complex suite of neurobiological processes involving the peripheral nervous system, brainstem and higher brain in this phenomenon. Cough can be a reflex or can be under volitional and cognitive control. It is typically initiated by irritant stimuli that activate airway mucosal sensory nerve fibres. These fibres convey this information to brainstem circuitry, which alters the normal breathing cycle to a cough motor pattern. Volitional and cognitively controlled cough is often accompanied by an irritant sensation known as the urge to cough. Volitional and cognitive control of cough and the perception of an urge to cough involve neural processing in subcortical and cortical brain sites.

Studying cough and cough hypersensitivity

Human neurophysiological studies have contributed to our understanding of cough and cough hypersensitivity, but they are limited by the types of measurements and interventions possible. Detailed mechanistic studies into 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\(^{24}\), and, as such, studies in these models have identified mechanisms that lead to sensory nerve activation, normal cough induction and neural pathways that mediate reflex coughing\(^{12}\). However, the use of animals to model the development and maintenance of cough hypersensitivity in humans has been debated\(^{14}\) as animals used to study pathological cough are largely devoid of any spontaneous coughing, requiring cough induction with an inhaled stimulus to assess the hypersensitivity. Moreover, although reflex cough hypersensitivity can be demonstrated in animal models, therapies that reverse this hypersensitivity have mostly not been clinically effective in humans\(^{12}\).

Peripheral neurophysiology

In guinea pigs, two peripheral sensory fibre subtypes can initiate cough when stimulated: thinly myelinated A\(\delta\) fibre subtype and nociceptive unmyelinated C-fibre subtype\(^{13-20}\) (FIG. 2). The cell bodies of cough A\(\delta\) fibres and C fibres arise from distinct vagal ganglia\(^{12,20}\) (nodose ganglion for A\(\delta\) fibres and jugular ganglion for C fibres), and their peripheral terminations are...
believed to reside predominantly in the major airways (larynx, trachea and large bronchi)\textsuperscript{16}, although terminations in the lung parenchyma cannot be discounted, as several parenchymal lung diseases present with chronic cough\textsuperscript{11}. Molecular analyses show differing patterns of gene expression and novel mechanisms of regulation\textsuperscript{11,12}. \(\alpha\text{-}\) Fibre-mediated cough is triggered by aspirated particulates, accumulated secretions and 

Table 2 | Additional conditions associated with chronic cough in adults and children

| Condition | Possible mechanism | Clinical picture |
|-----------|-------------------|-----------------|
| Obstructive sleep apnoea | Airway inflammation associated with excessive snoring, GERD, increased cough reflex sensitivity (cough hypersensitivity) and tracheobronchomalacia, a condition in which the walls of the trachea and bronchi are weak, leading to dilatation and easy collapsibility of the airways | Presence of nocturnal cough, snoring and nocturnal heartburn. Raised BMI and excessive daytime somnolence in older children or adults. Behavioural issues, tonsillar adenohypertrophy and facial abnormality in young children. Prevalence range 33–68% in patients with confirmed obstructive sleep apnoea\textsuperscript{17}. CPAP therapy may be effective in alleviating cough\textsuperscript{17}. |
| Ear diseases or obstructions, including excessive wax or foreign body | Activation of Arnold’s nerve cough reflex and 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\textsuperscript{18}. Can occasionally be identified as a cause of chronic cough when mechanical stimulation of the external auditory meatus is accompanied by features of cough hypersensitivity such as throat irritation and allotussia\textsuperscript{18}. |
| ‘Cardiac cough’: premature ventricular contractions, cardiac arrhythmias and heart failure | Haemodynamic changes in the pulmonary circulation, activation of cardiopulmonary C fibres or effect of pulmonary oedema | Ventricular arrhythmia-induced cough and of cough syncope may be present in 5% of cases of ventricular arrhythmia\textsuperscript{19}. 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 with or without 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 gastro-oesophageal reflux\textsuperscript{20}. |
| Tracheobronchomalacia or expiratory central airway collapse | Possible problems clearing airflow obstructions or 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 coexist with asthma, COPD and bronchiectasis. This condition is often associated with poor airway clearance of secretions. |
| Diffuse panbronchiolitis | Airway and lung inflammation | Chronic cough may be the sole or predominant symptom. Patients can have normal respiratory function or mild airflow limitation, normal chest X-ray findings and mild dilatation of the bronchiolar passages and a ‘tree-in-bud’ pattern on chest high-resolution CT. Cough can improve with long-term macrolide antibiotic therapy in some patients. |
| Lung and airway tumours | Lung cancer causes of cough include the direct effect of tumour mass leading to obstruction, collapse of lung or pleural or pericardial effusion, treatment of cancer with thoracic irradiation and chemo- and/or immunotherapy\textsuperscript{22}. | A change in cough pattern in a smoker can indicate lung cancer. |
| ILDs including interstitial pulmonary fibrosis and systemic sclerosis-associated ILD | Airway and lung inflammation or activation of cough receptors in fibrosis by neuroinflammatory factors | Cough and dyspnoea 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 apnoea, emphysema, lung cancer and asthma. 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 or habit cough in children (rare in adults) is possibly anxiety related, whereas somatic cough syndrome could be caused by psychological–functional disorder (transfer of psychological distress into a physical symptom) | Tic cough is a single repetitive cough, of maybe barking/honking character, usually absent in sleep. DSM-5 diagnostic criteria must be met for a diagnosis of somatic cough syndrome: “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)”\textsuperscript{23}. |
| Parasitosis | Airway and lung eosinophilic inflammation and mechanical stimulation | Parasitosis such as paragonimiasis, caused by a lung fluke, Paragonimus westermanni, which infects the lungs after eating an infected raw or undercooked crab or crayfish, or mammomonogamosis, caused by Mammomonogamus laryngeus, which inhabits the upper respiratory region in the human trachea, bronchi or larynx, is a rare but relevant cause in some tropical regions or in travellers. These disorders can often present as a dry persistent cough with normal chest X-rays. Blood eosinophilia is frequent\textsuperscript{24,25}. |
| Hypereosinophilic syndrome | Airway eosinophilic inflammation with or without FIP1L1–PDGFRA fusion gene and aberrant tyrosine kinase activity | Presents with chronic cough as the sole or predominant symptom, hypereosinophilia in blood and sputum, and responds well to imatinib\textsuperscript{26}. |

COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GERD, gastro-oesophageal reflux disease; ILD, interstitial lung disease.
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: first, a brief inspiratory phase to prime the lungs with a volume of air; second, a compression phase characterized by expiratory muscle contraction against a closed glottis, needed to ramp up intrapulmonary pressure; and finally, third, the expiratory phase during which the glottis opens and high-velocity expiratory airflow occurs.
- Some types of cough may not include an inspiratory phase, especially during bouts of repetitive coughing. In events with glottic closure and expiratory effort, without preceding inspiration, the event is referred to as an expiration reflex. In the clinic, expiration reflexes cannot be distinguished from cough as 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.
- 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, 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 behaviourally change the intensity of an evoked cough effort, or to suppress coughing entirely.
- Airway irritation can also give rise to perceivable sensations (such as 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 behavioural cough induction or regulation.

Glutamate (mediated by post-synaptic NMDA (N-methyl-d-aspartate) receptors) and, possibly, neurokinin (NK) receptors are involved in cough in guinea pigs. Indeed, NMDA and NK1 receptor blockade in animals and humans has antitussive actions, supporting a role for these receptors in cough. In rodents, brainstem neurons receiving cough sensory inputs are involved in autonomic, limbic and somatosensory processing (Fig. 2). In humans, functional brain imaging studies have found widely distributed brain activity accompanying inhalation of cough-evoking stimuli, in primary and secondary sensory cortical areas, and in the cingulate, insula and orbitofrontal cortices. This activity likely reflects the diverse autonomic responses, and the affective, hedonic and discriminative sensory experiences that accompany cough.

Peripheral sensitization of cough

Experimental induction of lung inflammation, for example, with allergens or respiratory viruses, in animals and in several airway diseases or treatments in humans, is accompanied by alterations in the excitability of the peripheral terminals of vagal sensory fibres that regulate cough (Fig. 3). For example, impaired metabolism of bradykinin, a potent activator of vagal C fibres is linked to coughing in patients using ACE inhibitor antihypertensive therapy. Similarly, excess release and/or impaired metabolism of ATP is associated with refractory chronic cough.

Inflammation can also cause plasticity of airway mucosal innervation, including changes in receptors, ion channels, neurochemistry, fibre density or the cells that contribute to fibre excitation. For example, patients with chronic cough had a ~30-fold increase in cough responsiveness to inhaled capsaicin that was accompanied by an increased density of TRPV1-expressing fibres in bronchial biopsy samples. In accordance with these data, studies in animal models have demonstrated a central role of upregulated TRP channel expression or activity, including TRPV1, TRPA1 and TRPV4, in development of hypersensitivity to inhaled cough challenges. Of note, however, clinical trials of TRPV1, TRPA1 and TRPV4 antagonists have failed to demonstrate any benefit against natural cough in patients, suggesting a disparity between animal and patient studies.

Animal studies also suggest that neural plasticity during pulmonary pathologies may relate to neuroinflammation 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. The cause of this neuroinflammation is unclear, but likely relates to both peripheral vagal detection of tissue inflammation and adverse effects of inflammation-induced persistent firing of action potentials in sensory neurons. Whether this occurs in humans is not proven, but is hypothesized as a cause of cough in some patients.

Functional interactions between sensory fibre subtypes in the brainstem can also affect cough. In humans, mechanical stimulation of the external ear can evoke coughing (Arnold’s reflex), which is attributed to mucosal acidification, as might happen after aspiration of gastric contents. Conversely, C-fibre-mediated cough is triggered by a range of irritant environmental chemicals and mediators of inflammation or tissue damage. Cough challenge studies and histochemical staining of airway biopsy samples suggest that these two cough pathways also exist in humans. A combination of animal and human studies has provided a comprehensive understanding of the wiring of central neurons and receptors responsible for excitation of cough sensory fibres (Fig. 2).
activation of the auricular branch of the vagus nerve, which projects to the paratrigeminal nucleus. Co-activation of cough Aδ fibres and C fibres may induce cough hypersensitivity, whereas coughing is inhibited by activation of nasal menthol-sensitive sensory fibres, lung stretch receptors and a subtype of C fibres innervating the lungs.

**Central sensitization of cough**

Airway inflammation in animal models of lung disease is accompanied by altered synaptic transmission, and glial cell mobilization and activation within the nucleus of the solitary tract, resulting in elevated inflammatory mediators in the brainstem, including neurotrophic factors (NGF, BDNF and GDNF) and cytokines (IL-1β, IL-6 and TNF). These processes are expected to contribute to cough hypersensitivity via amplifying inputs from cough sensory fibres. Consistent with this, upregulated cough network activity in the midbrain has been demonstrated in patients with cough hypersensitivity, in regions reportedly involved in the development of other sensory hypersensitivities.

In humans, cough and the urge to cough are highly responsive to placebo. The mechanisms of this phenomenon are comparable to those of placebo analgesia and involve recruitment of a descending neural pathway enacting opioid-dependent suppression of sensory processing in the brainstem.

Cough in humans can be voluntarily induced (or enhanced) and suppressed through higher brain motor control pathways. In some patients, especially children, behavioural coughing (somatic cough syndrome) may be the primary cause of chronic cough. Volitional cough suppression involves a brain network important for general motor response inhibition and non-acid reflux events are equally likely to precede coughing in patients with chronic cough, while application of capsaicin to the nose of healthy volunteers sensitizes cough, and nasal menthol reflex is technically challenging with no objective measures for validation and detection of microaspiration through pepsin or bile acids in saliva, sputum or airway samples may not be reliable. Of note, pepsin levels in patients with chronic cough are not different from those in healthy controls. Gaseous reflux might also be important in chronic cough, but supportive evidence is lacking. In patients with upper airway cough syndrome, inflammation or mucus from the nose or sinuses may extend or drip down the pharyngeal wall to the larynx and activate cough sensory fibres. However, 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.

**Indirect facilitation of cough**

Direct stimulation of the oesophagus or nose rarely evokes coughing. However, activating extrapulmonary sensory fibres can act synergistically with cough sensory fibres to produce cough hypersensitivity. Oesophageal acid instillation, for example, via a naso-oesophageal catheter, sensitizes cough evoked by inhaled capsaicin in healthy volunteers and causes coughing in patients with chronic cough, while application of capsaicin to the nose of healthy volunteers sensitizes cough, and nasal menthol inhibits coughing. Coughing follows reflux events in patients with chronic cough more often than would be expected by chance alone, of which both acid and non-acid reflux events are equally likely to precede coughing whereas reflux events extending to the proximal oesophagus are not 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.

**Diagnosis, screening and prevention**

Initial evaluation of patients with chronic cough generally occurs in primary care, where treatment is commenced in those with symptoms, clinical signs and/or investigations that point to one or more potential underlying causes. Referral to secondary care specialists often occurs for more detailed investigation in those with an
elusive cause of cough and in those who do not respond to treatment in primary care. Referrals are typically to pulmonary specialists, but may also be to allergists, ear, nose and throat specialists or gastroenterologists, depending on the clinical presentation. Adults with multiple comorbid conditions can be referred to multiple specialities, making the patient journey from diagnosis to assessment and treatment long. Patients with persistent cough despite detailed evaluation and further treatment trials in secondary care can be referred to specialist cough clinics. These clinics review the patients’ work-up to ensure optimal treatment of comorbid conditions that might be driving cough. In adults, attendance at a specialist cough clinic is often required to confirm a diagnosis of refractory cough or unexplained chronic cough, to use therapies that are of benefit in this patient
Fig. 2 | Neural pathways and mechanisms that contribute to the generation of cough. (1) Vagal sensory neurons that are involved in cough innervate the larynx, trachea and main bronchi and, possibly, the lung parenchyma (blue and green dashed lines). Vagal Aδ fibres (whose cell bodies reside in the nodose ganglia) are activated by mechanical stimuli (such as inhaled particulate matter, mucus and aspirated gastric contents) and protons whereas vagal C fibres (whose cell bodies reside in the jugular ganglia) are activated by irritant chemicals and inflammatory mediators. (2) Vagal fibres involved in cough express several ion channels and receptors needed for transduction of diverse sensory stimuli and the formation, conduction and regulation of action potentials and (3) project to brainstem nuclei to coordinate cough motor patterning. (4) Distinct networks in the higher brain are involved in the behavioural regulation of cough, encoding of the urge to cough and for cognitive and affective processing. (5) Central mechanisms in the higher brain are involved in the behavioural regulation of cough, encoding of the urge to cough and for cognitive and affective processing.

**Clinical characteristics**

Cough is an explosive effort associated with a characteristic sound (Box 1). The distinct quality of the sound can be characterized, for example, wet cough (moist, loose, productive or rattling) or dry (barking or hoarse). Wet chronic cough is thought to be associated with diagnoses characterized by mucus production such as chronic bronchitis, COPD and bronchiectasis. Although clinicians can distinguish reliably wet from dry cough, the ability to diagnose the cause of cough from sound is poor; only 34% of cases in one case series. In some patients, two or more distinct types of cough can coexist, for example, a wet and dry cough. In the clinic, the frequency of cough sounds can be counted and the intensity of individual cough efforts measured. However, patients seldom describe the frequency of cough and 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 weeks or months.

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. Throat clearing may also result from the feeling of mucus stuck at the back of the throat that needs to be cleared, 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. Whether patients distinguish throat clearing from cough, and the effect of this on patients' perception of their morbidity is unknown.

Adults 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. Another common symptom of cough hypersensitivity is the presence of an uncontrollable urge to cough. Sensations in the larynx (laryngeal parasthesia) or chest such as tickle, itch or irritation can trigger coughing and can be more bothersome than the cough itself. The presence of triggers and sensory symptoms may be the only feature to suggest the diagnosis of cough hypersensitivity. Although sensory symptoms are present in most adults with chronic cough, <5% report no triggers or urge to cough. Many patients with chronic cough, in addition to showing signs of cough hypersensitivity, also display laryngeal hypersensitivity.

Laryngeal hypersensitivity and dysfunction often present with chronic cough that is associated with vocal cord dysfunction, muscle tension dysphonia and globus (a sensation of a ‘lump’ in the throat) (Box 3).

**Diagnostic work-up**

Recommendations for the evaluation of adults with chronic cough (Fig. 4) are based on the anatomical diagnostic protocol first proposed more than 40 years ago and founded on the principle that structures innervated by vagal sensory fibres represent potential sites for generation of chronic cough. This remains a useful approach as it can assist with identifying possible treatable conditions in some patients. Any comorbid conditions involving these structures are initially presumed to be the 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, GERD and upper airway conditions (notably rhinitis, rhinosinusitis). A clinical history, focused on cough characteristics, associated sensations (such as urge to cough and need to clear throat), common cough triggers, comitant symptoms, combined with physical examination, represent the first important steps in evaluation of a patient with chronic cough. Concomitant symptoms associated with gastro-oesophageal reflux, and rhinosinusitis 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 of the cough.

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. Chest radiography and spirometry are mandatory for patients undergoing assessment for chronic cough. Measurement of markers of type 2 inflammation, such as fractional exhaled nitric oxide (FeNO) or sputum eosinophil count, may be useful in the early stage of work-ups of patients with chronic cough. Additional tests such as chest CT, polysomnography and bronchoscopy should be requested depending on the physician's review of the case as set out in Supplementary Table 1.

To help identify the underlying cause of chronic cough in children, paediatricians use the basic constructs...
of cough characterization, pointers (such as traits) and red flags (Fig. 5). These concepts are useful in current clinical practice, evidenced by calculation of likelihood ratios\textsuperscript{142} and incorporation of these facets in paediatric cough algorithms\textsuperscript{143,144}. Using cough algorithms to manage paediatric chronic cough is efficacious in improving clinical outcomes, demonstrated in cohort studies\textsuperscript{145}, randomized controlled trials (RCTs) based in specialist clinics\textsuperscript{145} and primary care\textsuperscript{144}. Further details of the paediatric diagnostic protocols are contained in the current guidelines\textsuperscript{143}.

**Cough assessment tools**

Several validated tools are available to assess cough in clinical practice (Supplementary Box 1). Subjective assessments of cough evaluate the patient’s perspective and

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**Fig. 3 | Peripheral and central processes contributing to cough hypersensitivity.** (1) Preclinical studies have described potential mechanisms that affect vagal sensory nerve fibres that are 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 various 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. Patients with cough hypersensitivity have (3) increased activity in midbrain areas, and (4) a reduced ability to suppress coughing owing to a failure to recruit descending brain networks that subserve cough suppression. (5) Patients with chronic cough have a range of effects 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 cough control, are all clinically useful antitussive options for patients with troublesome cough.
Box 2 | Cough in asthma and related disorders

- Cough is a common symptom of asthma. Patients with less well-controlled asthma than those with well-controlled asthma usually cough more frequently\(^\text{206,207}\) and bronchoconstriction and allergen exposure are known to sensitize and/or provoke coughing in people with asthma\(^\text{209,210}\). However, in the laboratory, bronchoconstriction and cough pathways can be separately inhibited\(^\text{211,212}\), and the severity of cough does not always reflect asthma severity. Some patients with well-controlled asthma may experience chronic cough. Chronic cough is the primary presenting symptom in patients with cough variant asthma\(^\text{213,214}\), while in the paediatric literature isolated cough is rarely asthma\(^\text{215}\).

- Patients with classical asthma have heightened responses to inhaled irritants such as capsaicin compared with healthy controls, although not to the same degree as those presenting with chronic cough\(^\text{212,216}\). The mechanisms leading to this remain elusive. Airway nerve density and neuronal branching are increased in bronchoscopic samples obtained from patients with classical asthma, like those seen in patients with chronic cough without asthma\(^\text{216,217}\).

- The precise mechanisms that underlie 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 than in typical asthma, and patients with cough variant asthma have normal ventilation function or less severe impairment of lung function\(^\text{218,219}\). However, patients with non-asthmatic eosinophilic bronchitis, without variable airway obstruction or hyper-responsiveness characteristic of asthma, also present with chronic cough\(^\text{220}\).

- The localization of mast cells within airway smooth muscle in patients with asthma but not in patients with non-asthmatic eosinophilic bronchitis has been proposed as an explanation for the lack of bronchial hyper-responsiveness in non-asthmatic eosinophilic bronchitis. However, other histological features are similar, so it is unclear why patients with non-asthmatic eosinophilic bronchitis present with chronic cough without airway obstruction and hyper-responsiveness\(^\text{221}\). The difference in airway function observed in subjects with eosinophilic bronchitis and asthma could be due to differences in mediator (such as prostaglandin E\(_2\), [REF.222]) production in the airways. Eosinophils may interact with airway sensory nerve fibres in people with asthma and promote increased airway sensory fibre density, nerve remodelling and airway hyper-reactivity\(^\text{223}\), while no relationship between eosinophils and increased nerve fibre density was noted in patients with chronic cough without asthma\(^\text{224}\).

- They are often not useful for assessing the efficacy of treatment as they are not predictive of a reduction in coughing in patients\(^\text{225}\). Although patients with cough have significantly lower thresholds for coughing during challenge tests compared with healthy individuals, the ranges can overlap, limiting their diagnostic potential\(^\text{226}\). Improving the sensitivity and specificity of cough challenge tests might be possible by standardizing equipment, protocols and analysis methods\(^\text{227}\).

Screening and prevention

Screening for chronic cough is not carried out in clinical practice. How screening could be done and whether it would lead to clinical benefit is unclear. Screening patients with chronic respiratory disease may be beneficial as cough is often overlooked during clinical evaluation. Moreover, early identification may improve the quality of life (QOL) of patients and possibly avoid over-treatment by specifically targeting cough. One simple screening method is a numerical rating scale that assesses cough severity and ascertains the duration of cough. Screening the general population could identify patients with respiratory disorders such as COPD, asthma, lung cancer and smoking-related chronic bronchitis at an earlier stage. The most important diagnosis is that of lung cancer, where development of a cough may be the first symptom, particularly in a smoker.

Whether non-smoking-related chronic cough is preventable is unknown. A greater understanding of the mechanism of cough, particularly cough hypersensitivity, is needed.

Management

The management of patients with chronic cough can be prolonged and complex, especially in patients with multiple comorbidities requiring treatment and when the cough may ultimately be refractory to such interventions. Therefore, management includes treatment of comorbid conditions that are potentially driving chronic cough and therapies directed at cough hypersensitivity in patients with refractory or unexplained cough.

Disease-specific therapy

For many adults with chronic cough, treatment of comorbid asthma, GERD or nasal disease (upper airway cough syndrome) improves their cough. However, few RCTs have assessed the efficacy of treatments compared with placebo in reducing cough in those with these conditions.

Asthma.

Several RCTs have assessed the efficacy of asthma therapies in patients with asthma and chronic cough, but few trials have been performed in the past decade, so more recent inhaled therapies are poorly represented\(^\text{228}\). The CHEST and European Respiratory Society guidelines suggest increasing inhaled corticosteroid dose and considering trials of leukotriene inhibitors and β-agonists in those for whom the treatment response to inhaled corticosteroids is incomplete, on the basis of evidence obtained in classical asthma\(^\text{229}\). 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 or signs are present\(^{152}\) and cough in paediatric asthma should not be regarded as a marker of severity.

**GERD.** Treatments for GERD include proton pump inhibitors (PPIs, which reduce the acidity of refluxate), histamine (\(\text{H}_\text{1}\)) receptor blockers (which have a similar, but more prolonged, effect to PPIs) and lifestyle measures such as weight loss, elevating the head of the bed and avoidance of eating before bedtime. Small RCTs of acid-suppressing therapy (PPIs and \(\text{H}_\text{1}\) receptor blockers) in patients with chronic cough have been performed but did not report positive results; a pooled analysis of these data suggests that adults with acid reflux on 24 h pH monitoring or symptoms of heartburn are most likely to experience benefit, which is now reflected in clinical guidelines\(^{4,141,153}\). Observational data support this approach, but response rates were low (28%) even in patients with chronic cough who reported heartburn\(^{144}\).

Treatments for non-acid reflux are limited. Promotility agents (such as the dopamine antagonists metoclopramide and domperidone) can be prescribed only for short-term use owing to their adverse effects and lack of evidence of efficacy in reflux-related chronic cough. Macrolide antibiotics promote gastric emptying, but small studies in patients with refractory chronic cough failed to show benefit\(^{155,156}\). Baclofen, a GABA\(_\text{B}\) agonist, blocks relaxation of the lower oesophageal sphincter, and therefore all types of reflux, but has unacceptable adverse effects for long-term use, whereas lesogabeneran (a peripherally acting GABA\(_\text{B}\) agonist with fewer adverse effects) did not reduce cough frequency in patients with refractory chronic cough in a RCT. Laparoscopic fundoplication, a keyhole surgical procedure whereby the upper part of the stomach is wrapped around the lower oesophagus so as to prevent the reflux of acid from the stomach into the oesophagus, in patients with GERD and chronic cough is rarely indicated owing to limited evidence for efficacy and high risk of long-term complications.

The management of children with GERD is dependent on age and disease severity. Acid-suppressive therapy should not be used solely for chronic cough in children with GERD and chronic cough\(^{157}\). Also, treatment of children with chronic cough is dependent on their age, feeding regimen and symptoms. PPIs and \(\text{H}_\text{1}\) receptor antagonists should not be used for longer than 4–8 weeks in paediatric patients, regardless of effectiveness, without further evaluation\(^{158}\). Should they prove to be successful in controlling the cough, they can be continued for longer periods, although the guidelines for managing paediatric GERD recommend a gastroscopy with biopsies and other tests to confirm anatomy and exclude other causes by histology of the biopsy samples\(^{158}\).

**Upper airway cough syndrome.** The treatment of patients with chronic cough and nasal disease is standard care for the diagnosed nasal condition. Allergic or nonallergic rhinitis is treated with 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\(^{159,160}\). Clinical trials evaluating the effectiveness of targeting concurrent nasal diseases to control chronic cough are lacking; therefore, predictors of improvement in chronic cough remain uncertain\(^{161}\).

**COPD, bronchiectasis and interstitial lung disease.** Cough, typically productive, is a common first symptom of COPD and is usually attributed to cigarette smoking and also as a result of exposure to environmental pollutants\(^{162}\). Chronic bronchitis is a distinct phenotype of COPD and is defined as chronic cough productive of sputum for 3 months over the course of a year for two consecutive years\(^{163}\). In established disease, cough is reported in 70% of patients\(^{17}\) and many consider it to be extremely severe. Moreover, cough is a prominent feature of disease exacerbations and is associated with adverse clinical outcomes\(^{164,165,166}\). Measuring the severity and burden of cough using symptom-based questionnaires is now recommended in the routine clinical evaluation of patients with COPD\(^{160}\). 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\(^{167}\). Impaired airway clearance, mucus retention and bacterial colonization cause inflammation and lung damage, which contribute to cough severity but are independent of cough reflex sensitivity\(^{168}\). Cough is a common and disabling symptom in idiopathic pulmonary fibrosis and may be due to inflammatory consequences

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**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**\(^{150}\). Laryngeal hypersensitivity and dysfunction represent an increased responsiveness of laryngeal protective reflexes triggered by mechanical or chemical stimuli and are considered to be part of the cough hypersensitivity syndrome.

- **Laryngeal hypersensitivity and dysfunction are present in many patients with chronic cough and cough hypersensitivity**\(^{19,251}\). They are often associated with comorbid post-nasal drip, rhinosinusitis, gastro-oesophageal reflux disease and asthma\(^{252}\).

- **Symptoms are usually localized to the laryngeal area, for example, ‘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**\(^{153}\). Other aspects of laryngeal dysfunction include muscle tension dysphonia that can be revealed during vocalization\(^{150}\).

- **Investigations include direct laryngoscopic examination of vocal fold motion during challenge (using external triggers such as exercise or scents), laryngeal electromyogram and voice assessment**\(^{134}\).

- **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**\(^{150}\). Cough neuromodulators such as amitriptyline and gabapentin might also be beneficial.
of the fibrosis itself or to comorbid reflux disease. No medicines are approved to treat cough in these patients, and current consensus is based on limited evidence.

Nonspecific pharmacological therapies
Pharmacological therapies directed at eliminating cough are required in cases in which treatment of comorbid disease associated with cough is unsuccessful at relieving coughing, or in those with no obvious cause for a chronic cough. These therapies are restricted to use in adults as, for cough management purposes, the age cut-off for use in children is usually 14 years. Whether patients other than those with refractory or unexplained chronic cough would benefit from adjunct nonspecific cough therapy is unclear, and controlled trials are needed.

Opiates. Codeine and morphine are commonly used antitussives in adult-based clinical practice and have antitussive effects via central opioid receptors. Accordingly, effective antitussive doses of opiates are likely to cause sedation. The opioid subtype by which opiates inhibit cough remains debatable, as μ-, κ- or δ-opioid receptor agonists are all antitussive. Opioid receptors are also localized to vagal sensory neurons, and their activation can suppress sensory fibre activity; however, unlike oral codeine or intravenous morphine, inhaled morphine or codeine does not inhibit inhaled capsaicin-induced cough, arguing against a peripheral antitussive effect of opiates. Opiates have no role in the management of children with chronic cough as they can cause death.

Codeine has a rapid onset of action. Although widely used, the efficacy of codeine is not supported by clinical studies. Several placebo-controlled RCTs for cough have been published without objective cough measurements, and other trials did not report significant benefits of codeine over placebo. Moreover, codeine has several concerns regarding safety, inter-individual variability in metabolism and dependence, although risk of dependence may be low in those without vulnerability to dependence. Adverse effects of codeine, such as nausea, constipation, dyspepsia, dizziness or somnolence, occur in up to 50% of patients and are mostly non-critical in adults.

Morphine is ~10 times more potent than codeine and is most often considered in patients with severe cough.
intractable cough. One trial demonstrated that low-dose slow-release morphine therapy was associated with significant improvements in subjective cough measures (Leicester Cough Questionnaire and daily cough severity scores) in patients with refractory chronic cough. The most common adverse effects were constipation and drowsiness. The effects of morphine were mostly observed within a week, but benefit was observed in <50% of patients. Morphine is associated with several safety concerns, including respiratory depression, drowsiness and addiction, depending on the dose.

**Gabapentinoids.** The GABA derivatives gabapentin and pregabalin are inhibitors of α2δ subunit-containing voltage-dependent calcium channels and possibly NMDA receptors. 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 one 10-week RCT, gabapentin significantly improved subjective cough measures and objective cough frequency in patients with chronic refractory cough; however, clinical benefits were not sustained after treatment cessation. No improvement in capsaicin cough reflex sensitivity was observed, suggesting a lack of effect on cough hyper-sensitivity. Of note, some patients do not experience any improvement in cough with gabapentin. Pregabalin, as an add-on to speech therapy, significantly improved subjective cough measures compared with speech therapy alone at week 14. However, the effects of pregabalin on objective cough frequency were not significant. Gabapentinoids cause common, and sometimes intolerable, adverse effects, including dizziness, disorientation, confusion, fatigue and blurred vision. The benefit of long-term use of gabapentinoids is difficult to predict given these adverse events.

**Tricyclic antidepressants.** Amitriptyline increases noradrenergic or serotoninergic neurotransmission by blocking presynaptic noradrenaline or serotonin transporters.
and has strong binding affinities for α-adrenergic, histamine (H1) and muscarinic (M1) receptors. In one randomized trial, treatment with low-dose amitriptyline at bedtime was significantly more effective than codeine and guaifenesin combinatorial treatment in improvement of subjective measures of cough in those with post-viral cough hypersensitivity. Moreover, one small observational study found an improvement of >50% in 67% of patients with idiopathic (refractory or unexplained) cough 2–3 months after starting treatment; however, only one-third of patients were still on the treatment after 2–3 years, with 53% reporting an improvement of >50%. A controlled, double-blind study of amitriptyline in chronic cough is needed. The most common adverse effects of amitriptyline are dry mouth, dizziness, headache and somnolence.

Nonspecific cough suppression and the risk of dystussia. Cough has an important protective function in the respiratory tract in 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 unwanted, excessive coughing without suppression of protective cough, essentially targeting the hypersensitive state. Studies in laboratory animals and humans have demonstrated that opiates and other centrally acting neuromodulators (gabapentin and baclofen) can inhibit cough evoked by a broad range of chemical and mechanical stimuli. This action is a dose-dependent generalized suppression of the nervous system (sedation), inhibition of the brainstem neurons involved in generating respiratory rhythm and/or direct suppression of cough sensory nerve activity. Consequently, some nonspecific cough suppressants might cause dystussia, although the prevalence of this is not well documented. One post hoc analysis of patients receiving morphine and codeine for cough suppression suggests that sedation is unlikely to contribute to their cough-suppressing properties, whereas gabapentin improved cough-specific QOL in patients with refractory cough without suppressing capsaicin cough reflex sensitivity. Risk of dystussia and aspiration is likely related to dosing, and some patient groups who are more prone to dystussia (such as the elderly and patients with spinal trauma or neurological disease) may be more susceptible to generalized cough suppression by centrally acting nonspecific cough therapies. At least one new peripherally acting nonspecific cough therapy in clinical trial (the P2X3 antagonist, gefapixant) has been shown not to produce generalized cough suppression at therapeutic doses.

Speech and language therapy

Speech and language therapy consists of education, cough control and suppression techniques, breathing exercises, vocal hygiene, hydration strategies and counselling. Two randomized controlled studies have evaluated the effectiveness of speech and language therapy for adults with unexplained or refractory chronic cough. One study found that 88% of participants in the treatment group showed improvement in symptom frequency and severity scores for breathing, cough, voice and upper airway symptoms, compared with 14% of participants in the placebo group. Another multicentre RCT found an improvement in cough-specific QOL and a reduction in cough frequency in the treatment group compared with the control group. No significant difference was found between therapy and control groups regarding subjective measures of cough and cough reflex sensitivity. The antitussive mechanisms of action of speech and language therapy remain unclear. One hypothesis is that improved understanding of the condition through education and counselling, along with training in suppression strategies, may affect the decreased inhibitory control of cough that is present in such patients. 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.

Treatment of children

Successfully managing a child with chronic cough (leading to cough resolution) is dependent on identifying the aetiology of the cough and treating it (see current clinical guidelines). Therefore, the suggested approach for managing children with chronic cough aims to identify the underlying cause, provide attention to contributing factors (such as tobacco smoke exposure) and understand the effect of the cough on the child and their parents or guardians. Children aged >14 years are usually managed in accordance with adult pathways.

Quality of life

QOL is one of the key end points in clinical trials with novel antitussives, and it also aids clinical practice guideline decision-making. Cough has significant effects on physical and mental health. Effects in adults include urinary incontinence, pain, sleep disturbance, interference with speech, anxiety and depression, avoidance of social situations and inability to work. Less common but severe complications include syncope and head injury, hernia, suicidal ideation and rib fracture. Stress urinary incontinence is under-recognized in adults with cough: ~65% of patients with chronic cough are...
female and 65% will experience cough-induced urinary incontinence\textsuperscript{204}. Patients with cough-induced urinary incontinence are often too embarrassed to mention it 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\textsuperscript{196}. In children, the key effects of chronic cough are annoyance, frustration, tiredness and effects on activities\textsuperscript{205}, whereas effects on parents of children with chronic cough are worries on aetiology of cough, helplessness and sleep disturbance\textsuperscript{206}. Data on the economic burden of chronic cough are lacking.

QOL can be assessed informally in the clinic by asking patients about the effects that are known to be associated with cough. HRQOL questionnaires can be used to quantify QOL in a validated and standardized manner. QOL tools have broad applicability, even in conditions with considerable heterogeneity that can limit the usefulness of objective tools. They capture aspects of disease severity that is not possible with objective tools, such as general health effects like fatigue and sleep disturbance, among others. In patients with cough, QOL tools can assess intensity and urge to cough, which cannot be assessed with cough frequency monitors\textsuperscript{207}. This is particularly important for patients who cough infrequently but are greatly bothered by it.

Studies of QOL in patients with chronic cough using validated tools have found significantly worse QOL in women than in men\textsuperscript{30}. Women had lower QOL owing to physical complaints, psychosocial issues and severe physical complaints. The greatest disparity between the sexes was due to stress urinary incontinence in women. Patients with a longer duration of cough, depression, younger age and interference with speech owing to cough also have worse QOL\textsuperscript{208}. The presence of urge to cough is also highly correlated with impairment in QOL\textsuperscript{209}. One longitudinal study of patients undergoing treatment for chronic cough found that improvement in cough was associated with a significant improvement in QOL at 3 months and continued improvement at 6 months\textsuperscript{206-210}. This improvement was associated with improvements in urinary incontinence, urge to cough and anxiety symptoms\textsuperscript{219}. Future studies to address gaps in knowledge should establish the frequency and characteristics of complications of cough to improve management and understand the direction of the relationship between cough, anxiety and depression. The economic impact of cough on individuals also needs to be investigated.

The Leicester Cough Questionnaire is the most widely used HRQOL tool in adults. This tool consists of 19 items that address physical, psychological and social domains\textsuperscript{211}, has good repeatability and responsiveness, and the minimal important clinical difference has been established\textsuperscript{212}. This questionnaire was used to demonstrate improvement in HRQOL in a randomized, placebo-controlled and double-blind phase III trial assessing antitussive activity of the P2X3 receptor antagonist, gefapixant\textsuperscript{213}. The Cough QOL Questionnaire (CQLQ) is another validated tool for adult patients with chronic cough\textsuperscript{219}. The CQLQ comprises 28 items, has good repeatability and responsiveness, and the minimal important clinical difference has been established\textsuperscript{214}. HRQOL assessments are also valuable in the paediatric setting and are performed using acute cough\textsuperscript{215} or child-specific chronic cough\textsuperscript{209} HRQOL tools. As a child’s illness and management affects the QOL of their family, 27-item and 8-item generic parent-proxy HRQOL tools are available for use in conjunction with cough-specific HRQOL assessments\textsuperscript{216,217}.

Little is known about the long-term outcomes of patients with chronic cough. In a study following patients for 7 years, only 14% of patients had resolution of cough although 26% reported a reduction in cough severity. No predictors of improvement in cough were found\textsuperscript{4}. Chronic cough may be associated with long-term health risks, such as risks of mortality, morbidity or drug adverse effects, although these have not been elucidated in patients with chronic cough.

**Outlook**

**Key gaps in knowledge**

Despite advances in understanding the mechanisms of chronic cough and improvements in therapeutic development, our understanding of the relationship between cough hypersensitivity and chronic cough is incomplete. For example, although some therapeutic benefit has been shown using treatments that target mechanisms putatively involved in establishing or maintaining hypersensitivity, these treatments do not work for all patients and they do not provide complete resolution of cough in most patients who do show responsivity\textsuperscript{11}. Whether this observation reflects the existence of multiple concurrent processes involved in cough hypersensitivity, yet-to-be-discovered ‘lynch pin’ processes or a lack of involvement of cough hypersensitivity in all patients is unclear. This is notable in children where evidence for cough hypersensitivity is lacking and targeting specific clinical conditions results in effective cough resolution.

We do not know whether any relationships exist with respect to the presentation of chronic cough across the lifespan. For example, an important question to answer is whether cough hypersensitivity evolves in some patients owing to the presence of a troublesome cough earlier in life. As such, whether children with chronic cough have a higher risk of cough hypersensitivity in adulthood is unknown. Indeed, genetic determinants might affect the risk of cough hypersensitivity, although this area of research is understudied. One challenge in investigating future health effects of chronic cough lies in the lack of a distinct diagnostic code for chronic cough in the International Classification of Diseases (ICD) system\textsuperscript{217}. Establishment of a code that categorizes chronic cough as a disease 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 are dependent on improved understanding of the multiple clinical dimensions of cough. As mentioned earlier, subjective patient reports of disease severity and effects on QOL do not always track linearly with objective measures of cough frequency. Moreover, the aspects of chronic cough that have the greatest effects on patients’ lives are poorly understood. This lack of knowledge is problematic in trials of therapies that rely...
on only one output as the primary end point measure; for example, only short-term (≤24 h) objective cough frequency is used by drug regulators in clinical trials of new antitussive 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 QOL are accepted as gold standard end point 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 analysis of the sound, intensity, cough bout duration and the time of day 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.

**Endotypes and personalized medicine**

Multiple mechanisms and aetiologies may underlie cough hypersensitivity. Recent suggestions of cough endotypes may help clinical management of cough. Conventionally, these endotypes relate to the underlying clinical condition (such as asthma, GERD or upper airway cough syndrome) but there may be other ways to endotype patients with cough; however, this needs to be explored. Clinical trials with P2X3 antagonists suggest that a subset of patients with refractory chronic cough respond well to purinergic inhibition, perhaps reflecting a currently unrecognized endotype. Trials of other antitussives have similarly shown heterogeneity in responsivity that may reflect differing pathological processes driving cough in different patients. A more careful assessment of this heterogeneity may identify clear endotypes, which then allows more personalized approaches to cough management.

**Emerging therapies**

Improved understanding of cough neurophysiology has advanced the development of new antitussive therapies, several of which are progressing through clinical trials (Supplementary Table 2). Molecules targeting P2X3 and P2X2/3 ATP receptors have demonstrated efficacy in reducing cough counts, and at least four companies have molecules in advanced clinical trials. Gefapixant is the first such compound to have completed phase III trials and demonstrated efficacy in adults with refractory chronic cough, while three other molecules have completed phase II trials (Supplementary Table 2). Trials have also been conducted with centrally acting neuropeptide I receptor antagonists, which have demonstrated some clinical benefit, notably in patients with lung cancer presenting with chronic cough. Drugs in earlier phases of clinical development are those targeting sodium channels involved in cough sensory neuron action potential conduction. Whether these therapies will show efficacy in patients is unknown. Trials with various TRP channel agents have been negative (Supplementary Table 2), and enthusiasm for these drugs as therapeutic targets has waned.

One challenge for these antitussive studies is overcoming the large placebo effect that accompanies current trial designs. The development of improved animal models that better recapitulate the processes that underpin chronic cough and cough hypersensitivity, along with reimagined clinical trial designs and/or improved end point measures may be required to identify true therapeutic efficacies. Furthermore, clinical trials for new compounds have only been assessed in adults, mostly those with refractory chronic cough, and it will be important to ascertain the clinical use of these new antitussives in other patients and in children.

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