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The Clinical Approach to Chronic Cough

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ABSTRACT

Chronic cough remains a significant clinical challenge, affecting approximately 10% of the population and leading to significant impairment in psychological, social and physical quality of life. In recent years, efforts have intensified to elucidate the mechanisms underlying chronic cough and to focus on investigating and treating refractory chronic cough (RCC). A 'treatable trait' approach, which focuses on identifying and addressing the specific associated causes of chronic cough, has gained traction. In some patients, refractory chronic cough is likely driven by a neuropathic mechanism due to dysregulation of the neuronal pathways involved in the cough reflex, often clinically described as cough hypersensitivity syndrome. While the initial treatment of underlying conditions remains central to managing treatable traits, the therapeutic options for RCC have expanded to include targeting cough hypersensitivity. First-line treatments now include neuromodulators and speech therapy with one P2X3 receptor antagonist (gefapixant) recently licensed in the EU, UK and Japan. Despite these advances, patient responses remain variable, underscoring the ongoing need for research into the pathophysiology and treatment of RCC. This article reviews current investigations and management options in treating chronic cough and RCC.

Introduction

Chronic cough, defined as cough lasting 8 weeks or longer, is a common troublesome condition that on average affects 10% of adults, but with large reported global variations ranging from 2-18%(1),(2). Chronic cough represents a leading cause of consultations in ambulatory and primary care settings(3-5). It is notably twice as common in women, with peak incidence occurring in individuals aged 50 to 60 years(6). Chronic cough is particularly distressing, frequently resulting in complications such as stress incontinence, chest discomfort, dizziness, fatigue, exhaustion and along with the stigma of coughing in public can lead to social isolation. All of these significantly diminish quality of life(7). The management of chronic cough poses significant challenges, as access to some investigations in primary and secondary can take a long time, most over-the-counter treatments are ineffective, and many current therapeutic options are 'off-label", have limited efficacy and associated with significant side effects. Although in many patients, chronic cough can be attributable to an underlying cause, treatment directed towards those conditions may be ineffective, or no cause is found. In rare cases, chronic cough can also signify serious underlying conditions, necessitating a careful approach to diagnosis and management. Recent reviews(8, 9), clinical statements(10) and guidelines published by the British Thoracic Society, European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP) can help primary and secondary care physicians to appropriately investigate and manage patients with chronic cough(11, 12). This review summarizes the clinical approach to managing chronic cough and also highlights issues related to diagnosing refractory, tools to assess cough, and provides a treatable traits approach to treating chronic cough in primary and secondary care.

Assessment of Chronic Cough

i) History and examination

The clinical history is crucial for assessing chronic cough, with a focus on cough duration, onset, severity, location, and associated features, as well as potential triggers and complications. Key associated conditions to consider include asthma, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS), alongside a detailed occupational and smoking history. Red flags such as hemoptysis, weight loss, and fever should also be noted.

Sudden breathlessness, dysphonia, choking, and swallowing difficulties may suggest inducible laryngeal obstruction(ILO)/vocal cord dysfunction(VCD). Wheezing, dyspnea, and exercise-induced cough maybe indicative of asthma. UACS often presents with post-nasal drip and nasal congestion, while GERD may cause heartburn and dysphonia, particularly postprandially or when lying down or bending forward.

Chronic productive coughs may indicate bronchiectasis, chronic bronchitis, or non-asthmatic eosinophilic bronchitis (NAEB). Common causes of chronic cough include UACS, asthma, eosinophilic bronchitis, and GERD, either individually or in combination(13, 14). Smoking in chronic obstructive pulmonary disease (COPD) is linked to increased cough frequency, and chronic bronchitis is associated with higher exacerbation risk(15, 16). Chronic productive cough is also an independent mortality risk factor(17). Congestive heart failure is a less frequent cause, with ACE inhibitors known to cause dry cough in 5-35% of patients(17-19). While some case series suggested sitagliptin might cause cough, this was not confirmed in large trials(20, 21).

Post-COVID-19 chronic cough prevalence beyond eight weeks is uncertain, with a systematic review estimating 18%, though with significant variability(22). Rarely, cough sound can provide diagnostic clues: pertussis causes a "whoop" sound, while tracheobronchomalacia and excessive dynamic airway collapse produce a "barking" cough with prolonged expiration and wheezing(23-26).

Tools to assess chronic cough

Both subjective and objective tools are commonly used in clinical trials for chronic cough, but not as frequently in routine practice. Even simple subjective assessments, like documenting cough severity and impact quality of life, are valuable for understanding the burden of refractory chronic cough (RCC) and evaluating treatment effectiveness over time.

a. Subjective Cough Assessment

Cough severity is often measured using a 0-10 numerical rating scale (NRS) either verbally or on paper, 0-100mm visual analogue scale (VAS), or verbal classifications (mild, moderate, very severe, maximum). Apart from the VAS which is validated, albeit, with moderate test re-test recall, there are not many specific validated tools for clinical practice. The Cough Severity Diary (CSD) is one option, though it is proprietary. New tools like the McMaster Cough Severity Questionnaire (MCSQ) and Cough Hypersensitivity Questionnaire (CHQ) are in development (27-29). For quality of life, validated questionnaires such as the Leicester Cough Questionnaire (LCQ, MID=1.3) and Cough Specific Quality of Life Questionnaire (CQLQ, MID=10.6) are widely used(30, 31).

b. Objective Cough Assessment

Objective cough frequency measurement is the gold standard for evaluating novel therapies for refractory or unexplained chronic cough in clinical trials. The VitaloJAK cough monitor, which is CE marked and 510(k) approved, measures 24-hour, awake, and nighttime cough frequencies, with the 24-hour frequency often serving as the primary endpoint (32). Recent data suggest cough bouts per hour and their duration may also correlate with patient-reported cough

severity(33). Whilst this has been very effective in clinical trials, the VitaloJAK is currently not used in clinical practice, but updated algorithms with fully automated capabilities may enhance further uptake in clinic.

Other cough monitors like the Leicester Cough Monitor (LCM), SIVA, Hyfe, and Strados offer varying sensitivity and specificity. The LCM has been used in studies of speech therapy and clinical trials, requiring minimal manual adjustment(34). The SIVA monitor(35), approved in the EU and the AI-driven Hyfe monitor have shown promising results(36), while the Strados monitor provides continuous wireless monitoring using an adhesive stethoscope sensor to monitor coughs. However, these systems have only been validated in small studies and have yet to be directly compared with the VitaloJAK in clinical trials. Future research is expected to validate their utility in routine practice.

Investigations in Primary Care

Given that there are many conditions associated with chronic cough in primary care, investigations should be focused and pragmatic in order to exclude serious underlying conditions or initiate treatments for an identified condition. In the absence of any clear history or asthma, reflux disease or nasal disease, empirical treatments should be avoided. Table 1 lists typical symptoms and investigations to consider in common conditions associated with chronic cough.

Perform CXR, Spirometry and Complete Blood Count

A chest x-ray (CXR) should be performed in all patients with chronic cough to exclude masses, consolidations, interstitial lung diseases, hilar lymphadenopathy, and evidence of emphysema. Although a CT scan of the thorax is not routinely indicated in patients with a normal CXR, but it should be considered if there is a high suspicion of carcinoma, bronchiectasis, or interstitial lung

disease (ILD). There is a particularly high burden of chronic cough in patients with ILD and greater cough severity has been associated with worse quality of life, larger decline in DLCO and reduced survival(37-39).

Spirometry, with pre- and post-bronchodilator measurements, is useful for diagnosing chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Blood tests are generally not beneficial in the routine evaluation of chronic cough; however, the presence of blood eosinophilia, elevated total or specific IgE may support diagnoses of asthma, allergy, or NAEB.

Investigations in Secondary and Tertiary Care

Airway hyperresponsiveness and inflammation.

Direct (e.g., methacholine), or indirect (e.g., exercise, mannitol, eucapnic voluntary hyperventilation) bronchoprovocation challenge tests can be utilized to identify airway hyperresponsiveness (AHR)(40-42). Although the BTS statement does not recommend this test in all patients, it can be particularly useful due to their negative predictive value, allowing withdrawal of unnecessary inhaled steroids and bronchodilators. Some specialist centers may have facilities to induce and process sputum to detect airway eosinophilia (>2%) to help diagnose NAEB(43). An alternative is to use fractional concentration of exhaled nitric oxide (FeNO), although this was not recommended for routine use in the diagnosis of chronic cough by the ERS taskforce on chronic cough(44), it was recommended by the more recent BTS clinical statement. However, both recognizes that there is a lack of quality evidence, and that trials are needed to assess its utility and optimum cut off values. A systematic review demonstrated that FeNO possesses moderate diagnostic accuracy for predicting cough-variant asthma (CVA),

NAEB and an improvement in cough response to ICS(45). A recent prospective study demonstrated patients with chronic cough who had a FeNO >25ppb, who were given ICS treatment for 3 weeks, showed improvements in LCQ and cough severity VAS(46). However, improvements in cough did not significantly correlate with changes in FeNO levels, there was no control arm and no measurements of cough frequency. The optimum cut-off for trial of ICS is also not well established but a recent meta-analysis suggests 25ppb to be associated with an increased odds of improvement in cough after initiating ICS(47). We therefore recommend using it if available.

Upper and Lower Airway Visualization

Bronchoscopy is generally not routinely recommended in the evaluation of chronic cough, unless there are signs of weight loss or hemoptysis, suspected foreign body inhalation, possible atypical or chronic infection (fungal, tuberculous or non-tuberculous mycobacteria), or tracheobronchomalacia (TBM), excessive dynamic airway collapse (EDAC) (48-50). The presence of eosinophilic infiltration on endobronchial biopsies or eosinophilia on broncho-alveolar lavage (>2%) may help confirm the diagnosis of NAEB, although in the majority of cases, induced sputum analysis will be sufficient. Laryngoscopy may aid in the assessment of muscle tension dysphonia (MTD), and inducible laryngeal obstruction (ILO)/vocal cord dysfunction (VCD) in patients with suggestive symptoms (51, 52), but this is not routinely recommended. A retrospective review of 80 refractory chronic cough patients showed bronchoscopy detected abnormalities in 42.5% of cases, including airway collapsibility and tracheopathia. Laryngoscopy revealed laryngeal obstruction or sensitivity in 35%. These findings led to treatment adjustments, highlighting the potential value of bronchoscopy in selected cases(53).

Similarly, CT scan of the sinuses or nasoendoscopy are not routinely recommended but may be useful to rule of nasal polps, sinusitis, and mucus impaction. The American Academy of Otolaryngology head and neck surgery strongly recommends the objective documentation of chronic sinusitis which can be obtained either by rhinoscopy, nasal endoscopy or CT scans. These modalities also pick up nasal polyps and mucus impactions which can have their own implications, for example a unilateral polyp masking malignancy. Nasal endoscopy should remain the first test for diagnosis due to accessibility and low cost, CT scans can be used in difficult cases as it has excellent sensitivity(54).

Identify Gastro-Esophageal Reflux Disease

The current gold standard for objectively diagnosing GERD is 24-hour pH impedance monitoring combined with high-resolution manometry, but this is only needed for those patients with persistent reflux symptoms despite lifestyle and anti-acid suppression. Testing is typically not available outside of specialized centers and often involves long wait times(55) and a specialist is required to interpret various parameters, including the number of reflux episodes, acid versus non-acid episodes, proximal versus distal episodes, total acid exposure times, and upper and lower esophageal sphincter pressure (UES/LES) along with abnormal motility patterns. Ideally, these tests should be conducted while the patient is not taking proton pump inhibitors or promotility agents. If the patient's reflux symptoms preclude cessation of treatment, these tests can be performed while the patient remains on medication.

In cases where these tests are not available, indirect evidence of reflux or aspiration can be gathered through alternative methods such as a barium swallow, video fluoroscopic evaluation of

swallowing, and upper gastrointestinal (GI) endoscopy. However, these indirect tests have lower sensitivity and specificities for diagnosing GERD or motility disorders.

Diagnosing Refractory or Unexplained Chronic Cough

After a thorough history, examination, and appropriate investigations, some patients with chronic cough may have an underlying disease identified, leading to complete or partial resolution of the cough. This type of cough is classified as "explained" and is a symptom of the identified condition. However, the exact proportion of patients who experience complete resolution remains unclear, representing an unmet need in understanding the burden of refractory chronic cough (RCC).

When an underlying condition is identified but the cough persists despite treatment, it is termed "refractory chronic cough" (RCC). If no cause is found, the cough is labeled "unexplained chronic cough" (UCC)(12). The term UCC assumes that all tests and treatment trials have been conducted, which may not always be the case. Additionally, UCC may be synonymous with the term "idiopathic" chronic cough, potentially leading to the misconception that no underlying pathology exists. This has prompted some to prefer the term "refractory and unexplained chronic cough" (RUCC).

Labeling a cough as "unexplained" can be frustrating for patients, as it may imply a lack of a cause. Studies show that patients with RCC or UCC often have underlying issues at the level of the airways, vagus nerve, brainstem, and/or central pathways(56-62). These mechanisms can be addressed through pharmacological treatment or speech therapy.

Recent data suggest that RCC and UCC occur in a 60:40 ratio, with allergic rhinitis, asthma, and GERD being common comorbidities in RCC(63, 64). Despite different terminologies, RCC and

UCC are considered part of the same condition, sharing similar features and pathophysiology, with no significant differences in treatment response(65, 66).

Management Options

Avoidance and withdrawal

Management plans should first start with smoking cessation, including E cigarette and marijuana, treatment of any underlying infections, excluding malignancy and replacing ACE inhibitors (Figure 1). Improvement can be seen within 4-8 weeks, although some cases report that the effect can last up to 6 months(19). Patients are recommended to switch to another class of antihypertensive e.g. angiotensin receptor blockers, which are not associated with increased cough (67).

Treatable Traits Approach

The treatable traits approach to managing chronic cough enhances care by focusing on modifiable traits rather than strict diagnostic categories. Please see figure 1 for a treatable trait approach concept in managing chronic cough. Instead of adhering strictly to traditional diagnostic categories, this approach identifies specific, modifiable traits associated with cough, such as airway eosinophilia, gastroesophageal reflux, or cough hypersensitivity. The advantage of this method is that it encourages clinicians to consider multiple traits in every patient, tailor treatments to the patient's unique phenotype, which can lead to better outcomes and more efficient use of healthcare resources. Additionally, this approach acknowledges that many patients with chronic cough have refractory chronic cough, where standard treatments have failed. In such cases targeting the underlying mechanism such as cough hypersensitivity maybe needed. This is the approach taken by the most recent British Thoracic Society guidelines. The

possible traits are outlined below but 2 important caveats should be acknowledged. First, while the treatable traits approach holds potential, its success depends on accurately being able identify the contributing traits and tailoring treatments accordingly. Second, the evidence that targeting such traits leads to benefit in all subjects with chronic cough is lacking, for e.g., treatment with ICS/LABA in patients with asthma may not resolve the coughing, in which case additional neuromodulator treatment may be needed.

i) Airway hyper-responsiveness and variable airflow obstruction.

Chronic cough in asthma is a prevalent and significant symptom, often indicating severe disease and poor prognosis(68). This condition can be identified by measuring airway hyper-responsiveness (AHR) and variable airflow obstruction, typically using methacholine challenge tests and spirometry with reversibility assessment, respectively. The mechanisms underlying chronic cough in asthma involve neuronal dysfunction, particularly in the airway sensory nerves. These nerves can become hypersensitive, leading to an exaggerated cough reflex, especially in the presence of bronchoconstriction and eosinophilic airway inflammation(69-73). Eosinophils may contribute to this process by increasing the length and branching of sensory nerves in the airway, which may further heighten cough reflex sensitivity(74).

The American College of Chest Physicians (ACCP) recommends treating asthma-related cough with bronchodilators and inhaled corticosteroids (ICS), while also considering a trial of oral steroids in cases with partial improvement. However, these treatments are not specifically targeted at cough, and existing studies, often graded as ‘low’ or ‘fair’ evidence, rely heavily on subjective measures like cough scoring systems or tussive challenges.

Leukotriene receptor antagonists have been shown to be effective in cough variant asthma (CVA) in two small randomized controlled trials and have been previously recommended in ACCP guidelines(75-77). In a pre-clinical study, tiotropium, a long-acting muscarinic antagonist (LAMA), has demonstrated effectiveness in reducing cough by inhibiting sensory nerve-mediated pathways, including TRPV1 and TRPA1. Uncontrolled pre-post studies after starting tiotropium showed improvement in LCQ, cough severity VAS and improvements in capsaicin sensitivity after tiotropium. However, these findings are not universally conclusive, and the effectiveness of treatments targeting airway inflammation. There are no placebo-controlled trials of anti-IL-5 biologics for the treatment of chronic cough with eosinophilic airways diseases. ICS have not been shown to reduce cough frequency in COPD (78), but long-acting muscarinic antagonists (LAMA) such as aclidinium have recently been shown to reduce cough and breathlessness in moderate COPD on a symptom severity questionnaire (79).

ii) Airway Eosinophilia

Airway eosinophilia can be a feature of classical asthma, cough variant asthma and non-asthmatic eosinophilic bronchitis (NAEB). The challenge in practice is how this can be measured. In an ideal situation, performance of induced sputum with hypertonic saline and counting the number of eosinophils to report the % of 400 total cells counted is the standard methodology. A value greater than 2.2% has been suggested to be above the upper limit of normal (2x S.D) or 1.60 (95^{th} centile)(80, 81). However, this process is not readily available in the majority of even secondary care hospitals, as it can be time consuming to perform and many patients cannot bring up sufficient sputum sample to process the sample. With this being the case the readily available blood eosinophil (BEC) (>0.3x109/L) and easy to measure fractional exhaled nitric oxide (FeNO>25ppb) have been suggested as a measure of type 2 high biomarker.

Both tests can serve as surrogate markers for a potential response to ICS. As a result, cough with raised T2 markers are trialed with ICS for minimum of 4 weeks, if there is inadequate response then the dose of ICS can be doubled or a LTRA added. Standard starting dose is budesonide DPI 200 mcg twice a day and dose can be doubled if effect is inadequate. Despite treatment if T2 markers remain high then course of oral corticosteroids (OCS) can be given (30mg prednisolone) for a 2 week trial(82-84). For patients with T2 low biomarkers and chronic cough a trial of ICS is unlikely to alleviate symptoms(85, 86). Patients with NAEB should be treated with medium to high dose ICS and/or oral glucocorticoids initially and then the dose tapered according to symptomatic improvement.

iii) Chronic Bronchitis/Neutrophilia

The presence of a cough with phlegm for 3 or more months in two consecutive years defines chronic bronchitis, a condition usually attributed in adults to cigarette smoking and other environmental (often occupational) exposures(87). The term ‘chronic bronchitis’ fails to address a more nuanced clinical perspective reflected in recent recognition of subclasses based on cough and phlegm including ‘chronic productive cough’ and ‘intermittent productive cough’(88). Irrespective, smoking cessation and irritant avoidance remains central to the management of this condition. Inflammatory changes associated with chronic bronchitis include airway neutrophilia which has also been reported in patients with dry or only minimally productive chronic cough (89). Precisely how neutrophils contribute to coughing and cough reflex hypersensitivity is not known (90).

iv) Gastro-esophageal reflux disease

Lifestyle changes, such as avoiding acid-exacerbating foods, heavy meals before sleep, and elevating the head of the bed, are crucial for managing GERD. Guidelines also suggest reducing or eliminating caffeine, alcohol, fatty or spicy foods, chocolate, and citrus products(91). The best predictor of therapy response is objective evidence of reflux or heartburn (44). A high-dose antacid trial (e.g., lansoprazole 30 mg BID) for 4 weeks is recommended in those with symptoms of heartburn or objective evidence; if ineffective, discontinue use. Evidence for H2 antagonists in nocturnal reflux is unclear, and the role of alginates in cough remains under investigation. PPIs have shown no benefit for chronic cough without symptomatic GERD and are not recommended in such cases due to their side effect profile. The optimal duration of PPI therapy is debated, with BTS guidelines suggesting 4 weeks, but a minimum of 8 weeks is likely necessary (92-94). Laparoscopic fundoplication should be considered only for patients with refractory reflux despite medical management, with referral to a gastroenterologist or upper GI surgeon recommended. Pre-surgery manometry is important to exclude motility disorders, as fundoplication may lead to complications like dysphagia, nausea, and bloating.

v) Promotility agents

There are no RCTs of treatment with metoclopramide or domperidone in patients with chronic cough. Macrolides are occasionally used as ~~a~~ promotility agents, but there is limited evidence of treatment benefit from long-term low dose macrolides in patients with chronic cough, and hence, they are generally not recommended outside specialist centers (11). One study showed significant benefit of a 12-week low dose regimen of azithromycin in COPD patients with the chronic bronchitis phenotype (95). In two other trials in RCC/UCC low dose erythromycin or azithromycin did not provide significant benefits over placebo on cough frequency, cough severity and quality of life (57, 96).

vi) Upper airway symptoms

Commonly called ‘Upper airway cough syndrome' (UACS) broadly encompasses both airway and nasal disease. Nasal disease is associated with allergic and non-allergic rhinitis (most commonly vasomotor), chronic rhinosinusitis and often presents in patients with a sensation of liquid dripping into the posterior nasopharynx. This is commonly described as post-nasal drip. Treatment for such symptoms precipitating cough is with intranasal steroid spray and saline irrigation for 6 weeks as the first line. Referral to ENT should be considered if symptoms persist beyond 12 weeks. There is a lack of strong evidence to guide therapy, however, guidelines recommend a trial of first/second generation non-sedating antihistamines (e.g., brompheniramine, fexofenadine, bilastine, rupatadine), intranasal steroids, ipratropium and/or decongestants (97-99). The latter should be used with care in patients with hypertension and are not recommended for long-term use. Patients with severe allergic rhinitis may undergo allergen immunotherapy, but its effects on cough have not yet been studied. It should be noted that many such patients have normal investigation including imaging and visual inspection but their coughing might be associated with laryngeal hypersensitivity.

vii) Inducible laryngeal obstruction(ILO)/Vocal cord dysfunction(VCD)

Inducible laryngeal obstruction (ILO)/vocal cord dysfunction (VCD), also known as paradoxical vocal fold movement or vocal cord dysfunction, is a condition characterized by inappropriate closure of the vocal folds during respiration, particularly during inhalation. This can lead to symptoms such as dyspnea, stridor, and, chronic cough(100-102). The condition is often triggered by irritants, stress, or physical exertion, and can be mistaken for asthma due to similar respiratory symptoms. The relationship between ILO/VCD and chronic cough is significant, as

the inappropriate vocal fold movements can cause airway irritation, leading to laryngeal dysfunction(103). The pathophysiology of ILO/VCD involves the hyperresponsiveness of the laryngeal adductor muscles, possibly due to heightened laryngeal sensitivity or altered central processing of sensory input. Management of ILO/VCD focuses on behavioral therapy, specifically speech therapy techniques aimed at retraining the laryngeal response to avoid inappropriate vocal fold closure. In addition, addressing contributory factors such as gastroesophageal reflux, which can exacerbate symptoms, is also critical. Both the BTS guidelines and the NEUROCOUGH international Delphi study have concluded the vital presence of speech and language therapists as part of the panel in managing patients with ILO, muscle tension dysphonia and VCD for chronic cough.

viii) Obstructive sleep apnea

The estimate prevalence of chronic cough in sleep disordered breathing is 33-44% (104-106). The mechanisms linking these conditions include gastroesophageal reflux disease (GERD), upper airway inflammation, and the mechanical impact of airway obstruction during sleep, which can exacerbate cough reflex sensitivity. Continuous positive airway pressure (CPAP) therapy, the standard treatment for OSA, has been shown to significantly reduce chronic cough symptoms by mitigating airway collapse and associated reflux events. A study comparing CPAP with sham therapy found that patients receiving CPAP experienced significant improvements in cough-related quality of life, as measured by the Leicester Cough Questionnaire (LCQ) scores, compared to those receiving sham therapy(107). This suggests that effective management of OSA can lead to substantial reductions in chronic cough symptoms, highlighting the importance of screening for and treating OSA in patients with excessive daytime sleepiness presenting with chronic cough.

ix) Mental Health Disorders

Chronic cough is closely linked with psychological conditions such as anxiety, depression, and low mood. These psychological factors can either exacerbate or result from chronic cough, creating a bidirectional relationship. This interaction may be due to the impact of chronic cough on social interactions, sleep, and overall quality of life, leading to increased psychological distress(108, 109) . Recent data from the Canadian Longitudinal Study of Aging demonstrated that higher psychological distress and depressive symptoms can independently increase the risk of developing chronic cough by 20%, but also chronic cough can worsen mental health symptoms (110). This suggests a complex interplay where treating psychological factors may significantly improve cough outcomes Amitriptyline, a tricyclic antidepressant, has been shown to alleviate chronic cough although this was an uncontrolled study without placebo and no validated endpoint.

x) Genetics

CANVAS syndrome, an acronym for Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome, is a rare neurodegenerative disorder characterized by a triad of cerebellar ataxia, sensory neuronopathy, and bilateral vestibular dysfunction. Chronic cough, a common and debilitating feature, is hypothesized to result from sensory neuropathy affecting vagal afferents and possible central nervous system involvement disrupting normal cough reflex pathways. Genetically, CANVAS is predominantly linked to biallelic expansions of an intronic AAGGG repeat in the RFC1 gene, inherited in an autosomal recessive manner. This genetic anomaly is believed to disrupt normal protein function, leading to the degeneration of neuronal cells and the syndrome. Currently, management focuses on symptomatic relief, including the use of

antitussives and neuromodulators for chronic cough, alongside supportive therapies like physical therapy for ataxia and balance training (111-113). Further research into the pathophysiological mechanisms and potential therapeutic targets is ongoing to improve outcomes for patients with this syndrome

xi) Cough Hypersensitivity Syndrome.

Cough hypersensitivity syndrome (CHS) is often recognized clinically as cough to low levels to thermal, chemical and mechanical triggers with frequent and severe urge to coughs sensations, often emanating from the throat, and coughing frequency which is disproportionately high despite treatment of underlying conditions. These features of hypersensitivity is a manifestation of neuronal dysfunction of the peripheral vagus nerve and/or central brain processes which underly the pathophysiology of patients with RCC. Management of cough hypersensitivity is non-pharmacological and pharmacological treatment. Pharmacological treatments can be peripheral or centrally acting.

Management of Refractory Chronic Cough

A) Centrally acting neuromodulators

Neuromodulator treatment includes low-dose morphine(114), gabapentin(115), and pregabalin (116). All three therapies demonstrate improved symptoms and QoL in RCTs; however, these trials have been small, and the doses used in the RCTs were associated with high rates of adverse events, such as dizziness, drowsiness, unsteadiness, and fatigue. Please see figure 2 for a clinical approach to the managing of chronic cough.

Use of low-dose slow release opioid therapy can be initially trialed for 2-weeks after discussion with the patient on the potential benefits and harms of treatment. Low-doses, between 5-10 mg slow or modified release morphine BID, are sufficient for those that respond, the benefit is often apparent within 3-7 days(114) whereas majority of patients report benefit in 5 days. A recent study showed treatment for 1-week can reduce objective cough frequency by up to 72%(117). Hence, if the patient does not benefit from a 1–2-week trial, low-dose morphine should be discontinued. If there is benefit, then the dose can be titrated to minimize side effects such as constipation, drowsiness and sedation bearing in mind to not exceed a dose of 10mg BID. If cough severity improves and side effects are mild, changing the dose and timing may be useful. Alternative regimes include once daily dosing at night, alternate day dosing, or when required 3-4 hours before socializing, teaching or attending important public events. Codeine is not routinely used due to evidence supporting lack of use in acute cough and COPD.

Gabapentinoids can also be considered in secondary care to improve QOL and symptom burden of caused by chronic cough. As these agents have a concern for abuse/ addiction they should be titrated and used cautiously, ensuring the lowest possible dose is used for effect or withdrawing the agent if there is no benefit. Gabapentin is started at a low dose of 100mg TIB and up titrated to a max dose of 600mg TID. The improvement in LCQ with gabapentin compared with placebo was 1.80 (95% CI 0·56–3·04; p=0·004; number needed to treat of 3·58). Pregabalin can be trialed at 25mg BID and slowly increased to 75 m BID (max dose 150mg BID) for therapeutic effect. Pregabalin was trialled in combination with speech therapy (SP) showing the change in LCQ score was greater with SP + pregabalin than with SP + placebo; mean difference in LCQ = 3.5 (1.2); 95% CI of difference, 1.1-5.8 (P = .024). Of note, despite an improvement in LCQ, there was no change in cough frequency using the Leicester cough monitor. One study using

amitriptyline 10mg at bedtime reported symptomatic improvement, but was unblinded, and lacked a placebo control or a validated tool to assess improvements in cough(108).

Baclofen, a peripheral and central GABAb agonist, have been trialed however there is limited value of these agents in clinical practice due to side effects and tolerability.

There can be concerns from physicians that cough suppression might be unsafe as it might be stopping clearance of mucus in the lower airways. However, the vast majority of patients with RCC who have normal spirometry, normal CXR and normal CT, there has been no documented evidence of cough suppression strategy leading to serious adverse events. Even those who present with coughing up mucus, the actual volume of mucus is usually very low, unlike patients with bronchiectasis or COPD with chronic mucus hyper-secretion. If there is doubt about structural lung diseases, then CT scan of the lung may help to exclude such conditions.

B) Peripheral antagonist; Gefapixant

Gefapixant (formerly AF-219) is a novel oral purinergic antagonist which blocks the P2X3 receptor on vagal afferent nerves. The initial phase 2a proof of concept study using 600 mg twice per day for only 2 weeks demonstrated a 75% reduction in objective cough frequency compared to placebo, however, all patients developed either loss of taste (ageusia), altered taste (dysgeusia) or reduced taste (hypogeusia) (118). Subsequently, a dose escalation study was completed to ascertain the ideal dose which would have a more tolerable side effect profile, and maintain clinically meaningful efficacy(119). Lower doses of between 7.5mg and 50mg twice daily were studied in a 12-week study, and the 50 mg twice per day showed a 37% reduction in cough rates compared with placebo(120). Two subsequent companion phase 3 studies have demonstrated the 45 mg BID dose met its primary outcome(63).-A dose response meta-analysis conducted also

concluded data from 9 RCTs that gefapixant did reduce cough frequency by 17.6% [95% CI, 10.6%-24.0%], moderate certainty], cough severity on the 100-mm VAS (mean difference, -6.2 mm [95% CI, -4.1 to -8.4]; high certainty), and cough-specific quality of life on the LCQ (mean difference, 1.0 points [95% CI, 0.7-1.4]; moderate certainty).However, taste related adverse events was approximately 69%, with 12% discontinuations due to taste adverse events. Based on this data, gefapixant was the first ever licensed drug for RCC/UCC by the European Medicine Agency (EMA) and regulatory authorities in the UK, Switzerland and Japan. However, the FDA did not approve the medication. Clinicians in countries where gefapixant is approved may consider trying this after informed discussion with patients knowing the benefits and risks above. Importantly, taste side effects do get better on treatment in 25%, and resolve in almost all patients after stopping gefapixant. It is not associated with any weight loss.

C) Speech and Language Therapy

Non-pharmacological treatments are delivered by speech and language therapists or physiotherapists and aimed at actively suppressing or controlling cough you are. These therapies can be used on their own or in conjunction with pharmacological treatment and are usually indicated for patients with refractory chronic cough to medical therapy. These interventions aim to educate patients about their cough, provide them with cough suppression techniques and breathing exercises, improve vocal/laryngeal hydration and psychoeducational counselling to help them gain greater control of their cough (121). At least six studies have been completed, consistently demonstrating non-pharmacological interventions help reduce cough frequency and improve quality of life(121). There is also evidence that they reduce cough hypersensitivity (121)In a multicentre randomised controlled trial (PSALTI), there was a 41% reduction in cough frequency assessed objectively with the Leicester Cough Monitor, and a clinically significant

improvement in quality of life (122). Importantly, the improvement in cough was sustained when therapy was discontinued. The addition of the Speech Pathology Treatment to neuromodulator drug therapy, Pregabalin has also been evaluated in a clinical trial (116). There was a clinically significant improvement in quality of life, and this was sustained when therapy was discontinued. Speech therapy may be particularly helpful when there is coexisting laryngeal disorders such as muscle tension dysphonia, inducible laryngeal obstruction and voice disturbance. Physiotherapy may be particularly helpful in the presence of disordered breathing patterns. The main limitation of nonpharmacological therapy is the lack of availability in primary and secondary care, trained staff and potentially patient compliance with exercises. Further research is needed to investigate when to refer patients, which components of therapy work, their optimal timing and delivery. There is currently ongoing work to investigate the benefits of delivering nonpharmacological therapy virtually, in a group therapy sessions are which could potentially be more cost-effective, reduce waiting lists and be more convenient for patients.

Conclusions

Chronic cough is a prevalent and distressing symptom that can significantly impact the physical, social, and psychological well-being of patients. Current guidelines advocate for the treatment of any identifiable underlying conditions or traits. In cases where the cough is refractory or unexplained, speech and language therapy, along with neuromodulatory treatments such as low-dose opioids, pregabalin, and gabapentin, can be considered. It is crucial for clinicians to monitor and limit the dosage and duration of centrally acting neuromodulator treatments to mitigate side effects and ensure tolerability, ideally within a respiratory or specialized cough clinic. Gefapixant is a novel peripherally acting P2X3 antagonist which is approved in Europe, UK,

Switzerland and Japan. Real world data on efficacy and tolerability will help to understand if this is a feasible option for patients with RCC.

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TABLE 1: Summary of Typical Symptoms, Investigations for Common Conditions associated with Chronic Cough.

Condition	Typical Symptoms	Investigations
Asthma	Episodic cough, wheeze, dyspnea	Spirometry with Reversibility, Bronchial Provocation Tests, FeNO
Cough Variant Asthma	Predominantly Cough only	Spirometry with Reversibility, Bronchial Provocation Tests, FeNO
NAEB	Mainly dry, occasionally productive cough. Minimal Wheeze.	No evidence of reversibility, or airway hyper-responsiveness. Sputum Cytology, FeNO, endobronchial biopsy
COPD	Progressive dyspnea, cough, wheeze, history of smoking	Spirometry, chest x-ray
GERD/Esophageal Dysmotility/Aspiration	Heartburn, indigestion, bloating, cough worse after eating/lying down.	24-hr pH impedance with high resolution manometry, barium swallow, video fluoroscopy, gastroscopy
Chronic Rhinosinusitis	Nasal Congestion, decreased sense of smell, facial pain-pressure-fullness.	Anterior rhinoscopy, naso-endoscopy, sinus CT
Bronchiectasis	Productive mucus and phlegm, recurrent infections,	CXR, HRCT, sputum culture (bacterial, fungal, atypical mycobacteria)
ILD including Sarcoidosis	Dry cough with progressive dyspnea	CXR, HRCT, transbronchial/VATS biopsy as per ILD MDT.
Inducible Laryngeal Obstruction/Vocal cord dysfunction	Sudden onset, breathlessness, cough, throat/chest tightness, voice disturbance.	Laryngoscopy with challenge, spirometry with flow volume loop.

Table 2: Investigation in Primary and Secondary Care.

Investigation		All patients	Selected Patients	Rarely	Research
CXR	PRIMARY CARE	✓			
CBC		✓			
Spirometry		✓			
Subjective Cough Assessment (0-10 NRS, VAS)		✓			
Bronchial Provocation	SECONDARY OR TERTIARY CARE		✓		
FeNO			✓		
CT Chest			✓		
Bronchoscopy			✓		
Sputum Induction			✓		
Sputum Culture			✓		
Laryngoscopy			✓		
CT Sinus			✓		
Naso/Laryngoscopy			✓		
Sleep Study				✓	
24-hr/Ph Impedence				✓	
Gastroscopy				✓	
Cough Challenge					✓
Cough Frequency Monitoring					✓

Figure 1. Chronic Cough: Treatable Traits Approach

The concept of a treatable traits approach in the management of chronic cough, with a focus on refractory chronic cough (RCC) and cough hypersensitivity syndrome (CHS). RCC is positioned overlapping at the center of the figure, representing its complex and often overlapping with CHS, a condition characterized by an exaggerated cough responses to low levels of thermal, mechanical and chemical stimulation. RCC and CHS can be associated with multiple and overlapping traits—specific clinical conditions that can contribute to chronic cough and are potentially modifiable through targeted therapeutic interventions. The overlapping nature of these traits highlights the multifactorial etiology of chronic cough, especially in refractory cases, emphasizing the importance of identifying and managing these underlying conditions to effectively treat chronic cough. It is important to note, although labelled 'treatable' not all of these traits, such as, CANVAS are treatable in clinical practice. ACE; angiotensin converting enzyme, CANVAS; Cerebellar ataxia, neuropathy and vestibular areflexia syndrome, ILO; inducible laryngeal obstruction; VCD, vocal cord dysfunction.

Figure 2. Clinical Approach to Managing Chronic Cough

A clinical approach to the investigation and management of chronic cough guides clinicians through a series of steps, starting with the assessment of the patient's history and physical examination, followed by targeted diagnostic tests to identify treatable traits and potentially overlapping cough hypersensitivity early on. The algorithm emphasizes regular assessment of cough severity and impact of cough on quality of life in order to evaluate if a patient has refractory chronic cough (RCC). In such cases specialized interventions for refractory cases, including peripheral antagonist and centrally acting neuromodulators with or without speech therapy.

*NRS- numeric rating scale, other scales to use are VAS for cough and the LCQ (Leicester cough Questionnaire)
** Gefapixant is currently only approved for use in the EU, Switzerland, Japan and UK
ACEi; angiotensin converting enzyme inhibitors, AHR; airway hyper-responsivness, BDR; bronchodilator response, CANVAS; Cerebellar ataxia, neuropathy and vestibular areflexia syndrome, CRS; chronic rhinosinusitis, GERD; gastroesophageal reflux disease, ILO; Inducible laryngeal obstruction, NRS; numeric rating scale, QoL; quality of life, OSA; obstructive sleep apnea, VCD; vocal cord dysfunction