BTS Clinical statement on chronic cough in adults

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INTRODUCTION

Chronic cough represents a significant part of everyday practice for practitioners in primary and secondary care. Since the last BTS Guideline on Chronic Cough (CC) in Adults in 2006 (1), we have seen major progress in the diagnosis, and therapy of this condition but it remains a challenging area with a limited evidence base (2,3). Clinical advances, particularly the recognition of cough hypersensitivity syndrome and the use of appropriate drug and non-pharmacological cough treatment has not yet embedded in most routine clinical practice in the UK. The objective of this statement is to distill recent progress into practical recommendations to improve the management of this common and frequently misunderstood disease.

Scope

This clinical statement provides practical advice for a wide range of healthcare practitioners in primary and secondary care looking after adult patients with chronic cough. The causes of chronic cough in children differ significantly to adults and has been addressed in a separate BTS guideline(4). This statement covers acute cough only briefly as it has been reviewed recently by a NICE guideline(5).

Methodology

The Clinical Statement Group (CSG) membership was drawn from respiratory medicine, general practice, physiotherapy, speech and language therapy, nursing, Ear Nose and Throat, a trainee and included lay/patient input. The CSG identified key areas requiring Clinical Practice Points. The overall content was developed to reflect the scope approved by the BTS Standards of Care Committee (SOCC). Following discussions of broad statement content, individual sections were drafted by group members. A final edited draft was reviewed by the BTS SOCC before posting for public consultation and peer review on the BTS website in November 2022. The revised document was re-approved by the BTS SOCC in XX before final publication. A summary of Clinical Practice Points is provided at Appendix A.

SECTION 1: BACKGROUND

The Cough Reflex

Cough is a protective reflex, to prevent aspiration of foreign bodies and expectorate secretions. The airways are innervated by sensory neurons, activation of which is carried via the vagus nerve to the brain stem and higher centres (Figure 1). Airway nerves sense irritant, noxious or mechanical stimuli through receptors on the nerve terminals (e.g., TRPV1 and TRPA1). In health or disease states, stimulation of these receptors may lead to an 'urge to cough', associated with a tickle sensation in the throat leading to coughing(9). Receptors such as the ATP gated P2X3 ion channel can also activate airway nerves; ATP may be released by cell damage, inflammation, and infection. Activation of cough peripheral nerve endings ultimately feeds into a complex central nervous system (CNS) network regulating the cough response. Within the CNS are important centres for the inhibition of peripheral excitatory inputs. Other anatomical areas innervated by the vagus nerve such as the ear (Arnold's reflex) and oesophagus may contribute to cough sensitivity.

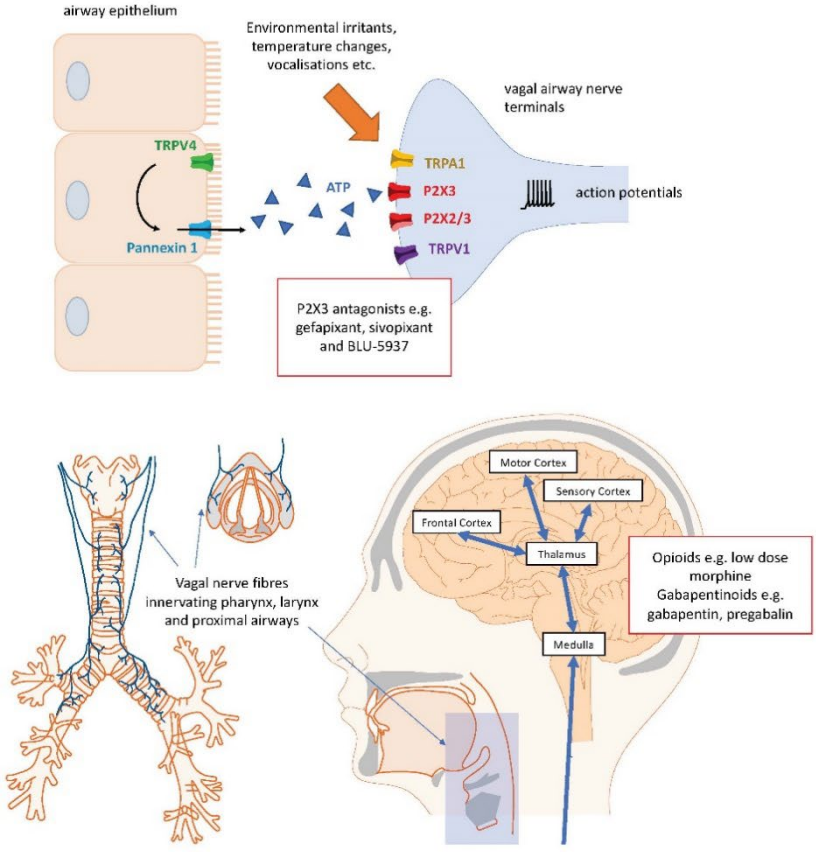

Figure 1. Coughing is initiated by activation of vagal sensory nerve fibres in response to irritant chemicals (via ion channels such as TRPA1 and TRPV1) and mechanical stimuli that generate action potentials. In patients with RCC, activation of vagal nerves by ATP, through P2X3 ion channels is thought to be important based on the efficacy of novel P2X3 antagonist treatments. ATP is likely released from structural cells e.g. epithelium, through pannexin channels activated by other ion channels such as TRPV4 (*J Allergy Clin Immunol. 2016 Jul;138(1):249-261.e12).* Vagal nerve fibres important in mediating cough innervate the oropharynx, hypopharynx, larynx and proximal airways. They transmit action potentials to the medulla in the brainstem, where synaptic transmission activates sensory and motor pathways in the central nervous system. Opioids and gabapentinoids are thought to inhibit coughing in the central nervous system through activation of opioid receptors (μ,δ,κ) and modulation of Ca^{2+} channels

Figure 1: Neurophysiology of the cough reflex

Terminology

Acute cough lasts ≤ 3 weeks and is usually self-limiting and due to a viral infection. Chronic cough lasts > 8 weeks. Various terminology(10) has been used to describe patients with persistent chronic cough in the literature, commonly used terms in current use are refractory and refractory unexplained chronic cough (RCC or RUCC, Table 1) We propose to simplify things. Where cough persists despite addressing co-morbidities or where no co-morbidities are identified we use the term 'Refractory chronic cough' (RCC). RCC should be considered an open multidimensional label, whereby treatment is based on the phenotype of the patient and identified treatable traits will vary or be absent. In many patients, the primary disorder is a hypersensitivity of sensory nerves.

Term	Definition
Acute Cough	Cough lasting < 3 weeks. Usually due to a viral infection
Chronic Cough	Cough lasting > 8 weeks
Refractory Chronic Cough (RCC)	Cause identified. Cough persists despite addressing treatable traits. May have symptoms suggestive of cough hypersensitivity.
Refractory Unexplained Chronic Cough (RUCC)	Unexplained; no treatable traits and no symptoms suggestive of cough hypersensitivity.
Cough Hypersensitivity Syndrome	Disorder characterised by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure. Thought to be mediated by sensitisation of the sensory neuronal pathways controlling cough including the vagus nerve and central nervous system.
Laryngeal Hypersensitivity	Neuronal hypersensitivity thought to underlie a range of laryngeal symptoms (including chronic cough, inducible laryngeal obstruction etc). Thought to be mediated by vagal and central nervous system innervation of laryngeal structures.

Table 1: Terminology

Epidemiology

The community prevalence of chronic cough is unclear, perhaps as high as 10% (11). Many sufferers don't access medical services, tolerating symptoms or possibly self-medicating. UK based primary care studies suggest CC affecting 1.2-2% (12,13) of the population but likely under-estimates the prevalence due to coding issues. Factors associated with CC included cigarette smoking, obstructive airways disease, obesity, reflux (14), rhinitis and ACE inhibitor use (12,13). Many patients may have no identified co-morbidity (13).

Impact of Chronic Cough

The impact on quality of life (QoL) is comparable to other respiratory diseases such as COPD(15). Patients experience numerous unpleasant symptoms; throat discomfort, chest pain, exhaustion, dizziness, syncope and urinary incontinence(16). Anxiety is common in CC (17–19) alongside low mood, fatigue, somatic symptoms, negative illness beliefs and a lack of a clear illness narrative when

their condition is unexplained. Concerns around serious underlying illness are common(19). Sufferers report embarrassment and significant social effort directed at managing negative reactions of others to the cough(20). Work absenteeism(21) and primary care attendance is frequent(22). Repetitive investigations, trials of treatment and referrals to secondary care increase healthcare costs (13). The proprietary cough remedy market is significant, around £400m/pa in the UK.

Summary of impact of cough

Chronic cough (CC) is common, predominantly affecting middle aged females.

Sufferers experience significantly impaired quality of life.

Cough is associated with increased healthcare costs.

Recent advances in the diagnosis and management of cough have not yet widely embedded in routine clinical practice in the UK.

SECTION 2: CAUSES OF CHRONIC COUGH

Moving beyond the anatomical diagnostic protocol

The usual approach to chronic cough, advocated by consensus panels(1,23,24) and informing most routine practice today, is based on the 'anatomical diagnostic protocol' developed in the late 1970's. The approach assumes that cough is 'caused' by a well-defined group of co-morbidities, particularly the familiar triad of asthma, upper airway disease and reflux. Early case series (no randomized controlled trials) suggested a rigorous protocol of investigation and empirical treatment of co-morbidities would cure most cases of cough. The anatomical diagnostic protocol has limitations (25,26) and most importantly, a significant number of patients (30-40%) don't get better with treating comorbidities or no obvious comorbidities exist(13). Clinicians often blindly treat possible causes of cough even when not indicated and RCT evidence suggests it is usually ineffective e.g. prescribing PPI's in the absence of heartburn symptoms(27). Elements of this approach remain valid but need refinement.

Treatable Traits and Cough

We propose to use the term 'treatable trait' to describe conditions that may cause cough. A trait is 'a therapeutic target identified by phenotypes or endotypes through a validated biomarker' and amenable to treatment. The biomarker could be any feature that can be objectively measured or evaluated(28). This approach has shown efficacy in airways disease(29)(30), is grounded in routine clinical practice and allows an open, multidimensional assessment of the various factors that may be causing chronic cough. Rather than labelling the patient as having 'reflux cough' or 'upper airway cough syndrome', consider using a general label (CC or RCC) and outlining contributing traits when describing a patient's presentation e.g., 'RCC with features of a) reflux b) ACEI use c) obesity d) cough hypersensitivity…etc. This approach is practical; a) facilitating a precision medicine approach, treatment is not empiric, rather directed at specifically identified traits and b) recognising the variable contribution of sometimes multiple common traits (presenting as diverse phenotypes). CC is not simply a symptom of traits such as asthma and reflux etc., many patients with CC have an underlying hypersensitivity of the cough reflex. This is often overlooked, explaining to some extent why treatment protocols focusing on other co-morbidities are sometimes ineffective (figure 2, table 2).

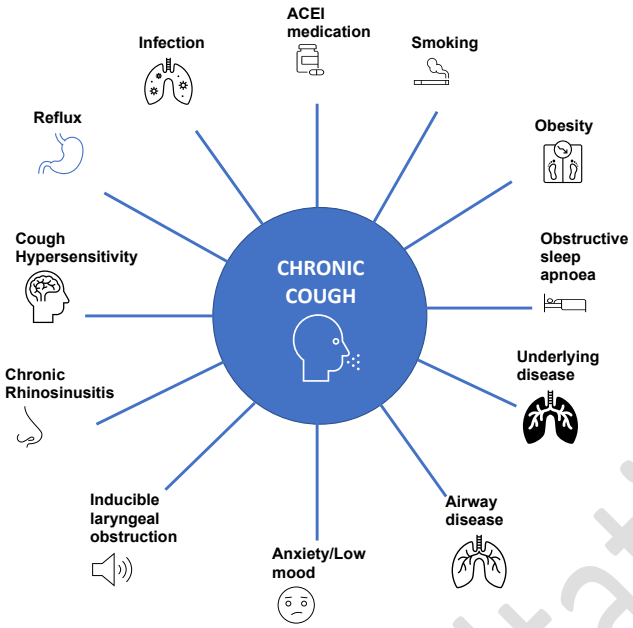

Figure 2: Treatable traits in chronic cough.

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152 Figure 2: Treatable traits of chronic cough

Trait	**Trait Identification Marker**	**Treatment**	**Expected Benefits of Treatment**
Smoking	Patient history. Urinary Cotinine. Exhaled CO.	Smoking cessation. Nicotine replacement therapy (NRT).	Resolving chronic bronchitis→ improvement in cough. May get worse initially as nicotine suppresses cough reflex. Use NRT.
Irritant exposure: cigarette smoking/vaping, occupational exposures chemical/particulates	History Occupational history	Reduce exposure	May improve cough
ACEI Treatment	History. Medication records.	Stop ACEI in <u>all</u> patients with chronic cough. Can use A2RB if needed instead.	Improvement in cough, may take 4 weeks or more.

Airway Eosinophilia	History FeNO >25ppb BEC (≥0.3 x 10^9/L) History	ICS Systemic corticosteroids Monoclonal antibodies	Improve cough and QoL Reduced exacerbations
Productive cough	History of significant sputum production. ? Underlying cause. Sputum C&S HRCT ? bronchiectasis	Airway clearance/physiotherapy Mucolytics Antimicrobials Macrolides	Limited evidence. May improve cough
Chronic Rhinosinusitis	History of two or more symptoms for ≥12 weeks, one of which should be either nasal blockage or nasal discharge (anterior or posterior), with or without facial pain/pressure or reduction or loss of smell	Nasal steroids Saline douching Consider ENT referral	Improvement in rhinosinusitis. Possible improvement in cough. Limited evidence.
Inducible laryngeal obstruction	History Laryngoscopy	Speech therapy intervention	May improve cough, limited evidence.
Obstructive Sleep apnoea	Clinical history Sleep study. Epworth Sleep Score.	CPAP therapy	May improve cough, limited evidence.
Gastroesophageal reflux disease	Clinical history- presence of heartburn best indicator of possible response to treatment. Reflux Symptoms Oesophageal manometry & pH/MII Endoscopy	PPIs Lifestyle measures Also consider; H2 antagonists, weight loss? Fundoplication?	Limited evidence. May improve cough for a subgroup of patients. Most don't improve.

Obesity	BMI Body habitus	Weight loss	May improve cough, no evidence.
Cough Hypersensitivity	Symptoms Cough completely/partially refractory to addressing treatable traits or no treatable traits obvious.	Cough control therapy (SLT) Low dose SR morphine Gabapentin/Pregabalin Clinical Trials of new therapies	Improvements in cough frequency and QoL.
Anxiety/Low mood	History HAD score	Reassurance and explanation Psychological intervention Antidepressants	May improve cough, no evidence.

Table 2: Treatable traits in chronic cough

Chronic cough as a neuropathic disorder. Increasing evidence supports the concept that dysregulation of the neuronal pathways controlling cough plays a role in patients presenting with CC and especially those with RCC(24). Patients cough in response to trivial exposures to environmental irritants (e.g. perfumes, cleaning products), activities not usually evoking cough (e.g. talking, laughing) and also without provocation, suggesting a cough hypersensitivity syndrome(9,31). Asthma, reflux, and rhinosinusitis are associated with chronic coughing, but this presentation is atypical for these common conditions, suggesting additional processes are operating. Finally, evidence shows heightened experimentally evoked cough responses, increased central nervous system activity and reduced cough controls in chronic cough patients, alongside clinical trials demonstrating the efficacy of a range of neuromodulating therapies(32–36). We don't yet have an objective test of cough hypersensitivity; the diagnosis is established by excluding a response to treatment of associated conditions.

Features of cough hypersensitivity are present in many respiratory conditions, not just CC (e.g. asthma, COPD, idiopathic pulmonary fibrosis), and can be considered a treatable trait in its own right(28,37,38). In patients presenting with chronic dry cough as their main symptom, it is often the dominant trait. The nature of the neuronal dysregulation underlying cough hypersensitivity may vary. This may explain why in some individuals CC/cough hypersensitivity resolves with treatment of traits such whereas in others it does not. Treatments targeting the mechanisms underpinning cough hypersensitivity are needed.

CLINICAL PRACTICE POINTS

Protocolised investigation and treatment of common comorbidities such as reflux, rhinitis and asthma is not always effective.

We advocate a 'treatable traits' approach to guide personalised treatment.

Cough hypersensitivity is a frequently overlooked treatable trait for many patients and requires specific treatment.

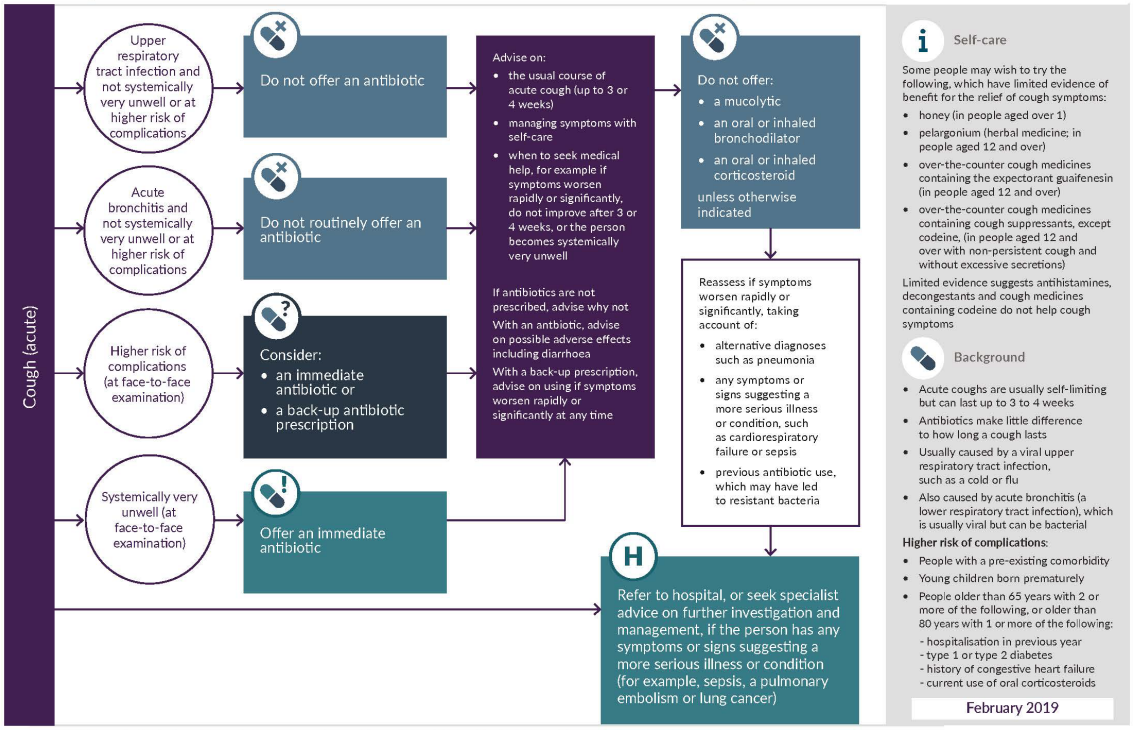
SECTION 3: CLINICAL ASSESSMENT

Acute cough

Cough is common in primary care; the practitioner needs to differentiate rare serious disease from what can be safely managed. Most cough is acute (<3 weeks), self-limiting and due to a viral upper respiratory tract infection (URTI) causing a transient cough hypersensitivity (39). COVID should be considered(40). Most cases settle in 7-10 days, but symptoms may persist for several weeks. There is no role for antibiotics (see Figure 3 and https://www.nice.org.uk/guidance/ng120)(5). Bacterial infection may cause acute bronchitis, antibiotics are usually not needed unless systemically very unwell or at high risk of complications (5). Inflammatory markers such as CRP(41) and procalcitonin(42) may guide decision making. 'Delayed' antibiotic strategies with a post-dated prescription for use if symptoms persist are as effective as immediate antibiotics(43). Prediction rules to identify those at highest risk are effective(44). Routine blood tests or chest x-ray are not recommended in the absence of worrying/atypical findings.

Cough (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



NICE uses 'offer' when there is more certainty of benefit and 'consider' when evidence of benefit is less clear.

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Cough (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

Choice of antibiotic: adults aged 18 years and over

Antibiotic[1]	Dosage and course length
First choice	
Doxycycline[2]	200 mg on first day, then 100 mg once a day for 4 days (5-day course in total)
Alternative first choices[3]	
Amoxicillin	500 mg three times a day for 5 days
Clarithromycin	250 mg to 500 mg twice a day for 5 days
Erythromycin	250 mg to 500 mg four times a day or 500 mg to 1000 mg twice a day for 5 days

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding
[2] Doxycycline should not be used in pregnancy, and the possibility of pregnancy should be considered in women of childbearing age
[3] Amoxicillin is the preferred antibiotic in pregnancy. Erythromycin is preferred if a macrolide is needed in pregnancy, for example, if there is true penicillin allergy and the benefits of antibiotic treatment outweigh the harms. See the Medicines and Healthcare products Regulatory Agency (MHRA) Public Assessment Report on the safety of macrolide antibiotics in pregnancy

Choice of antibiotic: children and young people under 18 years

Antibiotic[1]	Dosage and course length[2]
First choice	
Amoxicillin	1 to 11 months: 125 mg three times a day for 5 days 1 to 4 years: 250 mg three times a day for 5 days 5 to 17 years: 500 mg three times a day for 5 days
Alternative first choices[3]	
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 5 days 8 to 11 kg, 62.5 mg twice a day for 5 days 12 to 19 kg, 125 mg twice a day for 5 days 20 to 29 kg, 187.5 mg twice a day for 5 days 30 to 40 kg, 250 mg twice a day for 5 days 12 to 17 years: 250 mg to 500 mg twice a day for 5 days
Erythromycin	1 month to 1 year: 125 mg four times a day or 250 mg twice a day for 5 days 2 to 7 years: 250 mg four times a day or 500 mg twice a day for 5 days 8 to 17 years: 250 mg to 500 mg four times a day or 500 mg to 1000 mg twice a day for 5 days
Doxycycline[4]	12 to 17 years: 200 mg on first day, then 100 mg once a day for 4 days (5-day course in total)

[1] See BNF for children for appropriate use and dosing in specific populations, for example, hepatic impairment and renal impairment
[2] The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age.
[3] Amoxicillin is the preferred antibiotic in pregnancy. Erythromycin is preferred if a macrolide is needed in pregnancy, for example, if there is true penicillin allergy and the benefits of antibiotic treatment outweigh the harms. See the Medicines and Healthcare products Regulatory Agency (MHRA) Public Assessment Report on the safety of macrolide antibiotics in pregnancy
[4] Doxycycline should not be used in pregnancy, and the possibility of pregnancy should be considered in women of childbearing age

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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196 Figure 3: NICE Guideline - Cough (acute): antimicrobial prescribing NG120

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Treatment. Management prioritises reassurance and self-care (honey, OTC remedies)(45) (5) (figure 3). Evidence for effectiveness of OTC treatments is weak and many medications are likely no better than placebo(46). Careful explanation and 'safety netting' is good practice. A number of drugs are ineffective and should be avoided including; bronchodilators(47) and inhaled/oral steroids(48)(49) (unless underlying asthma/COPD), NSAID's, antihistamines and decongestants (50), mucolytics, codeine(51) and montelukast(52).

Systematic assessment of the patient with chronic cough

A systematic approach to management of CC is outlined in figure 4a and 4b.

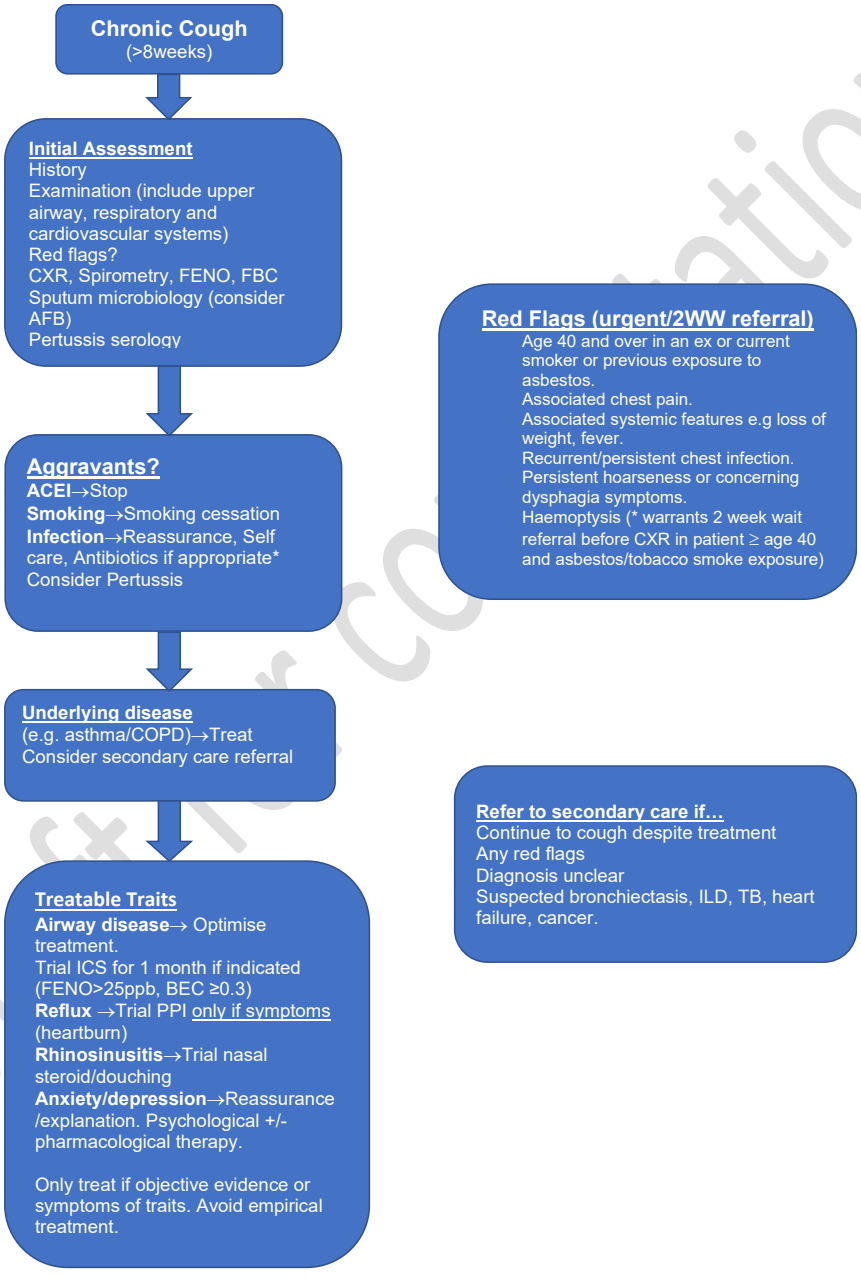

Figure 4a: Management of chronic cough in primary care

Most patients can be treated in primary care and all patients require a similar basic assessment. The process involves the recognition of serious disease and the systematic elimination and treatment of common traits causing cough. Some causes have an established and uncontroversial link with cough,

others are more controversial, and treatment may be less effective. Consider if cough hypersensitivity is a trait.

History and examination

All patients should undergo a face-to-face history and thorough examination including the upper airway and ears. Crackles on auscultation may suggest interstitial lung disease and requires prompt referral. Differentiating serious from non-serious causes of cough can be challenging(53). Figure 4a. shows red flag features requiring urgent chest x ray and/or urgent hospital referral. A normal CXR does not exclude lung cancer(54), refer/investigate if there is any concern. Prediction tools can be helpful(55).

The history can be quite nonspecific(56). Try and identify obvious aggravants such as smoking, ACE inhibitor use, recent viral infection, underlying disease (COPD etc) and treatable traits. Consider occupation and if the symptoms are work related. Ask about the duration of symptoms. The patient should describe the cough in their own words. Clarify that the patient is coughing and not throat clearing (frequently co-exists). Productive cough, particularly if sputum is thick or discoloured, suggests possible airways disease or infection. Many patients describe minimally productive (modest amounts of clear/white sputum) or dry cough. Associated symptoms (wheezing, rhinitis, heartburn etc) suggest an underlying cause. Consider possible symptoms of cough hypersensitivity. Ask about impact on quality of life, complications of chronic coughing and effects on mood. (19)(57)(20)(58). Several validated tools exist to measure cough frequency(59)(60) and quality of life, but they are largely research tools and their clinical utility is unclear(61).

Basic Investigations.

All patients with CC should have; Chest x ray (CXR), Spirometry (and preferably reversibility testing) to look for evidence of underlying airways disease. Sputum culture if infection is suspected. FeNO and Blood eosinophil count to identify eosinophilic/T2 high airway disease that may benefit from inhaled steroid treatment.

When should I refer the patient from Primary to Secondary Care?

Individuals who continue to cough despite treatment, if the diagnosis is unclear or there is suspected underlying disease such as bronchiectasis, interstitial lung disease, TB and heart failure. Red flag symptoms suggestive of malignancy should be referred urgently according to NICE guidelines (6). Patients will usually be seen in a respiratory clinic, but refer appropriately depending on the presentation (e.g., refer to ENT service if predominant upper airway symptoms).

Further Investigations

CT Scan

Chest CT scans should not be ordered routinely. Radiation exposure should be minimised (62), and the relevance of abnormalities picked up when performed routinely is questionable (63)(24)(64)(65). CT scans should be used to look for evidence of disease when indicated e.g. in chronic productive cough to exclude bronchiectasis(66), to exclude a neoplasm if lung cancer is suspected and/or the patient is in a high risk group (pick up rate 1-2%)(65), haemoptysis and a 'barking cough' suggestive of airway collapsibility (dynamic expiratory CT) (67).

Bronchoscopy

There is no role for routine bronchoscopy for most patients with CC. Tracheal abnormalities may be picked up (e.g., tracheopathia osteochondroplastica, airway collapsibility and tracheobronchomalacia) (68–70). Consider when there is suspicion of a) airway collapsibility ('barking'

quality to cough +/- relevant CT findings) b) a foreign body and c) to exclude infection and assess airway secretions when sputum culture is unhelpful/not possible.

Laryngoscopy

Laryngoscopy allows direct visualisation of the nasal passages and larynx and may be indicated in some patients with CC; a) symptoms of rhinosinusitis/rhinitis despite treatment b) hoarse voice symptoms c) where inducible laryngeal obstruction (ILO) is suspected(71).

Investigations not indicated in chronic cough

Methacholine/mannitol challenge tests for bronchial hyperreactivity are of limited value in the management of cough. Cough challenges (e.g., capsaicin) are research tools and should not be used to diagnose RCC. Further research is needed to determine if a cough challenge agent and protocol might discriminate between RCC and other causes of cough(72).

Secondary Care Assessment

Secondary care assessment (figure 4b) should; a) Clarify the diagnosis, particularly the recognition of cough hypersensitivity b) reassure when no serious disease is present c) help patients understand their condition d) provide targeted treatment. Clinicians should try and break the often-repetitive cycle of investigations, empirical treatment and worry experienced by these patients. The degree to which patients have been investigated is variable (73) so basic tests may be required. Further investigations depend on the individual's presentation.

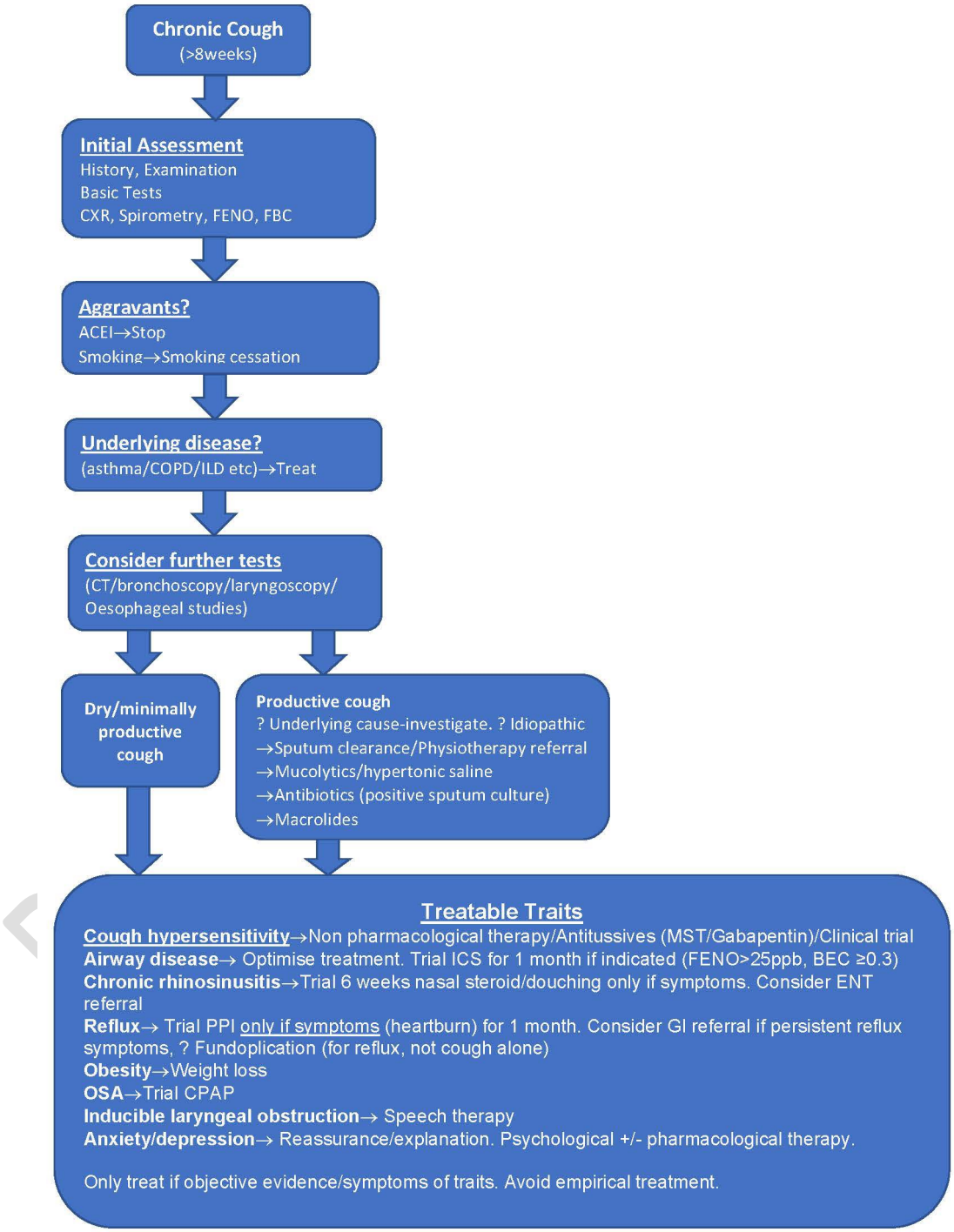

Figure 4b: Management of chronic cough in secondary care

CLINICAL PRACTICE POINTS

Establish who needs specialist referral or can be initially managed in general practice with a targeted trial of therapy. 'Red flags' should prompt urgent referral in line with NICE guidelines(6).

The history should identify possible underlying disease and treatable traits.

All patients with CC should have a chest x ray (CXR), full blood count (FBC), diagnostic spirometry and exhaled nitric oxide (FeNO) (if available).

CC in a patient with a normal CXR and no response to treatment of known or suspected triggers should be referred on to secondary care.

SECTION 4; TREATABLE TRAITS IN COUGH

Smoking

Smoking cessation improves cough by resolving chronic bronchitis(74). Nicotine withdrawal due to smoking cessation may enhancement cough hypersensitivity(75), hence patients may experience more coughing for a period after quitting. This can be attenuated and quit rates improved by using nicotine replacement. **ACE Inhibitors**

ACE inhibitor medication induces cough hypersensitivity(76) and should be discontinued in all patients, regardless of the underlying cause of cough or temporal relationship with symptoms.

Airway Disease

If airway disease is suspected, we advocate the 'treatable traits' approach; identifying and optimising treatment of pulmonary, extrapulmonary and behavioural traits, well described elsewhere(30)(28) and in disease specific guidelines(77)(78)(66). Optimising airway disease treatment is usually the key to managing cough in these patients. Cough hypersensitivity may be a trait in airway disease and need additional specific treatment. Some relevant traits are described in Figure 2 and Table 2.

Productive cough

Chronic productive cough is managed differently to a dry or minimally productive cough. The condition is not well understood. Patients suffer adverse health outcomes regardless of co-existent airflow limitation or smoking status(79). Consider early HRCT and sputum culture. Look for bronchiectasis and other airway disease (asthma, COPD), cigarette smoking, environmental exposure (dusts) and immune deficiency and possible tracheal abnormalities (e.g., tracheopathia osteochondroplastica, airway collapsibility and tracheobronchomalacia). An 'idiopathic productive cough'(80)(81) phenotype has been described, with persistent airway infection, relatively preserved lung function, neutrophilic airway inflammation and no clear radiological bronchiectasis.

Treatment There is limited evidence(82) so therapy is pragmatic; focus on optimising any underlying condition, treating airway infection, mucolytic therapy (e.g. Carbocisteine 750mg tds), and refer to physiotherapy to teach airway clearance techniques(83). Consider a trial of hypertonic saline. There is evidence to support the use of low dose macrolide treatment(84) for patients with productive cough that persists despite these interventions (e.g. Azithromycin 500mg 3 times per week). Macrolides should only be used for productive CC or where there is underlying airway disease as they are ineffective in patients with a dry/non-productive refractory CC(85,86). Macrolides should be initiated after assessment in secondary care. Appropriate follow up and precautions should be taken when commencing macrolide treatment in line with current BTS guidance(87)

Eosinophilic airway disease

A common cause of cough and amenable to treatment. Encompasses various labels including 'classic' asthma, 'cough variant asthma'(88) and 'non-asthmatic eosinophilic bronchitis(89) and may complicate other airway disease categories (COPD, bronchiectasis). Significant (>3%) sputum eosinophilia is the diagnostic gold standard but is technically challenging and not widely available. Exhaled nitric oxide (FeNO) levels and peripheral blood eosinophil count (BEC) indirectly reflect airway eosinophilia. BTS(77) and NICE(90) guidelines consider elevated FeNO levels (NICE specify >40 ppb) supportive of a diagnosis of (T2 high) asthma in an individual with typical symptoms. The usefulness of these markers in predicting response to inhaled corticosteroid (ICS) in CC is less certain. A recent meta-analysis noted the response rate to ICS treatment was significantly higher if FeNO was >25ppb (OR 13.5, sensitivity=77.4%, specificity=81.3%)(7), therefore a FeNO >25ppb should prompt a trial of ICS. A FeNO <25ppb is associated with a low rate of ICS response and should only be considered if there are other factors to suggest eosinophilic airway disease. A raised blood eosinophil count ($\geq 0.3 \times 10^9$/L) is supportive of a diagnosis of eosinophilic airway disease but not sensitive or specific enough to make a diagnosis alone(77); one study reported a weak correlation with treatment response(91).

Treatment

In patients with CC and no other features of airway disease, normal spirometry and low T2 biomarkers avoid the use of ICS and consider alternative causes.

In patients with other features of airways disease, optimise any traits and manage in line with published disease specific guidance. Consider a 1 month trial of ICS e.g. Budesonide DPI 200mcg bd or equivalent.

Cough with no other symptoms or airflow obstruction and raised T2 biomarkers (FeNO >25ppb and BEC $\geq 0.3 \times 10^9$/L). Consider trial of ICS for 4 weeks(7). If response is incomplete, consider escalating treatment e.g. double dose of ICS or add a leukotriene receptor antagonist (LTRA)(8) e.g. Montelukast 10mg nocte or equivalent. Also consider trial of oral corticosteroids e.g., Prednisolone 30 mg od for 2 weeks, and consider poor compliance if markers remain high.

Gastroesophageal Reflux disease

An area of considerable controversy, gastro-oesophageal reflux has long been associated with CC. Whether it is a major cause or just another aggravant in patients with cough hypersensitivity remains a matter of debate(92,93).

Acid Reflux: Proton pump inhibitors (PPIs) continue to be prescribed to treat CC, based on uncontrolled observational studies. Randomised controlled trials of PPIs, generally underpowered and of variable quality, have not demonstrated efficacy(27,94). Re-analysis of pooled data from the studies using 24h pH monitoring to characterise reflux, found therapeutic gain was greatest in patients with pathological oesophageal acid exposure(95). PPI's are not likely to benefit most patients with cough and long term use risks side effects (osteoporosis, infections, kidney disease) (96). A small subgroup may respond but evidence is weak. The presence of heartburn is the best indication for PPI treatment but the response rate is still low (28%)(97). No measure of reflux or questionnaire in chronic cough patients predicts who will respond to acid suppression.

Non acid reflux: There is much speculation about the roles of micro-aspiration, oesophageal dysmotility and other types of reflux (weakly acid, non-acid, gaseous and laryngo-pharyngeal). Micro-aspiration has been proposed to drive chronic coughing but objective studies utilising biomarkers (pepsin, bile acids) have consistently failed to show elevated levels in CC patients compared with healthy controls(98–100). Oesophageal dysmotility is frequently observed(101,102) and may reflect a broader autonomic disturbance(103). There are no good quality trials of prokinetic medications and use is limited due to side effects.

Studies evaluating reflux events in CC patients show the number of reflux events is elevated compared with healthy controls but still within normal limits(104,105). Also, irrespective of acidity, reflux precedes cough more frequently than expected by chance alone, in keeping with a generalised propensity for physiological levels of reflux to evoke coughing in CC (104)(105). Reflux events extending to the proximal oesophagus are no more likely to evoke coughing than those confined to the distal oesophagus. Reflux reaching the larynx/pharynx and gaseous reflux are challenging to measure reliably, hence conclusions are difficult to draw about their importance. Notably, a recent study of GABAb antagonism (lesogaberan) which reduces relaxations of the lower oesophageal sphincter and therefore reflux of all types, had little effect in patients with RCC; an insignificant reduction in cough frequency of ~25%(106). This would imply that reflux events, regardless of their nature are unlikely an important driver in this patient group.

Treatment

Recommendations are made based on evidence in patients with typical reflux symptoms (e.g., heartburn, regurgitation, upper abdominal/chest pain or discomfort)(107).The best predictor of treatment response is the presence of heartburn(97). Treatment should not be prescribed to patients with chronic cough in the absence of these symptoms.

Lifestyle measures including weight loss, dietary modification (not eating before bedtime, reduction of acidic, fatty or spicy foods and carbonated drinks) and raising the head of the bed may be valuable.

Trial of twice daily standard dose PPI for 1 month only in patient with heartburn and the dose only increased to control heartburn e.g. Lansoprazole 30mg bd or equivalent. Most effective if taken regularly 30-60 minutes before meals(108). Discontinue if no effect after 1 month. Re-bound heartburn occurs in the first few days after discontinuation and does not necessarily imply long term treatment is required.

Histamine-2 receptor antagonists taken at bedtime might be beneficial for nocturnal reflux symptoms but evidence is weak(109).

Weak evidence for using prokinetic drugs and should be restricted to specialist services.

Further investigations, including upper gastrointestinal endoscopy and oesophageal manometry plus 24h oesophageal pH-impedance monitoring should be reserved for patients with refractory reflux symptoms (i.e., heartburn, regurgitation) and those requiring high doses of acid suppression to maintain symptom control(107). Gastroenterology/upper GI surgery advice on management should also be sought.

Laparoscopic fundoplication is effective for gastroesophageal reflux disease but frequent complications include reflux recurrence, needing further surgery(96), dysphagia (11%), bloating (40%) and flatulence (57%)(110). A meta-analysis of the numerous published case series in CC (61 studies, 3869 patients)(111) suggested impressive outcomes but should be interpreted cautiously. Studies were of low quality, no RCT's and none utilising validated cough measures. There is good quality evidence to support fundoplication in patients with ongoing symptoms of heartburn and regurgitation, who have abnormal reflux on oesophageal studies, no significant dysmotility and have not responded to or are intolerant of lifestyle measures and acid suppression treatment. It is reasonable to consider fundoplication for patients in this group who also complain of cough but careful assessment and patient counselling is required(112). Fundoplication cannot be recommended for the treatment of cough alone in the absence of typical reflux symptoms and objective evidence of reflux.

Upper airway symptoms

A frequent diagnostic label in cough with a geographic variation in incidence(113), the 'upper airway cough syndrome' encompasses numerous symptoms. Diagnostic criteria have been unclear and

diagnosis based on the response to first generation antihistamines, which may have central antitussive effects(114). Upper airway/nasal disease is frequent in CC patients(115)(116) and other airway disease, making it unclear whether coughing arises from upper or lower airways. Convergence of trigeminal and vagal afferents in central cough pathways(117)(118) provides a possible mechanistic/neuronal link between upper airway disease and the development of cough hypersensitivity.

Nasal disease, in association with global airways inflammation and cough, should preferably be referred to as chronic rhinosinusitis (CRS). In adults CRS is a symptom-based diagnosis defined as the presence of two or more symptoms for ≥12 weeks, one of which should be either nasal blockage or nasal discharge (anterior or posterior), with or without facial pain/pressure or reduction or loss of smell(119). It can be difficult to discriminate between allergic rhinitis, non-allergic rhinitis, and CRS. Allergic rhinitis symptoms include rhinorrhoea (anterior or posterior), nasal congestion, nasal itching, itchy eyes and sneezing. Radiological investigations may be useful and guided by nasal symptoms. Incidental sinus changes may be present in up to one-third of CT scans(120) and two-thirds of MRI scans(121).

"***Post Nasal Drip" (PND)*** can be a symptom of underlying CRS and accompany persistent throat symptoms. There is doubt about the relationship with chronic cough(122).Only a minority of patients with demonstrable post nasal secretions, secondary to infective CRS, report cough as a symptom(123). When PND was mimicked by inserting hyperviscous solution into the nasal cavities of CRS patients and controls, coughing was not evoked(124).

Throat Symptoms; Many patients report persistent throat symptoms despite a normal otolaryngology examination; a feeling of a lump in throat (globus), dysphonia, throat mucus or "phlegm", "catarrh" or mucus entering the throat from the nose, throat clearing, throat discomfort, irritation, tickling and choking. These symptoms often co-exist with chronic cough and may represent a unifying underlying condition(125)(126). Attributed to underlying gastroesophageal reflux in the otolaryngology literature for many years(127,128), "laryngopharyngeal reflux" has remained a popular label to group these symptoms together, despite the lack of evidence supporting this mechanism and lack of effect of reflux treatment(129). Clinicians should explore other potential causes of chronic throat symptoms that have received little attention in the face of the reflux aetiology theory. Psychological distress(130), obesity(131), life events(132)(133), snoring, upper airway dryness, hormonal changes and laryngeal hypersensitivity have all been associated with chronic throat and voice symptoms(134). Laryngeal hypersensitivity could be a common mechanism(135).

'Red flag' symptoms suggestive of malignancy/demonstrable pathology are persistent dysphonia (every word of every sentence, not chronicity) or progressive dysphagia +/- localised pain; risk being greatest in smokers >45 years. Functional symptoms are more intermittent in nature.

Inducible laryngeal obstruction is a common finding in up to 2/3 of patients with CC. It is associated with voice disturbance and breathing pattern disorder and is likely to be a manifestation of laryngeal hypersensitivity(136). Diagnosis is by confirmed by functional laryngoscopy(137) and treatment is by speech therapy intervention.

Treatment

Evidence is limited, only uncontrolled case series suggest that nasal steroids improves cough symptoms (138)(139). For cough patients who report symptoms of CRS, treatment should

include an intranasal steroid spray with saline irrigation/douching for a minimum of 6 weeks, e.g., Mometasone furoate nasal steroid spray 100mcg twice daily, following the saline douching, reduced to 100mcg once daily thereafter.

Antibiotics should be avoided. Secondary care referral should be considered if the nasal symptoms are not improved after 12 weeks of therapy.

A recent large UK multicentre randomised controlled trial (Trial Of Proton-Pump Inhibitors in Throat Symptoms; TOPPITS) found that Lansoprazole 30mg twice-daily conferred no benefit over placebo(140). PPI's should not be used to treat upper airway symptoms.

Consider treatment of laryngeal hypersensitivity (see management of cough hypersensitivity)

Obstructive sleep apnoea (OSA)

The prevalence of OSA in the CC population may be significant (reportedly 39-68% (141)(142)) and CC is common in sleep clinic populations(143)(144). Continuous positive airways pressure (CPAP) therapy improved cough related quality of life in uncontrolled studies(144). A single centre RCT comparing CPAP with sham treatment showed a significant improvement in cough related quality of life but unfortunately did not record any objective cough counting data (145). OSA may enhance cough hypersensitivity via associated gastroesophageal reflux, rhinitis(146)(147), upper respiratory tract irritation and consequent inflammation (144)(145). Patients with cough and OSA may have obvious risk factors (snoring, excessive daytime sleepiness, obesity) but may not be sleepy and other more common causes of cough should be considered. OSA should be considered a possible treatable trait when assessing patients with CC.

Treatment If OSA is suspected, patients should undergo a sleep study and if appropriate a trial of CPAP. The success rate of CPAP therapy for CC is unknown and patients may struggle to tolerate therapy unless there is a marked and obvious improvement, which may be difficult to achieve in patients who aren't sleepy. Larger multicentre trials utilising objective cough recording are required to better assess the impact of intervention.

Obesity

A number of studies have suggested a link between obesity and chronic cough(148)(149). Obesity was more common in patients attending specialist care for chronic cough (24.3% vs 19% in controls)(150). Large population studies offer conflicting results (14)(151),most compelling is the Copenhagen General Population Study(152), 7.4% of obese individuals had a chronic cough, compared to 4.2% in the non-obese group. The prevalence of cough increased with increasing BMI. The main mediator of increased risk appeared to be gastroesophageal reflux disease. A study of patients seen in secondary care with CC suggested a higher incidence of reflux in obese patients and better response of cough to PPI treatment(153). Another possible mechanistic link is OSA (as outlined above) and possibly type 2 diabetes(148). The role of weight loss as a treatment for chronic cough has not been studied directly although weight loss improves OSA and gastroesophageal reflux(148). It is not unreasonable to consider obesity as a potential treatable trait in patients with CC and recommend weight loss strategies as part of a treatment plan.

CLINICAL PRACTICE POINTS

Smoking

Smoking cessation will reduce cough as chronic bronchitis resolves. Nicotine suppresses the cough reflex. Nicotine replacement therapy may prevent a rebound in cough hypersensitivity and worsening symptoms.

ACEI treatment

Stop in all patients with CC. Switch to an angiotensin 2 receptor blocker (A2RB) if needed. Improvement may take 4 weeks or more.

Airway disease: Productive cough

Productive cough is managed differently to a dry or minimally productive cough.

Look for infection, smoking and airways disease, particularly bronchiectasis.

Optimise airway clearance, treat infection. Consider low dose macrolide therapy e.g. Azithromycin 500mg three times per week (not to be used in chronic *dry* cough).

Eosinophilic airway disease

In patients with cough and no other features of airway disease, with normal spirometry and low T2 biomarkers, avoid the use of inhaled corticosteroids (ICS) and consider alternative causes.

In patients with other features of airways disease, optimise any traits and manage in line with published disease specific guidance. Consider a 1 month trial of ICS.

Cough with no other symptoms or airflow obstruction and raised T2 biomarkers (FeNO >25ppb and Blood eosinophil count (BEC) $\geq 0.3 \times 10^9$/L). Consider short trial of ICS for 4 weeks(7) e.g. Budesonide DPI 200mcg bd or equivalent.

If response is incomplete, consider add on treatment e.g. double dose of ICS or add a leukotriene receptor antagonist(LTRA)(8) e.g Montelukast 10mg nocte. Also consider a short trial of oral corticosteroids (e.g. Prednisolone 30mg od for 2 weeks) and consider compliance if markers remain high.

Gastroesophageal Reflux disease

A difficult area. Physiological levels of reflux can stimulate episodes in CC patients.

Only treat with Proton pump inhibitors (PPI's) if patient has heartburn or other definitive evidence of acid reflux e.g. Lansoprazole 30mg bd or equivalent for 4 weeks. Most patients don't respond.

Fundoplication cannot be recommended for the treatment of cough alone in the absence of more typical reflux symptoms and objective evidence of reflux.

Upper airway symptoms

Symptoms of chronic rhinosinusitis should prompt an empirical trial of a nasal steroid.

PPI's are not beneficial for throat symptoms.

Laryngeal dysfunction and hypersensitivity are common in CC.

Obstructive sleep apnoea (OSA)

Consider OSA as a potential treatable trait in refractory cough. Continuous positive airway pressure (CPAP) treatment might improve CC if there is objective evidence of OSA on a sleep study.

Obesity

Obesity is associated with chronic cough. Weight loss should be recommended in obese patients and might improve CC.

SECTION 5; COMPLICATIONS OF COUGH

Urinary incontinence

CC can lead to development of urinary incontinence. Predominantly affecting females and often under reported due to embarrassment, many patients go untreated. Urinary incontinence is associated with

worse quality of life and may impact on psychological health(57) The impact of specific interventions for urinary incontinence is unknown and the focus is usually on treating the cough. Specific interventions, including the input of a nurse specialist, to aid continence may also be beneficial. A trial looking at the impact of the antitussive, gefapixant, in females with urinary incontinence is ongoing(154).

Cough syncope

Cough syncope is a relatively uncommon(58) but consequences can be severe, particularly the potential for serious motor vehicle accidents. Increased intrathoracic pressure during coughing reduces cerebral blood flow (155) via cardioinhibitory baroreflex activation, peripheral vasodilatation and impaired responses to hypotension(156)(157)(158)(159) resulting in syncope. The diagnosis is usually clear from the history and the focus is on a) diagnosing and treating the cause of the cough and b) ensuring the patient is informed about restrictions on driving. There may be a number of specific conditions associated with cough syncope that should be considered (appendix-see table 1,2,3 (58)). In the UK, the Driver Vehicle Licensing Authority (DVLA) provides clear rules regarding driving after cough syncope. A patient who has suffered even a single episode of cough syncope, regardless of cause, should be advised not to drive and that they must inform the DVLA of their condition. https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive#cough-syncope for further information(160).

CLINICAL PRACTICE POINTS

Patients who suffer cough syncope should be advised not to drive and contact the DVLA. See https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive#cough-syncope for further guidance.

All patients presenting with CC should be asked if they are experiencing any symptoms of urinary incontinence (UI).

All patients reporting UI should be referred to their local MDT incontinence service for further specialist input and support.

SECTION 6: MANAGEMENT OF COUGH HYPERSENTIVITY

For patients with RCC, neuromodulating treatments targeting cough hypersensitivity are needed. Unfortunately, at present no treatments are licensed, but novel therapies are in development and non-pharmacological techniques have been found to have efficacy. Some licensed neuromodulator therapies are also beneficial. Cough treatments are likely to work via complex mechanisms and significant placebo effects are common(161).

Non-Pharmacological Treatment

A complex intervention(162), developed by speech and language therapists but also delivered by physiotherapists, based upon techniques that actively suppress coughing. There are 2 RCT's and a number of observational studies showing efficacy (163–168). The PSALTI study showed a 40% reduction in cough frequency and improved quality of life compared to sham therapy. Most patients respond (168) but the long term effect is unknown. Can be complimentary to pharmacological treatment(169) and allow a reduction of pharmacological treatment. It is best delivered by therapists experienced in managing chronic cough. Not widely available, we urge all secondary care organisations to look at ways of providing this therapy, preferably as part of an 'upper airway service' also treating ILO. Group therapy can be a cost-effective way of delivering treatment(170).

Pharmacological Treatment

Less evidence supports the use of pharmacological therapies for RCC and few studies have utilised validated endpoints. Initiation should usually be in secondary care only.

Opioids

Low dose slow-release morphine sulphate 5-10mg bd has been shown in an RCT to improve cough specific quality of life(36), and in patients reporting a clinical response, 24h cough frequency was reduced by 71% over placebo (171). The main side effect is constipation, managed with laxatives or the addition of oral naloxone. Around 50% of patients report benefit usually within about 5 days(130). Once daily dosing may be sufficient if cough symptoms are mainly troublesome during waking hours or overnight. Symptoms quickly return if treatment stops, so long-term use is required to maintain effects. Tolerance does not seem to occur and doses above 10mg bd should not be needed. Concerns remain about abuse/addiction potential and patients should be carefully monitored.

Codeine has frequently been used as an antitussive. It is a weak opiate with variable and unpredictable metabolism into active components including morphine(172). Clinical trials show it is ineffective in treating acute cough due to URTI(51,173) and in patients with COPD(174). It is unlikely to be a reliable antitussive and should not be used.

Gabapentinoids

Gabapentin improved cough specific quality of life in a single RCT(175). A second study assessed the effects of pregabalin versus placebo as an adjunct to non-pharmacological therapy, but found the effects confined to improvements in cough severity and quality of life without a change in cough frequency(169). Gabapentinoids have beneficial effects on anxiety and therefore improvements in mood may have contributed to the apparent benefit or changes in symptom perception or cough intensity. Side effects are common, wide ranging and can be difficult for patients to tolerate. Escalating the dose slowly may help minimise these and maximal doses may not be needed to afford some improvement in cough. Gabapentin and pregabalin are classed as controlled medicines in the UK due to the potential for misuse and addiction.

Gabapentin should be started at a low dose e.g. Gabapentin 100mg tds and then titrated up to a maximum dose of 600mg tds depending on clinical effects and side effects.

Pregabalin 25mg bd initially and increase in increments to 75mg bd.

Patients should be reassessed during does titration and therapy stopped if there are significant side effects or inadequate response to treatment.

Other neuromodulator therapies

A single study of low dose amitriptyline (10mg od) reported significantly improved cough over a combination of codeine/guaifenesin in a randomised trial of patients with chronic cough(176). Clinical experience however suggests more limited value. Baclofen has also been reported to have comparable effects to gabapentin in one trial but causes significant somnolence, dizziness and seizures on sudden withdrawal(177).

Novel therapies

Significant effort has been invested in the development of novel therapies for RCC in recent years, following the first report of the positive effects of a P2X3 antagonist(178) Subsequent studies have confirmed efficacy of gefapixant in RCC (35,179,180) and recently it has been licensed in Japan for the treatment, however disturbances in taste are a common side effect. More selective P2X3 antagonists (eliapixant, sivopixant and BLU-5937) are effective with less taste disturbance(32,141,142). There are currently ongoing clinical trials but the development of eliapixant has been halted due to toxicity

concerns. Placebo effects in more recent trials have made demonstrating treatment effects more challenging. The potential effects of these therapies outside of RCC is largely unexplored apart from one study in Idiopathic Pulmonary Fibrosis which gave borderline results (181). Other promising agents currently being investigated include a TRPM8 (menthol receptor) antagonist and mixed findings for neurokinin 1 receptor antagonists(182)(183). There have been negative trials of several TRP receptor antagonists (184–186) and a negative trial of a nicotinic receptor antagonist(187).

CLINICAL PRACTICE POINTS

Cough hypersensitivity is a treatable trait of many conditions and often the foremost problem in patients with chronic dry/minimally productive cough.

There are currently no tools to positively identify cough hypersensitivity.

Cough hypersensitivity may improve with treatment of other treatable traits, if not the patients has refractory chronic cough (RCC).

In RCC, the most effective treatments are those addressing cough hypersensitivity and include non-pharmacological therapy, low dose morphine and gabapentin.

Novel therapies are in development with P2X3 antagonists proving most promising.

SECTION 7: DELIVERY OF CARE FOR CHRONIC COUGH

Delivering care for patients with chronic cough

The healthcare systems across the UK are largely similar but local healthcare needs and how they are met vary considerably. Clinical assessment of cough does not usually require particularly specialised procedures or equipment and is focused on a thorough and systematic clinical assessment. Cough can almost always be dealt with quite adequately in general practice or a secondary care general respiratory clinic. There are a small and increasing number of tertiary cough clinics in the UK, often with a research focus that have evolved *ad hoc.*

Increasingly secondary care organisations have merged, and consultants work in large teams. This allows subspecialisation and development of special interests such as cough clinics. Work is simply redirected from general clinics to a specific cough clinic, there should not be any resource implications here and a special 'business case' should not be needed. A cough clinic offers certain advantages; The development of expertise and confidence in managing this difficult condition develops a better understanding of cough phenotypes/treatable traits, particularly the recognition of cough hypersensitivity. This allows a focus on treatments aimed at reducing cough hypersensitivity and draws a line under repetitive investigations and treatment trials. Recruitment into clinical trials of novel antitussives can be beneficial for patients when other measures have not been helpful. Trainees attending a cough clinic will get focused training in this area.

Care for patients with CC is multidisciplinary. Specialist nurse input is beneficial and the role should be developed(188). Access to specialist speech and language therapy and physiotherapy is essential for delivering non-pharmacological cough control therapy alongside the assessment and treatment of inducible laryngeal obstruction and breathing pattern disorder. Speech therapy services, particularly voice therapy, have been delivering 'vocal hygiene' and similar therapy for cough to ENT clinics for some time so local expertise may already exist. Speech therapy provision is likely to become a vital

component of all respiratory MDTs over time, not just tertiary services. Workforce planning within organisations should reflect this, but access to funding to deliver this within the UK remains challenging. Delivering this effective treatment should be economically beneficial over time by delivering effective therapy and minimising repetitive healthcare use by sufferers. The Royal College of Speech and Language Therapists have now formally identified the role of speech and language therapy in upper airway disorders within adult respiratory services and the RCSLT 2021 position paper recommends, as a minimum care standard, equitable patient access to appropriately trained staff for those individuals suffering with chronic cough. The RCSLT position paper and this document should be bused to support service development (189).

CLINICAL PRACTICE POINTS

Almost all CC can be dealt with in primary or secondary care.

Consider setting up a secondary care cough clinic. Secondary care organisations should look to providing specialist speech therapy and physiotherapy as part of an MDT to support the diagnosis and management of cough and other upper airway disorders.

SECTION 8: RESEARCH

As evident in this document, high quality evidence for the current clinical management of patients with CC is scant and therefore numerous opportunities exist to advance knowledge in this field. The development of validated tools to assess cough provides the ability to better evaluate therapies targeting treatable traits and perhaps more importantly identify predictors of treatment response that could guide therapy and improve the patient experience.

The development of P2X3 antagonists as the first novel, effective therapies for RCC has the potential to substantially improve the care of patients with RCC, assuming licensing of these treatments becomes widespread. However, treatments utilising other mechanisms to address cough hypersensitivity are required, as 25-30% of patients in clinical trials did not gain clinical meaningful improvements and the trials did not include those with less severe RCC. Care would also be improved by the optimisation/standardisation of non-pharmacological treatment. Including only the most effective components would likely facilitate more extensive adoption.

Finally, currently the diagnosis of RCC is a diagnosis of exclusion. This inevitably produces difficulty in establishing this diagnosis, the expense associated with investigations/treatment trials and prolongs the time to reach this diagnosis for patients. A better understanding of the mechanisms underlying cough hypersensitivity and the identification of biomarkers capable of positively identifying this trait has the potential to transform the management of CC for patients and clinicians and should also be a focus of future research efforts.

REFERENCES

1. Morice AH, McGarvey L, Pavord I, British Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. Thorax. 2006 Sep;61 Suppl 1:i1-24.

2. Mazzone SB, McGarvey L. Mechanisms and Rationale for Targeted Therapies in Refractory and Unexplained Chronic Cough. Clin Pharmacol Ther. 2021 Mar;109(3):619–36.

3. Morice A, Dicpinigaitis P, McGarvey L, Birring SS. Chronic cough: new insights and future prospects. Eur Respir Rev Off J Eur Respir Soc. 2021 Dec 31;30(162):210127.

4. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R, on behalf of the British Thoracic Society Cough Guideline Group. Recommendations for the assessment and management of cough in children. Thorax. 2007 Sep 28;63(Supplement 3):iii1–15.

5. Overview | Cough (acute): antimicrobial prescribing | Guidance | NICE [Internet]. NICE; [cited 2022 Apr 6]. Available from: https://www.nice.org.uk/guidance/ng120

6. Overview | Suspected cancer: recognition and referral | Guidance | NICE [Internet]. NICE; [cited 2022 Apr 7]. Available from: https://www.nice.org.uk/guidance/ng12

7. Ambrosino P, Accardo M, Mosella M, Papa A, Fuschillo S, Spedicato GA, et al. Performance of fractional exhaled nitric oxide in predicting response to inhaled corticosteroids in chronic cough: a meta-analysis. Ann Med. 2021 Dec;53(1):1659–72.

8. Côté A, Russell RJ, Boulet LP, Gibson PG, Lai K, Irwin RS, et al. Managing Chronic Cough Due to Asthma and NAEB in Adults and Adolescents. Chest. 2020 Jul;158(1):68–96.

9. Won HK, Kang SY, Kang Y, An J, Lee JH, Lee SM, et al. Cough-Related Laryngeal Sensations and Triggers in Adults With Chronic Cough: Symptom Profile and Impact. Allergy Asthma Immunol Res. 2019 Sep;11(5):622–31.

10. McGarvey L, Gibson PG. What Is Chronic Cough? Terminology. J Allergy Clin Immunol Pract. 2019 Aug;7(6):1711–4.

11. Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. Eur Respir J. 2014 Nov;44(5):1149–55.

12. Holden SE, Morice A, Birring SS, Jenkins-Jones S, Langerman H, Weaver J, et al. Cough presentation in primary care and the identification of chronic cough: a need for diagnostic clarity? Curr Med Res Opin. 2020 Jan 2;36(1):139–50.

13. Hull JH, Langerman H, Ul-Haq Z, Kamalati T, Lucas A, Levy ML. Burden and impact of chronic cough in UK primary care: a dataset analysis. BMJ Open. 2021 Dec 17;11(12):e054832.

14. Arinze JT, de Roos EW, Karimi L, Verhamme KMC, Stricker BH, Brusselle GG. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. ERJ Open Res. 2020 Apr;6(2):00300–2019.

15. Polley L, Yaman N, Heaney L, Cardwell C, Murtagh E, Ramsey J, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008 Aug;134(2):295–302.

16. Kum E, Guyatt GH, Devji T, Wang Y, Bakaa L, Lan L, et al. Cough symptom severity in patients with refractory or unexplained chronic cough: a systematic survey and conceptual framework. Eur Respir Rev. 2021 Sep 30;30(161):210104.

17. McGarvey LP, Carton C, Gamble LA, Heaney LG, Shepherd R, Ennis M, et al. Prevalence of psychomorbidity among patients with chronic cough. Cough Lond Engl. 2006 Jun 16;2:4.

18. Dicpinigaitis PV, Tso R, Banauch G. Prevalence of Depressive Symptoms Among Patients With Chronic Cough. CHEST. 2006 Dec 1;130(6):1839–43.

19. Hulme K, Deary V, Dogan S, Parker SM. Psychological profile of individuals presenting with chronic cough. ERJ Open Res. 2017 Jan;3(1):00099–2016.

20. Hulme K, Dogan S, Parker SM, Deary V. 'Chronic cough, cause unknown': A qualitative study of patient perspectives of chronic refractory cough. J Health Psychol. 2019 May;24(6):707–16.

21. Koskela HO, Lätti AM, Pekkanen J. The impacts of cough: a cross-sectional study in a Finnish adult employee population. ERJ Open Res [Internet]. 2018 Oct 1 [cited 2022 Mar 21];4(4). Available from: https://openres.ersjournals.com/content/4/4/00113-2018

22. Koskela HO, Lätti AM, Pekkanen J. Risk factors for repetitive doctor's consultations due to cough: a cross-sectional study in a Finnish employed population. BMJ Open. 2019 Jun 11;9(6):e030945.

23. Irwin RS, French CL, Chang AB, Altman KW, CHEST Expert Cough Panel*. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018 Jan;153(1):196–209.

24. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020 Jan;55(1):1901136.

25. Pavord ID, Chung KF. Management of chronic cough. Lancet Lond Engl. 2008 Apr 19;371(9621):1375–84.

26. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet Lond Engl. 2008 Apr 19;371(9621):1364–74.

27. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev. 2011 Jan 19;2011(1):CD004823.

28. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016 Feb;47(2):410–9.

29. McDonald VM, Gibson PG. Treatable traits in asthma: moving beyond diagnostic labels. Med J Aust. 2022 Apr 18;216(7):331–3.

30. Agusti A, Barnes N, Cruz AA, Gibson PG, Heaney LG, Inoue H, et al. Moving towards a Treatable Traits model of care for the management of obstructive airways diseases. Respir Med. 2021 Oct;187:106572.

31. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. Respir Med. 2015 Jun;109(6):701–7.

32. Hilton E, Satia I, Holt K, Woodcock AA, Belcher J, Smith JA. The Effect of Pain Conditioning on Experimentally Evoked Cough: Evidence of Impaired Endogenous Inhibitory Control Mechanisms in Refractory Chronic Cough. Eur Respir J. 2020 Jul 23;2001387.

33. Hilton ECY, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. J Allergy Clin Immunol. 2013 Oct;132(4):847-855.e1-5.

34. Prudon B, Birring SS, Vara DD, Hall AP, Thompson JP, Pavord ID. Cough and glottic-stop reflex sensitivity in health and disease. Chest. 2005 Feb;127(2):550–7.

35. McGarvey LP, Birring SS, Morice AH, Dicpinigaitis PV, Pavord ID, Schelfhout J, et al. Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet Lond Engl. 2022 Mar 5;399(10328):909–23.

36. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007 Feb 15;175(4):312–5.

37. Satia I, Tsamandouras N, Holt K, Badri H, Woodhead M, Ogungbenro K, et al. Capsaicin-evoked cough responses in asthmatic patients: Evidence for airway neuronal dysfunction. J Allergy Clin Immunol. 2017 Mar;139(3):771-779.e10.

38. Doherty MJ, Mister R, Pearson MG, Calverley PM. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax. 2000 Dec;55(12):1028–32.

39. Dicpinigaitis PV. Effect of viral upper respiratory tract infection on cough reflex sensitivity. J Thorac Dis. 2014 Oct;6(Suppl 7):S708-711.

40. Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE [Internet]. NICE; [cited 2022 Apr 6]. Available from: https://www.nice.org.uk/guidance/ng191

41. Lingard H, Zehetmayer S, Maier M. Bacterial superinfection in upper respiratory tract infections estimated by increases in CRP values: a diagnostic follow-up in primary care. Scand J Prim Health Care. 2008;26(4):211–5.

42. Odermatt J, Friedli N, Kutz A, Briel M, Bucher HC, Christ-Crain M, et al. Effects of procalcitonin testing on antibiotic use and clinical outcomes in patients with upper respiratory tract infections. An individual patient data meta-analysis. Clin Chem Lab Med. 2017 Nov 27;56(1):170–7.

43. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. Cochrane Database Syst Rev. 2017 Sep 7;9:CD004417.

44. Recommendations | Pneumonia (community-acquired): antimicrobial prescribing | Guidance | NICE [Internet]. NICE; [cited 2022 Apr 6]. Available from: https://www.nice.org.uk/guidance/ng138/chapter/Recommendations

45. Abuelgasim H, Albury C, Lee J. Effectiveness of honey for symptomatic relief in upper respiratory tract infections: a systematic review and meta-analysis. BMJ Evid-Based Med. 2021 Apr;26(2):57–64.

46. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev. 2014 Nov 24;(11):CD001831.

47. Lowry R, Wood A, Higenbottam T. The effect of anticholinergic bronchodilator therapy on cough during upper respiratory tract infections. Br J Clin Pharmacol. 1994 Feb;37(2):187–91.

48. El-Gohary M, Hay AD, Coventry P, Moore M, Stuart B, Little P. Corticosteroids for acute and subacute cough following respiratory tract infection: a systematic review. Fam Pract. 2013 Oct;30(5):492–500.

49. Hay AD, Little P, Harnden A, Thompson M, Wang K, Kendrick D, et al. Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults With Acute Lower Respiratory Tract Infection: A Randomized Clinical Trial. JAMA. 2017 Aug 22;318(8):721–30.

50. De Sutter AI, Eriksson L, van Driel ML. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database Syst Rev. 2022 Jan 21;1:CD004976.

51. Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. J Clin Pharm Ther. 1992 Jun;17(3):175–80.

52. Wang K, Birring SS, Taylor K, Fry NK, Hay AD, Moore M, et al. Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial. Lancet Respir Med. 2014 Jan;2(1):35–43.

53. Neal RD, Hamilton W, Rogers TK. Lung cancer. BMJ. 2014 Nov 6;349:g6560.

54. Stapley S, Sharp D, Hamilton W. Negative chest X-rays in primary care patients with lung cancer. Br J Gen Pract J R Coll Gen Pract. 2006 Aug;56(529):570–3.

55. Hamilton W, Green T, Martins T, Elliott K, Rubin G, Macleod U. Evaluation of risk assessment tools for suspected cancer in general practice: a cohort study. Br J Gen Pract J R Coll Gen Pract. 2013 Jan;63(606):e30-36.

56. McGarvey LPA. Patterns of cough in the clinic. Pulm Pharmacol Ther. 2011 Jun;24(3):300–3.

57. French CL, Crawford SL, Bova C, Irwin RS. Change in Psychological, Physiological, and Situational Factors in Adults After Treatment of Chronic Cough. Chest. 2017 Sep;152(3):547–62.

58. Dicpinigaitis PV, Lim L, Farmakidis C. Cough syncope. Respir Med. 2014 Feb;108(2):244–51.

59. Vertigan AE, Kapela SL, Birring SS, Gibson PG. Feasibility and clinical utility of ambulatory cough monitoring in an outpatient clinical setting: a real-world retrospective evaluation. ERJ Open Res. 2021 Oct;7(4):00319–2021.

60. Hall JI, Lozano M, Estrada-Petrocelli L, Birring S, Turner R. The present and future of cough counting tools. J Thorac Dis. 2020 Sep;12(9):5207–23.

61. Cho PSP, Birring SS, Fletcher HV, Turner RD. Methods of Cough Assessment. J Allergy Clin Immunol Pract. 2019 Aug;7(6):1715–23.

62. Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009 Dec 14;169(22):2071–7.

63. Truba O, Rybka A, Klimowicz K, Grabczak EM, Żukowska M, Dąbrowska M, et al. Is a normal chest radiograph sufficient to exclude pulmonary abnormalities potentially associated with chronic cough? Adv Respir Med. 2018;86(3).

64. Turner RD, Bothamley GH. Chronic cough and a normal chest X-ray - a simple systematic approach to exclude common causes before referral to secondary care: a retrospective cohort study. Npj Prim Care Respir Med. 2016 Mar 3;26(1):1–7.

65. Kuzniewski CT, Kizhner O, Donnelly EF, Henry TS, Amin AN, Kandathil A, et al. ACR Appropriateness Criteria® Chronic Cough. J Am Coll Radiol. 2021 Nov;18(11):S305–19.

66. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn SJ, Floto AR, et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019 Jan;74(Suppl 1):1–69.

67. Baroni RH, Feller-Kopman D, Nishino M, Hatabu H, Loring SH, Ernst A, et al. Tracheobronchomalacia: comparison between end-expiratory and dynamic expiratory CT for evaluation of central airway collapse. Radiology. 2005 May;235(2):635–41.

68. Decalmer S, Woodcock A, Greaves M, Howe M, Smith J. Airway abnormalities at flexible bronchoscopy in patients with chronic cough. Eur Respir J. 2007 Dec;30(6):1138–42.

69. Al-Sheklly B, Hennessey S, Badri H, Khalid S, Woodcock A, Smith JA, et al. Bronchoscopy in chronic cough; a real life review of practices. Eur Respir J [Internet]. 2019 Sep 28 [cited 2022 Apr 6];54(suppl 63). Available from: https://erj.ersjournals.com/content/54/suppl_63/PA611

70. Digby JW, King J, Smith J, Haines J, Hennessey S, Ludlow S, et al. Bronchoscopy and laryngoscopy findings in refractory chronic cough (RCC). Eur Respir J [Internet]. 2021 Sep 5 [cited 2022 Apr 6];58(suppl 65). Available from: https://erj.ersjournals.com/content/58/suppl_65/PA1936

71. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. Eur Respir J. 2017 Sep;50(3):1602221.

72. Holt K, Mcguinness K, Sheppard K, Smith J. How do cough patterns correlate with novel capsaicin cough challenge parameters? Eur Respir J [Internet]. 2021 Sep 5 [cited 2022 Apr 7];58(suppl 65). Available from: https://erj.ersjournals.com/content/58/suppl_65/OA4061

73. Mackley R, Schatzberger T, Parker SM. S34 Management of chronic cough in primary care. Thorax. 2013 Dec 1;68(Suppl 3):A20–A20.

74. Mullen JB, Wright JL, Wiggs BR, Paré PD, Hogg JC. Structure of central airways in current smokers and ex-smokers with and without mucus hypersecretion: relationship to lung function. Thorax. 1987 Nov;42(11):843–8.

75. Dicpinigaitis PV. Effect of tobacco and electronic cigarette use on cough reflex sensitivity. Pulm Pharmacol Ther. 2017 Dec;47:45–8.

76. Morice AH, Lowry R, Brown MJ, Higenbottam T. Angiotensin-converting enzyme and the cough reflex. Lancet Lond Engl. 1987 Nov 14;2(8568):1116–8.

77. Asthma | British Thoracic Society | Better lung health for all [Internet]. [cited 2022 May 9]. Available from: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/

78. COPD | British Thoracic Society | Better lung health for all [Internet]. [cited 2022 May 13]. Available from: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/copd/

79. Balte PP, Chaves PHM, Couper DJ, Enright P, Jacobs DR, Kalhan R, et al. Association of Nonobstructive Chronic Bronchitis With Respiratory Health Outcomes in Adults. JAMA Intern Med. 2020 May 1;180(5):676–86.

80. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J. 2009 Oct;34(4):812–8.

81. Martin MJ, Harrison TW. Causes of chronic productive cough: An approach to management. Respir Med. 2015 Sep;109(9):1105–13.

82. Malesker MA, Callahan-Lyon P, Madison JM, Ireland B, Irwin RS, CHEST Expert Cough Panel. Chronic Cough Due to Stable Chronic Bronchitis: CHEST Expert Panel Report. Chest. 2020 Aug;158(2):705–18.

83. Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax. 2009 May 1;64(Suppl 1):i1–52.

84. Martin MJ, Lee H, Clayton C, Pointon K, Soomro I, Shaw DE, et al. Idiopathic chronic productive cough and response to open-label macrolide therapy: An observational study. Respirol Carlton Vic. 2019 Jun;24(6):558–65.

85. Yousaf N, Monteiro W, Parker D, Matos S, Birring S, Pavord ID. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010 Dec;65(12):1107–10.

86. Hodgson D, Anderson J, Reynolds C, Oborne J, Meakin G, Bailey H, et al. The Effects of Azithromycin in Treatment-Resistant Cough: A Randomized, Double-Blind, Placebo-Controlled Trial. Chest. 2016 Apr;149(4):1052–60.

87. Smith D, Du Rand IA, Addy C, Collyns T, Hart S, Mitchelmore P, et al. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. BMJ Open Respir Res. 2020 Apr;7(1):e000489.

88. Irwin RS, French CT, Smyrnios NA, Curley FJ. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. Arch Intern Med. 1997 Sep 22;157(17):1981–7.

89. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. Lancet Lond Engl. 1989 Jun 17;1(8651):1346–8.

90. Recommendations | Asthma: diagnosis, monitoring and chronic asthma management | Guidance | NICE [Internet]. NICE; [cited 2022 May 9]. Available from: https://www.nice.org.uk/guidance/ng80/chapter/Recommendations#objective-tests-for-diagnosing-asthma-in-adults-young-people-and-children-aged-5-and-over

91. Rybka-Fraczek A, Dabrowska M, Grabczak EM, Bialek-Gosk K, Klimowicz K, Truba O, et al. Blood eosinophils as a predictor of treatment response in adults with difficult-to-treat chronic cough. ERJ Open Res. 2021 Oct;7(4):00432–2021.

92. Kahrilas PJ, Smith JA, Dicpinigaitis PV. A Causal Relationship Between Cough and Gastroesophageal Reflux Disease (GERD) Has Been Established: a Pro/Con Debate. Lung. 2014 Feb;192(1):39–46.

93. Houghton LA, Smith JA. Gastro-oesophageal reflux events: just another trigger in chronic cough? Gut. 2017 Dec;66(12):2047–8.

94. Kahrilas PJ, Altman KW, Chang AB, Field SK, Harding SM, Lane AP, et al. Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report. Chest. 2016 Dec;150(6):1341–60.

95. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. Chest. 2013 Mar;143(3):605–12.

96. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. JAMA. 2020 Dec 22;324(24):2536–47.

97. Badri H, Satia I, Bansal V, Mangi MA, Tangaroonsanti A, DeVault KR, et al. Heartburn as a Marker of the Success of Acid Suppression Therapy in Chronic Cough. Lung. 2021 Dec;199(6):597–602.

98. Decalmer S, Stovold R, Houghton LA, Pearson J, Ward C, Kelsall A, et al. Chronic cough: relationship between microaspiration, gastroesophageal reflux, and cough frequency. Chest. 2012 Oct;142(4):958–64.

99. Pauwels A, Decraene A, Blondeau K, Mertens V, Farre R, Proesmans M, et al. Bile acids in sputum and increased airway inflammation in patients with cystic fibrosis. Chest. 2012 Jun;141(6):1568–74.

100. Grabowski M, Kasran A, Seys S, Pauwels A, Medrala W, Dupont L, et al. Pepsin and bile acids in induced sputum of chronic cough patients. Respir Med. 2011 Aug;105(8):1257–61.

101. Almansa C, Smith JA, Morris J, Crowell MD, Valdramidou D, Lee AS, et al. Weak peristalsis with large breaks in chronic cough: association with poor esophageal clearance. Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2015 Mar;27(3):431–42.

991 102. Kastelik JA, Redington AE, Aziz I, Buckton GK, Smith CM, Dakkak M, et al. Abnormal
992 oesophageal motility in patients with chronic cough. Thorax. 2003 Aug;58(8):699–702.

993 103. Dockry RJ, Farrelly CL, Mitchell J, Corfield DR, Smith JA. Chronic cough is associated with
994 increased reporting of autonomic symptoms. ERJ Open Res. 2021 Jul;7(3):00105–2021.

995 104. Smith JA, Decalmer S, Kelsall A, McGuinness K, Jones H, Galloway S, et al. Acoustic cough-
996 reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology.
997 2010 Sep;139(3):754–62.

998 105. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients
999 with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring.
1000 Gut. 2005 Apr;54(4):449–54.

1001 106. Badri H, Gibbard C, Denton D, Satia I, Al-Shekllly B, Dockry RJ, et al. A double-blind randomised
1002 placebo-controlled trial investigating the effects of lesogaberan on the objective cough
1003 frequency and capsaicin-evoked coughs in patients with refractory chronic cough. ERJ Open
1004 Res. 2022 Jan;8(1):00546–2021.

1005 107. Overview | Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and
1006 management | Guidance | NICE [Internet]. NICE; [cited 2022 May 27]. Available from:
1007 https://www.nice.org.uk/guidance/cg184

1008 108. Waghray A, Waghray N, Perzynski AT, Votruba M, Wolfe MM. Optimal Omeprazole Dosing
1009 and Symptom Control: A Randomized Controlled Trial (OSCAR Trial). Dig Dis Sci. 2019
1010 Jan;64(1):158–66.

1011 109. Schuitenmaker JM, Kuipers T, Smout AJPM, Fockens P, Bredenoord AJ. Systematic review:
1012 Clinical effectiveness of interventions for the treatment of nocturnal gastroesophageal reflux.
1013 Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc. 2022 Apr 21;e14385.

1014 110. Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, et al. Laparoscopic antireflux
1015 surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial.
1016 JAMA. 2011 May 18;305(19):1969–77.

1017 111. Tustumi F, Bernardo WM, Mariano da Rocha JR, Szachnowicz S, Bernal da Costa Seguro FC,
1018 Bianchi ET, et al. Anti-reflux surgery for controlling respiratory symptoms of gastro-
1019 esophageal reflux disease: A systematic review and meta-analysis. Asian J Surg. 2021
1020 Jan;44(1):2–10.

1021 112. Spence JD. The need for clinical judgement in the application of evidence-based medicine.
1022 BMJ Evid-Based Med. 2020 Oct 1;25(5):172–7.

1023 113. Yasuda K. Upper airway cough syndrome may be the main cause of chronic cough in Japan: a
1024 cohort study. Fam Pract. 2021 Nov 24;38(6):751–7.

1025 114. Dicpinigaitis PV, Morice AH, Birring SS, McGarvey L, Smith JA, Canning BJ, et al. Antitussive
1026 drugs--past, present, and future. Pharmacol Rev. 2014;66(2):468–512.

1027 115. Dąbrowska M, Arcimowicz M, Grabczak EM, Truba O, Rybka A, Białek-Gosk K, et al. Chronic
1028 cough related to the upper airway cough syndrome: one entity but not always the same. Eur
1029 Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-
1030 Laryngol - Head Neck Surg. 2020 Oct;277(10):2753–9.

116. Marino MJ, Lal D. Association of cough with asthma in chronic rhinosinusitis patients. Laryngoscope Investig Otolaryngol. 2020 Apr;5(2):200–4.

117. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS, et al. WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation — Updates inCOVID-19. World Allergy Organ J. 2021 Nov 22;14(12):100618.

118. LUCANSKA M, HAJTMAN A, CALKOVSKY V, KUNC P, PECOVA R. Upper Airway Cough Syndrome in Pathogenesis of Chronic Cough. Physiol Res. 2020 Dec 1;69(Suppl 1):S35–42.

119. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1–464.

120. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clin Otolaryngol Allied Sci. 2002 Feb;27(1):11–7.

121. Hansen AG, Helvik AS, Nordgård S, Bugten V, Stovner LJ, Håberg AK, et al. Incidental findings in MRI of the paranasal sinuses in adults: a population-based study (HUNT MRI). BMC Ear Nose Throat Disord. 2014;14(1):13.

122. Smith JA, Woodcock A. Chronic Cough. N Engl J Med. 2016 Oct 20;375(16):1544–51.

123. O'Hara J, Jones NS. 'Post-nasal drip syndrome': most patients with purulent nasal secretions do not complain of chronic cough. Rhinology. 2006 Dec;44(4):270–3.

124. Rimmer J, Hellgren J, Harvey RJ. Simulated postnasal mucus fails to reproduce the symptoms of postnasal drip in rhinitics but only in healthy subjects. Rhinology. 2015 Jun;53(2):129–34.

125. O'Hara J, Fisher H, Hayes L, Wilson J. 'Persistent throat symptoms' versus 'laryngopharyngeal reflux': a cross-sectional study refining the clinical condition. BMJ Open Gastroenterol. 2022 Mar 25;9(1):e000850.

126. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough Lond Engl. 2014 Feb 19;10:1.

127. Hamilton NJI, Wilcock J, Hannan SA. A lump in the throat: laryngopharyngeal reflux. BMJ. 2020 Nov 2;371:m4091.

128. Powell J, O'Hara J, Wilson JA. Are persistent throat symptoms atypical features of gastric reflux and should they be treated with proton pump inhibitors? BMJ. 2014 Oct 9;349:g5813.

129. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005 May;54(5):710–7.

130. Deary IJ, Wilson JA, Harris MB, MacDougall G. Globus pharyngis: development of a symptom assessment scale. J Psychosom Res. 1995 Feb;39(2):203–13.

131. Bouchoucha M, Fysekidis M, Julia C, Airinei G, Catheline JM, Cohen R, et al. Body mass index association with functional gastrointestinal disorders: differences between genders. Results from a study in a tertiary center. J Gastroenterol. 2016 Apr;51(4):337–45.

132. Harris MB, Deary IJ, Wilson JA. Life events and difficulties in relation to the onset of globus pharyngis. J Psychosom Res. 1996 Jun;40(6):603–15.

133. Deary IJ, Smart A, Wilson JA. Depression and 'hassles' in globus pharyngis. Br J Psychiatry J Ment Sci. 1992 Jul;161:115–7.

134. Cathcart RA, Wilson JA. Catarrh - the patient experience. Rhinology. 2011 Oct;49(4):387–91.

135. Famokunwa B, Walsted ES, Hull JH. Assessing laryngeal function and hypersensitivity. Pulm Pharmacol Ther. 2019 Jun 1;56:108–15.

136. Vertigan AE, Kapela SL, Gibson PG. Chronic cough in Vocal Cord Dysfunction: Description of a clinical entity. Respir Med. 2020 Jul;168:105990.

137. Vertigan AE, Bone SL, Gibson PG. The Impact of Functional Laryngoscopy on the Diagnosis of Laryngeal Hypersensitivity Syndromes. J Allergy Clin Immunol Pract. 2022 Feb;10(2):597-601.e1.

138. Macedo P, Saleh H, Torrego A, Arbery J, MacKay I, Durham SR, et al. Postnasal drip and chronic cough: An open interventional study. Respir Med. 2009 Nov;103(11):1700–5.

139. Passali D, Spinosi MC, Crisanti A, Bellussi LM. Mometasone furoate nasal spray: a systematic review. Multidiscip Respir Med. 2016;11:18.

140. O'Hara J, Stocken DD, Watson GC, Fouweather T, McGlashan J, MacKenzie K, et al. Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial. BMJ. 2021 Jan 7;372:m4903.

141. Sundar KM, Daly SE. Chronic cough and OSA: a new association? J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 2011 Dec 15;7(6):669–77.

142. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. Cough Lond Engl. 2010 Apr 15;6(1):2.

143. Sundar KM, Daly SE. Chronic cough and OSA: an underappreciated relationship. Lung. 2014 Feb;192(1):21–5.

144. Chan K, Ing A, Birring SS. Cough in obstructive sleep apnoea. Pulm Pharmacol Ther. 2015 Dec 1;35:129–31.

145. Sundar KM, Willis AM, Smith S, Hu N, Kitt JP, Birring SS. A randomized controlled study of CPAP for patients with chronic cough and obstructive sleep apnea. Lung. 2020 Jun;198(3):449–57.

146. Chan KKY, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. Eur Respir J. 2010 Feb 1;35(2):368–72.

147. Wang TY, Lo YL, Liu WT, Lin SM, Lin TY, Kuo CH, et al. Chronic cough and obstructive sleep apnoea in a sleep laboratory-based pulmonary practice. Cough Lond Engl. 2013 Nov 5;9(1):24.

148. Chronic cough and obesity. Pulm Pharmacol Ther. 2019 Apr 1;55:84–8.

149. Morales-Estrella JL, Ciftci FD, Trick WE, Hinami K. Physical symptoms screening for cardiopulmonary complications of obesity using audio computer-assisted self-interviews. Qual Life Res. 2017 Aug 1;26(8):2085–92.

150. Zeiger RS, Schatz M, Butler RK, Weaver JP, Bali V, Chen W. Burden of Specialist-Diagnosed Chronic Cough in Adults. J Allergy Clin Immunol Pract. 2020 May;8(5):1645-1657.e7.

151. Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. Thorax. 2006 Nov;61(11):975–9.

152. Landt EM, Çolak Y, Nordestgaard BG, Lange P, Dahl M. Risk and impact of chronic cough in obese individuals from the general population. Thorax [Internet]. 2021 Jul 5 [cited 2021 Sep 29]; Available from: https://thorax.bmj.com/content/early/2021/07/05/thoraxjnl-2020-216351

153. Descazeaux M, Brouquières D, Didier A, Lescouzères M, Napoléon MF, Escamilla R, et al. Obesity Predicts Treatment Response to Proton Pump Inhibitor Therapy in Patients with Chronic Cough. Lung. 2020 Jun;198(3):441–8.

154. Merck Sharp & Dohme LLC. A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Women With Chronic Cough and Stress Urinary Incontinence [Internet]. clinicaltrials.gov; 2022 Apr [cited 2022 May 17]. Report No.: NCT04193176. Available from: https://clinicaltrials.gov/ct2/show/NCT04193176

155. Mattle HP, Nirkko AC, Baumgartner RW, Sturzenegger M. Transient cerebral circulatory arrest coincides with fainting in cough syncope. Neurology. 1995 Mar;45(3 Pt 1):498–501.

156. Krediet CTP, Wieling W. Edward P. Sharpey-Schafer was right: evidence for systemic vasodilatation as a mechanism of hypotension in cough syncope. Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol. 2008 Apr;10(4):486–8.

157. Benditt DG, Samniah N, Pham S, Sakaguchi S, Lu F, Lurie KG, et al. Effect of cough on heart rate and blood pressure in patients with 'cough syncope'. Heart Rhythm. 2005 Aug;2(8):807–13.

158. Dickinson O, Akdemir B, Puppala VK, Krishnan B, Detloff BLS, Sakaguchi S, et al. Blunted Chronotropic Response to Hypotension in Cough Syncope. JACC Clin Electrophysiol. 2016 Dec;2(7):818–24.

159. Waldmann V, Combes N, Narayanan K, Sharifzadehgan A, Bouzeman A, Beganton F, et al. Cough Syncope. Am J Med. 2017 Jul;130(7):e295–6.

160. Neurological disorders: assessing fitness to drive [Internet]. GOV.UK. [cited 2021 Sep 27]. Available from: https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive

161. Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. Lung. 2020 Feb;198(1):13–21.

162. Chamberlain Mitchell S a. F, Ellis J, Ludlow S, Pandyan A, Birring SS. Non-pharmacological interventions for chronic cough: The past, present and future. Pulm Pharmacol Ther. 2019 Jun;56:29–38.

163. Chamberlain Mitchell SAF, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. Thorax. 2017 Feb;72(2):129–36.

164. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006 Dec;61(12):1065–9.

165. Ryan NM, Vertigan AE, Bone S, Gibson PG. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough. Cough Lond Engl. 2010 Jul 28;6:5.

166. Patel AS, Watkin G, Willig B, Mutalithas K, Bellas H, Garrod R, et al. Improvement in health status following cough-suppression physiotherapy for patients with chronic cough. Chron Respir Dis. 2011;8(4):253–8.

167. Ryan NM, Vertigan AE, Gibson PG. Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement. Cough Lond Engl. 2009 Mar 17;5:4.

168. Mohammed S, Steer J, Ellis J, Parker SM. Nonpharmacological cough control therapy for chronic refractory cough and cough associated with underlying lung disease. ERJ Open Res. 2020 Jan;6(1):00243–2019.

169. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough: A Randomized Controlled Trial. Chest. 2016 Mar;149(3):639–48.

170. Selby J, Tidmarsh B, Bailey E, Hull J. Group-delivered speech and language therapy for chronic refractory cough: what do patients want? Eur Respir J [Internet]. 2019 Sep 28 [cited 2022 May 16];54(suppl 63). Available from: https://erj.ersjournals.com/content/54/suppl_63/PA4341

171. Al-Sheklly B, Mitchell J, Issa B, Badri H, Satia I, Collier T, et al. S35 Randomised control trial quantifying the efficacy of low dose morphine in a responder group of patients with refractory chronic cough. Thorax. 2017 Dec 1;72(Suppl 3):A24–5.

172. Nerenz RD, Tsongalis GJ. Pharmacogenetics of Opioid Use and Implications for Pain Management. J Appl Lab Med. 2018 Jan 1;2(4):622–32.

173. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997 Oct;49(10):1045–9.

174. Smith J, Owen E, Earis J, Woodcock A. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2006 Apr;117(4):831–5.

175. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet Lond Engl. 2012 Nov 3;380(9853):1583–9.

176. Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. The Laryngoscope. 2006 Dec;116(12):2108–12.

177. Dong R, Xu X, Yu L, Ding H, Pan J, Yu Y, et al. Randomised clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-oesophageal reflux-induced chronic cough. Aliment Pharmacol Ther. 2019 Mar;49(6):714–22.

178. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet Lond Engl. 2015 Mar 28;385(9974):1198–205.

179. Smith JA, Kitt MM, Morice AH, Birring SS, McGarvey LP, Sher MR, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. Lancet Respir Med. 2020 Aug;8(8):775–85.

180. Smith JA, Kitt MM, Butera P, Smith SA, Li Y, Xu ZJ, et al. Gefapixant in two randomised dose-escalation studies in chronic cough. Eur Respir J. 2020 Mar;55(3):1901615.

181. Martinez FJ, Afzal AS, Smith JA, Ford AP, Li JJ, Li Y, et al. Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial. Pulm Ther. 2021 Dec;7(2):471–86.

182. Turner RD, Birring SS. Neurokinin-1 Receptor Inhibition and Cough. Am J Respir Crit Care Med. 2021 Mar 15;203(6):672–4.

183. Smith JA, Harle A, Dockry R, Holt K, Russell P, Molassiotis A, et al. Aprepitant for Cough in Lung Cancer. A Randomized Placebo-controlled Trial and Mechanistic Insights. Am J Respir Crit Care Med. 2021 Mar 15;203(6):737–45.

184. Belvisi MG, Birrell MA, Wortley MA, Maher SA, Satia I, Badri H, et al. XEN-D0501, a Novel Transient Receptor Potential Vanilloid 1 Antagonist, Does Not Reduce Cough in Patients with Refractory Cough. Am J Respir Crit Care Med. 2017 Nov 15;196(10):1255–63.

185. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. J Allergy Clin Immunol. 2014 Jul;134(1):56–62.

186. Ludbrook VJ, Hanrott KE, Kreindler JL, Marks-Konczalik JE, Bird NP, Hewens DA, et al. Adaptive study design to assess effect of TRPV4 inhibition in patients with chronic cough. ERJ Open Res. 2021 Jul;7(3):00269–2021.

187. Kanemitsu Y, Smith J, Butera P, Canning B, Dicpinigaitis P, Iyer V, et al. The Efficacy of Bradanicline in Refractory Chronic Cough. Eur Respir J [Internet]. 2020 Sep 7 [cited 2022 Aug 8];56(suppl 64). Available from: https://erj.ersjournals.com/content/56/suppl_64/4564

188. Contributor NT. Developing a clinical nurse specialist role for patients with chronic cough [Internet]. Nursing Times. 2021 [cited 2022 May 19]. Available from: https://www.nursingtimes.net/clinical-archive/respiratory-clinical-archive/developing-a-clinical-nurse-specialist-role-for-patients-with-chronic-cough-14-06-2021/

189. Upper airway disorders within adult respiratory services [Internet]. RCSLT. [cited 2022 Aug 8]. Available from: https://www.rcslt.org/speech-and-language-therapy/clinical-information/upper-airway-disorders-adults/