Review Article

Patient-reported assessments of chronic cough in clinical trials: accessory or primary endpoints?

Ewan Christopher Mackay[1]^, Richard Douglas Turner[2,3]^, Peter Siu Pan Cho[1,4]^, Surinder S. Birring[1,4]^

[1]Department of Respiratory Medicine, Chest Unit, Cheyne Wing, King's College Hospital, London, UK; [2]Department of Respiratory Medicine, Princess Alexandra Hospital, Brisbane, Australia; [3]School of Medicine and Dentistry, Griffith University, Southport, Australia; [4]Centre for Human and Applied Physiological Sciences, King's College London, London, UK

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Correspondence to: Professor Surinder S. Birring, MD. Department of Respiratory Medicine, Chest Unit, Cheyne Wing, King's College Hospital, Denmark Hill, London SE5 9RS, UK; Centre for Human and Applied Physiological Sciences, King's College London, London, UK. Email: surinder.birring@nhs.net.

Abstract: Chronic cough is a complex disorder that affects up to 5–10% of the general population. It can be challenging to manage as there are few effective treatments, although several novel antitussives are in clinical development. The endpoints used to assess their efficacy in clinical trials should be optimal; most large clinical trials currently use objective measures as the primary outcome, especially cough frequency. There are strengths in this approach, although taking the view that other measures of chronic cough are less important, including patient-rated cough severity, psychosocial impact and other associated symptoms. Patient-reported outcome measures (PROMs) explore patients' personal experiences of health and disease, and the effects of particular conditions on their lives. Numerous validated PROMs exist for chronic cough, from simple visual analogue scales, to those that focus on cough hypersensitivity and cough-specific quality of life. Medicine regulators in the European Union (EU) and United States of America (USA) encourage the use of PROMs in clinical trials but have voiced concerns over their content validity, clinically meaningful thresholds for change, and discordance with objective measures. There are recent and ongoing studies to address these limitations. This review discusses currently available PROMs used to assess chronic cough and discusses their potential role as primary outcome measures in clinical trials.

Keywords: Clinical trials; quality of life; chronic cough; patient-reported outcome measures (PROMs); endpoints

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Introduction

Chronic cough, or a cough lasting more than 8 weeks (1,2), is a common condition affecting up to 9.6% of the global population, with a predominance for middle-aged women (2-4). It is by no means a benign phenomenon, having a variety of far-reaching effects on a person's physical, psychological and social wellbeing, including urinary incontinence, social embarrassment, interruption of speech, and sleep loss (5-7). There are different methods for assessing cough and its effects, with their own merits and limitations. Broadly, outcome measures can be split into objective measures that quantify the expulsive act of coughing, and subjective measures that rely upon self-reported patient experiences to evaluate cough and its

^ ORCID: Ewan Christopher Mackay, 0009-0006-8773-0146; Richard Douglas Turner, 0000-0002-3024-6971; Peter Siu Pan Cho, 0000-0001-8689-8541; Surinder S. Birring, 0000-0003-2525-6291.

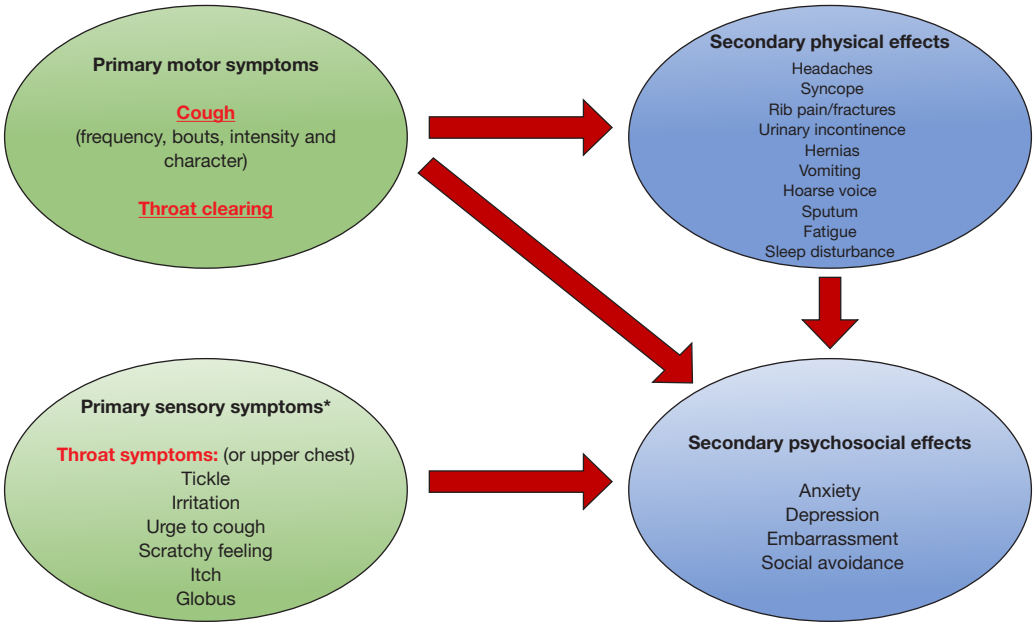

Figure 1 Symptoms of cough hypersensitivity syndrome**.

effects on an individual (8). It is likely that a combination of both is important when assessing clinical effectiveness in trials (9,10).

The objective measure of cough, particularly quantifying counts (frequency), assesses cough in a pre-defined period, typically over 24 hours (11,12). Cough frequency is currently the preferred primary endpoint for clinical trials, to evaluate the efficacy of antitussive medication (13,14). Objective cough counts can measure a directly observable phenomenon and potentially assess if antitussives have an impact on this absolute number. This removes subjectivity and arguably may better reflect the change in underlying disease pathophysiology than subjective measures (13). The limitation of objective measures is that they may not capture many aspects important to patients, particularly associated physical, social and psychological impacts (15), and as such correlate poorly or only moderately with patient-reported outcomes (8,13,16).

Patient-reported outcome measures (PROMs) are used in the assessment of many diseases. A recent meta-analysis identified multiple advantages of their use in the clinical setting, including encouraging patient involvement in consultations, sharing patient-clinician goal setting, and allowing clinicians to prioritise patient needs (17). PROMs are relevant as they capture the experience of the patients themselves, what matters most to their well-being, and in interpretating the clinical meaningfulness of interventions (13). As such, they are key assessments in clinical trials, although often as secondary endpoints (9,18).

In this article, we summarise commonly used patient reported outcomes for cough, and discuss their validity, strengths and limitations, and their potential for use as primary endpoints in clinical trials as a broader outcome measure.

Primary symptoms of chronic cough disorders

Cough is a normal protective feature of the respiratory system. It occurs in response to a number of different stimuli, with both reflex and volitional control (19,20). Chronic cough often represents a complex neurogenic disorder characterised by underlying neuronal hypersensitivity, termed "*cough hypersensitivity syndrome*" by a European Respiratory Society task force position paper (21). Cough hypersensitivity gives rise to other notable symptoms and effects in addition to the cough itself (22) and their interplay is depicted in *Figure 1*. We propose a new categorisation of the symptoms associated with chronic

cough disorders to facilitate better recognition of the wide-ranging symptoms that occur in addition to the cough and how they interact. The categories highlight the relationship between different types of symptoms but not their relative importance, which varies between patients.

Primary symptoms of chronic cough disorders reflect sensory and motor components of the cough reflex. Primary sensory symptoms include an urge to cough, which results from abnormal activation of cough sensory nerve fibres, often triggered by low levels of chemical, mechanical and thermal stimuli or in some cases, spontaneously (20,23). Patients may use a wide range of terms to report their abnormal laryngeal (or chest) sensations such as, 'scratch', 'tickling' or globus (11,23). An urge to cough is present in the majority of patients with chronic cough, although it is not universal (23). This to some patients can be more bothersome than the cough itself, and have a significant impact on a patient's perception of their disease (23,24).

Primary motor components include coughing, either singly or in bouts, and throat clearing. Coughs may be volitional in response to an urge to relieve the unpleasant irritation or sensation, or purely reflex in nature (20,23). Throat clearing and cough may be considered as part of a spectrum of motor responses to abnormal sensory stimulation (25). The frequency with which these actions occur is often quantified in the research setting, but their differentiation, character and wider effects are assessed less so.

Secondary effects: the wider impact of cough

Both sensory and motor symptoms can in isolation (or combination) lead to significant secondary effects on physical and psychological wellbeing (5,11). The subjective nature of PROMs allows a wider aspect of the cough disorder to be addressed than is possible with objective measures alone, better representing the patient's viewpoint and capturing the range of experiences related to the condition (13,26).

Physical effects

Chronic cough is associated with a number of secondary physical effects across multiple organ systems including sore throat, voice changes, headaches, syncope, arrhythmias, rib fractures, hernias and urinary incontinence (11,27). These can in turn lead to marked fatigue, poor sleep, and psychosocial effects (27).

Stress urinary incontinence as a result of coughing is a common problem, particularly in women with chronic cough, of whom up to 63% are affected (28). It is associated with a psychological burden from social anxiety and embarrassment that is likely to contribute to worse scores on quality-of-life measures (29). The disproportionate effect of urinary incontinence on women compared to men is important to capture, to obtain a fuller understanding of cough severity that does not discriminate against sex. This may however be best measured with specific urinary incontinence tools (30,31) so as not to reduce the responsiveness of cough PROMs when administered to a wider population with chronic cough, including males and younger patients, who generally do not report this complication (28).

Psychosocial effects

Cough can have a significant effect upon the psychological health of patients, with up to 53% of patients with chronic cough reporting significant depressive symptoms (32,33). A population-based study of 5,877 patients found that depressive symptoms were more common in those with chronic cough, with a previous history of depression making this more likely (34). The relationship between mood and cough is not yet fully understood, but there is a suggestion that anxiety and depression can have an effect on how patients perceive the severity of their cough (35). Other work has demonstrated that managing these related psychological conditions in addition to treating cough, can be helpful for optimising cough related quality of life (26).

The combined physical and psychological effects of persistent cough can have a marked deleterious effect on social circumstances and result in social isolation, embarrassment, exhaustion (34), and potentially affect employment (5,34,36). For the purpose of assessing the efficacy of medications, some medicine regulators consider psychosocial symptoms as a distal effect of cough and therefore secondary endpoints. A potential concern is that quality of life scores which place a significant weight on psychosocial symptoms can be influenced by a number of factors besides chronic cough, and this may therefore make them less specific in the measure of cough (24). Although the interplay between cough and psychosocial facets is likely complex (37), there is little evidence to support this view. Moreover, effective strategies at treating cough have been shown to improve psychosocial morbidity

in this cohort, which clearly demonstrates the relevance of assessing both together (26).

Objective measurement of cough and its limitations

Advantages and methods

As stated above, cough frequency (per unit time) is considered the gold standard for objective measures in clinical trials (11,14), because it is thought to give a faithful reflection of underlying pathology. Medicine regulatory authorities have traditionally preferred hard objective endpoints for evaluating treatments for pulmonary diseases, such as forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), number of exacerbations and mortality. They are less susceptible to subjectivity from both the patient and the clinician and may offer a direct insight into the disease mechanism (12). Cough is the major symptom of cough hypersensitivity disorders and is quantifiable objectively and therefore has rapidly become the primary outcome measure in most clinical trials (13,38-40).

One potential advantage of the use of objective endpoints in trials is in enabling smaller sample sizes than would otherwise be possible with subjective measures; this is due to greater variability between patients with PROMs (14). For example, one study in acute cough showed 24-hour cough frequency to be more repeatable than daytime cough frequency visual analogue scales (VAS) scores in the same patients with intra-class correlation coefficients 0.94 [95% confidence interval (CI): 0.90–0.97] *vs.* 0.78 (95% CI: 0.63–0.87) (41). Another study estimated that the sample sizes required to demonstrate a significant change (power 80%, α =0.05) for a parallel group study were almost twice as high for a PROM [Leicester Control Questionnaire (LCQ)] compared to objective cough frequency (42).

Cough monitors are typically worn by patients over 24 hours, and cough events per hour calculated either with interpretive software, or by manual analysis, which is more time intensive, but, at least at the time of writing, probably more reliable (8,43). A number of cough frequency monitors exist including the Leicester Cough Monitor (LCM) and Vitalojak monitor (14,44). Work is ongoing to develop monitors that are less intrusive, capable of data capture over prolonged periods, and use artificial intelligence for cough detection to fully automate analysis (45,46).

Limitations

Cough frequency, and the monitors currently in use for its measurement have limitations and drawbacks. Cough frequency is poorly related to subjective measures. As one of many examples, Marsden *et al.* investigated 56 patients with cough in asthma and found the correlation of both VAS scores and numerical cough scores with objective cough frequency was weak to moderate at best (r=0.45 and r=0.32 respectively), although LCQ scores correlated slightly better (r=–0.54) (47). This mirrors an earlier study by Birring *et al.* that demonstrated LCQ correlated only moderately with cough counts in those with chronic cough (r=–0.6) (48). This limited relationship between subjective assessments of chronic cough and cough frequency in effect hinders the clinical interpretation and meaningfulness of cough frequency data (8,13).

In terms of the duration of cough frequency measurement for assessing a baseline, or in response to treatment, 24 hours has become the standard, seemingly by default (12). However, accumulating data from cough frequency monitoring over longer durations in different groups of individuals is pointing to the extent that day-to-day cough frequency varies in the same subject in an apparently stable clinical state (49,50). One study following 178 patients with chronic cough for over 100 hours of monitoring, showed wide variation between days as well as a marked diurnal variation (49). A one-off 24-hour cough frequency recording could be therefore problematic as a means to establish a baseline, let alone in observing a response to a treatment, without greater knowledge of day-to-day variability in cough frequency in individuals (50). Reductions in cough frequency in clinical trials could theoretically be missed with periods of cough monitoring limited to 24-hour recordings, by one estimate using simulations based on longitudinal data, a true cough frequency reduction of 40% would be missed in as many as 17% of trials (49). It does seem recordings of greater than 24 hours are less susceptible to the problems associated with day-to-day variability in cough frequency and therefore may reflect a more accurate change in cough frequency over time, with a 47% error rate (significant difference compared to "actual" rate) noted with 24 hours of cough monitoring, reducing to 14% when monitoring was extended over 240 hours (49).

Cough monitoring periods longer than 24 hours therefore seem preferable, but more longitudinal intra-

individual cough frequency data are required to establish an optimal duration of recording for establishing cough frequency. This duration will however need to be balanced by practical issues relating to technology and acceptability for the patient. Indeed, using a cough monitor at all has drawbacks. However small, such devices are associated with a degree of intrusion, particularly as most recording systems currently capture speech and other sounds as well as cough, whether or not this is heard by a human observer. Although not fully substantiated, there are also concerns that wearing a cough monitor might theoretically create an observer effect and change the way that patients cough due to awareness, in a manner similar to 'white coat' hypertension (13). Less obtrusive monitors, such as wireless devices using smartphone technology or bespoke smartphone software with no additional hardware, could overcome some of these problems.

Cough monitors are also largely limited to recording the number of coughs, and tend not to record other important primary motor symptoms of chronic cough disorders, such as bouts of coughing, intensity, throat clearing or qualitative properties such as wet, dry, barking or bovine sounds (20). In addition, they do not capture the primary sensory symptoms of chronic cough disorders such as tickling in the throat or urge to cough. Coughing bouts and the character of the cough can have a marked impact on symptoms of physical discomfort and to some may be more impactful than the number of coughs (13,51). The respective weight of each component has not yet been studied and deserves further investigation.

PROMs

There are a number of different PROMs which are in common use by clinicians and researchers, including symptom scales, diaries and quality of life measures (see *Table 1* for a summary of their main characteristics) which can be used to assess cough severity, as well as other symptoms related to coughing which contribute to a patient's perception of the condition (13). The importance of assessing other cough characteristics was exemplified by a patient focus group study presented by Vernon *et al.* which highlighted cough intensity and disruption alongside cough frequency (including bouts of coughing as well as urge to cough) as being the key domains patients most associated with defining severity (51).

Furthermore, patients with chronic cough are unlikely to perceive their cough in absolute units of frequency and are more likely to present to healthcare providers due to psychosocial factors. In a study by French *et al.*, of the 15 most frequent reasons that patients with chronic cough sought medical attention, the majority (11 items) were psychosocial concerns. Four physical complaints (frequent retching, exhaustion, hoarseness and urinary incontinence) were mentioned, but cough frequency was not (5). It is worth noting that of the physical symptoms listed, all are secondary symptoms of cough, and although cough frequency may play a role in their severity, it is unclear if this relationship is linear. It is therefore of importance to ask about secondary effects of chronic cough disorders in clinical trials and use PROMs to establish what is most important to patients (32).

VAS

Perhaps the simplest measure that is often employed is a cough severity VAS. Comprising a 100-mm linear scale, the patient marks the scale in accordance with the severity of their symptoms between the labelled two possible extremes "worst cough ever" and "no cough" at opposite ends (56). This is a very quick method of assessment which could be utilised in busy clinics, and is easy for patients to understand (14). A potential drawback is that the scale is a continuous line without any graduated markers or severity descriptors along the scale to act as anchor points and as such, there are concerns that this may lead to intra-individual variability in scoring and therefore reduced repeatability (53). One study reported an intraclass correlation coefficient of 0.45–0.51 which at best implies only moderate test re-test correlation. The VAS does however correlate with more comprehensive cough assessment tools such as the LCQ or Cough Severity Diary (CSD) (56). In addition, severity categories have been reported for the VAS (57). Its ease of use has contributed to its utilisation as a screening tool for patient inclusion in the COUGH-1 and COUGH-2 clinical studies for gefapixant (39) and as a secondary endpoint in clinical trials for erythromycin (38) and gabapentin (52). However, it lacks an assessment of specific cough-related symptoms and important attributes such as psychosocial effects.

Numerical rating scale

Numerical rating scales are somewhat similar to VAS but with some important differences. They consist of a line with graduated anchor points which are labelled numerically

Table 1 Summary of the advantages and limitations of outcome measures often used to assess chronic cough in clinical trials

Outcome measure	Examples	Advantages	Limitations	Utility in clinical trials
24-hour cough frequency	Leicester Cough Monitor (semi-automated detection)	Provides objective and quantifiable cough counts (14)	Observer effect—patient awareness of device may influence cough counts (13) and also susceptible to placebo effect, similar to PROMs	Widely used in clinical trials as primary endpoint, including erythromycin (38) and gefapixant (39)
	VitaloJak monitor (manual cough detection)	Less likely to be affected by mood, personality	No assessment of impact of cough on patient	Secondary endpoint in trial of gabapentin amongst others (52)
	Newer interfaces using smartphone technology and AI automation in development (45,46)	Allows for relatively smaller samples sizes to establish MID (14)	Day to day variability associated with risk of missing treatment effect with 24-h recordings (49)	
			Technological—current need to capture/assess confidential speech and other patient audio data (13); short battery life, manual counting time consuming and expensive	
			Acceptability—continuous prolonged wearability required	
VAS	Cough VAS—100-mm scale with severity markers at both ends. No interval graduations	Quick and easy for patient to complete (14)	Lack of graduations may introduce variability (53)	Widely established as secondary endpoint in clinical trials (38,52) but also used as primary endpoint in some trials (54)
		Recommended for clinical use in European Respiratory Society 2020 guidelines (55)	Moderate repeatability (56)	Utilised as inclusion criteria for clinical trials, using threshold of 40 mm (39)
		MID of 20, 30 mm change for clinically important threshold (larger change) (56)	Does not assess psychosocial aspects of cough	Often used to validate other PROMs (57,58)
NRS	Cough NRS—scale with severity markers as extremes, interval graduations and numbers (0–10)	Quick and easy to complete (8), performance expected to be similar to VAS	Limited use in chronic cough to date. Needs validation study	Rarely used in assessment of chronic cough to date [2024]
		Potentially more consistent completion by patients compared to VAS due to its grading	Does not assess psychosocial aspects of cough	Primary outcome measure in phase 2B (IPF COMFORT-orvepitant) trial (59)

Table 1 (*continued*)

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Outcome measure	Examples	Advantages	Limitations	Utility in clinical trials
PGI-S	PGI-S in chronic cough (57)	Validated (57)	Ability to detect small changes may be less than other tools as it has fewer response categories	Commonly used in clinical trials outside of cough (60-62)
	One question-6 response options	Descriptors on Likert scale may be more intuitive than VAS/NRS as they are verbal and numerical		Useful anchor to aid interpretation of clinical benefit measured with other tools and to establish clinically meaningful thresholds for change (63,64)
		Good repeatability (57)		
Diaries	CSD (58): 7 items, 11-point response scale (0–10)	Brief, validated and repeatable (65)	Not as concise as VAS	CSD used as secondary endpoint in recent gefapixant study (66)
		Provides assessment of 3 domains: frequency, intensity and disruption (58)	Clinically meaningful thresholds need to be determined using PGI-S anchors to meet regulatory guidance	
		Developed in accordance with FDA guidance for PROMs (65,67)	Restricted access for commercial studies	
		MID of 1.3 established (65)		
	CET—developed in China (68): 5 items	Brief tools	Limited experience with these tools	Limited experience in clinical trials
		Cronbach alpha value for CET was 0.80 and intraclass correlation coefficient of 0.84, suggests good reliability. Correlated with LCQ-MC, r=−0.74, and LCQ-MC (r=−0.61) (68)	May need more detailed content validity studies to established items cover most important symptoms	
	COAT—developed in South Korea (69): 5 items	COAT demonstrated good test-retest reliability with intraclass correlation coefficient of 0.88. Correlated well with Korean LCQ (r=−0.71) (69)	Clinically important thresholds for change need defining in accordance to regulatory guidance	
		MID for COAT calculated to be 2.0 using a distribution method only (69)		
Quality of life measures	LCQ (70): 19 items	Comprehensive assessment of multiple aspects of cough symptoms and impact on patient quality of life	Can potentially be affected by psychosocial factors not related to cough (35)	LCQ used as primary endpoint in numerous clinical trials e.g., morphine (71), gabapentin (52), pregabalin/ speech therapy (72) and also widely established as secondary endpoints e.g., erythromycin, gefapixant (38,66)

Table 1 (*continued*)

Table 1 (*continued*)

Outcome measure	Examples	Advantages	Limitations	Utility in clinical trials
	CQLQ (73): 28 items	LCQ and CQLQ recommended for clinical use in European Respiratory Society 2020 guidelines (55)	Content validity studies need to be published to ensure they contain important items	CQLQ used as secondary endpoint in many trials e.g., gefapixant Phase 2 (74)
		Validated, repeatable and responsive (8,75)	Clinically important thresholds need to be reported in accordance to regulatory guidance	Often used to validate other PROMs (57,58)
		Vast experience of their utility and consistent performance in clinical trials		
		MID for LCQ is 1.3 (75,76)		
		MID for CQLQ calculated to be 21.89 (77)		
Cough challenge tests	Capsaicin, citric acid, ATP, mannitol, distilled water	Objective measurement and well-established test	Poor predictor of drug efficacy (78)	Demonstrate target engagement in clinical trials, e.g., TRPV1 antagonist (78)
		Useful to demonstrate target engagement in drug development at pre-clinical stage (14)	Time consuming to set up and test, not practical for routine use in clinic (79)	
			Significant overlap between healthy subjects and those with disease (80)	
			Characterised nebuliser with inspiratory flow limiter no longer manufactured. Existing nebulisers may administer slightly variable doses (81)	

AI, artificial intelligence; MID, minimal important difference; PROMs, patient-reported outcome measures; VAS, visual analogue scales; NRS, numerical rating scale; PGI-S, Patient Global Impression of Severity; CSD, Cough Severity Diary; CET, Cough Evaluation Test; COAT, Cough Assessment Test; FDA, Food and Drug Administration; LCQ-MC, Leicester Cough Questionnaire in Mandarin Chinese; CQLQ, Cough-Specific Quality of Life Questionnaire; ATP, adenosine triphosphate; TRPV1, transient receptor potential vanilloid 1.

which may facilitate consistency in the patient's response. These scales have seldom been used to assess chronic cough but could be expected to perform in a comparable fashion to VAS given their similarities, and may prove to be advantageous due to their anchor points (13). This form of scale could be considered in future studies and is currently being used as a primary outcome measure in the ongoing phase 2B trial IPF COMFORT (orvepitant) (59). Numeric rating scales are preferred over VAS by medicine regulators such as the Food and Drug Administration (FDA) in the United States of America (USA) (82).

Patient Global Impression of Severity (PGI-S) scale

The PGI-S consists of a question: "overall how would you rate the severity of your cough?", and has six numerical and descriptive values for the patient to choose from such as mild, moderate and severe (57). The potential advantage over VAS is the use of verbal response options which are more intuitive for the patient and fewer response options for simplification. The PGI-S has been recently validated in chronic cough and a study has demonstrated a statistically significant association with cough severity VAS and LCQ (57). PGI-S scores have also demonstrated utility as

anchors in studies to aid interpretation of clinical benefit, calculation of minimal important difference (MID) and validate other tools (63,64). Patient Global Impression of Change (PGI-C) scales have a similar structure to PGI-S scales but measure change in condition rather than its severity. They are potentially prone to recall bias but can be valuable in assessing the clinical meaningfulness of cough therapies (83).

Diaries

Cough symptom diaries are another commonly used PROM that can be used to assess chronic cough and may be a good compromise, with greater detail of cough characteristics than VAS, but are more concise than quality of life questionnaires. The CSD is a validated tool consisting of 7 items that are graded by patients from 0–10 on a Likert scale with verbal anchors alongside (e.g., never to constantly) and is completed daily for a pre-defined period of time (58). The questions are split across 3 domains relating to cough frequency, intensity of coughing and disruption to everyday life (51,58).

The CSD has been proven to be both reliable and valid (65) and has been used as an accessory endpoint in conjunction with VAS and quality of life measures in trials of gefapixant (84).

The Severity of Chronic Cough Diary (SCCD) is another tool currently in development, consisting of 14 items over 4 domains including: cough symptoms, symptoms related to cough, disruption to activities and sleep (85). Work is ongoing in establishing its role in clinical studies and MID is yet to be established.

Quality of life

Quality of life questionnaires are one of the best ways to provide an in-depth assessment of the effect that chronic cough has on patients (7,18). The most widely used is the LCQ (70) which has been in use for over 20 years (8,70,75). It has been translated into over 50 different languages and has been used in clinical trials as both primary and accessory endpoints (38,52,66,71,72). It consists of 19 questions which have been divided into 3 domains: physical symptoms, psychological and social impact. Each question is ranked on a 7-point Likert scale which also has written descriptions for each number on the scale. The questionnaire asks patients to assess their cough over the last 2 weeks and answers vary from 1: "all of the time" to 7: "none of the time" (70). It has been demonstrated to be valid, repeatable and responsive in multiple studies (70,75). Another quality-of-life measure sometimes used in the assessment of cough is the Cough-Specific Quality of Life Questionnaire (CQLQ) (14). It was developed in the USA and consists of 28 items for patients to complete across a Likert scale (73). It has demonstrated good validity as well as reliability in multiple settings including acute and chronic cough (14).

The Cough Evaluation Test (CET) which was developed in China, consists of only 5 questions relating to: daytime cough frequency, disturbance of sleep, cough intensity, interference with daily life and symptoms of anxiety or depression (68). Items are scored from 1 to 5 with accompanying text descriptors from "none" to "all of the time" (68). The CET correlated strongly with the LCQ, with a correlation coefficient of –0.74 (68). It can be completed in less than 1 minute which may facilitate its use in clinical settings. However, it has only 2 questions in relation to psychosocial wellbeing and therefore these health outcomes remain better covered by the LCQ or CQLQ.

The Cough Assessment Test (COAT) was developed in South Korea and is another promising short questionnaire that also has 5 items: frequency, effect on daily life, sleep disturbance, fatigue and cough hypersensitivity, all scored from 0–4 (69). It demonstrated good repeatability with test-retest correlation of 0.88 as well as concurrent validity which was assessed against the Korean version of the LCQ and a cough numerical rating scale (69). The COAT however, does not measure psychological effects of coughing, which is an important component of the disease (5).

PROMs to assess cough triggers and abnormal sensations

Patients with cough hypersensitivity experience cough in response to innocuous levels of different stimuli (86,87). Cough triggers and abnormal sensations (paraesthesia) are an important clinical feature which can help define this complex syndrome and these are difficult to quantify objectively. There are patient-reported outcome tools which can be used to ascertain the range of triggers and abnormal sensations experienced by patients. They may have potential for diagnosing refractory cough or cough hypersensitivity but this requires confirmation.

The Hull Airway Responsiveness Questionnaire (HARQ) is one such questionnaire, consisting of 14 items, scored from 0 to 5 (with worded anchors on the scale)

based on how often the patient has experienced particular symptoms in the past month (88). Responses vary from "no problem" to "severe/frequent problem" and scores are added together. It has been used to identify patients who have gastro-oesophageal reflux-associated chronic cough, so-called airway reflux (89). It has been suggested that it can also distinguish patients with chronic refractory cough from healthy subjects with a score >14 (out of 70) being associated with refractory chronic cough (88). Zhang *et al.* reported higher HARQ scores predict responsiveness to gabapentin therapy; a score >21.5 had a sensitivity of 84.6% and specificity of 63.6% for this purpose (90).

The Newcastle Laryngeal Hypersensitivity Questionnaire (NLHQ) is a questionnaire designed to assess laryngeal hypersensitivity which can manifest as a wide range of conditions such as chronic refractory cough, vocal cord dysfunction, muscle tension dysphonia and globus pharyngeus (91-93). It consists of 14 items across 3 domains (obstruction, pain/thermal and irritation) which are scored from 1 to 7 on a Likert scale with text descriptors. It includes many symptoms related to laryngeal irritation and throat sensations which are often experienced by chronic cough sufferers (91,93,94). The NHLQ has a moderate correlation with cough frequency (8,95) and has been validated for detecting laryngeal hypersensitivity (91) and can detect changes in laryngeal sensations after speech pathology treatment. In one study this was a decrease in NLHQ score of 2.3, and a clinically meaningful threshold of 1.7 (94,96). It has therefore been suggested that it may be a useful tool for evaluating success of behavioural interventions and neuromodulatory treatments in chronic cough (8,94,96). More recently, a modified form of the NLHQ has been used to measure laryngeal sensitivity in patients with artificial airways such as tracheostomies with comparative reliability and validity (97). The NHLQ is a useful tool for measuring laryngeal sensations in those with chronic cough, but it should be noted that this scale does not assess cough triggers which will require the use of other questionnaires.

The Cough Hypersensitivity Questionnaire (CHQ) is a recently developed measure of cough triggers and sensations (98). The CHQ was developed following detailed cognitive interviews of patients with chronic refractory cough to identify the range of triggers and sensations associated with cough (99). It contains 22 questions (16 triggers and 6 laryngeal sensations) related to coughing. A multi-centre cross-over trial in South Korea used the CHQ to assess patients referred to chronic cough clinics (22). This study reported a marked prevalence of laryngeal symptoms, with 69% of the 478 patients describing tickling in the throat (22). CHQ scores correlated moderately with LCQ (ρ=–0.50) and VAS scores (ρ=0.40) which suggests that cough hypersensitivity symptoms are a unique aspect of the disorder and have some impact on its severity (22). Further studies are needed to validate and evaluate existing tools, and also those in development such as Cough Hypersensitivity Assessment Tool (CHAT) and the ToPiC questionnaire, to assess their potential for identifying patients with chronic refractory cough and evaluating efficacy of treatments.

Limitations of patient reported outcomes

Patient reported outcomes by their very nature are subjective measures of disease severity and are therefore more likely to be affected by patient-related factors such as personality, socioeconomic background, age, gender and cultural values (100). Concerns have been raised that some PROMs (outside of cough) may be too complex for those that are cognitively impaired, the elderly or those with decreased literacy (17). Similarly, it is important to validate PROMs so that they are applicable across cultures and languages (100,101), although it is worth noting that longer established PROMs such as the LCQ have been converted into multiple different languages and validity of various translations has been established (102-104).

PROMs for cough assess patient perceptions of their condition, impact on their lives and mental health, which can all be influenced by other factors other than cough. It is possible that mood can influence a patient's perception of their cough and it could be argued this could make patient-reported outcomes less specific to the phenomenon being observed than objective measures. In a study by Ovsyannikov *et al.* (35), anxiety or depression was associated with discordance between subjective and objective measures of cough. VAS scores had a negative correlation with cough count (r=–0.38) in the subgroups with anxiety/depression compared to r=0.42 in groups without (35). Similarly, it has been suggested that external factors which improve mood or overall quality of life may also improve the perception of cough (26).

An advantage of the ability of PROMs to capture wide-ranging impacts of a condition is that they assess the overall health status (including mood), taking into account benefits of treatments and their side-effects. This is important when evaluating the effectiveness and value of therapy. Indeed, a

treatment which reduces absolute cough counts but causes debilitating side-effects is unlikely to improve a patient's overall perception of their disease.

PROM regulatory requirements

When considering outcome measures as clinical trial endpoints, it is important to review the requirements for PROMs that are set by regulatory bodies such as the European Medicines Agency (EMA) and FDA. The FDA has long recommended the use of PROMs especially in those diseases where objective measures do not capture all of the symptoms, both as primary and secondary end-points (67). The EMA guidelines from 2005 suggest that health-related quality of life measures can have an important role in clinical trials (105). Cough frequency tends to be the primary outcome in most clinical trials of novel antitussives, as demonstrated in recent phase 3 trials of gefapixant which used cough frequency as a primary outcome, with secondary outcomes (including quality of life) assessed with the LCQ (106). There have been concerns from medicine regulators about PROMs regarding their development methodology (specifically content validity), inclusion of psychosocial questions, how clinically meaningful thresholds for change were determined and their poor correlation with objective measures (67,82,105,107).

Content validity is vital to ensure that any outcome measure involves the input of patients (normally via structured interviews) such that it accurately reflects the range of symptoms that are experienced and what matters most to patients (82). For some older PROMs, such as the LCQ, content validity has recently been re-evaluated (75,108). The LCQ was developed in conjunction with patients to ensure it was a comprehensive tool, with items that were relevant to their symptoms, and had multiple iterations based on patient feedback (70). In a recent study, patients with refractory cough underwent detailed cognitive interviews to establish the impact of cough on their lives and also ascertain their feedback about the LCQ. All LCQ items were reported by patients as important problems related to their cough. In addition, patients found the LCQ to be a comprehensive measure, evaluating important concerns about cough and it was simple to understand and easy to complete (108).

Numerous studies have demonstrated the importance of psychosocial aspects of cough (32,33), and that these can be the most troublesome effects (5,109). From a regulatory perspective, psychosocial impact is considered a distal impact of cough and there is a preference to limit the primary evaluation of the efficacy of antitussive medications to physical items of PROMs. Caution should be taken in this approach because from the patient's perspective, psychosocial impact is paramount. Furthermore, the psychosocial impacts of cough are usually responsive to effective cough treatments (26) and this implies psychological symptoms may be a consequence of cough, rather than its cause, and the influence of other external factors such as mood may be over-stated. Indeed, it could be argued that a limitation of objective measures such as cough counts is an incomplete representation of the symptoms and burden experienced by patients with chronic cough.

Establishing clinical thresholds for PROMs to detect change is of vital importance for clinical trials as any difference identified in patient outcome measures has to be deemed clinically meaningful (67). Traditionally this has been performed by calculating the MID. More established PROMs such as the LCQ have had MID established [for LCQ a change of 1.3 units (75,76)], and a normative threshold for health has been reported in the LCQ (110). Similarly, (as shown in *Table 1*) MID for cough severity VAS, CSD, COAT and CQLQ have all been established (56,65,77). However, regulators suggest MIDs may be too small (107) and not meaningful, and that moderate and large changes should be assessed (67). Anchor-based scales (such as the PGI-S) can be helpful in establishing clinically meaningful thresholds for change (67). Establishing clinically meaningful differences for moderate change for endpoints is important, and further research is needed.

Another point of concern is the poor correlation between subjective and objective outcome measures in chronic cough. This is not surprising because objective measures such as cough frequency assess a very narrow and limited feature of the disorder and do not assess impact on patients. A patient with a low cough frequency but with resulting distressing episodes of urinary incontinence is more likely to report a significantly impaired quality of life (26) and a more severe cough. The discordance between tools may also be due to inaccuracies of the tools themselves but this is likely to be a minor factor. The relationship between changes in objective and subjective measures is likely to be much stronger than a cross-sectional comparison since this is more likely to be consistent between patients.

A discordance between objective and subjective measures was exemplified in a clinical trial of orvepitant (a novel neurokinin 1 antagonist) as an antitussive therapy (Volcano-1 trial) (16). Despite an improvement in a range

of PROMs compared to placebo, this effect was not corroborated by objective data such as improvement in daytime cough frequency (16). The discordance may be due to the limitation of cough frequency monitors solely measuring cough counts as individual events in a manner that is quite different to how patients perceive their cough. It may also be due to improvement in cough outcomes not measured by cough frequency monitors such as intensity, urge to cough and impact. Alternatively, there is a possibility that the medication's central nervous system effects altered patients' perceptions of the cough with no or little effect on cough frequency. Both objective and subjective endpoints provide complementary insights but only PROMs can summarise all aspects of the disease.

Conclusions

Should PROMs be used as primary end points in clinical trials?

Chronic cough is a complex disorder that has multiple symptoms, from primary sensory (urge to cough, throat tickling) (51,93) and primary motor (throat clearing, bouts of coughing) (22,51) to secondary effects such as urinary incontinence, feelings of depression and anxiety (5,32). The consequence of these can be profound on a patient's quality of life, particularly their psychosocial health (5,32). Objective cough counting assesses a limited aspect of the chronic cough condition and relates poorly with patient reported outcome measures. Can these tools be adapted and developed to show better agreement? This may be possible in future by incorporating cough bouts, intensity, timings of cough and other spectral characteristics into cough monitoring tools that may align better with the patient perception. Cough frequency may still play a role, especially if monitors can be smaller, less obtrusive, and run for several days at a time. The ideal trial might be one which weighs cough frequency (or some other related objective measure) equally with patient reported outcomes as co-primary endpoints in trials.

The limitations of PROMs are also their strength; they capture important psychosocial impacts and side-effects of treatments which are likely to outweigh their limitations. There are numerous PROMs for chronic cough and it is important to choose one that has been developed in the target patient population and used appropriate methodology to identify important and distressing symptoms for patients. They assess the impact of a wide range of manifestations of chronic cough disorders, are valid and responsive tools, and are simple to administer. Further work however is required to determine clinically important thresholds for change in PROMs using validated methods.

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