www.brn.cat

PERMANYER

BRN Rev. 2023;9(4):84-101

BRN Reviews

REVIEW ARTICLE

Impact of Chronic Cough on Quality of Life

Ana Oliveira, PhD[1,2], Ana Sofia Grave, MSc[1], Dina Brooks, PhD[2,3], and Imran Satia, MA, MB, BChir, MRCP, PhD[4,5,6,7,*]

[1]Lab 3R Respiratory Research and Rehabilitation Laboratory, School of Health Sciences, University of Aveiro (ESSUA), IBMED Aveiro, Portugal; [2]School of Rehabilitation Science, Faculty of Health Science, McMaster University, Hamilton; [3]Department of Respiratory Medicine, West Park Healthcare Centre, Toronto; [4]Department of Medicine, McMaster University; [5]Firestone Institute for Respiratory Health, St Joseph's Healthcare; [6]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University; [7]McMaster Institute for Research on Ageing, McMaster University. Hamilton, Ontario, Canada

ABSTRACT

Chronic cough affects approximately 10% of adults worldwide with large global variations from 2-18%. Despite its detrimental effects on physical, psychological, and social well-being, there is limited understanding of the specific impacts of chronic cough on individuals' daily lives. This review summarizes the impact of chronic cough across various life domains, including social interactions, work productivity, physical and psychological functioning, burden of investigations, treatment-related adverse events, and mortality. The review highlights the importance of considering different phenotypes of chronic cough in patient management to enable comprehensive evaluations that incorporate specific patient-reported outcomes for each phenotype. By adopting this approach, a comprehensive assessment can facilitate tailored interventions that improve patient-reported outcomes. Further research is needed to standardize the diagnosis of phenotypes, develop disease-specific patient-reported outcome measures, and conduct well-designed randomized controlled trials to evaluate both disease-specific and nonspecific therapies for individuals with chronic cough.

Keywords: Chronic cough. Impact. Quality of life.

Correspondence to:
Imran Satia
Email: satiai@mcmaster.ca

Received: 14-06-2023
Accepted: 24-07-2023
DOI: 10.23866/BRNRev:2023-M0090
www.brnreviews.com

INTRODUCTION

Cough is one of the most common symptoms for which people present to primary care and is a main complaint for patients seeking medical attention in specialist clinics[1,2]. Chronic cough (CC) refers to a cough that lasts for eight weeks or longer and poses high challenges and burden to individuals' physical, psychological, and social well-being[3]. CC can be manifested in a wide range of respiratory and non-respiratory conditions, such as asthma, gastroesophageal reflux disease (GERD), upper airway cough syndrome (UACS), and interstitial lung diseases[4,5]. Additionally, recent evidence suggests that CC may have clinical features described as cough hypersensitivity syndrome, which is characterized by coughing triggered by low levels of thermal, mechanical, or chemical exposure[6,7].

Globally, the prevalence of CC ranges from 2.5% to 18%[8-12] with an estimated prevalence in Europe of 10-15% in the general population[7]. However, certain subgroups, such as smokers and people with chronic respiratory diseases, may have higher rates of CC, with prevalence rising up to 90%[5,13]. Although it is challenging to estimate the incidence of CC due to the need for well-powered longitudinal studies, evidence suggests that its incidence ranges from 6.3% to 12.5%, and is increasing, especially in developing countries[14].

Several risk factors have been associated with CC, including aging, smoking, exposure to environmental irritants like air pollution, respiratory infections, asthma, GERD, and the use of certain medications, such as angiotensin-converting enzyme(ACE)-2 inhibitors[6]. Recent evidence from the Canadian Longitudinal Study of Aging (CLSA)[15] has also described an approximate 20% increased risk of developing CC in those with symptoms of psychological distress or depressive symptoms. The risk of developing CC is also higher in those with chronic pain as well suggesting shared pathobiology[12,16]. Despite its high prevalence, no licensed treatments for CC are currently available. Treatment options for CC typically involve managing the underlying triggers or causes, such as quitting smoking or treating asthma, GERD, UACS, but in some cases where the CC is refractory to treatment, cough suppressants or cough control strategies with a speech therapist or physiotherapist may be required[3,17,18]. However, the effectiveness and side effects of these treatments in objective and patient-reported outcomes can vary greatly[3], underscoring the need for further research to develop more effective and targeted therapies for CC.

This review provides a comprehensive overview of the phenotypes of CC, assessment tools, impact on individuals' lives, and the effects of available therapy on patient-reported outcomes.

PHENOTYPES OF CHRONIC COUGH

Phenotypes are observable properties of disorders resulting from the interaction between an individual's genes and environment[19]. These properties aid in grouping individuals with comparable clinical features, prognosis, and therapeutic requirements, making them beneficial in the clinical management of various disorders[20].

Chronic cough phenotypes are defined based on the individual and cough's clinical

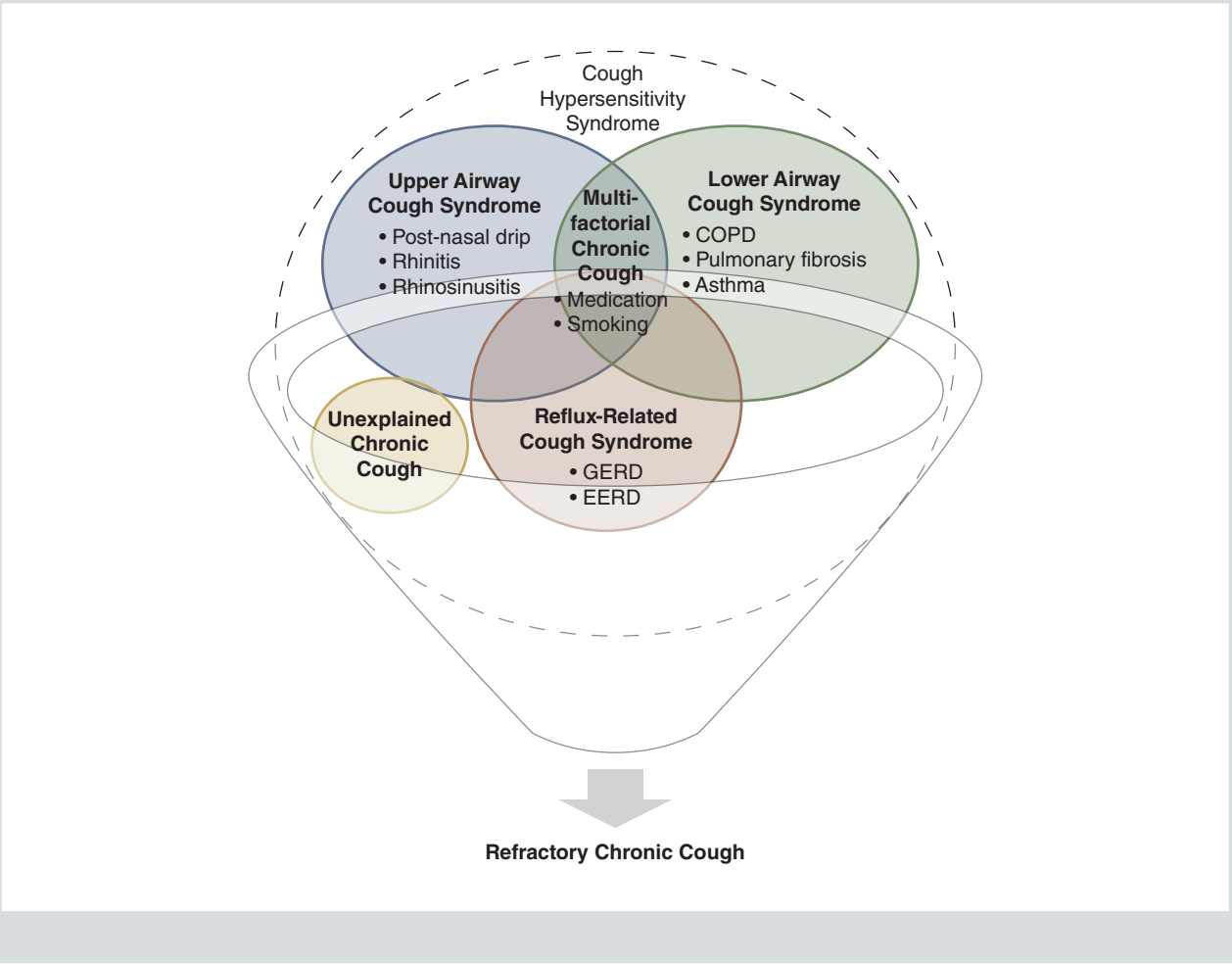

Figure 1. Commonly acknowledged phenotypes of chronic cough.
COPD: chronic obstructive pulmonary diseases; EERD: extra-oesophageal reflux disease; GERD: gastroesophageal reflux disease.

characteristics, underlying pathophysiology, and response to treatment. Although the investigation of phenotypes in CC is recent, with the first known work using clustering techniques published in 2020 by Koskela and colleagues[21], there is a growing interest in defining and exploring these phenotypes. Despite the area's novelty and ongoing evolution, some consensus exists on the following phenotypes (Fig. 1):

– Respiratory-related coughs: characterized by a cough that originates from the lower airways, including the trachea, bronchi, bronchioles and also the lung parenchyma. The cough is usually productive of sputum and may be associated with wheezing, shortness of breath, and chest tightness. The most common causes include asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and interstitial lung disease[22,23]. In endemic areas, tuberculosis or atypical mycobacteria also needs to be considered as potential causes.

– Upper airway cough syndrome: characterized by a cough that is caused by irritation

or inflammation in the upper airway, including the nasal cavity, sinuses, and pharynx. Symptoms may include nasal congestion, rhinorrhoea, post-nasal drip, and throat clearing. The most common causes include allergic rhinitis, non-allergic rhinitis, and chronic rhinosinusitis[3,22,23].

– Reflux-related cough syndrome: characterized by a cough that is triggered by GERD, which occurs when stomach acid and contents reflux into the oesophagus. Symptoms may include heartburn, indigestion, bloating, regurgitation, and a sour taste in the mouth. The cough is often worse at night or after meals[3,22,23].

– Iatrogenic cough: characterized by a CC caused by medications, the most common being the ACE inhibitors. This type of cough is caused by the accumulation of bradykinin and substance P in the airways, leading to sensitisation of the vagal c-fibres[24]. The onset of the cough may be delayed, occurring several weeks or months after starting the medication, and typically resolves within three months of discontinuing the drug[3,22,23].

– Unexplained CC: characterized by a cough that persists for more than eight weeks despite an extensive diagnostic evaluation that fails to identify an underlying cause[3,22,23].

– Multifactorial CC: characterized by a cough that is due to a combination of multiple factors, such as asthma, GERD, and UACS. This type of cough may be more difficult to treat because it requires a comprehensive approach that addresses all underlying factors[22].

– Refractory CC: a cough that persists for more than eight weeks despite optimal treatment for the underlying cause or causes of the cough[3,22,23].

Other cough phenotypes, such as the COVID-19 cough and smoking cough or those based on age and disease severity, have been described less frequently[21,25]. Regardless of the underlying phenotype, patients with CC may be predisposed to present a hypersensitivity disposition to cough[6]. The mechanisms underlying cough hypersensitivity syndrome are not completely understood, but it is believed to occur due to neuronal dysfunction as a consequence of three main processes that lead to increased activation of the neuronal pathways mediating cough[26,27]: i) excessive activation of airway vagal afferent terminals (e.g. by mucus, ATP, eosinophils), ii) neuroplastic changes in vagal afferent fibres, iii) neuroplastic changes in the central nervous system, i.e. central sensitization and/or impaired inhibitory control[28]. The exact cause of why these changes occur is unclear but they may result from chronic inflammation, viruses[29,30], or other pathological processes that lead to the neuronal dysfunction[6].

TOOLS USED TO EVALUATE THE IMPACT OF CHRONIC COUGH

Measuring cough parameters accurately is vital for both clinical practice and research, as it enhances our comprehension of cough mechanisms, helps in tailoring treatments, and in assessing the efficacy of novel therapies. To conduct a comprehensive cough assessment, both patient- and clinician/researcher-centred approaches are necessary and complementary. There are several tools available for assessing

cough, and guidelines and consensus statements have been established for their use[3,31]. We discuss the most commonly used and effective patient-reported and objective approaches for cough assessment, as well as emerging techniques and future prospects.

Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are vital for assessing the impact of CC on patients' quality of life, enabling them to express their symptoms, well-being, social interactions, and treatment satisfaction[32]. PROMs assist healthcare providers in monitoring disease progression, evaluating treatment efficacy, and making informed clinical decisions, serving as key endpoints in clinical trials[33,34].

Various PROMs currently exist to evaluate cough-related outcomes, including severity and quality of life. Cough severity encompasses multiple domains, such as frequency, intensity, control, duration, and associated effects[35]. Current PROMs used to assess cough severity, including the visual analogue scale (VAS)[36], cough symptom score (CSS)[37], cough severity diary (CSD)[38,39], and Cough Severity Index (CSI)[40], are simple and commonly employed in clinical practice but lack comprehensiveness. To address this, a new tool, the McMaster Cough Severity Questionnaire, is being developed[35]. This questionnaire aims to capture all domains reported by patients regarding cough severity, offering a comprehensive endpoint in clinical trials. However, further research is needed to refine and prioritize the questionnaire items and domains based on patient importance.

The Leicester Cough Questionnaire (LCQ) is widely recognized and recommended for assessing cough-related quality of life, including the European Respiratory Society (ERS) CC guidelines[3]. It evaluates the physical, social, and psychological effects of cough and has undergone robust validation in multiple languages with individuals experiencing a refractory CC[41,42], as well as those with COPD[43,44], cystic fibrosis[45], and bronchiectasis[46]. Other validated tools such as the CC Impact Questionnaire (CCIQ)[47], Cough Specific Quality of Life Questionnaire (CQLQ)[48], Cough Assessment Test (COAT)[49], and Cough Evaluation Test (CET)[50] also provide valuable insights into the subjective impact of cough symptoms on quality of life. Table 1 summarizes the characteristics, measurement properties, interpretability and time of application of commonly used PROMs to assess CC.

Moving forward, it is essential to develop disease-specific PROMs for CC, tailored to different phenotypes. This approach would enable a targeted evaluation of treatment outcomes specific to these conditions. Additionally, leveraging technology, such as mobile applications or web-based platforms may facilitate the implementation of PROMs in daily care and research. Online administration of PROMs has advantages over paper-based completion, including better data quality, faster completion time, lower cost, and the ability to guide clinical decision-making[51]. Simplified tools like VAS or numeric rating scales, especially when completed online, provide added value by reducing missing values and allowing frequent data collection in research and daily clinical practice[52-54].

Finally, there is a pressing need to develop tools that assess the quality of life and burden

of family members living with individuals experiencing CC. Parents of children with CC reported being affected by the psychological and social consequences of cough[55,56]. However, the impacts on partners or carers of adults of CC have not been investigated. By incorporating family-oriented outcome measures, such as caregiver burden scales or family impact questionnaires, a comprehensive assessment of the overall impact of CC on both patients and their families can be achieved. This would facilitate a more holistic approach to care and ensure that the needs of all individuals affected by CC are addressed.

Objective outcome measures

Objective tools for assessing CC provide valuable insights into cough characteristics, enabling accurate assessment and monitoring of cough frequency. The measurement of 24-hour cough frequency has become a key endpoint in clinical studies evaluating treatment effects[57,58]. Manual counting, though labour-intensive, remains the gold standard method, demonstrating high agreement among different listeners[59,60]. The VitaloJAK 24-hr cough monitoring system is currently the most used in clinical trials. It is a semi-automated cough monitoring system and has received regulatory approvals (510K and CE marked) for use in clinical trials[61]. It employs a filtering algorithm to remove non-cough sounds while retaining recorded cough sounds, and it has demonstrated efficiency in measuring cough frequency across different respiratory diagnoses[62-64]. Other fully automated cough monitors capable of monitoring coughs beyond 24 hours are currently being developed and validated but they lack the sensitivity, low false positive rates, and specificity compared to the VitaloJAK which has a sensitivity and specificity of around 99% due to the semi-automated process which requires manual tagging of cough.

Future development and refinement of objective tools for assessing CC are necessary. Rigorous validation studies should be conducted to enhance their accuracy and reliability across diverse populations and cough phenotypes. User-friendly interfaces, cost-effective versions, and standardized interpretation guidelines would improve accessibility and comparability. Integration of objective cough measures with patient-reported outcomes would enable a comprehensive assessment of cough-related outcomes. Exploring wearable devices, smartphone applications, and artificial intelligence can advance real-time monitoring and personalized interventions. Collaboration among researchers, clinicians, and technology developers is essential for driving innovation and improving the assessment and management of CC.

IMPACT OF CHRONIC COUGH

An internet survey conducted among the general population in Europe revealed that 96% of individuals with CC experienced a significant decline in their quality of life, resulting in social isolation, depression, and relationship difficulties[65]. A thorough examination of the multifaceted consequences of this condition is crucial to gain insights into the extensive burden it imposes. Addressing the various dimensions of CC is essential for optimizing patient care and improving outcomes. Clinicians and researchers should assess the impacts of CC

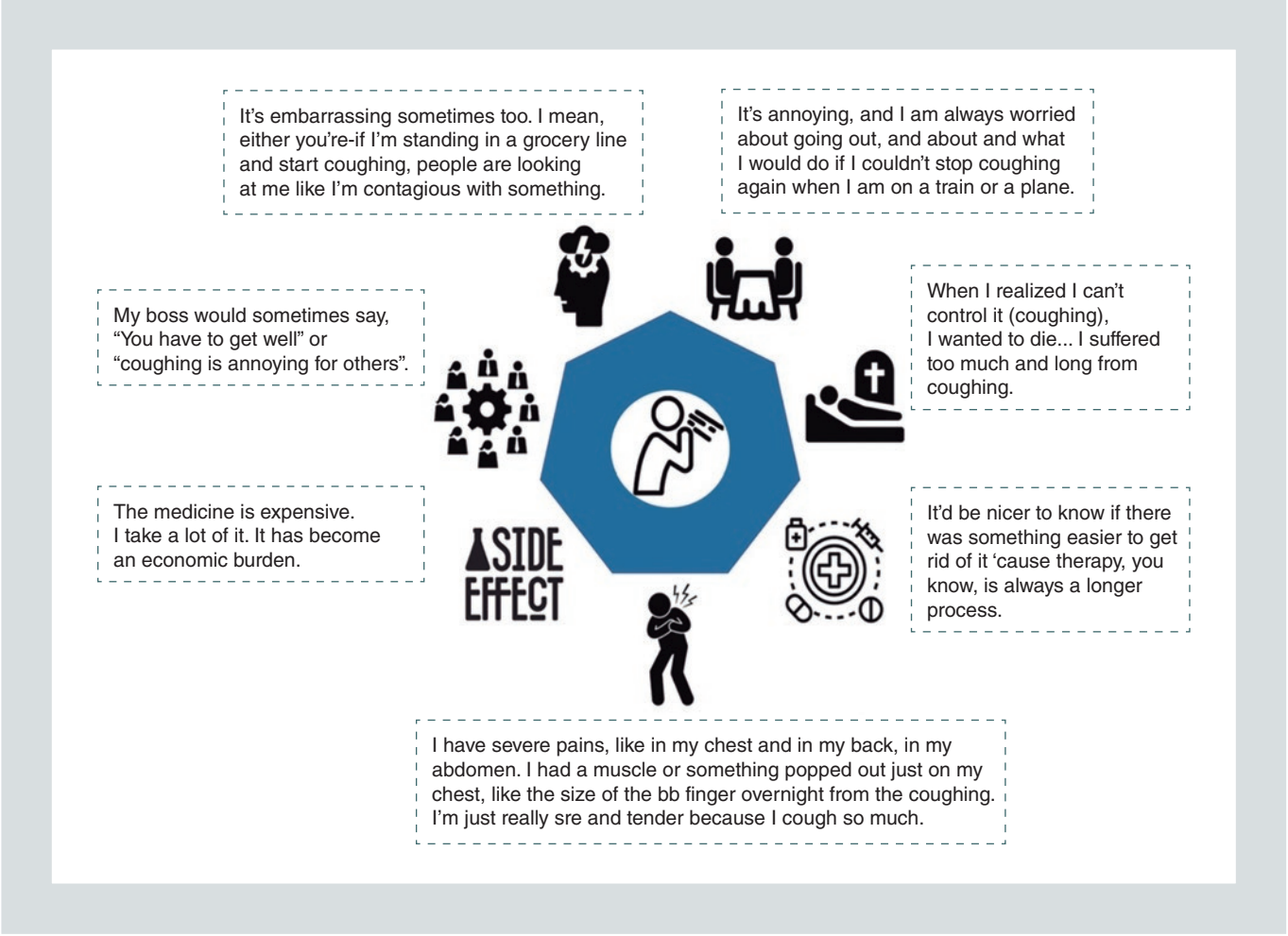

Figure 2. Impacts of chronic cough on social life, psychological and physical effects, work life, burden of investigations, adverse events of treatments, and mortality. Quotes are from the systematic review by Kayleigh et al.[66].

across multiple domains of an individual's life, including social life, work life, physical and psychological and function, burden of investigations, adverse events of treatments, and even mortality. Figure 2 summarizes the impacts of CC on the life domains addressed in this paper, accompanied by patients' quotes from qualitative literature[66].

Social life

Chronic cough can profoundly impact an individual's social life, leading to various challenges and limitations in their daily interactions and relationships. Surveys conducted in Asia (n=447)[67] and Europe (n=1120)[65] have shown that cough affects the daily activities of virtually all participants inquired (75 to 100%), disturbing their relationships with families and friends. The mean social LCQ scores varied between 3.5 and 5.8[68-71], significantly lower (i.e., worse) than the normal threshold of 6.06 in healthy populations[72].

Qualitative research also provides valuable insights into how CC affects individuals' social lives. Certain individuals express constant

concern about coughing in public due to the fear of how others will perceive them[66]. This fear leads to feelings of isolation and withdrawal from social interactions. In contrast, other individuals refuse to let the cough dominate their lives and employ strategies to minimize coughing[66]. However, those who do not limit their social interactions often attract unwanted attention and negative reactions, experiencing stigmatization as if they were contagious[66]. The unwelcome attention often prompts individuals to justify and explain their condition to others[66]. Some individuals even find it challenging to avoid public transportation to evade such attention and stigma, especially because coughing while driving poses a risk[66].

Furthermore, CC not only affects individuals but also significantly impacts those closest to them. This implies that CC has a ripple effect on the patient's immediate relationships. Nonetheless, gaining a better understanding of people in their surroundings can alleviate the burden[71]. Family members of patients are frequently concerned and supportive, offering valuable assistance in coping with the challenges posed by CC[71].

Work life

The impact of CC on a patient's personal experience with work or employment can be significant. Coughing episodes can disrupt concentration, communication, and productivity in the workplace[66,73]. The physical discomfort and embarrassment associated with coughing can also cause emotional distress, further affecting the individual's overall well-being, work motivation and work performance[66,71]. This can lead to decreased job satisfaction and limitations in career advancement. As a result, individuals may feel ashamed and stigmatized in the work environment, potentially leading to their withdrawal from or inability to continue working[66]. Indeed, CC is linked to increased sick leave. Approximately one in six participants experienced CC and reported taking more than seven days of sick leave in the previous year. This was significantly higher than the rates reported by those without cough. Both non-productive cough (21%) and productive cough (24%) were associated with higher sick leave rates compared to those with no cough (13%)[74].

Chronic cough among employees can have implications from an employer's perspective. While research specifically focused on the workplace is limited, studies conducted among school children suggest that frequent coughing can create a disruptive environment[75], similar to what may occur in a workplace setting. This disruption can negatively impact other employees' focus and productivity. Moreover, concerns about the contagiousness of CC may arise, leading to worries about the spread of illness within the workforce. Employers may need to consider implementing measures such as providing suitable workspaces or accommodations to minimize disruptions caused by CC.

The impact of CC extends beyond the individual and the workplace, affecting society as a whole. It contributes to increased healthcare utilization, with individuals seeking more doctor visits, diagnostic tests, and treatments. This places a burden on healthcare systems and resources[56,65,76]. Data suggests that the impact of CC on sick leave days is comparable to that of asthma in the general population,

highlighting the importance of recognizing the societal impact of this condition and allocating healthcare resources accordingly[74].

Physical function

Chronic cough exerts a profound and detrimental impact on individuals' physical health, impeding their ability to carry out basic and instrumental activities of daily living. Even simple tasks such as bathing, dressing, and eating, which are typically taken for granted, become triggers for coughing among those affected by CC[66]. Moreover, individuals report that more complex activities like housework, particularly those involving humidity such as doing the dishes or cleaning the bathroom, also elicit coughing episodes[71]. The relentless and forceful bouts of coughing make these activities arduous and draining, posing significant challenges to individuals with CC. In an effort to cope with these effects, participants employ strategies such as taking regular breaks or utilizing humidifiers during housework to alleviate the impact of cough on their daily routines[71].

Furthermore, CC imposes physical discomfort and elicits a range of associated symptoms. The repetitive coughing bouts can provoke a sore throat, chest pain, and strain in the abdominal and chest muscles[66]. Individuals may contend with frequent throat irritation, hoarseness, and a persistent tickling sensation that precipitates further coughing[77]. These symptoms not only engender discomfort but also disrupt sleep patterns, leading to fatigue and overall diminished quality of life. Additionally, the physical exertion associated with coughing can contribute to headaches, urinary incontinence, and in severe cases, even rib fractures[66]. Notably, the mean physical LCQ scores observed in previous studies ranged from 4.3 to 5.4[68-71], equalling or falling below the normal threshold of 5.4 in healthy populations, emphasizing the tangible physical toll of CC[72].

Psychological function

Chronic cough can have profound psychological impacts on individuals, stemming from the physical and social consequences associated with the condition. Research indicates that the mean LCQ scores obtained from people with CC vary between 4.0 and 5.4[68-71], falling below the normal threshold of 5.8 observed in healthy populations[72].

The persistent and disruptive nature of coughing episodes can evoke a wide range of negative emotions, including anxiety, depression, shame, frustration, and fear[66,70]. While the exact reasons behind the anxiety experienced by people with CC are not fully understood, it can be speculated that the unpredictable nature of the coughing fits, and the lack of a definitive diagnosis may play a role[66,78]. This anxiety may lead to a heightened sense of self-consciousness and fear of judgment from others, contributing to feelings of shame and embarrassment, as reported frequently in the literature[66,71]. The constant disruption and limitations in daily life activities can also lead to frustration and a sense of helplessness, as individuals struggle to fully engage in work, social interactions, and leisure activities[66].

The psychological impacts of CC are intricately connected to the physical and social

aspects of the condition. The physical discomfort, associated symptoms, and limitations in daily activities can contribute to feelings of frustration, irritability, and even anger[66]. The constant cycle of coughing, physical discomfort, and disrupted sleep patterns can result in fatigue and exhaustion, further exacerbating the psychological burden. The social consequences, including social isolation, stigma, and negative reactions from others, amplify feelings of shame and embarrassment. As reported frequently in the literature, CC can strip individuals of their identity, leaving them defined solely in terms of their cough[66].

Burden of investigations

People with CC often face a significant burden during investigations, a factor that is often overlooked in the literature and medical appointments. According to the latest European guidelines on diagnosing and treating CC[3], the initial approach involves identifying the underlying cause of the cough through various tests, including chest X-rays, pulmonary function tests, bronchoscopy, computed tomography scans, and sputum analysis. However, undergoing multiple investigations can be time-consuming, physically and emotionally demanding, and can incur financial costs[3,66]. Adding to the burden is the fact that the cause of CC remains unidentified in many cases, leading to a prolonged and frustrating diagnostic process[66]. Qualitative research highlights that individuals perceive the diagnosis process as lengthy, impersonal, and repetitive, leaving them burned out, desperate and exhausted without satisfactory answers[66]. Streamlining and optimizing the investigative process for CC is crucial to alleviate the burden on individuals and enhance their overall well-being.

Adverse events of treatments

Treatment for CC can have adverse effects that complicate the challenges faced by individuals. Medications commonly prescribed for CC, such as cough suppressants or neuromodulators, can lead to side effects including taste disorders, somnolence, fatigue, dizziness, dry mouth, and gastrointestinal disturbances[79,80]. Although research on the impacts of medication's side effects on individuals' lives is limited, studies on various health conditions have demonstrated that adverse effects of medications can significantly affect people's daily functioning and financing situation[81]. People with CC have reported a progressive increase in their medical costs, with the monthly cost of cough medication averaging around $74[71]. Furthermore, if the medications fail to provide the desired relief and lead to additional physical and mental consequences, individuals may become further frustrated and disappointed with the medical system, potentially leading them to discontinue medical investigations[71].

Invasive procedural treatments may also be considered for CC, such as nerve block injections of local anaesthetic and corticosteroid, surgical transection, bilateral thyroarytenoid botulinum toxin injection, and vocal fold augmentation with methylcellulose or hyaluronic acid[82]. While these procedures aim to target specific underlying causes of the cough,

they also carry the risk of complications or adverse effects. For example, nerve blocks can lead to temporary laryngospasm or throat paraesthesia, and thyroarytenoid botulinum toxin injection may cause temporary dysphagia and dysphonia. However, it is important to note that studies on procedural therapy have not reported any serious adverse effects such as death or aspiration pneumonia[82].

Treatment options for CC extend beyond medications alone. Non-pharmacological therapies, such as multimodal combinations of cough neuro-physiology education, cough suppression techniques, breathing exercises, hydration and cognitive-behavioural therapies delivered by a physiotherapist and/or speech-language therapists[83], are recommended as complementary treatments[3,84,85]. These therapies aim to address underlying triggers or modify cough behaviour and have shown no physiological adverse effects. However, it is important to acknowledge that some individuals may perceive these therapies as impractical or challenging to incorporate into their daily routines[66]. Engaging in physiotherapy, speech therapy or practicing breathing exercises may require significant time, commitment, and regular follow-up sessions, which can be demanding and difficult for certain individuals.

Each treatment option for CC presents its unique challenges. Therefore, healthcare professionals need to consider not only the physiological effects but also the practicality and feasibility of treatment approaches. This holistic approach is essential to provide comprehensive care that meets the specific needs and circumstances of individuals with CC.

Mortality

Chronic cough itself may not directly cause death but it can often indicate an underlying health condition that can contribute to increased mortality risk. Several studies have identified associations between CC and increased mortality rates, specifically productive cough[86-88]. This association is present even in the absence of lung function impairment[89] but also in people with respiratory conditions such as chronic obstructive pulmonary disease[90], and interstitial lung diseases[5]. These respiratory conditions, often characterized by chronic inflammation and lung damage, can lead to progressive respiratory decline and ultimately contribute to a higher risk of poor outcomes, including lung transplant and death[5]. Furthermore, CC can also be a symptom of other systemic illnesses, such as heart failure or certain types of cancer, which can further increase mortality risk[91,92].

Additionally, CC may lead to physical and psychological consequences known to be related to an increased risk of death, such as reduced physical activity[93] and increased levels of anxiety and depression[94]. Reduced physical activity resulting from CC can contribute to a sedentary lifestyle, which is a known risk factor for various chronic diseases and mortality[95-97]. Chronic cough can significantly affect an individual's mental well-being, leading to increased levels of stress, social isolation, anxiety and depression[66,70]. Psychological distress has been associated with an increased risk of mortality in the general population[98] and across various health conditions, such as cardiovascular diseases[99], respiratory disorders[100], and cancer[101].

TREATMENTS EFFECTS ON CHRONIC COUGH PATIENT-REPORTED OUTCOMES

Disease-specific treatments

Tailoring interventions to the underlying disease in individuals with known causes of CC, which make up around 60% of cases[102], holds promise for enhancing patient-reported outcomes. By targeting the specific underlying condition responsible for the CC (i.e., treatable traits), such as asthma, allergies, UACS, or GERD, improvements in cough-related quality of life and self-reported cough frequency may be attained. However, it is crucial to acknowledge that the current recommended approach, as outlined in international guidelines, is based on limited high-quality evidence from well-designed randomized controlled trials, which in some instances yield contradictory results[3].

The evidence regarding the effectiveness of inhaled steroids and bronchodilators, commonly prescribed for reducing airway inflammation and inducing smooth muscle relaxation, is inconsistent and of low quality. However, some studies have demonstrated their efficacy in reducing cough severity and improving cough-related quality of life in individuals with sub-acute and CC[103,104]. Based on the clinical benefits observed in certain patients with asthmatic cough (or airway eosinophilic inflammation) and the relatively low occurrence of adverse events, the current guidelines conditionally recommend the use of inhaled steroids in adults with CC[3]. Conversely, the evidence for acid suppression therapy (proton pump inhibitors or histamine-2 receptor antagonists) in individuals with GERD and allergy medications such as intra-nasal steroids and non-sedating H1-receptor antihistamines is inconsistent[105]. The guidelines advise against routine use of anti-acid drugs in adult patients with CC[3]. As for non-sedating H1-receptor antihistamines, despite their widespread use in patients with CC, evidence suggests that improvements in patient-reported cough scores may only be observed in specific subgroups, particularly those with seasonal allergic rhinitis-associated cough (with a cough frequency score improvement of -44.0 ± 7.3% and cough intensity score improvement of -65.7 ± 8.3%) or atopic cough (relative improvement in cough frequency score of -36.6 ± 8.4%)[106].

Refractory or unexplained chronic cough

Up to four in every ten individuals with CC develop an unexplained or refractory cough that has no or little response to guideline-based treatment and it has a substantial impact on quality of life and healthcare utilization[102]. In this context, neuromodulators such as morphine, gabapentin, and pregabalin, non-pharmacological therapies, including physiotherapy and/or speech language therapy, and P2X3 antagonists including gefapixant and camlipixant have been investigated[107,108].

Nonspecific therapies, such as neuromodulators, target the nervous system to modulate cough reflex sensitivity. While the evidence for their effectiveness is limited and inconsistent, some studies suggest that medications like morphine, gabapentin, and pregabalin may offer potential benefits in reducing cough severity and improving cough-related

quality of life[109-112]. However, their use should be approached with caution, as they may be associated with important side effects, including respiratory depression, drowsiness dizziness, confusion and fatigue[109-112]. The benefit of long- term use of neuromodulators is difficult to predict due to these adverse events.

Non-pharmacological therapies, such as physiotherapy and speech-language therapy, have demonstrated promising outcomes in individuals with refractory CC. These therapies have been associated with a significant reduction in cough severity (decreases of over 20 mm on the VAS) and in cough-related quality of life (mean difference between groups of 1.53; 95% CI 0.21 to 2.85 on the LCQ), without physiological side effects[113,114]. Current clinical guidelines recommend the use of non-pharmacological therapy in individuals with refractory CC[3,84,85]. However, to ensure widespread implementation in clinical practice, further evidence from well-designed randomized controlled trials is necessary, as well as more trained healthcare professionals who can effectively apply these therapies[3,84,85,115]. It is worth noting that research on the mechanisms of action of non-pharmacological therapy is also lacking, and conducting mechanistic studies would be beneficial in establishing the relevance and efficacy of these therapies[83].

P2X3 antagonists, such as gefapixant and camlipixant, represent a novel class of medications targeting the P2X3 receptor involved in the cough reflex[80,116-118]. By blocking the activation of these receptors, these drugs aim to reduce cough sensitivity and frequency. Gefapixant, the first-in-class, successfully completed phase III trials and showed promising results in improving cough-related quality of life. The overall effect estimates were favorable, with a significantly higher odds ratio observed for increasing LCQ scores above the minimal clinically important difference of 1.3 points compared to the placebo group[118]. Moderate or high doses (≥ 45 mg) of gefapixant showed significant therapeutic effects[116]. The efficacy of camlipixant (BLU-5937) was evaluated in the SOOTHE phase 2b trial. Significant improvements above the minimal clinically important difference (1.3 points) for the LCQ and the cough severity VAS (30 mm) were observed with camplixant doses of 12.5 mg or above and 50 mg or above, respectively, over the 29-day treatment period[118,119]. The phase 3 CALM-1 and CALM-2 program are currently underway.

Nalbuphine in an oral extended release formulation is an opioid agonist-antagonist which has recently been evaluated in patients with refractory chronic cough secondary to IPF. This phase 2a cross-over trial demonstrated 52.5% placebo-adjusted reduction in 24-hr cough frequency, with a corresponding improvement in subjective cough frequency scores and breathlessness scores. Further larger studies including all patients with RCC are in development[127].

Given the significant impact of CC on health-related quality of life and the absence of a single effective therapy, it is imperative to prioritize comprehensive management and support. A multidisciplinary approach that combines medical treatment, education, self-management strategies, psychological support, and social interventions becomes crucial in addressing the complex biopsychosocial

Table 1. Characteristics of patient-reported outcome measures commonly used to assess chronic cough

Instrument	Characteristics	Validated populations	Measurement properties				Interpretability	Time of application
			Validity*	Test-retest reliability¥	Internal consistency	Responsiveness		
Visual Analog Scale (VAS)[36]	100 mm scale ranging from 0 (no cough) and 100 mm (worst cough). Measures cough severity and frequency.	Refractory chronic cough or unexplained chronic cough	High correlations with LCQ (r = –0.72) and CSD (r = 0.84)	Moderate reliability 0.45 < ICC < 0.51	n/a	Large effect sizes for responders (> 1.3)	Higher scores indicate higher severity. MCID: 30mm	1 min
Cough Symptom Score (CSS)[37]	Two-part questionnaire to measure cough severity during day- and night-time.	Asthma Chronic cough	Very high correlations with cough counts on audio and EMG signals (0.96 < r0.99)	n/r	n/r	n/r	Higher scores indicate higher severity. MCID: n/r	2 min
Cough Severity Diary (CSD)[38,39]	Seven-item daily diary to assess cough severity along three dimensions: frequency, intensity, disruptiveness	Refractory chronic cough Unexplained chronic cough	Moderate to high correlations with LCQ (r = 0.62) and VAS (r = 0.84)	Moderate to excellent reliability 0.68 < ICC < 0.94	Adequate: Cronbach α 0.923	n/r	Higher scores indicate higher severity. MCID: n/r	10 min
Cough Severity Index (CSI)[40]	Ten question survey to assess cough severity and impact on daily life	Upper airway cough syndrome	Moderate relation with CQLQ (r = 0.60)	High reliability r = 0.86	Adequate: Cronbach α 0.928	Significant changes after cough suppression	Higher scores indicate higher severity. MCID: n/r	10 min
Leicester Cough Questionnaire (LCQ)[41-43,45,46,120]	19 question survey on physical, phycological and social domains of quality of life	Chronic cough Cystic fibrosis Acute cough Bronchiectasis COPD	Low to high correlations with VAS (–0.72 < r < –0.41), SGRQ-T (–0.70 < r < –0.54), and CSD (–0.64) and CFQ-R (–0.78)	Good to excellent reliability ICC = 0.80-0.96	Adequate: Cronbach α 0.884-0.950	Large effect sizes for responders (> 1.2)	Higher scores indicate higher health-related quality of life. MCID: 1.3 points	20 min
Chronic Cough Impact Questionnaire (CCIQ)[47]	21-item survey to assess cough severity on daily activities, social activities, mood and sleep/attention	Chronic Cough	Low correlations with SF-36 items	Moderate to good reliability 0.67 < r < 0.88	Inadequate to adequate: Cronbach α 65.41 < α < 86.98	Significant changes after asthma treatment	Higher scores indicate higher impact. MCID: n/r	20 min.
Cough Specific Quality of Life Questionnaire (CQLQ)[48,121-123]	28-item survey to assess quality of life in the following domains: somatic symptoms, extreme somatic symptoms, social psychology, functional ability, emotional state, and personal safety fears	Chronic Cough IPF COPD Cystic fibrosis	Low to high correlations with objective total time spent coughing (r = 0.36), VAS (0.63), SGRQ-T (0.79)	Good reliability ICC = 0.89	Adequate: Cronbach α 0.89 < α < 0.92	Significant changes after treatment	Higher scores indicate less cough related quality of life. MCID: 13	30 min
Cough Assessment Test (COAT)[49]	5-item survey to assess cough frequency, limitation on daily activities, sleep disturbance, fatigue and hypersensitivity to irritants	Chronic cough	Moderate to high correlations with LCQ (r = –0.71) NRS (r = 0.69)	High reliability 0.75 < r < 0.84	n/r	Moderate to high correlations Δ LCQ (r = –0.66) and Δ NRS (r = 0.72) after treatment	Higher scores indicate higher impact. MCDI: 2 points	5 min
Cough Evaluation Test (CET)[50]	5-item survey to assess cough frequency, intensity, sleep disturbance, interference with daily life and feelings of depression and anxiety	Chronic cough	High correlations with LCQ (r = –0.74), VAS (r = 0.70) and CSS (r = 0.71)	Good reliability ICC = 0.84	Adequate: Cronbach α 0.80	Moderate to high correlations Δ LCQ (r = –0.70) and Δ NRS (r = 0.72) and CSS (r = 0.66) after treatment	Higher scores indicate higher impact. MCDI: 2 points	5 min

CCIQ: Chronic Cough Impact Questionnaire; CET: Cough Evaluation Test; CCS: Cough Symptom Score; COPD: chronic obstructive pulmonary disease; COAT: Cough Assessment Test; CFQ-R: Cystic Fibrosis Questionnaire–Revised; CQLQ: Cough Specific Quality of Life Questionnaire; CSS: Cough Severity Score; CSI: Cough Severity Index; CSD: Cough Severity Diary; EMG: electromyography; ICC: intraclass correlation coefficient; LCQ: Leicester Cough Questionnaire; MCID: minimal clinically important difference; n/a: not applicable; n/r: not reported; NRS: numeric rating scale; SGRQ-T: St. George Respiratory Questionnaire Total; VAS: Visual Analog Scale.
Correlations (r) were interpreted as 0-0.30: negligible no correlation; 0.31-0.5: low; 0.51-0.70: moderate; 0.71-0.90: high; 0.91-1.00: very high[124]; ICC were interpreted as < 0.5; poor, 0.5-0.75: moderate; 0.75-0.9: good; > 0.90 excellent[125]; internal consistency was considered adequate when Cronbach's $\alpha \geq 0.70$[126]. Data for the LCQ, CQLQ, COAT and CET are reported for total scores only.

challenges faced by individuals. Cognitive-behavioral therapies can play a valuable role in managing anxiety and depression while aiding in the development of effective coping strategies. Additionally, education and awareness programs are essential for reducing stigma and fostering a supportive environment. To establish the effectiveness of comprehensive interventions aimed at improving quality of life, trials focusing on multimodal therapies, including PROMs covering various domains such as psychological factors and social interactions, are necessary.

CONCLUSIONS

This review summarizes evidence on four significant themes related to the quality of life in CC: cough phenotypes, assessment tools, impacts, and treatments. Understanding diverse phenotypes enables tailored treatment approaches and improves patient-reported outcomes. However, further research and standardization are needed to enhance their clinical utility. Comprehensive assessment includes PROMs and objective tools. PROMs reveal cough severity and quality of life, while objective tools provide data on cough frequency. Advancing assessment tools requires refinement, standardization, and disease-specific PROMs. Chronic cough profoundly impacts various aspects of individuals' lives, necessitating a holistic approach for optimal care and outcomes. Tailoring treatments for different cough phenotypes can enhance PROMS, although evidence for medications like inhaled steroids and acid suppression therapy is limited and inconsistent. Neuromodulators and non-pharmacological interventions require further research. Novel P2X3 antagonists show promise but need additional investigation for efficacy and safety.

CONFLICTS OF INTEREST

I.S. reports grants from ERS Respire 3 Marie Curie Fellowship, grants and personal fees from Merck Canada and GSK, grants from Bayer and Bellus, personal fees from Respiplus, Genentech and AstraZeneca, outside the submitted work.

FUNDING

The study was funded by Merck Canada. I.S. is currently supported by the E.J. Moran Campbell Early Career Award, Department of Medicine, McMaster University. Dina Brooks holds a National Sanitarium Association (NSA) Chair in Respiratory/Pulmonary Rehabilitation Research.

REFERENCES

1. Cherry DK, Burt CW, Woodwell DA. National Ambulatory Medical Care Survey: 2001 summary. Adv Data. 2003:1-44.
2. Irwin RS, Baumann MH, Bolser DC et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1s-23s.
3. Morice AH, Millqvist E, Bieksiene K et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020; 55(1).
4. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371:1364-74.
5. Ryerson CJ, Abbritti M, Ley B et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology. 2011;16:969-75.
6. Chung KF, McGarvey L, Song WJ et al. Cough hypersensitivity and chronic cough. Nat Rev Dis Primers. 2022;8:45.
7. Mazzone SB, Satia I, McGarvey L, Song WJ, Chung KF. Chronic cough and cough hypersensitivity: from mechanistic insights to novel antitussives. The Lancet Respiratory Medicine. 2022 Dec 1;10(12):1113-5.
8. Song WJ, Chang YS, Faruqi S et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J. 2015; 45:1479-81.

9. Koo HK, Jeong I, Lee SW et al. Prevalence of chronic cough and possible causes in the general population based on the Korean National Health and Nutrition Examination Survey. Medicine (Baltimore). 2016;95:e4595.
10. Arinze JT, de Roos EW, Karimi L et al. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. ERJ Open Res. 2020;6.
11. Holden SE, Morice A, Birring SS et al. Cough presentation in primary care and the identification of chronic cough: a need for diagnostic clarity? Curr Med Res Opin. 2020;36:139-50.
12. Satia I, Mayhew AJ, Sohel N et al. Prevalence, incidence and characteristics of chronic cough among adults from the Canadian Longitudinal Study on Aging. ERJ Open Res. 2021;7.
13. Mac Aogáin M, Chotirmall SH. Bronchiectasis and cough: An old relationship in need of renewed attention. Pulmonary Pharmacology & Therapeutics. 2019;57:101812.
14. Bergmann M, Haasenritter J, Beidatsch D et al. Prevalence, aetiologies and prognosis of the symptom cough in primary care: a systematic review and meta-analysis. BMC Fam Pract. 2021;22:151.
15. Satia I, Mayhew AJ, Sohel N et al. Impact of mental health and personality traits on the incidence of chronic cough in the Canadian Longitudinal Study on Aging. ERJ Open Res. 2022;8.
16. Arinze JT, Verhamme KMC, Luik AI,et al. The interrelatedness of chronic cough and chronic pain. Eur Respir J. 2021;57.
17. Kaplan A. Improving the assessment of adults with chronic cough in primary care. : The International Primary Care Respiratory Group; 2021 [Available from: https://www.ipcrg.org/11541].
18. Irwin RS, French CL, Chang AB et al. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153:196-209.
19. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18:716-25.
20. Sidhaye VK, Nishida K, Martinez FJ. Precision medicine in COPD: where are we and where do we need to go? Eur Respir Rev. 2018;27: 180022.
21. Koskela HO, Selander TA, Lätti AM. Cluster analysis in 975 patients with current cough identifies a phenotype with several cough triggers, many background disorders, and low quality of life. Respir Res. 2020;21:219.
22. Rouadi PW, Idriss SA, Bousquet J et al. WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation - Updates in COVID-19. World Allergy Organ J. 2021;14:100618.
23. Abozid H, Baxter CA, Hartl S et al. Distribution of chronic cough phenotypes in the general population: A cross-sectional analysis of the LEAD cohort in Austria. Respir Med. 2022;192:106726.
24. Morice AH, Lowry R, Brown MJ et al. Angiotensin-converting enzyme and the cough reflex. Lancet. 1987;2:1116-8.
25. Kang J, Seo WJ, Kang J et al. Clinical phenotypes of chronic cough categorised by cluster analysis. PLoS One. 2023;18:e0283352.
26. Smith JA, Satia I, Badri H, et al. Mini-review: Hypertussivity and allotussivity in chronic cough endotypes. Neurosci Lett. 2023;792:136934.
27. Mazzone SB, Satia I, McGarvey L et al. Chronic cough and cough hypersensitivity: from mechanistic insights to novel antitussives. Lancet Respir Med. 2022;10:1113-5.
28. Hilton E, Satia I, Holt K et al. The Effect of Pain Conditioning on Experimentally Evoked Cough: Evidence of Impaired Endogenous Inhibitory Control Mechanisms in Refractory Chronic Cough. Eur Respir J. 2020; 2001387.
29. Tatar E, Öcal B, Korkmaz H et al. Postviral Vagal Neuropathy: What Is the Role of Laryngeal Electromyography in Improving Diagnostic Accuracy? J Voice. 2015;29:595-9.
30. García-Vicente P, Rodríguez-Valiente A, Górriz Gil C et al. Chronic cough in post-COVID syndrome: Laryngeal electromyography findings in vagus nerve neuropathy. PLoS One. 2023;18:e0283758.
31. Boulet LP, Coeytaux RR, McCrory DC et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. Chest. 2015;147:804-14.
32. Nelson EC, Eftimovska E, Lind C et al. Patient reported outcome measures in practice. BMJ. 2015;350:g7818.
33. Administration USFaD. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: U.S. Food and Drug Administration; 2009 [updated 2019, October 17. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims].
34. Speight J, Barendse SM. FDA guidance on patient reported outcomes. Bmj. 2010;340:c2921.
35. Kum E, Guyatt GH, Devji T et al. Cough symptom severity in patients with refractory or unexplained chronic cough: a systematic survey and conceptual framework. Eur Respir Rev. 2021;30: 30:210104 .
36. Martin Nguyen A, Bacci ED, Vernon M et al. Validation of a visual analog scale for assessing cough severity in patients with chronic cough. Ther Adv Respir Dis. 2021;15:17534666211049743.
37. Hsu JY, Stone RA, Logan-Sinclair RB et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J. 1994;7:1246-53.
38. Vernon M, Leidy NK, Nacson A et al. Measuring cough severity: Perspectives from the literature and from patients with chronic cough. Cough. 2009;5:5.
39. Vernon M, Kline Leidy N, Nacson A et al. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. Ther Adv Respir Dis. 2010;4:199-208.
40. Shembel AC, Rosen CA, Zullo TG et al. Development and validation of the cough severity index: a severity index for chronic cough related to the upper airway. Laryngoscope. 2013;123:1931-6.
41. Birring SS, Prudon B, Carr AJ et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58:339-43.
42. Nguyen AM, Schelfhout J, Muccino D et al. Leicester Cough Questionnaire validation and clinically important thresholds for change in refractory or unexplained chronic cough. Ther Adv Respir Dis. 2022;16:17534666221099737.
43. Berkhof FF, Boom LN, ten Hertog NE et al. The validity and precision of the Leicester Cough Questionnaire in COPD patients with chronic cough. Health Qual Life Outcomes. 2012;10:4.
44. Haukeland-Parker S, Hasvik E, Jelsness-Jørgensen LP et al. Cross-cultural adaptation and validation of the Norwegian version of the Leicester Cough Questionnaire in chronic obstructive pulmonary disease. Physiother Theory Pract. 2022;38:2175-84.
45. Ward N, Stiller K, Rowe H et al. The psychometric properties of the Leicester Cough Questionnaire and Respiratory Symptoms in CF tool in cystic fibrosis: A preliminary study. J Cyst Fibros. 2017;16:425-32.
46. Murray MP, Turnbull K, MacQuarrie S et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34:125-31.
47. Baiardini I, Braido F, Fassio O et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60:482-8.
48. French CT, Irwin RS, Fletcher KE et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121:1123-31.
49. Koo HK, Jeong I, Kim JH et al. Development and validation of the COugh Assessment Test (COAT). Respirology. 2019;24:551-7.
50. Zhan W, Zhang L, Jiang M et al. A new simple score of chronic cough: cough evaluation test. BMC Pulmonary Medicine. 2020;20:68.
51. Meirte J, Hellemans N, Anthonissen M et al. Benefits and disadvantages of electronic patient-reported outcome measures: systematic review. JMIR perioperative medicine. 2020;3:e15588.
52. Moor CC, Mostard RLM, Grutters JC et al. The use of online visual analogue scales in idiopathic pulmonary fibrosis. Eur Respir J. 2022;59:2101531.
53. Nolan CM, Birring SS. PROMising developments in IPF patient-reported outcome measures. Eur Respir J. 2022;59:2102312 .

54. Scallan C, Strand L, Hayes J et al. R-scale for pulmonary fibrosis: a simple, visual tool for the assessment of health-related quality of life. Eur Respir J. 2022;59: 2100917.
55. Waring G, Kirk S, Fallon D. The impact of chronic non-specific cough on children and their families: A narrative literature review. Journal of Child Health Care. 2020;24:143-60.
56. Marchant JM, Newcombe PA, Juniper EF et al. What is the burden of chronic cough for families? Chest. 2008;134:303-9.
57. Zhang M, Sykes DL, Brindle K et al. Chronic cough-the limitation and advances in assessment techniques. J Thorac Dis. 2022;14:5097-119.
58. Turner RD, Birring SS. Measuring cough: what really matters? J Thorac Dis. 2023;15:2288-99.
59. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6.
60. Turner RD, Bothamley GH. How to count coughs? Counting by ear, the effect of visual data and the evaluation of an automated cough monitor. Respir Med. 2014;108:1808-15.
61. Smith JA, Holt K, Dockry R et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. Eur Respir J. 2021;58:2004271.
62. Key AL, Holt K, Hamilton A et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough. 2010;6:4.
63. Marsden PA, Satia I, Ibrahim B et al. Objective Cough Frequency, Airway Inflammation, and Disease Control in Asthma. Chest. 2016;149:1460-6.
64. Singh D, Beier J, Astbury C et al. The novel bronchodilator navafenterol: a phase 2a, multicentre, randomised, double-blind, placebo-controlled crossover trial in COPD. Eur Respir J. 2022;59.
65. Chamberlain SA, Garrod R, Douiri A et al. The impact of chronic cough: a cross-sectional European survey. Lung. 2015;193:401-8.
66. Kayleigh B, Alyn M, Natalie C et al. The "vicious circle" of chronic cough - The patient experience. A qualitative synthesis. ERJ Open Research. 2023: 00094-2023.
67. Kang SY, Won HK, Lee SM et al. Impact of Cough and Unmet Needs in Chronic Cough: A Survey of Patients in Korea. Lung. 2019;197:635-9.
68. Kubo T, Tobe K, Okuyama K et al. Disease burden and quality of life of patients with chronic cough in Japan: a population-based cross-sectional survey. BMJ Open Respir Res. 2021;8: e000764(.
69. Jan van den B, Carl B, Mireille E et al. The demographics, clinical characteristics and quality of life of chronic cough in patients from the Isala Cough Clinic in the Netherlands. ERJ Open Research. 2022;8:00232-2022.
70. Lai K, Huang L, Zhao H et al. A multicenter survey on the current status of chronic cough and its impact on quality of life in Guangdong, China. J Thorac Dis. 2022;14:3624-32.
71. Ueda N, Yakushiji A, Schelfhout J et al. Impact of refractory and unexplained chronic cough on disease burden: a qualitative study. BMC Pulm Med. 2022;22:372.
72. Reynolds JE, Jetté ME, Wright ML et al. Normative Values for the Leicester Cough Questionnaire in Healthy Individuals. Ann Otol Rhinol Laryngol. 2023;132:705-8.
73. Won HK, Song WJ. Impact and disease burden of chronic cough. Asia Pac Allergy. 2021;11:e22.
74. Johansson H, Johannessen A, Holm M et al. Prevalence, progression and impact of chronic cough on employment in Northern Europe. Eur Respir J. 2021;57:2003344.
75. Blum NJ. Repetitive Behaviour and Tics. In: Feldman HM, Coleman WL, Carey WB, et al., editors. Developmental-Behavioral Pediatrics. 4rd ed. Philadelphia: SAUNDERS Elsevier; 2009. p. 629-41.
76. Zeiger RS, Schatz M, Hong B et al. Patient-Reported Burden of Chronic Cough in a Managed Care Organization. J Allergy Clin Immunol Pract. 2021;9:1624-37.e10.
77. Kum E, Guyatt GH, Munoz C et al. Assessing cough symptom severity in refractory or unexplained chronic cough: findings from patient focus groups and an international expert panel. ERJ Open Res. 2022;8:00667-2021.
78. Hulme K, Deary V, Dogan S et al. Psychological profile of individuals presenting with chronic cough. ERJ Open Res. 2017;3:00099-2016.
79. Zheng Z, Huang J, Xiang Z et al. Efficacy and Safety of Pharmacotherapy for Refractory Chronic Cough: A Systematic Review and Network Meta-Analysis 2023 [Available from: http://dx.doi.org/10.2139/ssrn.4420756].
80. Brister D, Wahab M, Rashad M et al. Emerging drugs in the treatment of chronic cough. Expert Opin Emerg Drugs. 2023:1-11.
81. O'Donovan B, Rodgers RM, Cox AR et al. 'You feel like you haven't got any control': A qualitative study of side effects from medicines. Journal of Patient Safety and Risk Management. 2019;24:13-24.
82. Wamkpah NS, Peterson AM, Lee JJ et al. Curbing the Cough: Multimodal Treatments for Neurogenic Cough: A Systematic Review and Meta-Analysis. Laryngoscope. 2022;132:107-23.
83. Chamberlain Mitchell SAF, Ellis J, Ludlow S et al. Non-pharmacological interventions for chronic cough: The past, present and future. Pulm Pharmacol Ther. 2019;56:29-38.
84. Birring SS, Kavanagh JE, Irwin RS et al. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. Chest. 2018;154:904-17.
85. De Vincentis A, Baldi F, Calderazzo M et al. Chronic cough in adults: recommendations from an Italian intersociety consensus. Aging Clin Exp Res. 2022;34:1529-50.
86. Putcha N, Drummond MB, Connett JE et al. Chronic productive cough is associated with death in smokers with early COPD. COPD. 2014;11:451-8.
87. Fortis S, Shannon ZK, Garcia CJ et al. Association of Nonobstructive Chronic Bronchitis With All-Cause Mortality: A Systematic Literature Review and Meta-analysis. Chest. 2022;162:92-100.
88. Satia I, Mayhew AJ, Sohel N et al. Impact of productive and dry chronic cough on mortality in the Canadian Longitudinal Study on Aging (CLSA). J Thorac Dis. 2022;14:5087-96.
89. Landt EM, Çolak Y, Nordestgaard B et al. Productive vs non-productive chronic cough associated with worse lung health and higher morbidity and mortality in the general population. Eur Respir J. 2022;60(suppl 66): 4029.
90. Lindberg A, Sawalha S, Hedman L et al. Subjects with COPD and productive cough have an increased risk for exacerbations and death. Respir Med. 2015;109:88-95.
91. Kvale PA. Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):147s-53s.
92. Emilsson ÖI. The burden and impact of chronic cough in severe disease. Curr Opin Support Palliat Care. 2022;16:183-7.
93. Landt E, Çolak Y, Lange P et al. Chronic Cough in Individuals With COPD: A Population-Based Cohort Study. Chest. 2020;157:1446-54.
94. Li Y, Cao C, Ji Y et al. Anxiety and depression are associated with reduced quality of life and increased cough severity in chronic cough. Asian Pac J Allergy Immunol. 2022.
95. Biswas A, Oh PI, Faulkner GE et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015;162:123-32.
96. Furlanetto KC, Donária L, Schneider LP et al. Sedentary Behavior Is an Independent Predictor of Mortality in Subjects With COPD. Respir Care. 2017;62:579-87.
97. Paluch AE, Bajpai S, Bassett DR et al. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. Lancet Public Health. 2022;7: e219-e28.
98. Russell R, Minhas S, Chandan JS et al. The risk of all-cause mortality associated with anxiety: a retrospective cohort study using 'The Health Improvement Network' database. BMC Psychiatry. 2023;23:400.
99. Celano CM, Millstein RA, Bedoya CA et al. Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. Am Heart J. 2015;170:1105-15.
100. Vikjord SAA, Brumpton BM, Mai XM et al. The association of anxiety and depression with mortality in a COPD cohort. The HUNT study, Norway. Respir Med. 2020;171:106089.

101. Wang YH, Li JQ, Shi JF et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol Psychiatry. 2020;25:1487-99.
102. Gibson PG, Vertigan AE. Management of chronic refractory cough. BMJ. 2015;351:h5590.
103. Johnstone KJ, Chang AB, Fong KM et al. Inhaled corticosteroids for subacute and chronic cough in adults. Cochrane Database Syst Rev. 2013;2013: Cd009305.
104. Matera MG, Rogliani P, Zanasi A et al. Bronchodilator therapy for chronic cough. Pulm Pharmacol Ther. 2017;47:88-92.
105. Kahrilas PJ, Altman KW, Chang AB et al. Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report. Chest. 2016;150:1341-60.
106. Lee JH, Lee JW, An J et al. Efficacy of non-sedating H1-receptor antihistamines in adults and adolescents with chronic cough: A systematic review. World Allergy Organ J. 2021;14:100568.
107. Satia I, Wahab M, Kum E et al. Chronic cough: Investigations, management, current and future treatments. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2021;5:404-16.
108. Satia I, Badri H, Al-Sheklly B et al. Towards understanding and managing chronic cough. Clin Med (Lond). 2016;16(Suppl 6):s92-s7.
109. Morice AH, Menon MS, Mulrennan SA et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175:312-5.
110. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012; 380:1583-9.
111. Vertigan AE, Kapela SL, Ryan NM et al. Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough: A Randomized Controlled Trial. Chest. 2016;149:639-48.
112. Oh JY, Kang YR, An J et al. Codeine prescription pattern and treatment responses in patients with chronic cough: a routinely collected institutional database analysis. J Thorac Dis. 2023;15:2344-54.
113. Ilicic AM, Oliveira A, Habash R et al. Non-pharmacological Management of Non-productive Chronic Cough in Adults: A Systematic Review. Front Rehabil Sci. 2022;3:905257.
114. Dasouki S, Quach S, Mancopes R et al. A Non-Pharmacological Cough Therapy for People with Interstitial Lung Diseases: A Case Report. Physiotherapy Canada. 2022(aop):e20210081.
115. Ilicic AM, Brooks D, Kho M et al. Cough Assessment and Management in Pulmonary Rehabilitation- A Canadian Survey. Copd. 2023;20:71-9.
116. Chuang MH, Chen IW, Chen JY et al. Efficacy and safety of gefapixant for chronic cough: a meta-analysis of randomised controlled trials. Eur Respir Rev. 2023;32: 220219 .
117. Smith J, Birring SS, Dicpinigaitis P et al. Response in Patient-reported Cough Severity in Soothe, a Phase 2b Trial of Camlipixant in Refractory Chronic Cough. A99 CLINICAL TRIALS IN CHRONIC LUNG DISEASE. p. A2533-A.
118. McGarvey LP, Birring SS, Morice AH et al. Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet. 2022; 399:909-23.
119. Benamar R. Bellus Health - Investor Presentation NASDAQ/TSX - BLU 2023 [Available from: https://ir.bellushealth.com/static-files/5dcac9ff-f01d-4533-b5a2-ec99afbbc286].
120. Rebelo P, Oliveira A, Paixão C et al. Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Cough and Sputum in Patients with COPD. Int J Chron Obstruct Pulmon Dis. 2020;15:201-12.
121. Smith J, Owen E, Earis J et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006; 130:379-85.
122. Fletcher KE, French CT, Irwin RS et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63:1123-31.
123. Lechtzin N, Hilliard ME, Horton MR. Validation of the Cough Quality-of-Life Questionnaire in patients with idiopathic pulmonary fibrosis. Chest. 2013;143:1745-9.
124. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24:69-71.
125. Portney LG, Watkins MP. Foundations of Clinical Research: Applications To Practice: Pearson/Prentice Hall; 2015.
126. Terwee CB, Bot SD, de Boer MR et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60:34-42.
127. Maher TM, Avram C, Bortey E, Hart SP, Hirani N, et al. Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis. NEJM Evidence. 2023: EVIDoa2300083.