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British Thoracic Society Clinical statement on chronic cough in adults

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Terminology, epidemiology and impact

- 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.

Causes of chronic cough

- Protocolised investigation and treatment of common comorbidities such as reflux, rhinitis and asthma is not always effective.
- A 'treatable traits' approach is advocated~~,~~ to guide personalised treatment.
- Cough hypersensitivity is a frequently overlooked treatable trait for many patients and requires specific treatment including antitussives and non-pharmacological treatment.

Clinical Assessment

- 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(1).
- 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.

Treatable traits in cough

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 250mg three times per week initially, titrating up to 500mg three times per week depending on clinical response (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) ≥0.3 x 10^9/L). Consider short trial of ICS for 4 weeks (2) 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)(3) 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.

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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.

Complications of chronic cough

- 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.

Management of Cough Hypersensitivity

- 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.

Delivery of care of chronic cough

- 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 and language therapy and physiotherapy as part of an MDT to support the diagnosis and management of cough and other upper airway disorders.

BTS Clinical statement on chronic cough in adults

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 (4), there has been major progress in the diagnosis, and therapy of this condition but it remains a challenging area with a limited evidence base (5,6). 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(7,8). This statement covers acute cough only briefly as it has been reviewed recently by a NICE guideline(9).

Methodology

The Clinical Statement Group (CSG) was jointly chaired by SP and JAS. Membership was drawn from respiratory medicine, general practice, physiotherapy, speech and language therapy, nursing, Ear Nose and Throat, and a trainee. Lay/patient input was received from patient groups linked to the statement authors. 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) and methodology is described in the clinical statement production manual. 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 June 2023 before final publication.

SECTION 1: Terminology, epidemiology, and impact of chronic cough

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(10). 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: 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(11) 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). This statement simplifies things. Where cough persists despite addressing co-morbidities or where no co-morbidities are identified the term 'Refractory chronic cough' (RCC) is used. 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 for Chronic Cough Condition

Epidemiology

The community prevalence of chronic cough is unclear, perhaps as high as 10% (12,13). Both sexes and any age may be affected but the condition appears most prevalent in later middle aged females (14–16).Many sufferers don't access medical services, tolerating symptoms or possibly self-medicating. UK based primary care studies suggest CC affecting 1.2-2% (15,16) 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 (17), rhinitis and ACE inhibitor use (15,16). Many patients may have no identified co-morbidity (13,15).

Impact of Chronic Cough

The impact on quality of life (QoL) is comparable to other respiratory diseases such as COPD(18). Patients experience numerous unpleasant symptoms; throat discomfort, chest pain, exhaustion, dizziness, syncope and urinary incontinence(19). Anxiety is common in CC (20–22) alongside low mood, more likely if pre-existing depression(23)), fatigue, physical symptoms, negative illness beliefs and a lack of a clear illness narrative when their condition is unexplained. Concerns around serious underlying illness are common(22). Sufferers report embarrassment and significant social effort directed at managing negative reactions of others to the cough(24). Work absenteeism(25) and primary care attendance is frequent(26). Repetitive investigations, trials of treatment and referrals to secondary care increase healthcare costs (15). The 'over the counter' cough remedy market is significant, around £400m/pa in the UK.

CLINICAL PRACTICE POINTS

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(4,27,28) 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 (29,30) and most importantly, a significant number of patients (30-40%) don't get better with treating comorbidities or no obvious comorbidities exist(15). 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(31). Elements of this approach remain valid but need refinement.

Treatable Traits and Cough

This statement proposes 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(32). This approach has shown efficacy in airways disease(33,34), 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 i) reflux ii) ACEI use iii) obesity iv) cough hypersensitivity v) dysphonia…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 of chronic cough

Table 2: Treatable Traits in Chronic Cough

Trait	Trait Identification Marker	Treatment	Expected Benefits of Treatment
Smoking	Patient history (cigarette smoking, chronic productive cough, worse in mornings). 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 Pets and Hobbies	Reduce exposure	May improve cough
ACEI Treatment	History (dry cough, throat symptoms). 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 (cough, possibly asthma type symptoms wheeze/breathless/nocturnal symptoms) FeNO >25ppb BEC (≥0.3 x 10^9/L) History	ICS Systemic corticosteroids	Improve cough and QoL Reduced exacerbations
Productive cough	History (significant sputum production, may be purulent). ? Underlying cause. Sputum C&S HRCT ? bronchiectasis Bronchoscopy	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 if symptoms do not improve with medical management and lifestyle changes.	Improvement in rhinosinusitis. Possible improvement in cough. Limited evidence.
Inducible laryngeal obstruction	History (wheeze, breathless, cough, inspiratory difficulties, dysphonia, symptoms variable) Laryngoscopy	Speech therapy intervention	May improve cough, limited evidence.
Obstructive Sleep apnoea	History (snoring, daytime sleepiness, obesity) Sleep study. Epworth Sleep Score. High BMI	CPAP therapy Lifestyle advice Weight loss Mandibular advancement device	May improve cough, limited evidence for CPAP. No evidence for other measures.
Gastroesophageal reflux disease	History-presence of heartburn best indicator of possible response to treatment. Reflux Symptoms Oesophageal manometry & pH/MII Endoscopy Barium swallow High BMI	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	History (dry cough, triggered by trivial exposures eg cold air/perfumes/talking, frequent laryngeal symptoms)	Cough control therapy (SLT) Low dose SR morphine	Improvements in cough frequency and QoL.

	Cough completely/partially refractory to addressing treatable traits or no treatable traits obvious.	Gabapentin/Pregabalin Clinical Trials of new therapies	
Anxiety/Low mood	History Screening tool e.g. HAD score	Reassurance and explanation Psychological intervention Antidepressants	May improve cough, no evidence.

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(28). 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(10,35). 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(36–40). There is currently no 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(32,41–43). 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.

A ‘treatable traits’ approach is advocated, to guide personalised treatment.

Cough hypersensitivity is a frequently overlooked treatable trait for many patients and requires specific treatment including antitussives and non-pharmacological 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 (44). COVID should be considered(45). 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)(9). Bacterial infection may cause acute bronchitis, antibiotics are usually not needed unless systemically very unwell or at high risk of complications (9). Inflammatory markers such as CRP(46) and procalcitonin(47) may guide decision making. ‘Delayed’ antibiotic strategies with a post-dated prescription for use if symptoms persist are as effective as immediate antibiotics(48). Prediction rules to identify those at highest risk are effective(49). Routine blood tests or chest x-ray are not recommended in the absence of worrying/atypical findings.

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

Treatment. Management prioritises reassurance and self-care (honey, OTC remedies)(50) (9) (figure3). Evidence for effectiveness of OTC treatments is weak and many medications are likely no better than placebo(51). Careful explanation and ‘safety netting’ is good practice. A number of drugs are ineffective and should be avoided including; bronchodilators(52) and inhaled/oral steroids(53,54) (unless underlying asthma/COPD), NSAID’s, antihistamines and decongestants (55), mucolytics, codeine(56) and montelukast(57).

Systematic assessment of the patient with chronic cough

A systematic approach to management of CC is outlined in figure 4 (primary care) and figure 5 (secondary care).

Figure 4: 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. Appropriate follow up should be arranged to assess response to treatment trials.

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(58). Figure 4 shows red flag features requiring urgent chest x ray and/or urgent hospital referral. A normal CXR does not exclude lung cancer(59), refer/investigate if there is any concern. Prediction tools can be helpful(60).

The history can be quite nonspecific(61). 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. Environmental factors such as air pollution may be relevant(62). 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. (22,24,63,64). Several validated tools exist to measure cough frequency(65,66) and quality of life, but they are largely research tools and their clinical utility is unclear~~(67)~~.

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 (1). 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 such as nasal obstruction and discharge and voice change).

Further Investigations

CT Scan

Chest CT scans should not be ordered routinely. Radiation exposure should be minimised (68), and the relevance of abnormalities picked up when performed routinely is questionable (28,69–71). CT scans should be used to look for evidence of disease when indicated e.g. in chronic productive cough to exclude bronchiectasis(72), to exclude a neoplasm if lung cancer is suspected and/or the patient is in a high risk group (pick up rate 1-2%)(69), haemoptysis and a 'barking cough' suggestive of airway collapsibility (dynamic expiratory CT) (73).

Bronchoscopy

There is no role for routine bronchoscopy for most patients with CC but may be helpful in some circumstances(74). Tracheal abnormalities may be picked up (e.g., tracheopathia osteochondroplastica, airway collapsibility and tracheobronchomalacia) (74–76). Consider when a) productive cough and no clear cause, b) suspicion of airway collapsibility ('barking' quality to cough +/- relevant CT findings) c) a foreign body and d) to exclude infection and assess airway secretions when sputum culture is unhelpful/not possible.

Flexible nasendoscopy and Laryngoscopy

Flexible nasendoscopy and 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(77).

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(79).

Secondary Care Assessment

Secondary care assessment (figure 5) 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 (79) so basic tests may be required. Further investigations depend on the individual's presentation.

Figure 5: 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(1).

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(80). Nicotine withdrawal due to smoking cessation may enhancement cough hypersensitivity(81), hence patients may experience more coughing for a period after quitting. This can be attenuated and quit rates improved by using nicotine replacement. There are a number of interventions that can help smokers quit outlined in NICE guidelines(82).
https://www.nice.org.uk/guidance/ng209/chapter/Recommendations-on-treating-tobacco-dependence#stop-smoking-interventions

ACE Inhibitors

ACE inhibitor medication induces cough hypersensitivity(83) 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, the 'treatable traits' approach is advocated; identifying and optimising treatment of pulmonary, extrapulmonary and behavioural traits, well described elsewhere(32,33) and in disease specific guidelines(72,84,85). 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(86). Consider early HRCT and sputum culture. Look for bronchiectasis and other airway disease (asthma, COPD), cigarette smoking, environmental exposure (dusts), immune deficiency and possible tracheal abnormalities (e.g., tracheopathia osteochondroplastica, airway collapsibility and tracheobronchomalacia). Bronchoscopy may be helpful for some patients(74). An 'idiopathic productive cough'(87,88) 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(89) 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(90). Consider a trial of hypertonic saline. There is some evidence to support the use of low dose macrolide treatment(91) for patients with productive cough that persists despite these interventions (e.g. Azithromycin 250mg 3 times per week could be used initially with subsequent titration to 500mg depending on clinical response). 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(92,93). 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(94)

Eosinophilic airway disease

A common cause of cough and amenable to treatment. Encompasses various labels including 'classic' asthma, 'cough variant asthma'(95) and 'non-asthmatic eosinophilic bronchitis(96) 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 estimate airway eosinophilia but this is a difficult area and FeNO is affected by various factors (elevated in allergic rhinitis, atopy and eczema, reduced in smokers, variably affected by viral infections)(97).BTS(84), NICE(98), ERS (99) and Global initiative for asthma (GINA) guidelines consider elevated FeNO levels (NICE and ERS specify >40 ppb, GINA a

lower level of >20ppb) 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 uncertain. 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%)(2), therefore a FeNO >25ppb should prompt a trial of ICS. A FeNO <25ppb is associated with a low rate of ICS response so ICS should be avoided unless there are other factors to suggest eosinophilic airway disease.

A raised blood eosinophil count (≥0.3 x 10^9/L) is supportive of a diagnosis of eosinophilic airway disease but not sensitive or specific enough to make a diagnosis alone(84); one study reported a weak correlation with treatment response(100).

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 ≥0.3 x 10^9/L). Consider trial of ICS for 4 weeks(2). If response is incomplete, assuming inhaler technique and compliance are adequate, consider escalating treatment e.g. double dose of ICS or add a leukotriene receptor antagonist (LTRA)(3) 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(101,102).

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(31,103). 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(104). PPI's are not likely to benefit most patients with cough and long term use risks side effects (osteoporosis, infections, kidney disease) (105). 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%)(106). 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)(107–109). 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 . Oesophageal dysmotility is frequently observed(110,111) and may reflect a broader autonomic disturbance(112). 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(113,114). 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 (113,114). 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%(115). 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)(116).The best predictor of treatment response is the presence of heartburn(106). 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(117). 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(118).

Weak evidence for using prokinetic drugs, should not be used routinely for cough and use restricted to specialist services due to potential side effects(119,120).

Alginates are frequently used in ENT practice to treat 'laryngopharyngeal reflux'. The only placebo controlled study is negative(121,122) and the findings from an ongoing placebo controlled RCT of alginates in patients with throat symptoms are eagerly awaited(123). There is almost no evidence in cough and no RCT's. Observational studies showing efficacy (124) are of limited value given the prominent placebo effects seen with cough treatments. Alginates are well tolerated and effective for typical reflux symptoms such as heartburn so may be prescribed for that. They are not indicated for cough where there are no typical reflux symptoms.

Further investigations, including upper gastrointestinal endoscopy and oesophageal manometry plus either 24h oesophageal pH-impedance monitoring or 96h wireless oesophageal pH capsule monitoring (BRAVO) 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(116). 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(105), dysphagia (11%), bloating (40%) and flatulence (57%)(125). A meta-analysis of the numerous published case series in CC (61 studies, 3869 patients)(126) 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(127). 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(128), 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(129). Upper airway/nasal disease is frequent in CC patients(130,131) 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(132,133) 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(134). 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(135) and two-thirds of MRI scans(136).

"***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(137).Only a minority of patients with demonstrable post nasal secretions, secondary to infective CRS, report cough as a symptom(138). When PND was mimicked by inserting hyperviscous solution into the nasal cavities of CRS patients and controls, coughing was not evoked(139).

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(140,141). Attributed to underlying gastroesophageal reflux in the otolaryngology literature for many years(142,143), "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(144). 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(145), obesity(146), life events(147,148), snoring, upper airway dryness, hormonal changes and laryngeal hypersensitivity have all been associated with chronic throat and voice symptoms(149). Laryngeal hypersensitivity could be a common mechanism(150).

'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 (ILO) is defined as "inappropriate laryngeal closure at the glottic and/or supraglottic level, which leads to dynamic airflow obstruction and causes breathing difficulties". Previously referred to as 'vocal cord dysfunction'. It may manifest as cough, wheeze, breathlessness, and voice disturbance. Symptoms may be episodic, usually inspiratory and associated with certain triggers. ILO can co-exist with a number of conditions including asthma and CC. In a tertiary RCC population, ILO is a common finding(151,152) often associated with voice disturbance and breathing pattern disorder and may be a manifestation of laryngeal hypersensitivity(153). Diagnosis is confirmed by functional laryngoscopy(154) and treatment is by speech and language therapy intervention.

Treatment: Evidence is limited, only uncontrolled case series suggest that nasal steroids improves cough symptoms (155,156). For cough patients who report symptoms of CRS, treatment should include an intranasal steroid spray with saline irrigation/rinses 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(157). 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% (158,159)) and CC is common in sleep clinic populations(160,161). Continuous positive airways pressure (CPAP) therapy improved cough related quality of life in uncontrolled studies(160). 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 (162). OSA may enhance cough hypersensitivity via associated gastroesophageal reflux, rhinitis(163,164), upper respiratory tract irritation and consequent inflammation (160,162). Patients with cough may have obvious risk factors for OSA (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(165,166). Obesity was more common in patients attending specialist care for chronic cough (24.3% vs 19% in controls)(167). Large population studies offer conflicting results (17,168),most compelling is the Copenhagen General Population Study(169), 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(170). Another possible mechanistic link is OSA (as outlined above) and possibly type 2 diabetes(166). The role of weight loss as a treatment for chronic cough has not been studied directly although weight loss improves OSA and gastroesophageal reflux(166). 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 250mg three times per week initially, titrating up to 500mg three times per weekdepending on clinical response (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(2) 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)(3) 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 contribute to the development of stress 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(64) 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 and pelvic health physiotherapy, to aid continence may also be beneficial(171). A trial looking at the impact of the antitussive, gefapixant, in females with urinary incontinence is ongoing(172).

Cough syncope

Cough syncope is a relatively uncommon(63) but consequences can be severe, particularly the potential for serious motor vehicle accidents. Increased intrathoracic pressure during coughing reduces cerebral blood flow (173) via cardioinhibitory baroreflex activation, peripheral vasodilatation and impaired responses to hypotension(174–177) 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 (see tables 1 and 1 (63)). 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(178).

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 unlicensed neuromodulator therapies are also beneficial. Cough treatments are likely to work via complex mechanisms and significant placebo effects are common(179).

Commented [SP2]: Typo-should have said 'unlicensed'

Non-Pharmacological Treatment

Commented [SP3]: Need to link potential 'respiratory futures' website online resources here-will be helpful

A complex intervention(180), 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(181–185) . The PSALTI study showed a 40% reduction in cough frequency and improved quality of life compared to sham therapy. Most patients respond (186) but the long term effect is unknown. Can be complimentary to pharmacological treatment(187) and allow a reduction of pharmacological treatment. It is best delivered by therapists experienced in managing chronic cough. Not widely available, this statement urges all secondary care organisations to look at ways of providing this therapy, preferably as part of an 'upper airway service' also diagnosing and treating ILO. Group therapy can be a cost-effective way of delivering treatment(188).

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(40), and in patients reporting a clinical response, 24h cough frequency was reduced by 71% over placebo (189). 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(190). Clinical trials show it is ineffective in treating acute cough due to URTI(56,191) and in patients with COPD(192). 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(193). 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(187). 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(194). 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(195).

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(196) Subsequent studies have confirmed efficacy of gefapixant in RCC (39,197,198) however disturbances in taste are a common side effect. More selective P2X3 antagonists are effective with less taste disturbance(199–202). There are currently ongoing clinical trials of camlipixant but the development of eliapixant and sivopixant has been halted. Placebo effects in more recent trials have made demonstrating treatment effects more challenging. The potential effects of P2X3 antagonists outside of RCC is largely unexplored apart from one study in Idiopathic Pulmonary Fibrosis which gave borderline results (203). Licensing of Gefapixant in the USA has been held up by the FDA, but the drug is currently used in Japan and recently been approved for use in refractory cough by regulatory authorities in the EU(204).

Commented [SP4]: Need to comment further re UK authorisation

Other promising agents currently being investigated include a TRPM8 (menthol receptor) agonist (205) and mixed findings for neurokinin 1 receptor antagonists(206,207). There have been negative trials of several TRP receptor antagonists (208–210) and a negative trial of a nicotinic receptor antagonist(211). The dual-acting ƙ opioid receptor agonist/μ opioid receptor antagonist nalbuphine has demonstrated impressive effects on IPF cough in phase 2 studies, further clinical trials are awaited including for RCC(212).

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 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. 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 cough clinic, there should not be any resource implications here and a special 'business case' should not be needed. A cough clinic offers 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 empirical 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(170). 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 and language 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 and language 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 used to support service development (212).

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 and language 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.

ABBREVIATIONS

ACEI= Angiotensin converting enzyme inhibitor

A2RB= Angiotensin 2 receptor blocker/antagonist

ATP= Adenosine triphosphate

BEC= Blood eosinophil count

BMI= Body mass index

BTS= British Thoracic Society

CC= Chronic cough

CNS= Central nervous system

CO= Carbon monoxide

COPD= Chronic obstructive pulmonary disease

CPAP= Continuous positive air pressure

CRS= Chronic rhinosinusitis

CSG= Clinical statement group

CT= Computerised tomography scan

CXR= Chest x ray/radiograph

DPI= Dry powder inhaler

DVLA= Driver vehicle licensing agency (UK)

ENT= 'Ear nose and throat', also referred to as otorhinolaryngology

FDA= US Food and drug administration

FBC= Full blood count

FENO= Fraction of exhaled nitric oxide

GINA= Global initiative for asthma

HAD= Hospital anxiety and depression scale

HRCT= High resolution CT scan

ICS= Inhaled corticosteroids

ILO= Inducible laryngeal obstruction (previously termed vocal cord dysfunction)

LTRA= Leukotriene receptor antagonist

MDT= Multidisciplinary team

NICE= National institute for health and care excellence (UK)

NRT= Nicotine replacement therapy

NSAID= Non-steroidal anti-inflammatory drug

OSA= Obstructive sleep apnoea

OTC= ‘Over the counter’ medicine, usually remedies bought without prescription.

PPI=Proton pump inhibitor

P2X= ATP gated P2X receptor cation channel, family of sensory receptors involved in nociception

QoL= Quality of life

RCC= Refractory chronic cough

RCT= Randomised controlled trial

RUCC= Refractory unexplained chronic cough

SALT= Speech and language therapy

SLT= Speech and language therapy (see above)

SOCC= Standards of care committee (BTS)

TRPA1= Transient receptor potential cation channel, subfamily A, member 1, also known as the ‘wasabi receptor’, an irritant receptor

TRPM8= Transient receptor potential cation channel subfamily M (melastatin) member 8, also known as the ‘menthol receptor’, a cold sensing receptor

TRPV1= transient receptor potential cation channel subfamily V member 1, also known as ‘capsaicin receptor’, temperature/irritant receptor

UI= Urinary incontinence

URTI= Upper respiratory tract infection

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