

ADVANCING OUTCOME MEASUREMENT IN REFRACTORY OR UNEXPLAINED
CHRONIC COUGH

Advancing Outcome Measurement in Refractory or Unexplained Chronic Cough

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LAY ABSTRACT

Drug development in refractory or unexplained chronic cough (RCC/UCC) faces two key challenges: suboptimal endpoints and large placebo responses. This thesis addresses these challenges through a series of studies. To quantify drug efficacy across doses and characterize the magnitude of the placebo response, we first conducted a dose-response meta-analysis of gefapixant, a novel P2X3 antagonist. Based on the gefapixant development program, regulators separately identified a need for endpoints that better capture patient-important benefits and meet fit-for-purpose standards. We subsequently developed and validated the McMaster Cough Severity Questionnaire (MCSQ), an 8-item patient-reported outcome measure designed to capture key aspects of cough severity from the patient perspective. Finally, we applied the MCSQ in a 2x2 factorial randomized trial protocol evaluating low-dose morphine, pregabalin, and cough control therapy. Collectively, this work strengthens the methodological foundation for clinical trials in RCC/UCC and supports more patient-centered evaluation of emerging therapies.

ABSTRACT

Refractory or unexplained chronic cough (RCC/UCC) is a debilitating condition that substantially impacts patients' quality of life. No licensed therapies exist in Canada, and suboptimal clinical trial endpoints, coupled with large placebo responses, have hindered drug development. This thesis advances outcome measurement in RCC/UCC to improve the detection and interpretation of treatment effects.

To characterize drug efficacy and placebo responses, we conducted a dose-response meta-analysis of gefapixant, the first P2X3 antagonist to reach phase 3 trials. This analysis quantified gefapixant's modest efficacy and confirmed a substantial placebo response. To better understand this response and inform future trial designs, we described underlying neurobiological mechanisms as well as non-specific contributors, including regression-to-the-mean and patient expectancy.

During review of the gefapixant development program, major regulatory agencies emphasized the need for outcome measures that better capture patient-important benefits and meet fit-for-purpose standards. We thus developed and evaluated the McMaster Cough Severity Questionnaire (MCSQ), an 8-item patient-reported outcome measure comprising two domains and a one-week recall period. Using mixed methods, classical test theory, and Rasch modelling, we demonstrated the MCSQ's strong content validity, construct validity, and test-retest reliability, supporting its use as a promising endpoint for future clinical trials. To illustrate its application, we designed a 2x2 factorial randomized trial protocol evaluating the comparative effectiveness and harms of two commonly prescribed neuromodulators, low-dose morphine and pregabalin, and a non-pharmacologic intervention, cough control therapy, for RCC/UCC. This trial will further evaluate the MCSQ's longitudinal validity, responsiveness, and minimal important differences.

Collectively, this work strengthens the methodological foundation for clinical trials in RCC/UCC and supports more patient-centered evaluation of emerging therapies.

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TABLE OF CONTENTS

Chapter 1	Introduction.....	1
Chapter 2	Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose-response meta-analysis.....	12
Chapter 3	Placebo Responses in Clinical Trials of Refractory Chronic Cough: Mechanisms, Challenges, and Mitigation Strategies	67
Chapter 4	Cough symptom severity in patients with refractory or unexplained chronic cough: a systematic survey and conceptual framework	75
Chapter 5	Assessing cough symptom severity in refractory or unexplained chronic cough: findings from patient focus groups and an international expert panel.....	128
Chapter 6	The McMaster Cough Severity Questionnaire (MCSQ): a cough severity instrument for patients with refractory chronic cough.....	169
Chapter 7	Test-Retest Reliability of the McMaster Cough Severity Questionnaire in patients with refractory or unexplained chronic cough	218
Chapter 8	A 2x2 factorial, randomized, open-label trial to evaluate neuromodulators and cough control therapy in patients with refractory or unexplained chronic cough: the FORTITUDE trial protocol	235
Chapter 9	Discussion and Conclusions	287

LIST OF FIGURES

Figure 1-1: Pathophysiology of RCC/UCC	3
Figure 2-1: Literature search flow diagram in a study of gefapixant for chronic cough	35
Figure 2-2: Estimated effects of gefapixant by dose compared to placebo estimated by a study-level meta-analysis.....	37
Figure 2-3: Dose-response relationship between gefapixant dose and 24-hour, awake, and sleep cough frequency.	39
Figure 2-4: Dose-response relationship between gefapixant dose and cough severity, cough-specific quality of life, taste-related adverse events, and adverse events leading to discontinuation	41
Figure 3-1: Factors underlying the placebo effect and the placebo response	74
Figure 4-1: Study selection flow chart.....	118
Figure 4-2: Conceptual framework of cough severity in patients with chronic cough.....	119
Figure 5-1: Conceptual framework of cough symptom severity in patients with RCC/UCC	147
Figure 5-2: Assessing cough in patients with RCC/UCC	148
Figure 6-1: Overview of the steps involved in the development of the MCSQ	198
Figure 6-2: Item person map.....	199
Figure 6-3: Convergent validity of the MCSQ total score.....	200
Figure 6-4: McMaster Cough Severity Questionnaire.....	202
Figure 7-1: Bland-Altman plots demonstrating test-retest agreement for (A) MCSQ Total Score, (B) MCSQ Frequency Score, and (C) MCSQ Intensity Score.	233
Figure 8-1: FORTITUDE study design.....	275

LIST OF TABLES

Table 1-1: Concerns Raised by the U.S. Food and Drug Administration Regarding Cough-Specific PROMs.....	8
Table 2-1: Characteristics of included studies	42
Table 4-1: Characteristics of included studies	96
Table 4-2: Characteristics of patients in included studies.....	99
Table 4-3: Domains and items related to measurement of cough severity in adult patients with chronic cough.....	108
Table 5-1: Characteristics of 16 focus group patients.....	149
Table 5-2: Domains and items related to measurement of cough symptom severity in patients with RCC/UCC	150
Table 5-3: Open-ended responses among 11 experts regarding items/domains to assess of cough symptom severity	165
Table 6-1: Patient baseline characteristics	191
Table 6-2: Impact scores of items	193
Table 6-3: Rotated component matrix of the loading factors for the 10-item MCSQ	195
Table 6-4: Summary statistics of the 8-item MCSQ.....	196
Table 7-1: Baseline demographics of participants (n=75)	230
Table 7-2: Test-retest reliability	231
Table 7-3: Change scores by Patient Global Impression of Change responses at visit 2	232
Table 8-1: Dosing schedule of pregabalin	276
Table 8-2: Summary of cough control therapy	277
Table 8-3: Study visits and procedures	278
Table 8-4: Summary of statistical analysis plan for the 6-week randomized phase	281

LIST OF APPENDICES

eMethods 2-1: Search strategy	46
eMethods 2-2: Study characteristics and baseline patient information collected from trials	49
eMethods 5-1: Focus group interview guide	166
eMethods 6-1: Item reduction questionnaire	212
eMethods 6-2: Instructions for the think-aloud and verbal probing procedures.....	215
eMethods 6-3: Verbal probing interview questions	216
eFigure 2-1: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and cough-specific quality of life using restricted cubic spline regression	63
eFigure 2-2: Pooled dose-response relationship between gefapixant dose and relative risk for treatment-related adverse events compared to placebo	64
eFigure 2-3: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and adverse events leading to discontinuation using restricted cubic spline regression.....	65
eFigure 2-4: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and taste-related adverse events using restricted cubic spline regression	66
eTable 2-1: Risk of bias in included studies	50
eTable 2-2: GRADE evidence profile.....	54
eTable 2-3: Goodness of fit statistics for all dose-response models	60
eTable 2-4: Risk differences for achieving a benefit greater than or equal to the MID for gefapixant (45 mg twice daily)	61
eTable 2-5: Results of sensitivity analyses including 2 unpublished trials.....	62

eTable 4-1: Search strategy	120
eTable 4-2: Characteristics of cough-specific PROMs included in the review	124
eTable 6-1: Item tracking matrix.....	204
eTable 6-2: Cognitive debriefing interview summary	206
eTable 6-3: Final conceptual framework	211
eTable 6-4: MCSQ Scoring Sheet.....	217

LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
ATP	Adenosine 5'-triphosphate
ATS	American Thoracic Society
AEs	Adverse events
BID	Twice daily
CASA-Q	Cough and Sputum Questionnaire
CCIQ	Chronic Cough Impact Questionnaire
CCM	Conditioned cough modulation
CCT	Cough control therapy
CET	Cough Evaluation Test
CI	Confidence interval
COAT	Cough Assessment Test
COMT	Catechol-O-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPM	Conditioned pain modulation
CQLQ	Cough Quality of Life Questionnaire
CSD	Cough Severity Diary
CSI	Cough Severity Index
CSS	Cough symptom score
CS-VAS	Cough Severity Visual Analogue Scale
DMC	Data monitoring committee
eCRF	Electronic case report forms
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
eRM	Extended Rasch Modelling
ERS	European Respiratory Society
FDA	U.S. Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FORTITUDE	FactOrial Randomized TrIal To evalUate neuromoDulators and cough control thErapy
FVC	Forced vital capacity
GERD	Gastro-esophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GROC	Global Rating of Change
HARQ	Hull Airway Reflux Questionnaire
ICC	Intraclass correlation coefficient
ICJME	International Committee of Medical Journal Editors
ITT	Intention-to-treat
LCQ	Leicester Cough Questionnaire
LHQ	Newcastle Laryngeal Hypersensitivity Questionnaire
LLN	Lower limit of normal
MCSQ	McMaster Cough Severity Questionnaire
MD	Mean difference

MID	Minimal important difference
MNAR	Missing-not-at-random
OPRM1	μ -opioid receptor gene
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRISM	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRN	As needed
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PSALTI	Physiotherapy with a speech and language therapy intervention
PSI	Person separation index
QoL	Quality of life
REDCap	Research Electronic Data Capture
RCC	Refractory chronic cough
RCT	Randomized controlled trial
REB	Research ethics board
RoB	Risk of bias
RR	Relative risk
SD	Standard deviation
SOP	Standard operating protocol
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TAM	Test Analysis Modules
UACS	Upper airway cough syndromes
UCC	Unexplained chronic cough
VPC	Variance partition coefficient

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a sandwich thesis comprised of 9 chapters.

Chapter 1 (Introduction) is unpublished. EK is the sole author.

Chapter 2 is published in *JAMA*. EK, GHG, and IS conceived the study design. EK developed the search strategy. EK, MP, ND, and MW screened studies. EK and MP extracted the data and performed risk of bias assessments. EK performed the statistical analysis. EK and IS assessed the certainty of the evidence. EK, DKC, DZ, PMOB, GHG, and IS interpreted the data. EK wrote the first draft of the manuscript, with revision from DKC, PMOB, GHG, and IS. All authors critically reviewed and approved the manuscript.

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expertise. EK wrote the first draft of the manuscript. All authors provided critical review and final approval of the manuscript.

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Chapter 1 Introduction

What is Refractory or Unexplained Chronic Cough (RCC/UCC)?

Chronic cough, defined as a cough lasting for 8 weeks or more, is a common condition affecting 16% of Canadians over the age of 45.¹ Although some patients respond well to treatments targeting identifiable causes (e.g., asthma, gastro-esophageal reflux disease, and upper airway disease), 26% have refractory or unexplained chronic cough (RCC/UCC).²

RCC/UCC is associated with significant healthcare utilization.^{3,4} Diagnosis often involves multiple failed treatment trials and/or years of investigations to exclude alternative causes. As a result, patients can experience symptoms for 8 years or more before receiving a formal diagnosis.⁵

The condition has a profound impact on patients' quality of life.^{6,7} Patients frequently experience urinary incontinence, chest or abdominal discomfort, vomiting, syncope, sleep disturbance, anxiety, depression, social isolation, and work impairment. Improving quality of life in these patients represents a large unmet need.

Pathophysiology of RCC/UCC

The pathophysiology of RCC/UCC involves cough hypersensitivity syndrome, which refers to dysfunction of the neuronal pathways that control coughing (**Figure 1-1**).⁸ Cough normally serves as a defensive reflex to protect the airways from thermal, mechanical, and/or chemical damage. Activation of two main vagal afferent fiber types in the larynx, trachea, carina, and large intrapulmonary bronchi can evoke coughing.⁹ The first includes jugular C-fibers, which are unmyelinated epithelial nerves that respond to stimuli such as capsaicin, bradykinin, acidity, inflammatory mediators, and adenosine 5'-triphosphate (ATP).¹⁰ The second includes A δ fibers,

which are myelinated subepithelial nerves that respond primarily to mechanical stimuli such as mucus, as well as changes in pH and osmolarity.¹⁰

Activation of these airway sensory afferents generates action potentials that synapse in the brainstem, particularly within the nucleus tractus solitarius.^{10,11} From there, neural inputs can induce coughing by modifying activity of the respiratory central pattern generator, a collection of neurons that generate respiratory rhythm.¹⁰ Signals from the nucleus tractus solitarius can also relay through second-order neurons to the thalamus. Third-order neurons in the thalamus then project to higher cortical regions, including the primary somatosensory cortex, insula, prefrontal cortex, and posterior parietal cerebral cortex.¹⁰ These higher cortical regions encode the conscious perception of an urge-to-cough.¹⁰ They can also exert top-down suppression of the cough reflex through both voluntary and non-voluntary inhibitory control pathways.¹⁰

In RCC/UCC, dysfunction of the neuronal pathways regulating cough can occur through several mechanisms: (i) increased activation and/or hyperexcitability of vagal afferents; (ii) hypersensitivity and/or hyperresponsiveness of the brainstem and higher cortical processing networks; (iii) impaired voluntary control and/or descending inhibition; or (iv) a combination of these mechanisms (**Figure 1-1**).⁸

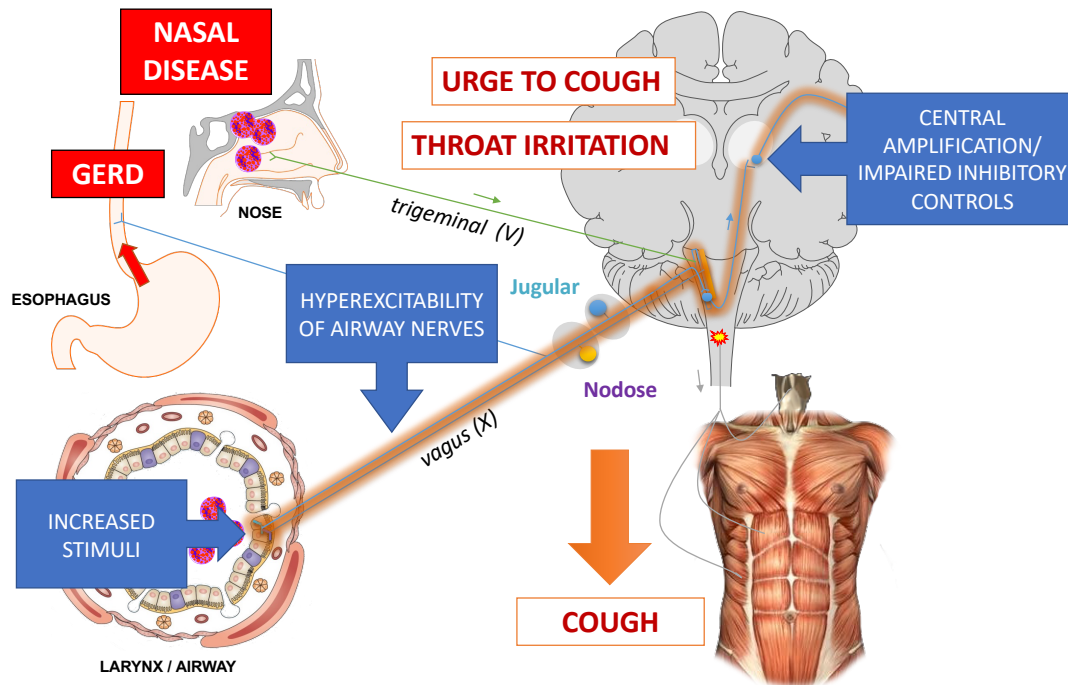


Figure 1-1: Pathophysiology of RCC/UCC

Current Treatments for RCC/UCC

In Canada and many countries globally, there remains no licensed treatments for RCC/UCC. Clinical practice guidelines^{12,13} therefore recommend physiotherapy or speech and language therapy,^{14,15} or off-label use of neuromodulators, including low-dose morphine,^{16,17} pregabalin,¹⁸ gabapentin,¹⁹ and amitriptyline.²⁰ Neuromodulators primarily act on the central nervous system pathways controlling cough.

Low-dose morphine

Low-dose morphine acts primarily as a mu-opioid receptor agonist, with weaker activity on other opioid receptor subtypes.²¹ These receptors have expression throughout the central nervous system and, to a lesser extent, in peripheral tissues including the respiratory tract and vagal

afferent pathways.²¹ Centrally, mu-opioid receptors are expressed in the anterior cingulate cortex, insula, amygdala, brainstem, and spinal cord.²¹ Researchers hypothesize that low-dose morphine reduces cough reflex sensitivity through agonism of mu-opioid receptors primarily in the brainstem and higher cortical regions.

Two small randomized trials have studied low-dose morphine given at 5-10 mg twice daily (BID) for 2-4 weeks in patients with RCC/UCC.^{16,17} The first trial in 27 patients found that, compared to placebo, morphine reduced cough severity by 2 points (95% CI 1.1 to 2.1) on a 10-point scale.¹⁶ The second trial in 22 known responders found that morphine improved 24-hour cough frequency by 71.8% and cough severity on the 100-mm visual analogue scale (CS-VAS) by 27.2 mm compared to placebo.¹⁷ In both trials, the most common side effects included constipation and drowsiness.^{16,17}

Pregabalin/Gabapentin

Although the exact mechanism of action of gabapentinoids remains unclear in RCC/UCC, these medications may bind the $\alpha_2\delta$ subunit of voltage-gated calcium channels rather than acting directly on GABA_A or GABA_B receptors.²² In doing so, this reduces calcium influx and decreases the release of excitatory neurotransmitters, thereby reducing neuronal hyperexcitability of the cough reflex.

One randomized trial of 62 patients demonstrated that gabapentin given at a maximum tolerable dose of 600 mg three times daily improved cough quality of life by 1.80 points (95% CI 0.56 to 3.04) on the Leicester Cough Questionnaire (LCQ) compared to placebo.¹⁹ Adverse effects occurred in 31% of patients receiving gabapentin and commonly included nausea and fatigue. In a randomized trial of 40 patients examining pregabalin (150 mg BID) plus speech therapy, the

combination improved scores on the LCQ by 3.5 points (95% CI 1.1 to 5.8) and the CS-VAS by 25.1 mm (95% CI 10.6 to 39.6 mm) compared to speech therapy alone.¹⁸ Treatment discontinuation occurred in 5% of patients due to drowsiness, nausea, or weight gain.

Amitriptyline

Amitriptyline, a tricyclic antidepressant, inhibits the reuptake of serotonin and norepinephrine to increase their synaptic concentrations in the central nervous system. The evidence supporting amitriptyline (10 mg nightly) comes from a single randomized trial of 28 patients demonstrating a higher proportion achieving complete cough response compared to codeine/guaifenesin.²⁰

The evidence in favour of neuromodulators remains very limited, with additional limitations including intolerable side effects in some patients, lack of sustained benefits after treatment discontinuation, and concerns regarding long-term use (e.g., abuse, dependency, and addiction). Consequently, recent drug development has focused on therapies that act peripherally on sensory nerve afferents or mixed opioid receptor agonist/antagonists that may pose fewer side effects.

Emerging Treatments for RCC/UCC

Nalbuphine

Nalbuphine extended-release oral represents a new therapy under phase 2b investigation for the treatment of RCC/UCC. The medication acts as a mixed kappa-opioid receptor agonist and mu-opioid receptor antagonist on both central and peripheral cough pathways. The RIVER phase

2a, dose-escalation, cross-over trial in RCC/UCC demonstrated that nalbuphine (108 mg BID) reduced cough frequency by 57% compared to placebo.²³ Common adverse effects included constipation, somnolence, nausea, dizziness, headache, and fatigue. A phase 2b trial has also evaluated nalbuphine extended-release in patients with chronic cough and idiopathic pulmonary fibrosis.²⁴ A phase 2b trial in RCC/UCC is currently being planned.

P2X3 antagonists

P2X3 antagonists represent another new class of therapy targeting peripheral sensory nerve receptors in the airways. These drugs block ATP from activating homomeric P2X3 and heteromeric P2X2/3 ligand-gated ion channels expressed on sensory nerve afferents innervating the larynx, trachea, carina, and intrapulmonary airways.^{8,25}

The most extensively studied P2X3 antagonist includes gefapixant, with multiple phase 2 and phase 3 trials demonstrating reductions in 24-hour cough frequency.²⁶⁻²⁹ Regulators in the European Union, United Kingdom, Switzerland, and Japan have approved gefapixant for the treatment of RCC/UCC; however, the drug remains unapproved in Canada and the United States. Camlipixant, a more selective P2X3 antagonist, is currently under evaluation in the CALM-1/CALM-2 phase 3 trials.

Challenges Facing Drug Development

Despite promising biological mechanisms, clinical trials of P2X3 antagonists, particularly gefapixant, have revealed two key challenges: modest efficacy of unclear patient importance and large placebo responses. When reviewing gefapixant's phase 3 trials (COUGH-1 and COUGH-2),³⁰ regulatory agencies faced difficulty interpreting whether observed reductions in cough

frequency represented patient important improvements. Although cough frequency reduced compared to placebo, the magnitude of change was modest, and it remained uncertain whether frequency alone captured the aspects of cough most important to patients. Large placebo responses further complicated the interpretation of treatment effects.

COUGH-1 and COUGH-2 included patient-reported outcome measures (PROMs) as secondary endpoints to capture the patient experience of cough. The Cough Severity Visual Analogue Scale (CS-VAS) provided a single-item assessment in which patients rated their cough severity over the past day on a 0-100 mm scale.³¹ The Leicester Cough Questionnaire (LCQ), consisting of 19 items with a 2-week recall period, assessed the impact of cough on physical, psychological, and social domains of health.³² The Cough Severity Diary (CSD), a daily diary, included 7 items evaluating cough frequency, intensity, and disruption.³³ Modest improvements in these PROMs with gefapixant further contributed to uncertainty regarding the overall benefit of the drug.

Aside from the observed treatment effects, the U.S. Food and Drug Administration (FDA) also raised several methodological concerns regarding the PROMs (**Table 1-1**). For the CS-VAS, concerns included potential inconsistency in scale length, high rates of missing data, absence of numeric ratings along the scale, and reliance on a single anchor (the Patient Global Impression of Change [PGIC]) rather than multiple anchors (e.g., PGIC and Patient Global Impression of Severity [PGIS]) for estimating the minimal important difference (MID). For the LCQ, the FDA noted that psychological and social domains represent distal constructs to coughing itself, potentially reducing sensitivity to changes (responsiveness) in cough severity. Additional concerns included low-to-moderate correlations with related measures (e.g., cough frequency) and disagreement with the use of a transition instrument, the Global Rating of Change (GROC), to

define MID thresholds. Finally, for the CSD, they raised similar concerns regarding reliance on a single anchor (PGIC) to estimate the MID and the appropriateness of the PGIC response categories.

Table 1-1: Concerns Raised by the U.S. Food and Drug Administration Regarding Cough-Specific PROMs

Measure	Key Concerns
Cough Severity Visual Analogue Scale (CS-VAS)	• Potential inconsistency in the scale length due to formatting issues. • High rates of missing or incomplete data. • Lack of numbers on the scale, making small changes difficult to interpret. • Minimal important difference (MID) estimated using only a single anchor, the Patient Global Impression of Change (PGIC); regulators preferred multiple anchors (PGIC and Patient Global Impression of Severity [PGIS]).
Leicester Cough Questionnaire (LCQ)	• Measures the impact of cough on physical, psychological, and social domains, but the FDA viewed psychological and social domains as potentially influenced by factors unrelated to cough treatment; FDA focused on the physical domain alone. • Lack of confirmatory factor analysis for the 3-domain structure. • LCQ-Total Score showed low-to-moderate correlations with related measures, such as 24-hour cough frequency. • COUGH-1/COUGH-2 trials defined responders using a ≥ 1.3-point increase in the LCQ-Total Score. However, the anchor to derive this MID was the Global Rating of Change (GROC) Scale, a 15-point scale prone to recall bias. Regulators also did not agree with combining improvement and worsening response options on the GROC to define the MID. • Other thresholds (≥ 3.3-point or ≥ 4.1-point increase) lacked sufficient evidence of meaningfulness to patients.
Cough Severity Diary (CSD)	• No supporting evidence for thresholds of ≥ 1.3- and ≥ 2.7-point reductions in responder analyses. • Regulators questioned the use of “Somewhat improved” on the PGIC to derive the MID of 1.3 points. • Regulators questioned using “Improved”/“Very much improved” on the PGIC to derive the 2.7-point threshold. • Only a single anchor used; regulators preferred multiple anchors (PGIC + PGIS) and anchors specific to constructs of interest.

From a broader research perspective, the PROMs also have other conceptual and practical limitations. The CS-VAS, while simple, oversimplifies the multidimensional experience of cough and demonstrates only modest test-retest reliability.³¹ If not administered daily, its daily recall may also risk capturing an unrepresentative period of cough. The LCQ, while more comprehensive,

consists of 19 items, making it lengthy and cumbersome for use in clinical practice. Finally, CSD is proprietary, which limits its accessibility and widespread adoption across studies and clinical settings.

Together, the limitations highlighted by regulatory agencies and these additional considerations underscore the need for a widely available, sensitive, and patient-important outcome measure with clear evidence of interpretability.

Thesis Rationale and Objectives

This thesis aims to advance outcome measurement and improve the interpretation of treatment effects in trials of RCC/UCC. Specifically, the forthcoming chapters will:

1. Quantify drug efficacy and placebo responses within gefapixant's drug development program, the first P2X3 antagonist to reach phase 3 trials (Chapter 2);
2. Describe mechanistic and methodological contributors to the placebo response (Chapter 3);
3. Develop and evaluate the measurement properties of a new patient-reported outcome measure, the McMaster Cough Severity Questionnaire (MCSQ) (Chapters 4-7);
4. Outline a protocol for a 2×2 factorial randomized trial evaluating low-dose morphine, pregabalin, and cough control therapy for RCC/UCC, while assessing the validity, responsiveness, and MID of the MCSQ (Chapter 8); and
5. Summarize the thesis and future research steps (Chapter 9).

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Chapter 2 Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose-response meta-analysis

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Abstract

Importance: Gefapixant represents an emerging therapy for patients with refractory or unexplained chronic cough.

Objective: To evaluate the efficacy and tolerability of gefapixant for the treatment of adults with refractory or unexplained chronic cough.

Data Sources: We searched MEDLINE, EMBASE, CENTRAL, and the Web of Science from November 2014 to July 2023.

Study Selection: Two reviewers independently screened for parallel and crossover randomized controlled trials (RCTs) that compared, in patients with refractory or unexplained chronic cough, either gefapixant with placebo, or two or more doses of gefapixant with or without placebo.

Data Extraction and Synthesis: Two reviewers independently extracted data. We conducted a frequentist random-effects dose-response meta-analysis or pairwise meta-analysis for each outcome. Using the GRADE approach, we rated our certainty in whether patients would perceive the effects as important (greater than the minimal important difference [MID]) or small (less than the MID).

Main Outcomes and Measures: Cough frequency (measured using the VitaloJAK cough monitor; MID, 20%), cough severity (measured using the 100-mm visual analog scale [VAS]; higher is worse; MID, 30 mm), cough-specific quality of life (measured using the Leicester Cough Questionnaire [LCQ]; score range, 3 [maximal impairment] to 21 [no impairment]; MID, 1.3 points), treatment-related adverse events, adverse events leading to discontinuation, and taste-related adverse events.

Results: We identified 9 RCTs including 2,980 patients. Compared to placebo, gefapixant (45 mg twice daily) had small effects on awake cough frequency (17.6% reduction [95% CI, 10.6% to

24.0%], moderate certainty), cough severity on the 100-mm VAS (mean difference [MD] of -6.2 mm [95% CI, -4.1 to -8.4], high certainty), and cough-specific quality of life on the LCQ (MD 1.0 points [95% CI, 0.7 to 1.4], moderate certainty). Compared to placebo, gefapixant (45 mg twice daily) probably caused an important increase in treatment-related adverse events (32 more per 100 patients [95% CI, 13 to 64 more], moderate certainty) and taste-related adverse events (32 more per 100 patients [95% CI, 22 to 46 more], high certainty). High certainty evidence suggests that gefapixant (15 mg twice daily) had small effects on taste-related adverse events (6 more per 100 patients [95% CI, 5 to 8 more]).

Conclusions and Relevance: Compared with placebo, gefapixant 45 mg orally twice daily led to modest improvements in cough frequency, cough severity, and cough-specific quality of life but increased taste-related adverse events.

Background

Chronic cough affects 2-18% of adults globally¹ and can substantially impact quality of life.² Although some patients respond well to treatments targeting possible causes of cough, 10-60% have refractory or unexplained chronic cough.³⁻⁵

Faced with no licensed treatments for refractory or unexplained chronic cough, guidelines recommend treatment with speech pathology or neuromodulators.^{6,7} Neuromodulators include morphine,⁸ gabapentin,⁹ pregabalin,¹⁰ and amitriptyline,¹¹ but these therapies have dose-limiting adverse effects, poor response in some patients, and concerns about long-term use.⁶ Alternative therapies for refractory or unexplained chronic cough remain an unmet need.

A new class of antitussives for refractory or unexplained chronic cough includes P2X3 antagonists.¹²⁻¹⁴ These agents bind to the P2X3 receptor, an adenosine triphosphate (ATP) gated ion channel on chemically-sensitive airway c-fibres.¹⁵⁻¹⁷ Blocking this receptor prevents ATP from opening the channel, thereby reducing activation of c-fibres that transmit action potentials to the brainstem and somatosensory cortex that control cough.

Clinical trials have highlighted the efficacy of P2X3 antagonism for treatment of refractory or unexplained chronic cough.^{12-14,18,19} Two phase 3 trials evaluating gefapixant met the primary endpoint of reducing 24-hour cough frequency compared to placebo.¹⁹ Given these trials, Japan and Switzerland have licensed gefapixant for treatment of refractory or unexplained chronic cough, while the FDA, European Medicines Agency, Health Canada, and other major regulatory authorities deliberate. Although gefapixant is not yet approved by the FDA for use in the United States, there remains a possibility that gefapixant could become the first licensed treatment for refractory or unexplained chronic cough in multiple countries globally.

Evidence of gefapixant's magnitude of effect on outcomes of benefit and tolerability should precede its widespread use. No studies have previously evaluated all randomized trial evidence addressing this therapy – findings that can inform regulatory agencies, guideline developers, payers, clinicians, and patients. We therefore performed a systematic review and dose-response meta-analysis evaluating the effects of gefapixant in patients with refractory or unexplained chronic cough.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁰ Prior to data analysis, we registered our protocol on PROSPERO (CRD42022383872). This paper differs from the protocol in that it focuses on gefapixant rather than all P2X3 antagonists. Several reasons informed this protocol deviation: (1) out of all P2X3 antagonists, gefapixant was most likely to become imminently available for use in clinical practice; (2) while conducting this work, drug development programs for eliapixant²¹ and sivopixant²² discontinued after their phase 2b trials; and (3) we believed that evidence syntheses on camlipixant were premature with phase 3 trials still ongoing.

Eligibility criteria

We included parallel and crossover randomized controlled trials (RCTs) that compared gefapixant to placebo or alternative doses of the drug in adults (≥ 18 years old) with refractory or unexplained chronic cough lasting >8 weeks. We excluded trials in which $<80\%$ of patients had refractory or unexplained chronic cough lasting >8 weeks.

Data sources and search

We searched MEDLINE, EMBASE, CENTRAL, and the Web of Science from November 2014 to July 2023 with no restrictions on language or publication status (**eMethods 2-1**). To ensure an exhaustive search for unpublished data, we hand-searched websites of the FDA, EMA, and pharmaceutical company.

Study selection

Paired reviewers independently screened titles, abstracts, and full-texts. Title, abstract and full-text screening required agreement between reviewers. Reviewers resolved disagreements by discussion and, if necessary, by consultation with an adjudicator.

Data extraction

Two reviewers extracted data independently using a standardized, pilot-tested form. **eMethods 2-2** lists the study characteristics and baseline patient information captured from trials. Reviewers resolved discrepancies by discussion, and when necessary, by adjudication with a third reviewer.

Reviewers extracted (1) 24-hour, (2) awake, and (3) sleep cough frequencies, each measured using the VitaloJAK cough monitor²³; (4) cough severity, measured using the Visual Analogue Scale (VAS)²⁴; (5) cough-specific quality of life, measured using the Leicester Cough Questionnaire (LCQ)²⁵ or Cough Quality of Life Questionnaire (CQLQ)²⁶; (6) treatment-related adverse events (AEs); (7) AEs leading to discontinuation; and (8) taste-related AEs. We captured all outcomes at the longest follow-up. For AEs, we recorded the number of patients with ≥ 1 event.

Risk of bias assessments

Two independent reviewers used a modified Cochrane RoB 2.0 tool for assessing risk of bias in RCTs.²⁷ Reviewers rated both parallel and crossover trials at “low risk of bias”, “probably low risk of bias”, “probably high risk of bias”, or “high risk of bias” across each domain. For crossover trials, we considered risk of bias arising from period and carryover effects.²⁷ Reviewers resolved discrepancies by discussion, and when necessary, by adjudication with a methodologist.

Data synthesis

We conducted random-effects dose-response meta-analysis with the restricted maximum likelihood estimator.^{28,29} Dose-response meta-analysis summarizes, across studies, the relationship between treatment dose and an outcome. We modelled non-linearity using one-stage restricted cubic splines³⁰ with knots set at 10%, 50%, and 90%. Wald-type tests tested non-linearity, and goodness-of-fit statistics informed model fit.

For outcomes in which we found no evidence of a dose-response relationship, we assumed the same effect across doses and performed a random-effects pairwise meta-analysis.

For cough frequency outcomes, we calculated pooled mean differences in log-transformed coughs/hour and 95% confidence intervals. For studies in which only means and standard deviations of the unlogged data were available, we approximated means and standard deviations on the log scale.³¹ When reported, we preferentially pooled mean changes in log-transformed coughs/hour from baseline estimated using ANCOVA or linear mixed-effects models that adjusted for baseline covariates. To calculate percent reductions, we exponentiated mean differences in log-transformed coughs/hour using $100*(e^{\text{diff}}-1)$.

For patient-reported outcomes, we calculated pooled mean differences and 95% confidence intervals. For cough-specific quality of life, if a trial reported the outcome using the CQLQ instead

of the LCQ, we assumed both instruments measured the same construct and transformed mean differences on the CQLQ into natural units of the more widely-used LCQ.³²

For all efficacy outcomes apart from sleep cough frequency, we modelled risk differences and 95% confidence intervals for achieving at least the minimal important difference (MID). The MID is the smallest change in an outcome that patients would perceive as important. Based on prior work, we considered MIDs as a 20% reduction in cough frequency,³³ a 30 mm reduction on the 100-mm cough severity VAS,³⁴ and a 1.3-point increase on the LCQ.³⁵ Given that regulators would most likely approve 45 mg twice daily, we focused our modelling of risk differences for achieving the MID based on summary mean differences comparing the effects of gefapixant at this dose to placebo.³⁶

We calculated pooled relative risks (RR) and 95% confidence intervals for AE outcomes. We also report absolute risk increases using estimates of baseline risk from the median of the control group from eligible trials.

For crossover trials, we prioritized analysis of both periods over an analysis of the first period only. We pooled crossover trials with parallel designs using methods outlined in the Cochrane Handbook.³⁷

In our primary analyses, we included only published trials. To test the impact of including unpublished trials, we ran, for applicable outcomes, *post hoc* sensitivity analyses including unpublished trials.

Analyses were among the intention-to-treat population with complete case data. Although we included trials that evaluate any dose of gefapixant, to avoid spurious judgments based on imprecise models, we limited our inferences to clinically-relevant doses and for which the model

yielded credible results (0 to 60 mg twice daily). We ran analyses with *dosresmeta* and *metafor* packages in R (version 4.2.1).

Heterogeneity and meta-regression

For two-stage linear dose-response models, we examined, across studies, heterogeneity in the study-specific dose-response association through a combination of visual inspection of dose-response plots, χ^2 tests, and the I^2 statistic. For one-stage dose-response models using restricted cubic splines, we examined heterogeneity through visual inspection of the dose-response plots and the variance partition coefficient (VPC).³⁰ The VPC is a study-specific and dose-specific statistic that represents the percentage of heterogeneity out of the total variability specific to the study. For non-referent doses in each study, we calculated a VPC and took the average of the study-specific VPCs by dose to be interpreted as the dose-specific I^2 .³⁰

To explain heterogeneity, we ran meta-regression to test the following *a priori* hypotheses about study-level covariates: (1) crossover trials show larger effects than parallel trials; and (2) trials with higher risk of bias show larger effects than trials with lower risk of bias. We performed the last meta-regression only if we found considerable variability within a risk of bias component. Tests of interaction established whether treatment effects differed significantly.

Rating the certainty of evidence

Using the GRADE approach, two reviewers assessed the certainty in evidence for all doses and outcomes.³⁸ We rated our certainty in whether patients would perceive effects to be important (i.e., greater than the MID) or small (less than the MID). To ascertain MIDs for AE outcomes, we surveyed 5 patient partners with refractory or unexplained chronic cough. They informed absolute

MIDs of 15% for treatment-related AEs, 10% for AEs leading to discontinuation, and 10% for taste-related AEs.

Results

After screening 713 titles and abstracts, and 100 full texts, we identified 11 RCTs, two of which were unpublished and only had results on the clinical trial registration (**Figure 2-1**). For the primary analysis, we included 9 published RCTs, 4 of which had a crossover^{12,39,40} and 5 of which had a parallel design.⁴¹⁻⁴³ All trials, apart from one that addressed alternative doses of gefapixant⁴³, compared one or more doses with a placebo. Industry funded all trials. Trials excluded current smokers, had a mean age of 58.5 years, enrolled a mean of 75.7% female patients, and had a median cough duration of 11.6 years – characteristics that are typical for those with refractory or unexplained chronic cough. **Table 2-1** lists the characteristics of the 9 included studies.

Risk of bias in included studies

Among 9 RCTs, reviewers rated 2 at risk of bias for at least one domain (**eTable 2-1**). One trial did not adequately describe concealed allocation, and one trial had $\geq 20\%$ missing outcome data that could lead to bias.

Outcome data

eTable 2-2 presents evidence profiles for the effects of gefapixant at doses 15, 30, 45, and 60 mg twice daily. **eTable 2-3** reports the goodness-of-fit statistics for all dose-response models.

24-hour cough frequency

Six RCTs including 2472 patients reported 24-hour cough frequency measured by the VitaloJAK ambulatory cough recorder.^{12,19,40,42} We did not find evidence of a nonlinear relationship between increasing gefapixant dose and reduction in 24-hour cough frequency (**Figure 2-3A**). The linear model demonstrated that, compared to placebo, gefapixant (45 mg twice daily) probably had a small effect on 24-hour cough frequency (16.0% reduction [95% CI, 9.4% to 22.0%]; risk difference for achieving at least the MID, 4.7% [95% CI, 0.6% to 8.7%]; moderate certainty; **Figure 2-2; eTable 2-4**), whereas at 60 mg twice daily, gefapixant probably caused an important reduction in 24-hour cough frequency (20.7% reduction [95% CI, 12.5% to 28.3%]; moderate certainty).

Awake cough frequency

Six RCTs including 2452 patients reported awake cough frequency measured by the VitaloJAK ambulatory cough recorder.^{12,19,40,42} Although we found evidence of a nonlinear relationship between dose and reduction in awake cough frequency, we found heterogeneity explained by a significant difference between parallel and crossover trials. Since crossover trials demonstrated larger effects than parallel trials, we modelled the dose-response relationship only among the parallel trials (3 RCTs, 2145 patients).^{19,42} The dose-response model demonstrated that, compared to placebo, gefapixant (45 mg twice daily) probably had a small effect on awake cough frequency (17.6% reduction [95% CI, 10.6% to 23.7%]; risk difference for achieving at least the MID, 6.9% [95% CI: 3.3% to 10.5%]; moderate certainty; **Figure 2-2; Figure 2-3B; eTable 2-4**). At 60 mg twice daily, gefapixant probably caused an important reduction in awake cough frequency (22.8% reduction [95% CI, 14.0% to 30.7%]; moderate certainty). A sensitivity analysis including one unpublished RCT⁴⁴ found similar results (**eTable 2-5**).

Sleep cough frequency

Four RCTs including 541 patients reported sleep cough frequency measured by the VitaloJAK ambulatory cough recorder.^{12,40,42} We found no evidence of a relationship between gefapixant dose and reduction in sleep cough frequency. In a pairwise meta-analysis treating all doses as having the same effect, we found low certainty evidence that gefapixant reduced sleep cough frequency compared to placebo (13.1% [95% CI, 47.8% reduction to 44.8% increase]; low certainty; **Figure 2-2; Figure 2-3C**).

Cough severity

Eight RCTs including 2666 patients reported cough severity using the VAS.^{12,19,39,40,42,45} We found evidence of a nonlinear relationship between gefapixant dose and reduction in cough severity, but parallel and crossover trials significantly differed. Since crossover trials demonstrated larger effects than parallel trials, we modelled the dose-response relationship only among parallel trials (4 RCTs, 2292 patients).^{19,42,45} The dose-response model demonstrated that, compared to placebo, gefapixant (45 mg twice daily) had a small effect on cough severity measured by the 100-mm VAS (mean difference of -6.2 mm [95% CI, -4.1 to -8.4]; risk difference for achieving at least the MID, 11.0% [95% CI, 6.8% to 15.2%]; high certainty; **Figure 2-2; Figure 2-4A; eTable 2-4**).

Cough-specific quality of life

Eight RCTs including 2651 patients reported cough-specific quality of life.^{12,19,40,42,43,45} The dose-response model suggested that, compared to placebo, use of gefapixant 45 mg twice daily resulted in a mean increase of 1 point (95% CI, 0.7 to 1.4) on the LCQ measuring cough-specific

quality of life (risk difference for achieving at least the MID, 9.2% [95% CI, 5.6% to 12.8%]; moderate certainty; **Figure 2-2; Figure 2-4B; eTable 2-4**).

Treatment-related AEs

Five RCTs including 2580 patients reported treatment-related AEs.^{19,40,42} The dose-response model demonstrated that, compared to placebo, use of gefapixant 45 mg twice daily resulted in more treatment-related AEs (RR, 2.7 [95% CI, 1.7 to 4.4]; moderate certainty). Treatment-related AEs were lower with gefapixant 15 mg twice daily, but were still increased compared with placebo (RR 1.4 [95% CI, 1.2 to 1.6]; moderate certainty; **Figure 2-2; eFigure 2-2**).

Taste-related AEs

Nine RCTs including 2974 patients reported taste-related AEs.^{12,19,39,40,42,43,45} The dose-response model suggested that, compared to placebo, gefapixant (45 mg twice daily) caused a significant increase in taste-related AEs (RR, 9.0 [95% CI, 6.5 to 12.6]; high certainty), whereas at 15 mg twice daily, gefapixant caused a smaller increase (RR, 2.5 [95% CI, 2.2 to 2.9]; high certainty; **Figure 2-2; Figure 2-4C**). To explore the impact of including two unpublished RCTs,^{44,46} we included these trials in a sensitivity analysis, which found similar results (**eTable 2-5**).

AEs leading to discontinuation

Nine RCTs including 2974 patients reported AEs leading to discontinuation.^{12,19,39,40,42,45} Modelling of the dose-response relationship found significant nonlinearity between gefapixant

dose and AEs leading to discontinuation. The nonlinear model suggested that, compared to placebo, gefapixant (45 mg twice daily) caused an important increase in AEs leading to discontinuation (RR, 4.3 [95% CI, 3.2 to 5.8]; moderate certainty), and that gefapixant (15 mg twice daily) caused a small increase (RR, 1.9 [95% CI, 1.6 to 2.2]; high certainty; **Figure 2-2; Figure 2-4D**). A sensitivity analysis including two unpublished RCTs^{44,46} found similar results (**eTable 2-5**).

Discussion

Compared to placebo, gefapixant (45 mg twice daily) resulted in improvements in cough frequency, severity, and quality of life that were less than the MID – thresholds for patient-importance. Gefapixant at this dose increases treatment-related AEs by an absolute 32% and taste-related AEs by 35% – frequencies greater than the thresholds our patient partners considered important. At 60 mg twice daily, gefapixant caused significant reductions in cough frequency, but high certainty evidence suggests that this dose not only increased treatment-related and taste-related AEs, but also increased AEs that led to discontinuation of gefapixant.

Because reporting of average effects rests on an assumption that all patients experience similar benefit, the risk differences were modelled for achieving at least the MID for gefapixant at 45 mg twice daily. For awake cough frequency, compared to placebo, only 6.9% more patients receiving gefapixant would achieve a 20% change from baseline. However, greater risk differences were found for achieving at least a 30 mm reduction on the 100-mm cough severity VAS (11.0%) and a 1.3-point increase on the LCQ (9.2%). This modelling has statistical flaws including reduced power for statistical tests and failure to discern variation in treatment effects from random error;⁴⁷ nevertheless, some may consider these proportions benefiting.

Although this study focused on the effects of gefapixant compared with placebo, substantial improvements in cough were found with administration of placebo in these studies. Among patients who received placebo, awake cough frequency improved by 54.8%, cough severity VAS decreased by 24.2 mm, and cough-specific quality of life increased by 3.0 points on the LCQ. The reasons for such large placebo responses, and whether placebo effects occur in clinical practice, remain unclear. Researchers have speculated that responses to placebo might occur due to changes in expectation among trial participants; investigator enthusiasm influencing patient expectation; natural disease progression; regression to the mean; activation of the Hawthorne Effect among trial participants who receive regular observation;⁴⁸ and/or re-activation of descending inhibitory control neurons by release of endogenous opioids.⁴⁹⁻⁵¹ Future studies should better understand the reasons for such large placebo responses.

The results of this study align with the largest trials¹⁹ evaluating gefapixant for refractory or unexplained chronic cough. At 12 weeks, COUGH-1 reported that gefapixant (45 mg twice daily) led to a 18.5% reduction (95% CI, 0.9% to 32.9%) in 24-hour cough frequency compared to placebo, while COUGH-2 reported that, at 24 weeks, gefapixant (45 mg twice daily) led to a 14.6% reduction (95% CI, 1.4% to 26.1%).¹⁹ Similar effect sizes were found, but with greater precision, for gefapixant at this dose (16.0% reduction [95% CI, 9.4% to 22.0%]). Findings of a dose-dependent increase in the risk for AEs, particularly taste-related, relate to studies that document unselective blocking of P2X3 and P2X2/3 receptors by gefapixant.^{12,19} Inhibition of P2X2/3 heterotrimeric receptors on taste buds may lead to taste disturbances including ageusia, hypogeusia, and dysgeusia. One recent study reassures, however, that taste-related AEs resolve, with 25% of patients having resolution of all taste AEs while taking gefapixant, 63% experiencing

resolution after stopping therapy, and 8% having resolution of ≥ 1 taste AE before and after treatment.⁵²

Implications for practice and research

Future clinical trials including both placebo and untreated controls should discern what proportion of the placebo response in these trials relates to true placebo effects and/or non-specific factors (i.e., natural course of disease, regression to the mean).

As current therapies for refractory or unexplained chronic cough pose substantial harms and have only low-quality evidence to support its benefits, gefapixant, despite its limited effectiveness, may still prove superior to these treatments. If such is the case, gefapixant may provide an option for patients who have tried and failed all other therapies for identifiable causes. The small benefits of gefapixant and limitations of existing therapies underscore the urgent need for research to identify interventions with greater impact.

Strengths

This study has several strengths. By treating dose as a continuous variable, the study avoided misleading aggregation of treatment effects across studies that evaluated different doses. A comprehensive search of databases, regulatory sites, and conference proceedings mitigated the risk of publication bias. To further reduce bias, two reviewers independently screened studies, abstracted data, and performed risk of bias assessments. Using the GRADE approach, the certainty in whether patients would consider the effects of gefapixant across doses and outcomes as important was highlighted, thus providing possible insights regarding how patients are likely to experience the trade-off between its benefits and harms.

Limitations

This study has several limitations. First, it is limited by the dose range for which credible inferences can be drawn. Due to fewer trials examining doses beyond 60 mg twice daily, the study's models yielded less precise results at higher doses. Second, studies excluded current smokers or ex-smokers with >20 pack-year history. It remains unclear whether gefapixant has any role in current smokers or those with chronic obstructive pulmonary disease. Third, although trials recruited patients who had chronic cough refractory to at least two months of stable guideline-suggested therapy, lack of reporting regarding objective confirmation of diagnosis (i.e., asthma reversibility, bronchial challenges), assessment of compliance with prior treatment trials, and/or independent adjudication that investigators followed the American College of Chest Physicians⁷ or European Respiratory Society⁶ guidelines reduced certainty about whether patients received adequate workup before entering the trials. Fourth, the modelling of risk differences for achieving at least the MID assumed similar standard deviations of the outcome measurements in the treatment and control groups, and that change from baseline scores in both groups are normally distributed. There remains a possibility that these assumptions were not met. Finally, responder analyses have statistical limitations, a crucial one being that they fail to discern variation in treatment effects from random error.⁴⁷ Strong inferences about patients who potentially benefit from gefapixant solely based on the responder analyses are cautioned against.

Conclusions

Compared with placebo, gefapixant 45 mg orally twice daily led to modest improvements in cough frequency, cough severity, and cough-specific quality of life but increased taste-related adverse events.

Author contributions:

EK, GHG, and IS conceived the study design. EK developed the search strategy. EK, MP, ND, and MW screened studies. EK and MP extracted the data and performed risk of bias assessments. EK performed the statistical analysis. EK and IS assessed the certainty of the evidence. EK, DKC, DZ, PMOB, GHG, and IS interpreted the data. EK wrote the first draft of the manuscript, with considerable revision from DKC, PMOB, GHG, and IS. All authors critically reviewed and approved the manuscript.

Conflicts of interest: EK has received consulting fees from Respiplus outside of the submitted work. ND is funded by the Canadian Asthma, Allergy and Immunology Foundation Type II Inflammation award supported by Sanofi Genzyme, and the Canadian Institute of Health Research (CIHR) – Canadian Lung Foundation (CLA) Fellowship award, and reports personal fees from AstraZeneca outside of the submitted work. PMOB reports receiving research grants from AstraZeneca, Novartis, Medimmune, Biohaven, Merck, and Bayer outside of the submitted work, and has received personal fees for consulting or speaking from AstraZeneca, GSK, Medimmune, Chiesi, Menarini and Covis. IS is supported by the E.J. Moran Campbell Early Career Award, McMaster University and reports grants from Merck, GSK, and MITACS outside of the submitted work, and speaker and/or consulting fees from Merck, GSK, AstraZeneca, Roche, Genentech and Respiplus. MP, MW, DZ, DKC, and GHG report no conflicts of interest.

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Data sharing: The data that support the study findings are available on Open Science Framework (<https://osf.io/c2msz/>).

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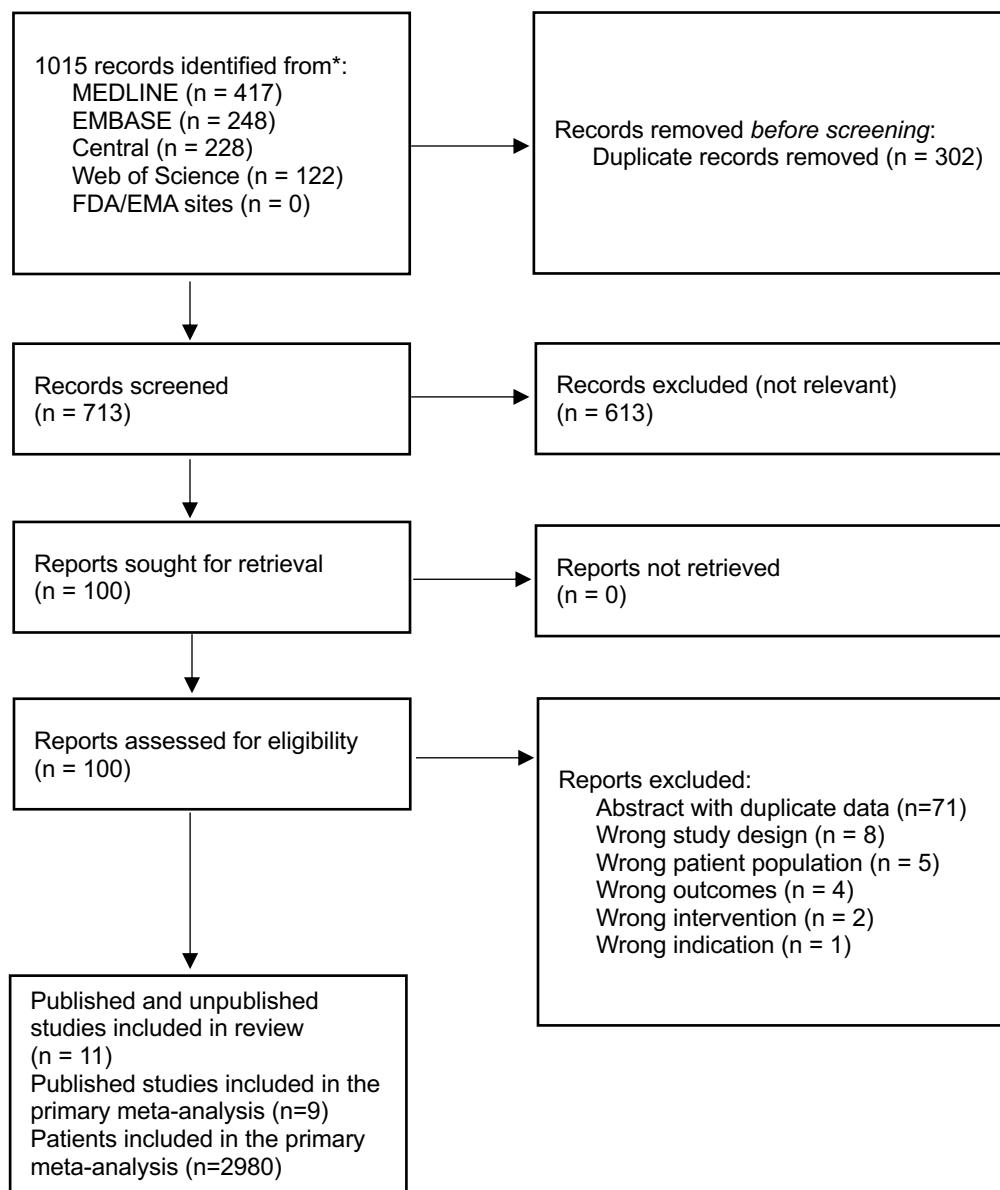


Figure 2-1: Literature search flow diagram in a study of gefapixant for chronic cough

	No. of studies	No. of patients	Baseline risk ^a	15 mg twice daily	30 mg twice daily	45 mg twice daily	60 mg twice daily
24-hour cough frequency, % reduction (95% CI)	6	2472	49.7%	5.6% (3.3% to 8.0%)	11.0% (6.4% to 15.3%)	16.0% (9.4% to 22.0%)	20.7% (12.5% to 28.3%)
Awake cough frequency, % reduction (95% CI)	3	2145	54.8%	6.2% (3.7% to 8.7%)	12.1% (7.2% to 16.7%)	17.6% (10.6% to 24.0%)	22.7% (13.9% to 30.6%)
Sleep cough frequency, % reduction (95% CI)	4	541	22.7%	13.1% (-44.8% to 47.8%) ^b			
Cough severity on the 100 mm VAS, ^c mean difference (95% CI)	4	2292	-24.2 mm	-2.1 mm (-1.4 to -2.8 mm)	-4.2 mm (-2.7 to -5.6 mm)	-6.2 mm (-4.1 to -8.4 mm)	-8.3 mm (-5.4 to -11.2 mm)
Cough-specific quality of life on the LCQ, ^d mean difference (95% CI)	8	2651	3.0 points	0.5 points (0.3 to 0.7 points)	0.8 points (0.5 to 1.2 points)	1.0 points (0.7 to 1.4 points)	1.1 points (0.7 to 1.5 points)
Treatment related adverse events, absolute risk difference per 100 patients (95% CI)	5	2580	19 per 100	8 more (4 to 12 more)	18 more (8 to 32 more)	32 more (13 to 64 more)	53 more (19 to 100 more)
Taste-related adverse events, ^e absolute risk difference per 100 patients (95% CI)	9	2974	4 per 100	6 more (5 to 8 more)	17 more (13 to 24 more)	32 more (22 to 46 more)	47 more (31 to 63 more)
Adverse events leading to discontinuation, absolute risk difference per 100 patients (95% CI)	9	2974	4 per 100	3 more (2 to 5 more)	8 more (6 to 12 more)	13 more (9 to 19 more)	17 more (11 to 26 more)

^a The expected risk or change from baseline with placebo.

^b We found no evidence of a dose-response relationship for sleep cough frequency. Estimate is based on a pairwise meta-analysis treating all doses as having the same effect.

^c Cough severity visual analogue scale (VAS); higher is worse; score range, 0 (no cough) to 100 mm (worst possible cough); MID, 30 mm.

^d Leicester Cough Questionnaire (LCQ); higher is better; score range, 3 (maximal impairment) to 21 (no impairment); MID, 1.3 points.

^e Taste-related adverse events include ageusia, dysgeusia, and/or hypogeusia.

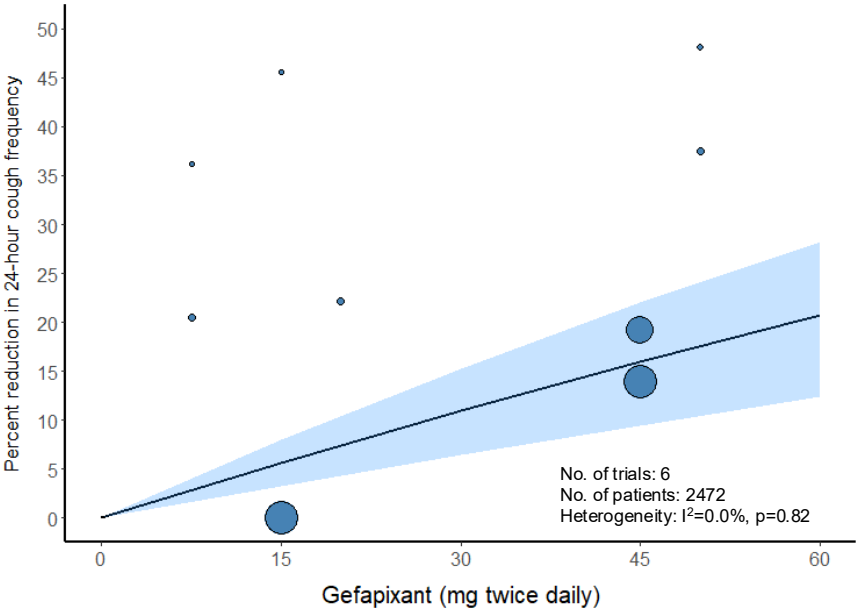
Legend

	Important benefit	Not importantly different	Important harm
High certainty			
Moderate certainty			
Low certainty			
Very low certainty			

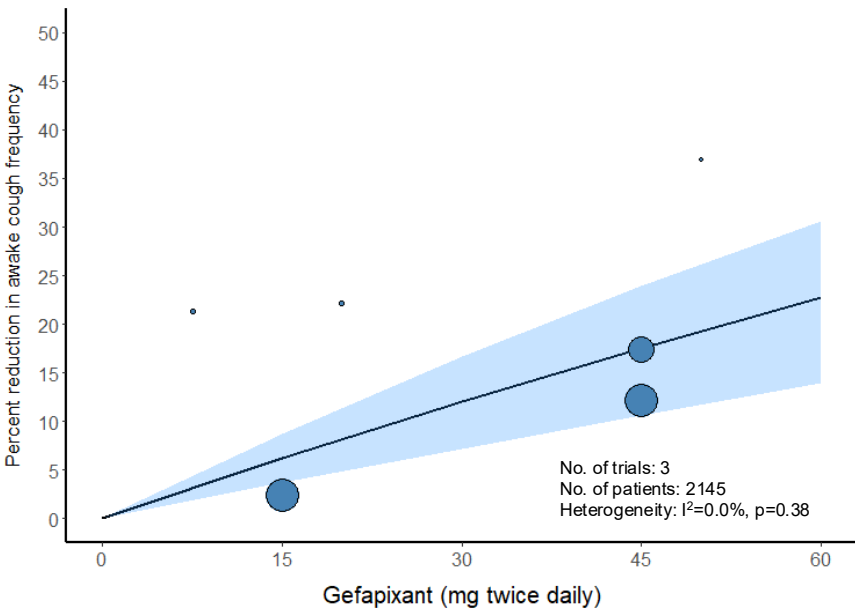
Figure 2-2: Estimated effects of gefapixant by dose compared to placebo estimated by a study-level meta-analysis

We list model estimates at clinically-relevant doses from 0 to 60 mg twice daily at equal intervals (every 15 mg twice daily). Cells show effect estimates and 95% CIs in parentheses. Green indicates benefit whereas red indicates harm. The shading corresponds to the GRADE certainty rating in whether patients would perceive effects to be important (i.e. greater than the MID) or not importantly different (less than the MID). We considered MIDs as a 20% reduction in cough frequency, a 30-mm reduction on the 100-mm cough severity VAS, a 1.3-point increase on the LCQ, a 15% increase for treatment-related AEs, a 10% increase for AEs leading to discontinuation, and a 10% increase for taste-related AEs. Outcomes are ordered by the frequency with which studies consider the outcome as a primary, secondary, or safety outcome. **eTable 2-2** reports the GRADE evidence profiles for each outcome and dose.

A Pooled dose-response relationship between gefapixant dose and percent reduction in log-transformed 24-hour cough frequency



B Pooled dose-response relationship between gefapixant dose and percent reduction in log-transformed awake cough frequency



C Pooled mean difference in log-transformed sleep cough frequency among patients with refractory or unexplained chronic cough who received gefapixant versus placebo in 4 randomized clinical trials

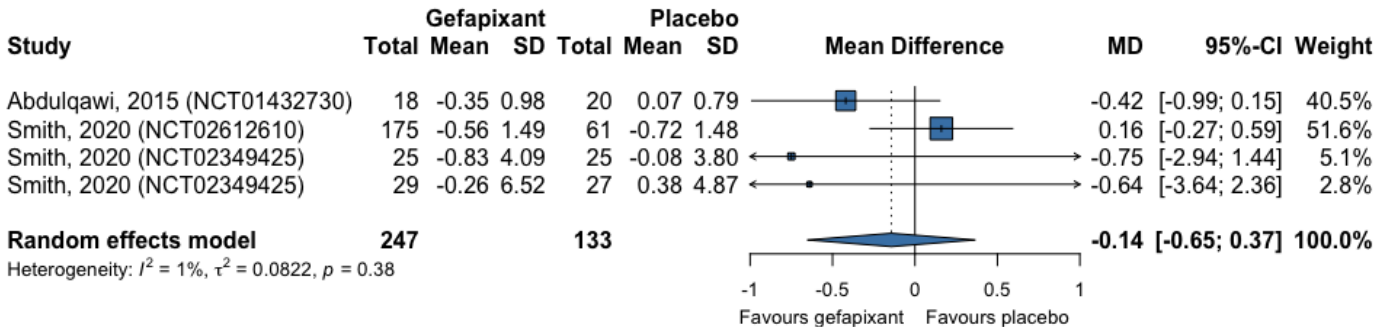


Figure 2-3: Dose-response relationship between gefapixant dose and 24-hour, awake, and sleep cough frequency.

A-B, Mean differences are in comparison to placebo (dose=0). The shaded regions represent 95% CIs. Circles represent mean differences observed in individual trials, and the diameters are proportional to the inverse variance of the study. Trials evaluating different doses may have contributed more than one circle in the graph. **A-B**, Doses are truncated at the largest dose for use in clinical practice (60 mg twice daily). **C**, Effects for sleep cough frequency are represented as mean differences in log-transformed coughs/hr. Percent reduction compared to placebo is calculated as $100*(e^{\text{diff}}-1)$, where diff is the mean difference in log-transformed coughs/hour.

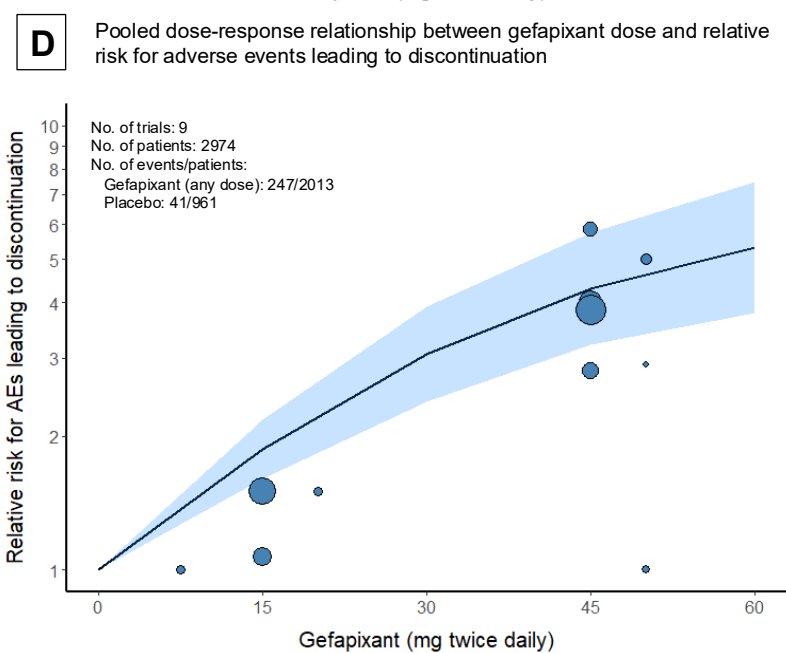
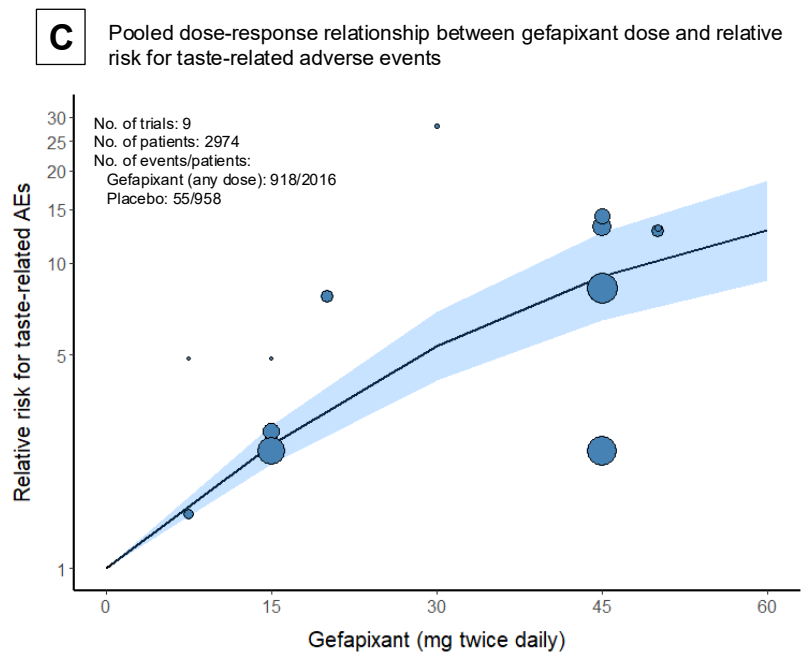
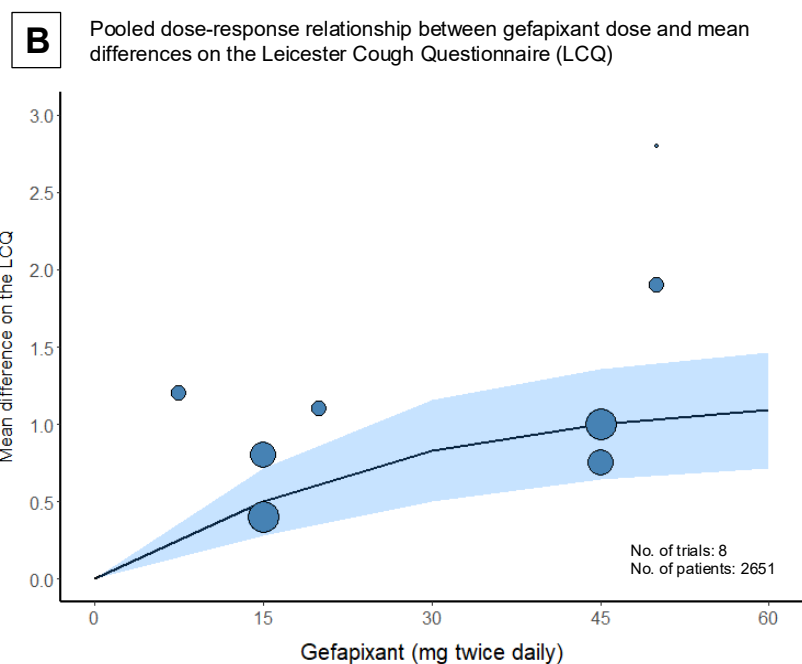
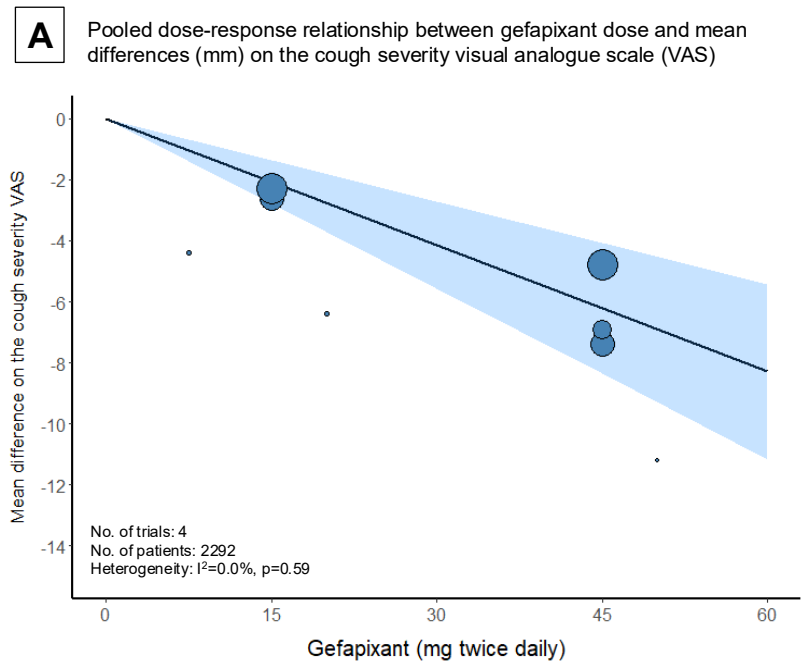


Figure 2-4: Dose-response relationship between gefapixant dose and cough severity, cough-specific quality of life, taste-related adverse events, and adverse events leading to discontinuation

A-D, Mean differences or relative risks are in comparison to placebo (dose=0). The shaded regions represent 95% CIs. Circles represent mean differences or relative risks observed in individual trials, and the diameters are proportional to the inverse variance of the study. Trials evaluating different doses may have contributed more than one circle in the graph. Doses are truncated at the largest dose for use in clinical practice (60 mg twice daily). **B-D**, Outcomes were analyzed using a one-stage dose-response model using restricted cubic splines. We examined heterogeneity through visual inspection of the dose-response plots and the variance partition coefficient (**eFigure 2-1, eFigure 2-3, eFigure 2-4**). **A**, Cough severity visual analogue scale (VAS); higher is worse; score range, 0 (no cough) to 100 mm (worst possible cough); MID, 30 mm. **B**, Leicester Cough Questionnaire (LCQ); higher is better; score range, 3 (maximal impairment) to 21 (no impairment); MID, 1.3 points. **C**, Taste-related adverse events include ageusia, dysgeusia, and/or hypogeusia.

Table 2-1: Characteristics of included studies

Study	Phase	N	Design	Country	Age, years, mean (SD)	Female, %	Duration of cough, year, mean (SD)	Eligibility threshold	Intervention	Outcomes
McGarvey, ¹ 2022; COUGH-2 (NCT03449147)	Phase 3	1314	Parallel	Multinational	58.1 (12.1)	74.9	11.2 (9.8)	Cough severity VAS $\geq$ 40 mm	Gefapixant (15 mg orally BID for 52 weeks); gefapixant (45 mg orally BID for 52 weeks); placebo	24-hour cough frequency, awake cough frequency; cough severity; cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste-related AEs
McGarvey, ¹ 2022; COUGH-1 (NCT03449134)	Phase 3	730	Parallel	Multinational	59.0 (12.6)	74.2	11.6 (9.5)	Cough severity VAS $\geq$ 40 mm	Gefapixant (15 mg orally BID for 52 weeks); gefapixant (45 mg orally BID for 52 weeks); placebo	24-hour cough frequency, awake cough frequency; cough severity; cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste-related AEs
McGarvey, ² 2023 (NCT04193202)	Phase 3b	419	Parallel	Multinational	52.6 (13.7)	64.7	0.6 (0.2)	Cough duration >8 weeks for <12 months	Gefapixant (45 mg orally BID for 12 weeks); placebo	Cough severity; cough-specific quality of life; AEs leading to discontinuation; taste-related AEs
Smith, ³ 2020 (NCT02612610)	Phase 2b	253	Parallel	UK, USA	60.2 (9.9)	76.3	14.5 (11.7)	Cough severity VAS $\geq$ 40 mm	Gefapixant (7.5 mg orally BID for 12 weeks); gefapixant (20 mg orally BID for 12 weeks); gefapixant (50 mg orally BID for 12 weeks); placebo	24-hour cough frequency, awake cough frequency; sleep cough frequency; cough severity; cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste-related AEs

Niimi, ⁴ 2022 (NCT03696108)	Phase 3	169	Parallel	Japan	57.9 (15.0)	62.7	9.2 (10.5)	NA	Gefapixant (15 mg orally BID for 52 weeks); gefapixant (45 mg BID for 52 weeks)	Cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste- related AEs
Smith, ⁵ 2020 (NCT02349425)	Phase 2	30	Crossover	USA	60.2 (11.1)	80.0	13.2 (1.9- 42.8) ^a	Cough severity VAS $\geq$ 40 mm	Gefapixant (7.5/15/30/50 mg orally BID each for 4 days); placebo	24-hour cough frequency, awake cough frequency; sleep cough frequency; cough severity; cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste- related AEs
Smith, ⁵ 2020 (NCT02349425)	Phase 2	29	Crossover	USA	63.2 (7.4)	86.2	15.4 (1.4- 55.3) ^a	Cough severity VAS $\geq$ 40 mm	Gefapixant (50/100/150/2 00 mg orally BID each for 4 days); placebo	24-hour cough frequency, awake cough frequency; sleep cough frequency; cough severity; cough-specific quality of life; treatment-related AEs; AEs leading to discontinuation; taste- related AEs
Abdulqawi, ⁶ 2015 (NCT01432730)	Phase 2	24	Crossover	UK	54.5 (11.1)	75.0	9.0 (3-25) ^b	NA	Gefapixant (600 mg orally BID for 2 weeks); placebo	24-hour cough frequency; awake cough frequency; sleep cough frequency; cough severity; cough-specific quality of life; AEs leading to discontinuation; taste- related AEs
Morice, ⁷ 2019 (NCT02476890)	Phase 2	12	Crossover	UK	61.1 (8.7)	87.5	14.6 (9.9)	HARQ score $>$ 20	Gefapixant (50 mg orally BID for 1 day); placebo	24-hour cough frequency; cough severity; AEs leading to

										discontinuation; taste-related AEs
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Abbreviations: HARQ, Hull Airway Reflux Questionnaire; AEs, adverse events; NR, not reported.

^a Only reported median (range).

^b Only reported median (IQR).

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6. Abdulqawi R, Dockry R, Holt K, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015; **385**(9974): 1198-205.
7. Morice AH, Kitt MM, Ford AP, et al. The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. *European Respiratory Journal* 2019; **54**(1): 1900439.

Supplemental Online Content

Kum E, Patel M, Diab N, Wahab M, Zeraatkar D, Chu DK, O'Byrne PM, Guyatt GH, Satia I. Efficacy and tolerability of gefapixant for treatment of refractory or unexplained chronic cough: a systematic review and dose-response meta-analysis.

eMethods 2-1: Search strategy

eMethods 2-2: Study characteristics and baseline patient information collected from trials

eTable 2-1: Risk of bias in included studies

eTable 2-2: GRADE evidence profile

eTable 2-3: Goodness of fit statistics for all dose-response models

eTable 2-4: Risk differences for achieving a benefit greater than or equal to the MID for gefapixant (45 mg twice daily)

eTable 2-5: Results of the sensitivity analyses excluding unpublished trials

eFigure 2-1: Plot of variance partition coefficient for the meta-analysis between gefapixant dose and cough-specific quality of life

eFigure 2-2: Dose-response model between gefapixant dose and treatment-related adverse events

eFigure 2-3: Plot of variance partition coefficient for the meta-analysis between gefapixant dose and adverse events leading to discontinuation

eFigure 2-4: Plot of variance partition coefficient for the meta-analysis between gefapixant dose and taste-related adverse events

eMethods 2-1: Search strategy

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

- 1 Cough/
- 2 (cough* adj5 (chronic* or persistent* or refractory)).mp.
- 3 1 or 2
- 4 *Antitussive Agents/tu [Therapeutic Use]
- 5 purinergic agents/ or purinergic antagonists/ or purinergic p2 receptor antagonists/ or purinergic p2x receptor antagonists/
- 6 exp receptors, purinergic p2x/ or receptors, purinergic p2x3/
- 7 purinergic.ti.ab.
- 8 purinoceptor.ti.ab.
- 9 P2X3.ti.ab.
- 10 gefapixant.mp.
- 11 Sivopixant.mp.
- 12 Eliapixant.mp.
- 13 AF-219.mp.
- 14 S-600918.mp.
- 15 or/4-14
- 16 3 and 15
- 17 randomized controlled trial.pt.
- 18 controlled clinical trial.pt.
- 19 randomi?ed.ab.
- 20 placebo.ab.
- 21 drug therapy.fs.
- 22 randomly.ab.
- 23 trial.ab.
- 24 groups.ab.
- 25 or/17-24
- 26 exp animals/ not humans.sh.
- 27 25 not 26
- 28 16 and 27

EMBASE (OVID)

Database: Embase <1974 to 2023 July 04>
Search Strategy:

- 1 coughing/ or chronic cough/
- 2 (cough* adj5 (chronic* or persistent* or refractory)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
- 3 1 or 2
- 4 *antitussive agent/dt [Drug Therapy]
- 5 purinergic P2 receptor antagonist/
- 6 purinergic p2x receptor/ or exp purinergic p2 receptor/
- 7 exp purinergic receptor affecting agent/
- 8 purinergic.ti.ab.
- 9 purinoceptor.ti.ab.
- 10 P2X3.ti.ab.
- 11 gefapixant.mp. or gefapixant/

12 sivopixant.mp. or sivopixant/
 13 eliapixant.mp. or eliapixant/
 14 AF-219.mp.
 15 S-600918.mp.
 16 or/4-15
 17 3 and 16
 18 randomized controlled trial/
 19 Controlled clinical study/
 20 random\$.ti,ab.
 21 randomization/
 22 intermethod comparison/
 23 placebo.ti,ab.
 24 (compare or compared or comparison).ti.
 25 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or
 comparing or comparison)).ab.
 26 (open adj label).ti,ab.
 27 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 28 double blind procedure/
 29 parallel group\$1.ti,ab.
 30 (crossover or cross over).ti,ab.
 31 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or
 patient\$1 or subject\$1 or participant\$1)).ti,ab.
 32 (assigned or allocated).ti,ab.
 33 (controlled adj7 (study or design or trial)).ti,ab.
 34 (volunteer or volunteers).ti,ab.
 35 human experiment/
 36 trial.ti.
 37 or/18-36
 38 (random\$ adj sampl\$ adj7 ("cross section\$" or questionnaire\$1 or survey\$ or database\$1)).ti,ab.
 not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
 39 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled
 study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.)
 40 (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab.
 41 (Systematic review not (trial or study)).ti.
 42 (nonrandom\$ not random\$).ti,ab.
 43 "Random field\$".ti,ab.
 44 (random cluster adj3 sampl\$).ti,ab.
 45 (review.ab. and review.pt.) not trial.ti.
 46 "we searched".ab. and (review.ti. or review.pt.)
 47 "update review".ab.
 48 (databases adj4 searched).ab.
 49 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or
 rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or
 marmoset\$1).ti. and animal experiment/
 50 Animal experiment/ not (human experiment/ or human/)
 51 or/38-50
 52 37 not 51
 53 17 and 52

Cochrane Library (Wiley)

ID	Search Hits
#1	MeSH descriptor: [Cough] explode all trees
#2	(cough* near/5 (chronic* or persistent* or refractory))
#3	#1 or #2

#4	MeSH descriptor: [Antitussive Agents] explode all trees and with qualifier(s): [therapeutic use - TU]	
#5	MeSH descriptor: [Purinerbic Agents] explode all trees	
#6	MeSH descriptor: [Purinerbic Antagonists] explode all trees	
#7	MeSH descriptor: [Purinerbic P2 Receptor Antagonists] explode all trees	
#8	MeSH descriptor: [Purinerbic P2X Receptor Antagonists] explode all trees	
#9	MeSH descriptor: [Receptors, Purinerbic P2X] explode all trees	
#10	MeSH descriptor: [Receptors, Purinerbic P2X3] explode all trees	
#11	purinerbic	
#12	purinoceptor	
#13	P2X3	
#14	gefapixant or Sivopixant or Eliapixant or AF-219 or S-600918	
#15	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	1140
#16	#3 and #15	
#17	#16 in Trials	

Web of Science (Clarivate)

3 #1 AND #2 98

2 ALL=(purinerbic or purinoceptor or P2X3 or gefapixant or Sivopixant or Eliapixant or AF-219 or S-600918)

1 TS=((cough* NEAR/5 (chronic* or persistent* or refractory)))

eMethods 2-2: Study characteristics and baseline patient information collected from trials

- Publication status (i.e., peer-reviewed publication, trial registration, abstract)
- Geographic location
- Design (i.e., parallel or crossover)
- Funder (i.e., industry, government, institutional, not-for-profit)
- Age (mean [SD], median [IQR or range])
- Sex (%)
- Smoking history
 - Current (%)
 - Former (%)
 - Never (%)
- Duration of cough (mean [SD], median [IQR or range])
- Comorbid conditions (i.e., asthma, allergic rhinitis, gastroesophageal reflux) (%)
- Eligibility criteria
- Number randomized to each intervention
- Dose
- Frequency, route of administration

eTable 2-1: Risk of bias in included studies

Author (trial registration)	Randomization	Deviation from the intended intervention	Missing outcome data	Measurement of outcome	Selection of the reported results	Period and carryover effects
24-hour cough frequency						
Abdulqawi 2015 (NCT01432730)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Morice 2019 (NCT02476890)	Probably high risk of bias ^a	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Awake cough frequency						
Abdulqawi 2015 (NCT01432730)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sleep cough frequency						
Abdulqawi 2015 (NCT01432730)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	NA

Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Cough severity						
Abdulqawi 2015 (NCT01432730)	Low risk of bias	Low risk of bias	High risk of bias ^b	Low risk of bias	Low risk of bias	Low risk of bias
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Morice 2019 (NCT02476890)	Probably high risk of bias ^a	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
McGarvey 2023 (NCT04193202)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Cough-specific quality of life						
Abdulqawi 2015 (NCT01432730)	Low risk of bias	Low risk of bias	High risk of bias ^b	Low risk of bias	Low risk of bias	Low risk of bias
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Niimi 2022 (NCT03696108)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2023 (NCT04193202)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Treatment-related adverse events						

McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	NA
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias
Niimi 2022 (NCT03696108)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Adverse events leading to discontinuation						
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	NA
Morice 2019 (NCT02476890)	Probably high risk of bias ^a	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias
Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias
Niimi 2022 (NCT03696108)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2023 (NCT04193202)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Taste-related adverse events						
McGarvey 2022; COUGH-1 (NCT03449134)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
McGarvey 2022; COUGH-2 (NCT03449147)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Smith 2020 (NCT02612610)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA
Morice 2019 (NCT02476890)	Probably high risk of bias ^a	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Probably low risk of bias
Smith 2020; Study 1 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias

Smith 2020; Study 2 (NCT02349425)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	Low risk of bias
Niimi 2022 (NCT03696108)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Probably low risk of bias	NA
McGarvey 2023 (NCT04193202)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	NA

^a Did not adequately describe concealed allocation.

^b Had $\geq 20\%$ missing outcome data that could lead to bias.

eTable 2-2: GRADE evidence profile

24-hour cough frequency												
Number of studies	Number of patients	Dose (mg BID)	Mean difference versus placebo in log-transformed coughs/hour (95% CI)	Absolute percent reduction versus placebo (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
6	2472	15	-0.058 (95% CI: -0.083 to -0.033)	49.69% (mean)	55.32% (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) has a small effect on 24-hour cough frequency (5.63% reduction [95% CI: 3.25% to 7.96%]; high certainty).
				5.63% (95% CI: 3.25% to 7.96%)								
6	2472	30	-0.116 (95% CI: -0.166 to -0.066)	49.69% (mean)	60.64% (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (30 mg BID) has a small effect on 24-hour cough frequency (10.95% reduction [95% CI: 6.39% to 15.30%]; high certainty).
				10.95% (95% CI: 6.39% to 15.30%)								
6	2472	45	-0.174 (95% CI: -0.249 to -0.099)	49.69% (mean)	65.66% (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (45 mg BID) probably has a small effect on 24-hour cough frequency (15.97% reduction [95% CI: 9.43% to 22.04%]; moderate certainty).
				15.97% (95% CI: 9.43% to 22.04%)								
6	2472	60	-0.232 (95% CI: -0.332 to -0.133)	49.69% (mean)	70.40% (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (60 mg BID) probably causes an important reduction in 24-hour cough frequency (20.71% reduction [95% CI: 12.45% to 28.25%]; moderate certainty).
				20.71% (95% CI: 12.45% to 28.25%)								
Awake cough frequency												
Number of studies	Number of patients	Dose (mg BID)	Mean difference versus placebo in log-transformed coughs/hour (95% CI)	Absolute percent reduction versus placebo (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							

3	2145	15	-0.064 (95% CI: -0.091 to -0.037)	54.78% (mean)	61.01% (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) has a small effect on awake cough frequency (6.23% reduction [95% CI: 3.67% to 8.73%]; high certainty).
		6.23% (95% CI: 3.67% to 8.73%)										
3	2145	30	-0.129 (95% CI: -0.183 to -0.075)	54.78% (mean)	66.86% (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (30 mg BID) has a small effect on awake cough frequency (12.08% reduction [95% CI: 7.21% to 16.70%]; high certainty).
		12.08% (95% CI: 7.21% to 16.70%)										
3	2145	45	-0.193 (95% CI: -0.274 to -0.112)	54.78% (mean)	72.34% (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (45 mg BID) probably has a small effect on awake cough frequency (17.56% reduction [95% CI: 10.61% to 23.98%]; moderate certainty).
		17.56% (95% CI: 10.61% to 23.98%)										
3	2145	60	-0.258 (95% CI: -0.366 to -0.150)	54.78% (mean)	77.48% (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (60 mg BID) probably causes an important reduction in awake cough frequency (22.70% reduction [95% CI: 13.90% to 30.62%]; moderate certainty).
		22.70% (95% CI: 13.90% to 30.62%)										
Sleep cough frequency												
Number of studies	Number of patients	Dose (mg BID)	Mean difference versus placebo in log-transformed coughs/hour (95% CI)	Absolute percent reduction versus placebo (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
4	380		-0.14 (95% CI: -0.65 to 0.37)	22.70% (mean)	35.76% (mean)	Not serious	Not serious	Not serious	Very serious	Not serious	Low	Compared to placebo, gefapixant may not importantly reduce sleep cough frequency (13.06% reduction [95% CI: 47.80% reduction to 44.77% increase]; low certainty).
		13.06% (95% CI: -44.77% to 47.80%)										
Cough severity												
Number of studies	Number of patients	Dose (mg BID)		Mean difference on the 100-mm VAS (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							

4	2292	15		-24.17 mm (mean)	-26.24 mm (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) has a small effect on cough severity (-2.07 mm on a 100-mm VAS [95% CI: -2.79 to -1.36 mm]; high certainty).
				-2.07 mm (95% CI: -2.79 to -1.36 mm)								
4	2292	30		-24.17 mm (mean)	-28.32 mm (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (30 mg BID) has a small effect on cough severity (-4.15 mm on a 100-mm VAS [95% CI: -5.58 to -2.71 mm]; high certainty).
				-4.15 mm (95% CI: -5.58 to -2.71 mm)								
4	2292	45		-24.17 mm (mean)	-30.39 mm (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (45 mg BID) has a small effect on cough severity (-6.22 mm on a 100-mm VAS [95% CI: -8.37 to -4.07 mm]; high certainty).
				-6.22 mm (95% CI: -8.37 to -4.07 mm)								
4	2292	60		-24.17 mm (mean)	-32.46 mm (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (60 mg BID) has a small effect on cough severity (-8.29 mm on a 100-mm VAS [95% CI: -11.15 to -5.43 mm]; high certainty).
				-8.29 mm (95% CI: -11.15 to -5.43 mm)								
Cough-specific quality of life												
Number of studies	Number of patients	Dose (mg BID)		Mean difference on the LCQ (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
8	2651	15		2.99 points (mean)	3.49 points (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) has a small effect on cough-specific quality of life (0.50-point increase on the LCQ [95% CI: 0.28 to 0.72 points]; high certainty).
				0.50 points (95% CI: 0.28 to 0.72 points)								
8	2651	30		2.99 points (mean)	3.82 points (mean)	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (30 mg BID) has a small effect on cough-specific quality of life (0.85-point increase on the LCQ [95% CI: 0.50 to 1.16 points]; high certainty).
				0.83 points (95% CI: 0.50 to 1.16 points)								
8	2651	45		2.99 points (mean)	3.99 points (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (45 mg BID) probably has a small effect on cough-specific quality of life

				1.00 points (95% CI: 0.65 to 1.36 points)								(1.00-point increase on the LCQ [95% CI: 0.65 to 1.36 points]; moderate certainty).
8	2651	60		2.99 points (mean)	4.08 points (mean)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (60 mg BID) probably has a small effect on cough-specific quality of life (1.09-point increase on the LCQ [95% CI: 0.72 to 1.47 points]; moderate certainty).
				1.09 points (95% CI: 0.72 to 1.47 points)								
Treatment-related adverse events												
Number of studies	Number of patients	Dose (mg BID)	Relative risk (95% CI)	Absolute risk difference (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
5	2580	15	1.40 (95% CI: 1.19 to 1.64)	19 per 100	27 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) causes a small increase in treatment-related adverse events (8 more per 100 patients [95% CI: 4 more to 12 more]; moderate certainty).
				8 more per 100 patients (95% CI: 4 more to 12 more)								
5	2580	30	1.95 (95% CI: 1.42 to 2.68)	19 per 100	37 per 100	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (30 mg BID) probably causes an important increase in treatment-related adverse events (18 more per 100 patients [95% CI: 8 more to 32 more]; moderate certainty).
				18 more per 100 patients (95% CI: 8 more to 32 more)								
5	2580	45	2.72 (95% CI: 1.69 to 4.39)	19 per 100	51 per 100	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (45 mg BID) probably causes an important increase in treatment-related adverse events (32 more per 100 patients [95% CI: 13 more to 64 more]; high certainty).
				32 more per 100 patients (95% CI: 13 more to 64 more)								
5	2580	60	3.81 (95% CI: 2.02 to 7.18)	19 per 100	72 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (60 mg BID) importantly increases treatment-related adverse events (53 more per 100 patients [95% CI: 19 more to 100 more]; high certainty).
				53 more per 100 patients (95% CI: 19 more to 100 more)								
Adverse events leading to discontinuation												

Number of studies	Number of patients	Dose (mg BID)	Relative risk (95% CI)	Absolute risk difference (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
9	2974	15	1.87 (95% CI: 1.61 to 2.18)	4 per 100	7 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) causes a small increase in adverse events leading to discontinuation (3 more per 100 patients [95% CI: 2 more to 5 more]).
				3 more per 100 patients (95% CI: 2 more to 5 more)								
9	2974	30	3.06 (95% CI: 2.40 to 3.91)	4 per 100	12 per 100	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (30 mg BID) probably causes a small increase in adverse events leading to discontinuation (8 more per 100 patients [95% CI: 6 more to 12 more]).
				8 more per 100 patients (95% CI: 6 more to 12 more)								
9	2974	45	4.30 (95% CI: 3.22 to 5.75)	4 per 100	17 per 100	Not serious	Not serious	Not serious	Serious	Not serious	Moderate	Compared to placebo, gefapixant (45 mg BID) probably causes an important increase in adverse events leading to discontinuation (13 more per 100 patients [95% CI: 9 more to 19 more]).
				13 more per 100 patients (95% CI: 9 more to 19 more)								
9	2974	60	5.32 (95% CI: 3.79 to 7.49)	4 per 100	21 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (60 mg BID) importantly increases adverse events leading to discontinuation (17 more per 100 patients [95% CI: 11 more to 26 more]).
				17 more per 100 patients (95% CI: 11 more to 26 more)								
Taste-related adverse events												
Number of studies	Number of patients	Dose (mg BID)	Relative risk (95% CI)	Absolute risk difference (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Plain language summary
				Placebo	Gefapixant							
9	2974	15	2.54 (95% CI: 2.20 to 2.94)	4 per 100	10 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (15 mg BID) causes a small increase in taste-related adverse events (6 more per 100 patients [95% CI: 5 more to 8 more]).
				6 more per 100 patients (95% CI: 5 more to 8 more)								
9	2974	30	5.35 (95% CI: 4.13 to 6.92)	4 per 100	21 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (30 mg BID) causes an important increase in taste-related adverse events (17

				17 more per 100 patients (95% CI: 13 more to 24 more)								more per 100 patients [95% CI: 13 more to 24 more]).
9	2974	45	9.04 (95% CI: 6.49 to 12.61)	4 per 100	36 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (45 mg BID) causes an important increase in taste-related adverse events (32 more per 100 patients [95% CI: 22 more to 46 more]).
				32 more per 100 patients (95% CI: 22 more to 46 more)								
9	2974	60	12.78 (95% CI 8.75 to 16.66)	4 per 100	51 per 100	Not serious	Not serious	Not serious	Not serious	Not serious	High	Compared to placebo, gefapixant (60 mg BID) causes an important increase in taste-related adverse events (47 more per 100 patients [95% CI: 31 more to 63 more]).
				47 more per 100 patients (95% CI: 31 more to 63 more)								

eTable 2-3: Goodness of fit statistics for all dose-response models

Outcome	Linear					Nonlinear					
	Deviance	df	p value	r ²	Adjusted r ²	Deviance	df	p value	r ²	Adjusted r ²	pnonlinearity
24-hour cough frequency	6.749	15	0.964	0.756	0.739	6.452	14	0.954	0.766	0.733	0.59
Awake cough frequency	58.043	15	0.000	0.413	0.374	28.951	14	0.011	0.707	0.666	0.0032
Parallel trials only	5.450	6	0.488	0.800	0.767	4.240	5	0.515	0.845	0.783	0.27
Cough severity	48.377	17	0.000	0.527	0.500	23.710	16	0.096	0.768	0.739	0.0074
Parallel trials only	2.701	7	0.911	0.923	0.912	2.378	6	0.882	0.932	0.909	0.57
Cough-specific quality of life	36.137	11	0.000	0.383	0.327	15.814	10	0.105	0.730	0.676	0.0063
Treatment-related adverse events	144.127	14	0.000	0.644	0.618	26.915	13	0.013	0.933	0.923	0.55
Adverse events leading to discontinuation	64.448	18	0.000	0.462	0.432	11.823	17	0.811	0.901	0.890	0.000
Taste-related adverse events	289.228	18	0.000	0.486	0.457	26.981	17	0.058	0.952	0.946	0.000

eTable 2-4: Risk differences for achieving a benefit greater than or equal to the MID for gefapixant (45 mg twice daily)

Outcome	Proportion of patients who achieved the MID		Risk difference for achieving the MID, % (95% CI)	Mean difference (95% CI)
	Placebo	Gefapixant (45 mg twice daily)		
24-hour cough frequency	491/779 (63.0%)	1146/1693 (67.7%)	4.7% (0.6% to 8.7%)	16.0% reduction (9.4% to 22.0%)
Awake cough frequency	546/706 (77.3%)	1230/1460 (84.2%)	6.9% (3.3% to 10.5%)	17.6% reduction (10.6% to 24.0%)
Cough severity, measured on the 100-mm VAS	329/828 (39.7%)	742/1464 (50.7%)	11.0% (6.8% to 15.2%)	6.2 mm reduction (4.1 to 8.4 mm reduction)
Cough-specific quality of life, measured on the LCQ	624/915 (68.2%)	1344/1736 (77.4%)	9.2% (5.6% to 12.8%)	1.0 point increase (0.7 to 1.4 point increase)

MIDs included a 20% change in 24-hour and awake cough frequency, 30-mm reduction on the cough severity VAS, and a 1.3-point increase on the LCQ

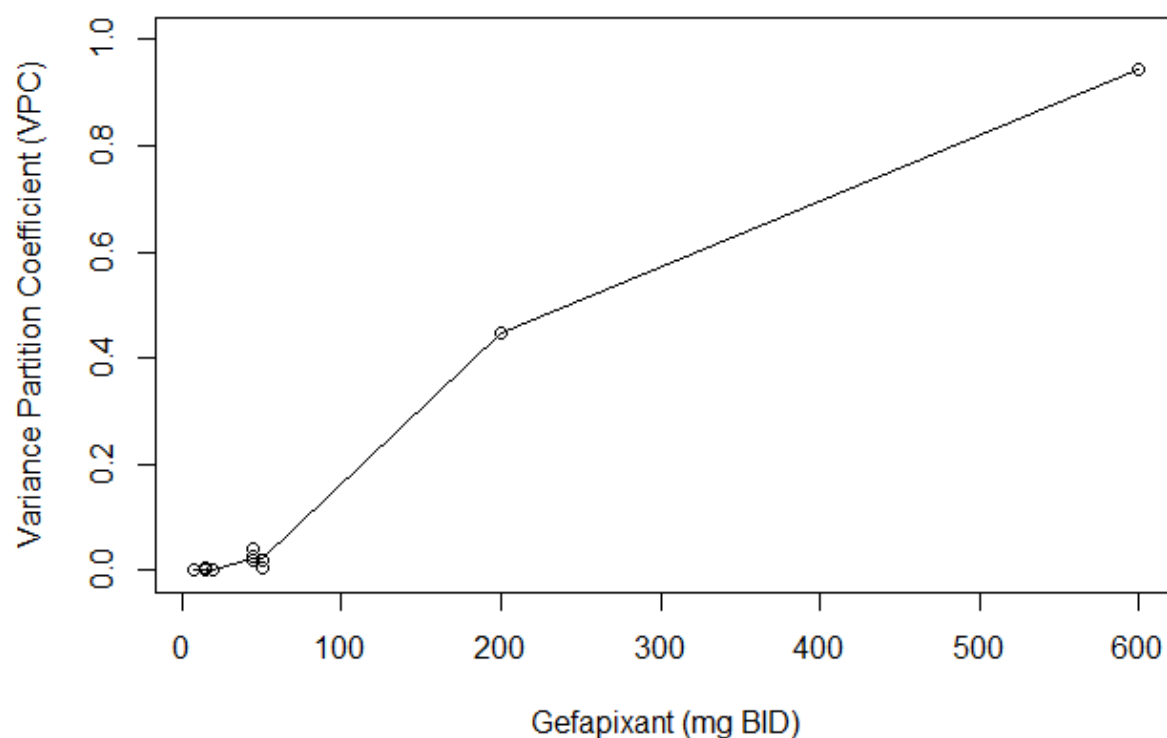
eTable 2-5: Results of sensitivity analyses including 2 unpublished trials

Awake cough frequency	Dose (mg BID)	Primary analysis			Sensitivity analysis		
		Studies	Patients	Absolute percent reduction versus placebo (95% CI)	Studies	Patients	Absolute percent reduction versus placebo (95% CI)
	15	3	2145	6.24% (3.67% to 8.73%)	4	2166	6.29% (3.73% to 8.79%)
	30	3	2145	12.08% (7.21% to 16.70%)	4	2166	12.19% (7.32% to 16.80%)
	45	3	2145	17.56% (10.61% to 24.00%)	4	2166	17.63% (10.77% to 24.04%)
	60	3	2145	22.70% (13.89% to 30.62%)	4	2166	22.81% (14.02% to 30.71%)
Adverse events leading to discontinuation	Dose (mg BID)	Studies	Patients	Absolute risk difference per 100 patients (95% CI)	Studies	Patients	Absolute risk difference per 100 patients (95% CI)
	15	9	2974	3 more (2 more to 5 more)	11	3021	3 more (2 more to 5 more)
	30	9	2974	8 more (6 more to 12 more)	11	3021	8 more (5 more to 12 more)
	45	9	2974	13 more (9 more to 19 more)	11	3021	13 more (8 more to 18 more)
	60	9	2974	17 more (11 more to 26 more)	11	3021	17 more (10 more to 26 more)
Taste-related adverse events	Dose (mg BID)	Studies	Patients	Absolute risk difference per 100 patients (95% CI)	Studies	Patients	Absolute risk difference per 100 patients (95% CI)
	15	9	2974	6 more (5 more to 8 more)	11	3020	7 more (6 more to 9 more)
	30	9	2974	17 more (13 more to 24 more)	11	3020	20 more (15 more to 27 more)
	45	9	2974	32 more (22 more to 46 more)	11	3020	35 more (24 more to 48 more)
	60	9	2974	47 more (31 more to 70 more)	11	3020	44 more (31 more to 64 more)

Two unpublished trials:

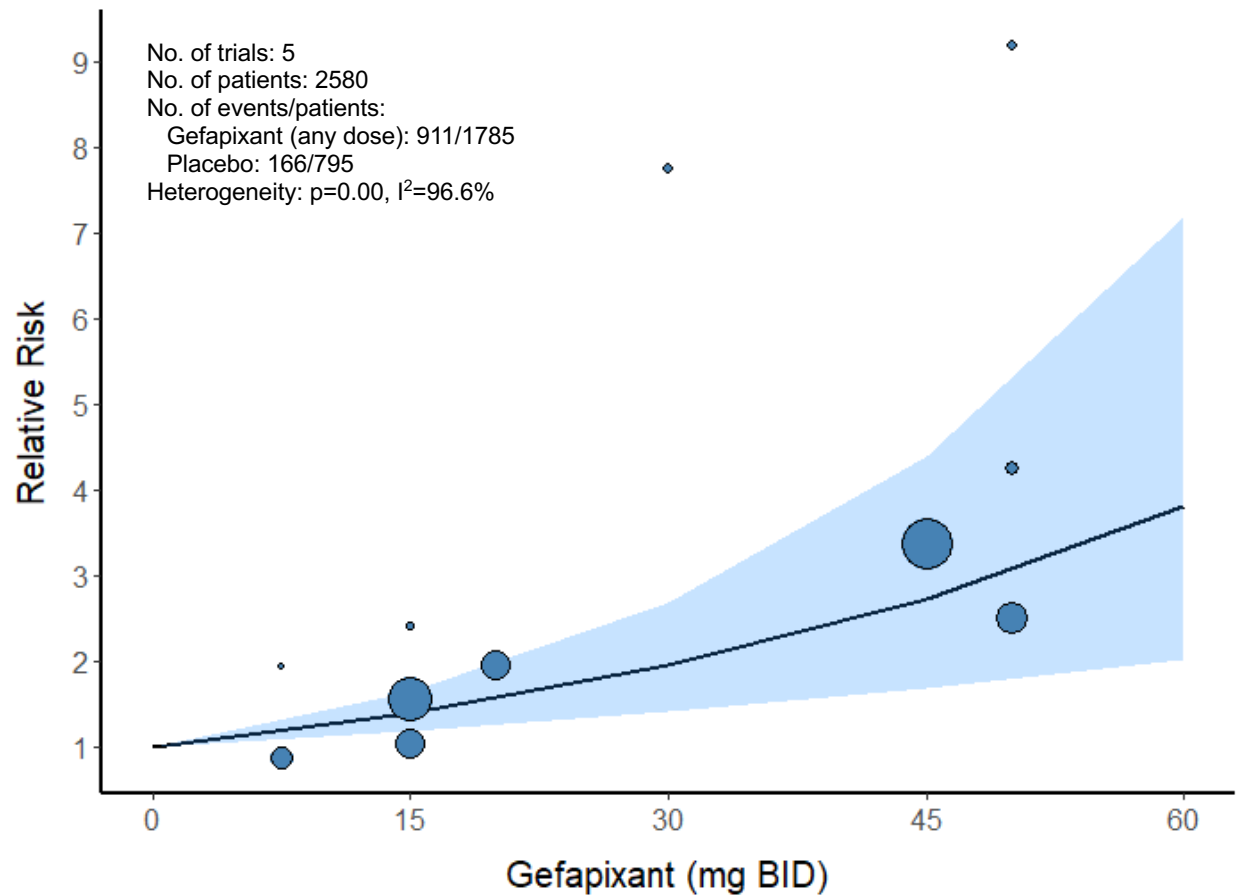
1. Afferent Pharmaceuticals I. An 8-Week Refractory Chronic Cough Study (MK-7264-021). <https://ClinicalTrials.gov/show/NCT02612623>; 2015.
2. Sharp M, LLC D. Study of Gefapixant (MK-7264) in Adult Japanese Participants With Unexplained or Refractory Chronic Cough (MK-7264-033). <https://ClinicalTrials.gov/show/NCT03482713>; 2018.

eFigure 2-1: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and cough-specific quality of life using restricted cubic spline regression



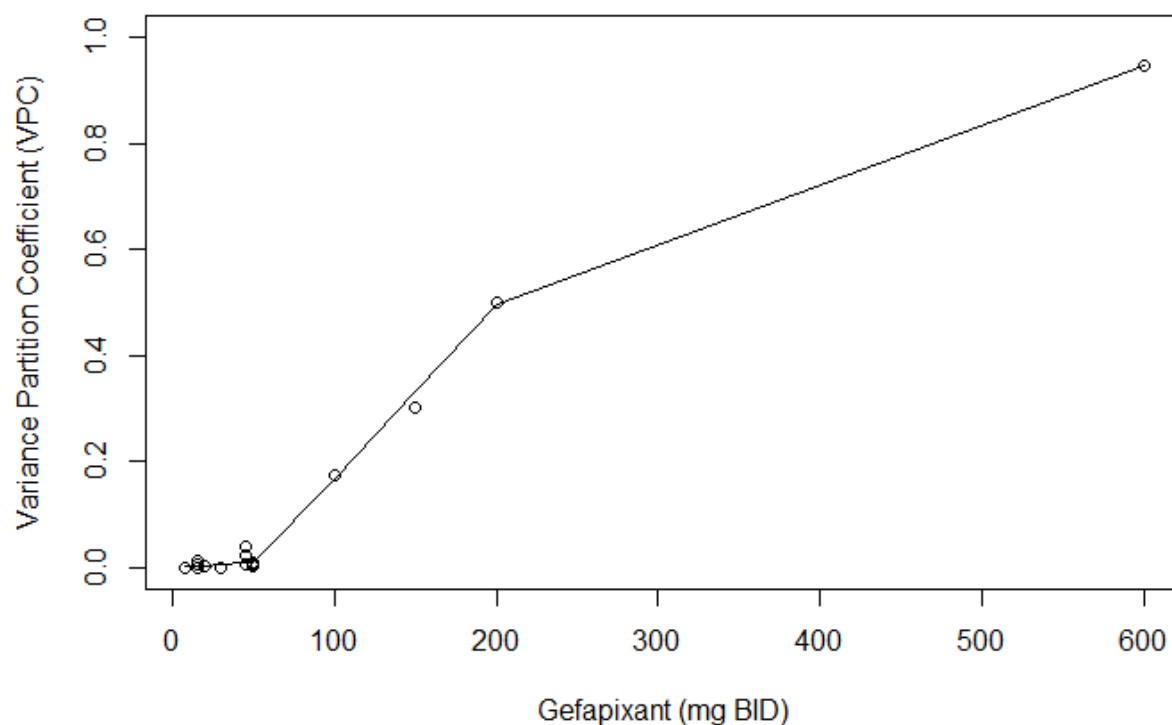
Each circle represents a study; the fitted line represents the LOWESS curve.

eFigure 2-2: Pooled dose-response relationship between gefapixant dose and relative risk for treatment-related adverse events compared to placebo



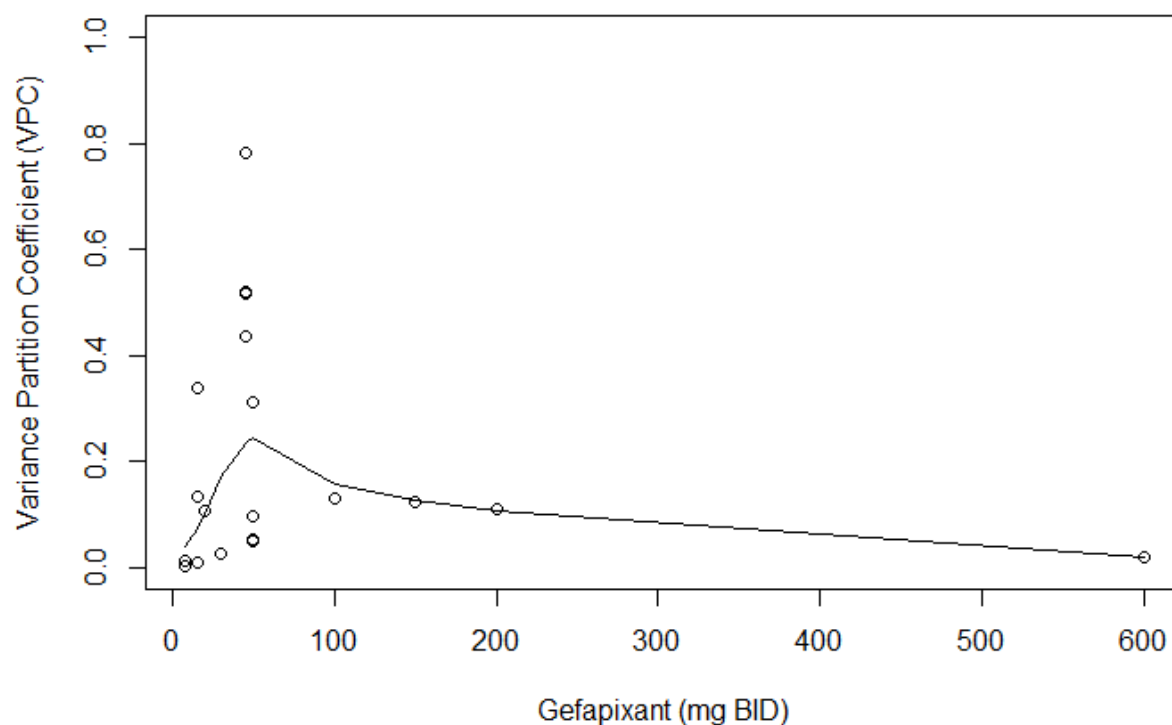
Placebo (dose=0) serves as the reference group. The shaded regions represent 95% CIs. Circles represent relative risks observed in individual trials, and the diameters are proportional to the inverse variance of the study. Trials evaluating different doses may have contributed more than one circle in the graph.

eFigure 2-3: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and adverse events leading to discontinuation using restricted cubic spline regression



Each circle represents a study; the fitted line represents the LOWESS curve.

eFigure 2-4: The variance partition coefficient of each observed dose (non-reference dose in each study) for the meta-analysis between gefapixant dose and taste-related adverse events using restricted cubic spline regression



Each circle represents a study; the fitted line represents the LOWESS curve.

Chapter 3 Placebo Responses in Clinical Trials of Refractory Chronic Cough: Mechanisms, Challenges, and Mitigation Strategies

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Refractory chronic cough (RCC) is a cough that persists for >8 weeks and does not respond to treatment of any underlying cause. Recent randomized trials for RCC have demonstrated substantial placebo responses that have complicated the interpretation of drug treatment effects. This article explores potential mechanisms for the placebo response in RCC, the challenges they present, and potential design solutions to mitigate their impact.

While the terms “placebo response” and “placebo effect” are often used interchangeably, “placebo response” refers to changes among participants receiving placebo during a clinical trial, whereas “placebo effect” refers to the therapeutic effect of receiving a drug that is not caused by its biologically active ingredients. While placebo effects may contribute to the placebo response, other factors can comprise the placebo response (**Figure 3-1**). In RCC, it remains unknown to what extent placebo effects versus other factors underlie the placebo response.

Various environmental and psychosocial factors can elicit a placebo response. One that might contribute to a true placebo effect may be the expectation of treatment benefit activating inhibitory neurons that can suppress coughing.¹ Most patients with RCC have tried and failed multiple therapies. The opportunity to participate in a randomized trial offering a potentially new treatment can elicit hope and expectation. This expectation may cause top-down modulation of the urge-to-cough in the somatosensory cortex.^{1,2} Indeed, neuroimaging studies in healthy individuals show that placebo administration reduces the urge-to-cough sensation during capsaicin inhalation challenge, and this associates with an increase in prefrontal and parietal activity that mediate cough suppression.¹ Expectation of treatment benefit might further generate endogenous opioids, dopamine, and serotonin in the affective and cognitive brain regions that exert descending inhibition of cough in the brainstem.^{3,4} These neurobiological mechanisms might explain true placebo effects occurring in patients with RCC.

Another phenomenon explaining the placebo response may be regression to the mean. Patients with RCC often have day-to-day cough variability.⁵ A study that longitudinally monitored cough frequency over 30 days in patients with chronic cough found that mean daily cough rates varied from 6.5 to 182 coughs per hour, with standard deviations varying from 0.99 to 124.⁵ In trials of RCC that often select patients at the peak of their disease (i.e., those with a baseline 24-hour cough frequency ≥ 25 coughs/hour or a cough severity visual analogue scale score ≥ 40 mm), an apparent improvement might result from values on remeasurement being, on average, closer to individual means even without the effect of treatment. While larger treatment differences in patients with higher baseline cough frequencies may indeed reflect greater treatment responsiveness,⁶ responses could also be influenced by regression to the mean.

A final factor may be the Hawthorne effect – a phenomenon whereby patients modify their behavior under the knowledge that they are being observed.⁷ Patients in a randomized trial may become acutely aware of their cough, leading them to unconsciously adjust how they perceive, report, or manage their symptoms. This heightened self-awareness may improve cough even while patients receive placebo.

Substantial placebo responses (up to 57% reductions in 24-hour cough frequency)⁶ in trials of RCC pose challenges related to the estimation of treatment effects. Firstly, higher placebo responses reduce the likelihood of a drug demonstrating superiority over placebo. This has implications for regulatory approval, sample size, cost, and feasibility to detect statistically significant differences. Secondly, patients with RCC may have varying susceptibilities to placebo response based on factors including expectation and prior treatment trials. Variability in the proportion of placebo responders can render comparison of results across trials more challenging.

This occurred with the gefapixant development program in which the magnitude of the placebo response increased from 33% to 57% from phase 2b to phase 3 trials.^{6,8-10}

Some trials in RCC have attempted to mitigate the placebo response by excluding patients whose cough frequencies improved or worsened substantially during a single-blind placebo run-in period. While excluding patients with a highly variable cough pattern might reduce the placebo response, it renders the trial less pragmatic and can screen fail patients whose symptoms fluctuate due to the natural history of their disease rather than true placebo effects.

An alternative strategy might involve using two (or more) measurements of cough frequency for baseline assessment. Regression to the mean occurs when participants are selected based on extreme values of a variable (i.e., high cough frequency), which are influenced by both true severity and random variation. On remeasurement, these extreme values tend to move closer to an individual's average, not because of any intervention, but due to random measurement variability. Instead of taking a single baseline measurement – which might represent an outlier due to random variability – investigators should consider averaging two (or more) baseline measurements to provide a more stable estimate of a patient's baseline level. Future developments in cough frequency monitoring beyond 24 hours could provide a more representative sample of cough variability at baseline and over time.

Evidence from an asthma trial investigating montelukast demonstrates that enhanced messaging about treatment benefits can importantly influence patient-reported outcomes.¹¹ Investigators should minimize expectation that might contribute to the placebo effect by framing information neutrally and avoiding verbal or nonverbal cues that could bias participants.

Investigators should also judiciously select participants with truly RCC. Within tertiary cough clinics, chronic cough can respond to treatment of an identifiable cause in up to 36% of

patients and can spontaneously resolve in up to 5% of patients.¹² Investigators planning trials in RCC should carefully design inclusion criteria and select study sites to only recruit those with truly RCC.

Advancing our understanding of the placebo response in trials of RCC requires further investigation. One that remains crucial is a study including an untreated control arm to estimate the proportion of the placebo response representing true placebo effects versus natural disease progression and regression to the mean. We also need neuroimaging studies to better understand the neuronal mechanisms behind placebo effects, studies on contextual and design factors influencing placebo responses, and studies identifying biomarkers linked to prefrontal activation to screen placebo responders. All of these may help us to better design trials leading to more effective evaluation of new therapies in RCC.

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Conflict of Interest Disclosure: I.S. is supported by a Canada Research Chair and reports grants from Merck, MITACS, GSK, Bellus, Trevi Therapeutics, Bayer, Genentech; personal speaker fees from Merck, GSK, AstraZeneca, Sanofi-Regeneron; and consulting fees from Merck, GSK, Bellus, Sanofi-Regeneron, Methapharm outside the submitted work. E.K and W.H. have nothing to disclose.

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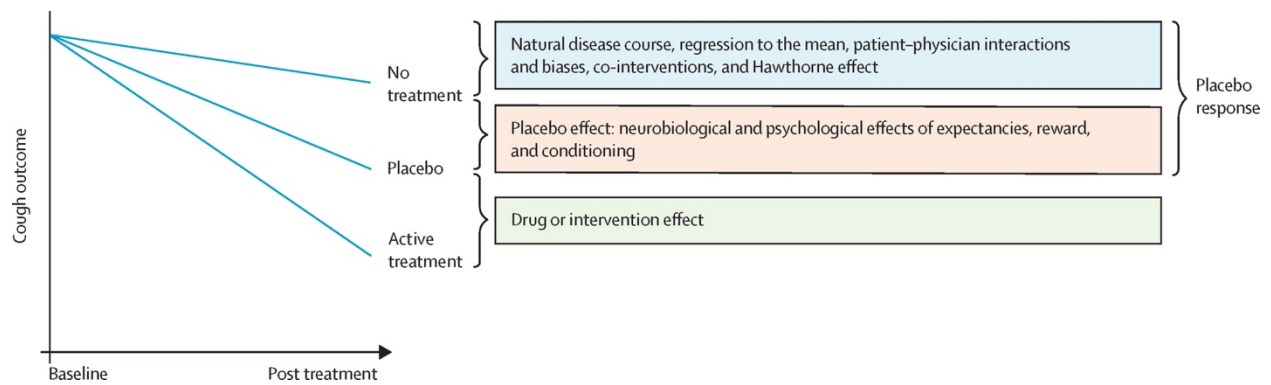


Figure 3-1: Factors underlying the placebo effect and the placebo response

(adapted from Haflíðadóttir et al)¹

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Chapter 4 Cough symptom severity in patients with refractory or unexplained chronic cough: a systematic survey and conceptual framework

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Abstract

Background: Cough severity represents an important subjective endpoint in assessing the effectiveness of therapies for patients with chronic cough. Although cough-specific quality of life questionnaires exist, a widely available cough severity instrument with established measurement properties remains unavailable.

Objective: To identify and summarize the results of studies reporting on the experience of patients with chronic cough and, in the process, develop a conceptual framework to inform development of a patient-reported outcome measure (PROM) addressing cough severity.

Design: Systematic survey and iterative brainstorming toward a conceptual framework.

Results: We identified 61 eligible studies reporting on patient experience with chronic cough. Studies provided 82 potential items, of which 43 proved unique and relevant to cough severity. The urge-to-cough sensation and the cough symptom itself represented broad domains of cough severity. Two subdomains under urge-to-cough included frequency (1 item) and intensity (1 item). Five subdomains under cough symptoms included control (2 items), frequency (6 items), bout duration (1 item), intensity (8 items), and associated features/sequelae (24 items).

Conclusions: Our systematic survey and conceptual framework identified items and domains of cough severity in patients with refractory or unexplained chronic cough. The results support item generation and content validity for a PROM assessing cough severity.

Introduction

Chronic cough lasting for more than 8 weeks is a common health problem that affects between 2-18% of adults worldwide.¹ Although clinicians can often identify and effectively treat known causes of cough—including asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, gastro-esophageal reflux disease (GERD), and upper airway cough syndromes (UACS)—up to 60% of patients experience persistent coughing despite treatment targeting these underlying conditions (refractory chronic cough), while in others, no cause can be identified (unexplained chronic cough).²⁻⁴

Chronic cough can result in important impairment in quality of life. Physical symptoms associated with chronic cough include chest pain, urinary incontinence, cough syncope, and headaches.⁵ Patients may also experience depression, anxiety, sleep disorders, and social disability.⁵ Improving quality of life in these patients requires investigation and administration of effective therapies.

Objective measurement of cough frequency represents the current gold standard to assess the efficacy of novel therapies for refractory or unexplained chronic cough in clinical trial settings, particularly for regulatory approval. Limitations of cough frequency monitoring include, however, restricted time frame (typically over 24 hours), burden for patients over repeated measurements, and expense. Together, these render the technology unfeasible for use in routine clinical practice. Although objective cough frequency is an important endpoint and a dominant aspect of severity, there may be other patient-important factors that contribute to patients' overall perception of cough severity.

Patient-reported outcomes (PROs) represent measures of patients' health status that are obtained from direct patient inquiry without interpretation by a clinician or anyone else.⁶ PROs

including the Leicester Cough Questionnaire (LCQ),⁷ Chronic Cough Impact Questionnaire (CCIQ),⁸ Cough Specific Quality of Life Questionnaire (CQLQ),⁹ Cough Assessment Test (COAT),¹⁰ and Cough Evaluation Test¹¹ provide insight into patients' subjective experience of chronic cough. Most of these measures focus on the impact of cough symptoms on quality of life and are thus limited in that they only indirectly address cough severity. This is important because improvement in the subjective experience of cough may be not only due to cough suppression, but also due to central neuromodulatory effects from agents such as opioids, pregabalin, and gabapentin that diminish the aversive nature of the cough experience. Thus, alongside cough-specific quality of life, full insight into therapeutic efficacy requires assessment of cough symptom severity itself.

The visual analogue scale (VAS), in which patients use a 100 mm scale ranging from “no cough” to “the worst cough severity”, provides a measure of patients' experience of cough severity.¹² Limitations of the cough severity VAS include, however, lack of evidence supporting its measurement properties, difficulty comparing VAS scores between and within individuals due to lack of interpretability, and limitations of single-item instruments in fully capturing complex patient experiences.¹³

The cough symptom score (CSS), a two-part diary that includes questions related to cough frequency, severity, and impact during the day and night, provides another subjective measure of cough severity.¹⁴ Clinical experience with this instrument is, however, limited, and the tool lacks a conceptual framework. Validity, responsiveness, and interpretability of the CSS also remain untested.

In contrast to the cough severity VAS and the CSS, the Cough Severity Diary (CSD), a seven-item daily diary including domains of frequency, intensity, and disruption, has undergone

psychometric testing.¹⁵⁻¹⁷ It is, however, currently a proprietary questionnaire that's use for clinical or research purposes remain restricted. Furthermore, it lacks conceptual clarity in that the domain “disruption” measures cough impact on daytime activities and sleep, which represent measurements of cough-specific quality of life rather than cough symptom severity. A widely available instrument with established measurement properties that subjectively measures cough symptom severity rather than cough-specific quality of life remains unavailable.

Apart from the CSD, an important limitation of the cough severity measures we have discussed is that they were not informed by a thorough systematic survey of the available literature documenting patients' experience of chronic cough. Failure to conduct a comprehensive survey risks omission of important items and limits the development of a conceptual framework to optimally define the underlying construct and domains for a cough severity instrument.¹⁸⁻²⁰ Therefore, we conducted a systematic survey to identify both relevant domains and items to assess cough severity.

Methods

We conducted a systematic survey following a protocol registered on Open Science Framework (reference: <https://osf.io/tnjba>). This report adheres to preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards.²¹ A steering group (E. Kum, G. Guyatt, and I. Satia) developed the plan for the study, the detailed methodology, and led the development of the conceptual framework.

Data sources and search

We searched the databases of MEDLINE, EMBASE, CINAHL, PsycINFO, PubMed, and HaPI from January 2007 to August 2020. The search strategy, adapted to each database and without

language restrictions, included terms representing cough and terms representing PRO measures (PROMs) (**eTable 4-1**). To identify relevant studies prior to 2007, we referred to a systematic survey¹⁶ that included related articles within the literature from 2002 to 2006, as well as reviewed reference lists of all eligible studies from our updated search.

Eligibility criteria

We included studies meeting any of the following criteria: (1) studies addressing item generation of a cough-specific PROM (including PROMs that assess cough symptom severity, urge-to-cough severity, and/or their impacts); (2) qualitative studies (interviews and focus groups) addressing the experience of chronic cough; (3) cross-sectional studies addressing the experience of chronic cough; and (4) longitudinal cohort studies (prospective or retrospective) addressing the prognosis of chronic cough, in which cough was the independent predictor of a patient-important outcome. Eligible studies reported at least one relevant domain or item that informed the concept of cough severity.

We included studies that enrolled adult patients (age ≥ 18 years old) with chronic cough of any etiology. Chronic cough was defined as cough lasting more than 8 weeks.²² Studies including mixed cough populations (i.e. chronic cough, subacute cough, and acute cough) or that defined chronic cough with a threshold duration of less than 8 weeks were deemed eligible if the study reported data stratified for patients with cough lasting more than 8 weeks, or if $\geq 80\%$ of the patients had cough lasting more than 8 weeks.

We excluded the following studies: (1) randomized clinical trials in which cough serves as a primary or secondary endpoint; (2) case reports related to chronic cough; (3) reviews addressing chronic cough; (4) editorials; (5) letters to the editor; (6) conference abstracts; (7) studies that failed to explicitly define chronic cough or failed to report the average duration of chronic cough;

and (8) studies including only patients with lung cancer, cystic fibrosis, pulmonary hypertension, or heart failure.

Study selection

Using Covidence systematic review software, a pair of reviewers, following training and calibration exercises, first independently screened all titles and abstracts, and subsequently the full texts of studies identified as potentially eligible. Reviewers resolved disagreements by discussion and, when necessary, by adjudication with a third reviewer (E. Kum, G. Guyatt, or I. Satia).

Data extraction

For each eligible study, a pair of reviewers, following training and calibration exercises, extracted data independently using a standardized, pilot tested data extraction form. Reviewers collected information on study characteristics (study design and sample size) and patient characteristics (country, setting, type of care, age, sex, smoking habits, smoking pack years, causes of chronic cough, and duration of cough). For studies addressing item generation or development of a PROM, we extracted information on the questionnaires' target population, content (construct(s) assessed, number of items, number of domains, and labelling of domains), and format (scoring and recall period).

Reviewers extracted statements informing candidate items and domains of cough severity. Informative statements included those on (1) precipitants and sensations leading up to a cough; (2) characteristics of coughing while it is happening; and (3) symptoms in the immediate period (approximately 10 mins) after coughing that patients perceive to be caused by coughing. Reviewers extracted relevant statements verbatim from the articles.

Statements deemed uninformative of cough severity included those that referred to domains and items related to cough-specific quality of life, including cough impacts on daily life,

mental/psychological health, and social life. Statements referring to symptoms that may co-occur with coughing but that are not due to coughing itself were also considered uninformative. Reviewers resolved discrepancies by discussion and, when necessary, by adjudication with a third reviewer. To ensure consistency of judgements, one researcher (E. Kum) was a member of all reviewer pairs. A senior investigator (G. Guyatt or I. Satia) adjudicated any conceptual issues that proved particularly challenging.

Qualitative synthesis

In parallel with the data extraction process, a steering group (E. Kum, G. Guyatt, and I. Satia) developed a separate list of domains and items using our own phrasing (a taxonomy), adding domains and items as new themes from extracted statements emerged. For each item or domain, the taxonomy specified a collection of common terms and statements used to convey the same or related ideas. By assigning the most closely related keywords, reviewers used the taxonomy to organize the statements they extracted according to its meaning and content.²³ Reviewers could suggest new items or domains when a quotation did not fit existing ones. The continuous updating of the taxonomy provided a method to involve all reviewers in the qualitative synthesis process.

After completion of data extraction, the steering group reviewed the taxonomy and suggested improvements to the wording. Potential items suggested by reviewers could be eliminated if judged ineligible by the steering group. These ineligible items included those that provided redundant, uninterpretable, or irrelevant concepts. The steering group subsequently developed a draft conceptual framework that, through interactive discussion, led to arrangement of eligible items and domains, and to some domains being subsumed within existing categories, given less prominence. We used vote counting, comprising the number of studies mentioning either

the domain or an item under that domain, to identify the frequency with which authors mentioned items or domains presented in the final conceptual framework.

Results

After screening 6,425 titles and abstracts and 334 full texts, 61 studies proved eligible.

Table 4-1 presents the characteristics of the included studies that typically used cross-sectional designs (n=38; 62.3%) and were conducted in the United Kingdom (n=20; 32.8%), United States (n=13; 21.3%), and Australia (n=7; 11.5%). Studies commonly defined chronic cough with a threshold duration of greater than 8 weeks (n=40; 65.6%).

Typical patients proved to be females over the age of 50 years who had never smoked and were receiving care from secondary or tertiary care settings (**Table 4-2**). One qualitative study interviewed a sample of international respiratory specialists, rather than patients with chronic cough.²⁴

The search identified eligible studies addressing item generation or development of a number of cough-specific PROMs: the Chronic Cough Impact Questionnaire (CCIQ),⁸ Cough and Sputum Questionnaire (CASA-Q),²⁵ Cough Assessment Test (COAT),¹⁰ Cough Evaluation Test (CET),¹¹ Cough Severity Diary (CSD),¹⁵ Cough Severity Index (CSI),²⁶ Cough Specific Quality of Life Questionnaire (CQLQ),⁹ Cough Symptom Score (CSS),¹⁴ Hull Airway Reflux Questionnaire (HARQ),²⁷ Leicester Cough Questionnaire (LCQ),⁷ Newcastle Laryngeal Hypersensitivity Questionnaire (LHQ),²⁸ and Punum Ladder.²⁹ **eTable 4-2** lists the characteristics of these PROMs. One study provided information on item generation for both the CQLQ and the Punum Ladder.³⁰

Saturation of the taxonomy

A taxonomy of potential items and domains was largely established after the first 20 studies. Few additional items or domains were added to the taxonomy when extracting the remaining 41 studies.

Item identification

From included studies, reviewers identified a total of 82 items. Each candidate item was carefully reviewed by the steering group for eligibility. Items judged ineligible on review included those that represented objective physiologic measurements (i.e. compressive phase duration, esophageal pressure, expiratory muscle activation, gastric pressure, and peak cough flow) rather than subjective measurements of cough intensity; conditions rather than symptoms associated with coughing (i.e. cardiac rhythm disturbance and subconjunctival hemorrhage); vague descriptions (i.e. worsening cough, character of cough); or concepts unrelated to cough severity (i.e. interference, disturbance, cough triggers, hemoptysis). Items referring to synonymous concepts (i.e. shortness of breath, dyspnea, and breathlessness) were grouped into a single item. This resulted in 43 unique items reflected in our final taxonomy (**Table 4-3**).

Concept elicitation from included studies

Through iterative discussion of the taxonomy with the steering group, both the urge-to-cough sensation (noted in 31 studies) and the cough symptom itself (in 58 studies) emerged as broad domains of cough severity under which eligible items were classified (**Table 4-3; Figure 4-2**).

Urge-to-cough sensation

Regarding the urge-to-cough sensation, we identified two subdomains that mediate its impact: urge frequency (n=5) and intensity (n=6) (**Table 4-3; Figure 4-2**). Urge-to-cough sensations, commonly described as an “irritation” (n=8) or “tickle” (n=9) within the throat or chest region, can precede a cough. Patients who experience urge-to-cough sensations frequently report that the urge almost always leads to coughing, although not all coughs are preceded by an urge.³¹ Patients described the urge-to-cough as being linked to how frequently one coughs and whether one is able to control their cough: *“Well I think the more you try and like think ‘Don’t let the tickle ... don’t let the tickle bother you and don’t cough’, sometimes the tickle comes like to a point where you just can’t stop it”*.³² Thus, the frequency and intensity of urge-to-cough sensations may be related to the subjective experience of coughing and therefore relevant in assessing cough severity. Both urge frequency and intensity were characterized as single-item subdomains (**Table 4-3**).

Cough symptoms

The study team identified five subdomains for assessing severity of the cough symptom itself: control (n=10), frequency (n=33), fit/bout duration (n=4), intensity (n=17), and associated features/sequelae (n=44) (**Table 4-3; Figure 4-2**).

Cough control refers to the ability, or lack thereof, to voluntarily or involuntarily suppress a cough from starting or once started. Because it captured whether coughing was a conscious act or an uncontrollable, involuntary reflex, the study team characterized cough control as a separate subdomain from cough frequency (**Table 4-3; Figure 4-2**). Some patients described voluntarily coughing to clear mucous, “something stuck”, or in response to an irritating urge in the throat; other patients described uncontrollable bouts of coughing that are highly unpleasant. Suppression

of cough from starting (n=3) or once started (n=3) represented two items under the domain cough control that the study team identified.

Cough frequency represented another subdomain in assessing cough severity (**Table 4-3; Figure 4-2**). In some studies, cough frequency referred to the frequency of any coughs (individual or bouts of coughing) (n=28); other studies referred to the frequency of bouts (n=12). Suggested periods to assess cough frequency included overall (throughout the day and night) (n=28), during the day (n=14), during the night (n=21), in the morning (n=6), and prandial or postprandial (n=8). Studies identified that the frequency of coughing may be variable depending on the time of day (i.e. less frequent at night versus during the day), and that timing dictated various cough impacts to quality of life, such as daytime activities or sleep disruption. Thus, the study team captured six candidate items under the domain frequency: frequency of any coughs (assessed day and night), frequency of coughs during the day, frequency of coughs during the night, frequency of coughs in the morning, frequency of coughs in the prandial/postprandial period, and frequency of bouts.

The study team identified duration of bouts as a subdomain of cough severity (**Table 4-3; Figure 4-2**). The team defined a bout as a prolonged series of explosive phases of coughing, either after a single breath or with several breaths interspersed.³³ Patients may describe greater cough severity when they occur in bouts, potentially as they are “less controllable” and involve greater amounts of “effort”: “... [a bout is] one of those that goes on and on and on and I think ‘I can’t do with that, it’s tired me out’ ... you know drained”.³² Further, longer bouts of coughing may lead to a higher frequency and intensity of adverse sequelae: “To me that strikes me as always a very serious bout of coughing, because obviously, oxygen wasn’t getting where it was supposed to be getting. Um, and I find this is freaky, especially if you’re driving, you know, and you’re coughing, and all of a sudden you’re dizzy”.¹⁶ Therefore, the frequency of bouts, along with the duration of

each bout, is likely to influence cough severity. The team characterized duration of bouts as a single-item subdomain.

The study team identified cough intensity as another subdomain (**Table 4-3; Figure 4-2**). Single-word descriptions of cough intensity provided seven items under this subdomain, including harsh (n=2), deep (n=2), hacking (n=2), barking (n=1), honking (n=1), strong (n=2), and intense (n=1). The team also classified patients' description of the effort to cough (n=6), defined as the physical effort to expectorate an urge, as another item under intensity.

Related to intensity, patients described symptoms that they experience during and immediately after coughing. The study team classified this as a separate subdomain called associated features/sequelae of coughing (**Table 4-3; Figure 4-2**). Under this subdomain, eight items representing experiences while coughing included dizziness (n=4), wheeze (n=13), syncope (n=6), dyspnea or shortness of breath (n=15), incontinence (n=15), distress (n=3), tightness of throat (n=4), and tightness of chest (n=5). The team also identified sequelae of coughing, depending on patient susceptibility, as sixteen other items under this subdomain, including general pain (n=6), rib pain or fracture (n=6), chest pain (n=13), abdominal pain (n=6), back pain (n=2), aches (n=1), headache (n=8), sore throat (n=3), exhaustion (n=15), voice change or hoarseness (n=15), retching or vomiting (n=12), expectoration of mucous or phlegm (n=19), umbilical hernia (n=1), excessive sweating (n=1), watery eyes (n=1), and runny nose (n=1).

Discussion

We report the first systematic survey synthesizing items and domains of cough severity in patients with refractory or unexplained chronic cough. The survey identified 82 potential items, of which 43 proved unique and clearly related to cough severity. The study team categorized these

final items under two broad domains: the urge-to-cough sensation (two subdomains: urge frequency and intensity) and the cough symptom itself (five subdomains: cough control, frequency, duration of bouts, intensity, and associated features/sequelae).

Strengths and limitations

Our work follows established methodology and guidance for optimal development of PROMs.²⁰ A preliminary step in PROM development is to establish the measurement construct, a theoretically-derived notion of the domain(s) to be measured.¹⁸⁻²⁰ An understanding of the construct will lead to expectations about how an instrument should behave if it is valid.¹⁹ Therefore, the systematic survey and conceptual framework in itself represent strengths in terms of development of a cough severity PROM.

Other strengths of our systematic survey include transparent eligibility criteria and rigorous methods for systematic data abstraction; flexibility in development of the taxonomy allowing incorporation of the views of involved reviewers while abstracting; and achieving a saturation effect (i.e. few new items/domains) after abstraction of approximately 20 eligible studies. It is therefore unlikely that we missed any key items or domains. Inclusion of studies from different geographic and care settings ensured that items and domains are likely to reflect experiences from a diversity of chronic cough patients. Further, development of our conceptual framework involved iterative discussion with a steering group of chronic cough and health status measurement experts, thereby strengthening the clarity and face validity of our framework.

Our survey, however, has limitations. The database search primarily focused on studies from the year 2007 onwards, although articles published before 2007 were still hand-searched and included if eligible. The focus on more recent studies was based on developing conceptual insights

relying on current, rather than historical, patient experiences of cough severity. Because the study achieved saturation in the taxonomy, a more exhaustive search would unlikely change the results.

The process of synthesizing verbatim quotations to characterize items and domains introduced subjectivity, as did the decisions regarding combining, reducing, and separating of items. For example, a number of statements addressed frequency of coughing during different periods of the day, and we labeled these items as daytime frequency, nighttime frequency, morning frequency, and prandial/postprandial frequency. Others may have classified these into fewer or greater items.

Findings in context of other studies

A study by Vernon et al.¹⁶ explored factors relevant to assessment of cough severity in a literature review and a semi-structured focus group study. Their conceptual framework consisted of frequency, intensity, and disruption, and informed development of the CSD.¹⁵ Our results are consistent with several of the themes presented in their conceptual framework, although our survey identified additional important concepts. Firstly, we identified both the frequency and intensity of the urge-to-cough sensation as subdomains that should be assessed in measuring cough severity. The conceptual framework of the CSD includes an item related to urge frequency, although assessment of urge intensity is not considered.

Secondly, our conceptual framework identifies cough control as a subdomain. Recent mechanistic studies demonstrate that patients with refractory chronic cough have impaired ability to voluntarily suppress coughing,³⁴ but also provide evidence of impairment in the inhibitory control neurons that represent a sub-conscious and involuntary process.³⁵ This distinction may be mechanistically relevant. Lack of sub-conscious inhibitory control pathways intuitively seems

more important in starting a cough, given that healthy people do not consciously suppress their coughing throughout the day. In contrast, once a cough has started, impaired voluntary suppression may perpetuate longer duration and bouts of coughing.

Functional brain magnetic resonance imaging also corroborates the relevance of central cortical pathways in the conscious and sub-conscious control of coughing.³⁶⁻³⁸ As speech therapy aims to increase control of cough, the concept seems highly relevant in assessing the effectiveness of therapies. The conceptual framework of the CSD does not identify this as a stand-alone concept, and few other cough-specific PROMs have included cough control as a domain.

Thirdly, although we identified this as potentially relevant, the CSD does not consider duration of bouts in their conceptual framework. In a study comparing objective and subjective measurements of cough, investigators reported moderate correlation of frequency of cough epochs (bouts) with subjective quality of life and cough severity VAS scores.³⁹ As the frequency of coughing bouts ignores the length of each bout, the study suggested that duration of bouts may be an important factor in the perception of cough severity that remains unaccounted for with objective bout frequency. Therefore, we have included duration of bouts as a subdomain in our conceptual framework.

Although the CSD framework includes cough intensity, their conceptual framework is non-specific in terms of the subcategories that comprise this domain. The authors identify harshness and physical discomfort as comprising cough intensity. Our survey, however, identified 32 items describing intensity, including the effort to cough, descriptors of coughing (i.e. strong, harsh, intense, deep, barking, honking), and associated features/sequalae (i.e. chest pain, syncope, dizziness, hoarseness, sore throat) (**Figure 4-2**).

Finally, the CSD framework identifies disruption to daytime activities and sleep as concepts of cough severity. We strove for conceptual clarity by excluding domains or items related to cough impact on quality of life. Several validated and widely available PROMs already assess the impact of cough symptoms on quality of life, including the LCQ,⁷ CCIQ,⁸ CQLQ,⁹ COAT,¹⁰ and CET.¹¹ Our conceptual framework defines concepts to measure symptom severity, which would inform an instrument complementary to existing quality of life questionnaires.

Conclusions

We report a systematic survey and conceptual framework that identified candidate items and domains to measure cough severity. Studies provided 43 unique items that contributed to our conceptual framework. The urge-to-cough sensations, a linked component of the cough experience, classified as a domain. The study team identified frequency (1 item) and intensity (1 item) as subdomains under the urge-to-cough sensation. The cough symptom itself represented another domain, subdomains of which included control (2 items), frequency (6 items), fit/bout duration (1 item), intensity (8 items), and associated features/sequelae (24 items). Qualitative studies could address the comprehensiveness and appropriateness of the items, domains, and subdomains we have identified, and lead to refinement of our evolving approach to measurement of cough severity. These studies, including focus groups with chronic cough patients and consultation with international cough experts, are currently underway. Our findings support item generation and content validity of a PROM assessing cough symptom severity in patients with refractory or unexplained chronic cough. The PROM will be designed for both discriminative and evaluative purposes for use in health research and clinical practice.

Author contributions

E. Kum, G. Guyatt, T. Devji, Y. Wang, P. O’Byrne, and I. Satia conceived the study. E. Kum, G. Guyatt, and I. Satia comprised the steering group. E. Kum and R. Couban developed the search strategy. E. Kum, L. Bakaa, L. Lan, E. Liu, A. Mastrodonardo, and R. Couban searched and extracted the data. E. Kum performed the analysis. E. Kum, G. Guyatt, and I. Satia interpreted the data. E. Kum drafted the manuscript. All authors critically reviewed and approved the final manuscript.

Conflicts of interest

I. Satia reports grants from ERS Respire 3 Marie Curie Fellowship, grants and personal fees from Merck Canada, and personal fees from GSK and AstraZeneca, outside the submitted work. P. O’Byrne reports grants and personal fees from AstraZeneca, personal fees from GSK, grants from Novartis, grants and personal fees from Medimmune, and personal fees from Chiesi, outside the submitted work. All other authors report no conflicts of interest.

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Table 4-1: Characteristics of included studies

Study	Total sample size	Country	Definition of chronic cough	Study type
Adams, 2009 ¹	3960	Australia	cough lasting >12 weeks	Cross-sectional analysis of a prospective cohort study
Baiardini, 2005 ²	166	Italy	cough lasting >3 weeks	Study addressing item generation of a PROM (Chronic Cough Impact Questionnaire)
Birring, 2003 ³	104	United Kingdom	cough lasting >3 weeks	Study addressing item generation of a PROM (Leicester Cough Questionnaire)
Campi, 2020 ⁴	1204	Italy	cough lasting >8 weeks	Cross-sectional study
Chamberlain, 2015 ⁵	1120	United Kingdom, Germany, France, Italy, Poland, Russia, Ukraine, Latvia, Lithuania, Moldova, Romania, Bulgaria, Turkey, Greece, Czech Republic, Austria, Switzerland, Spain, Portugal, Ireland, Iceland, Norway, Sweden, Belgium, Netherlands, Denmark, Cyprus, Luxembourg	cough lasting >8 weeks	Cross-sectional study
Chan, 2010 ⁶	55	Australia	cough lasting >8 weeks	Cross-sectional study
Cheng, 2017 ⁷	176	Canada	NR	Cross-sectional study
Çolak, 2019 ⁸	14740	Denmark	cough lasting >8 weeks	Cross-sectional analysis of a prospective cohort study
Çolak, 2017 ⁹	14669	Denmark	cough lasting >8 weeks	Cross-sectional analysis of a prospective cohort study
Cornford, 1998 ¹⁰	30	United States	cough lasting >3 weeks and who consulted due to cough as the primary illness	Qualitative study
Crawford, 2008 ¹¹	41	Germany, Spain, France, Japan, United States	daily cough and sputum production >3 months	Study addressing item generation of a PROM (Cough and Sputum Assessment Questionnaire)
Decalmer, 2007 ¹²	62	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Everett, 2007 ¹³	373	United Kingdom	NR	Cross-sectional study
Everett, 2007 ¹⁴	47	United Kingdom	demonstrable abnormality of oesophageal manometry or Ph monitoring or both	Cross-sectional study
Faruqi, 2014 ¹⁵	86	United Kingdom, United States, Japan, Germany	NA	Qualitative study
Faruqi, 2011 ¹⁶	25	United Kingdom	cough lasting >6 months	Prospective cohort study
Ford, 2006 ¹⁷	3883	United Kingdom	cough lasting >8 weeks	Cross-sectional study
French, 2017 ¹⁸	80	United States	cough lasting >8 weeks	Cross-sectional analysis of a prospective cohort study
French, 1998 ¹⁹	39	United States	cough lasting >3 weeks	Prospective cohort study; study addressing item generation of a PROM (Cough-Specific Quality of Life Questionnaire; Punum Ladder)
Fujimura, 2012 ²⁰	1000	Japan	cough lasting >8 weeks	Qualitative study
Hilton, 2015 ²¹	100	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Hsu, 1994 ²²	47	United Kingdom	cough lasting >6 months	Study addressing item generation of a PROM (Cough Symptom Score)
Hulme, 2019 ²³	14	United Kingdom	cough lasting >8 weeks	Qualitative study

Kang, 2019 ²⁴	447	Korea	cough lasting >8 weeks	Cross-sectional study
Kelsall, 2011 ²⁵	62	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Kelsall, 2008 ²⁶	70	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Koo, 2019 ²⁷	401	Korea	cough lasting >8 weeks	Study addressing item generation of a PROM (Cough Assessment Test)
Koskela, 2018 ²⁸	3697	Finland	cough lasting >8 weeks	Cross-sectional study
Koskela, 2019 ²⁹	3695	Finland	cough lasting >8 weeks	Cross-sectional study
Kuznair, 2007 ³⁰	136	United States	cough lasting >3 weeks	Cross-sectional study
Lai, 2020 ³¹	1162	China	cough lasting >8 weeks	Cross-sectional study
Lan, 2020 ³²	164	Australia	cough lasting >8 weeks	Cross-sectional study
Landt, 2020 ³³	41545	Denmark	cough lasting >8 weeks	Cross-sectional analysis of a prospective cohort study
Lätti, 2018 ³⁴	3673	Finland	cough lasting >8 weeks	Cross-sectional study
Lee, 2015 ³⁵	49	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Lee, 2012 ³⁶	100	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Lee, 2017 ³⁷	32	United Kingdom	cough lasting >8 weeks	Cross-sectional study
Ma, 2009 ³⁸	200	China	cough lasting >8 weeks	Prospective cohort study
Mello, 1996 ³⁹	88	United States	cough lasting >3 weeks	Cross-sectional study
Morice, 2011 ⁴⁰	255	United Kingdom	cough lasting >8 weeks	Study addressing item generation of a PROM (Hull Airway Reflux Questionnaire)
Murry, 2010 ⁴¹	16	United States	NR	Retrospective cohort study
Ojoo, 2013 ⁴²	112	United Kingdom	cough lasting >8 weeks	Prospective cohort study
Ozge, 2005 ⁴³	165	Turkey	cough lasting >4 weeks	Cross-sectional study
Sato, 2019 ⁴⁴	129	Japan	NR	Cross-sectional study
Shariat, 2009 ⁴⁵	360	United States	NR	Cross-sectional study
Shembel, 2013 ⁴⁶	365	United States	cough lasting >8 weeks	Study addressing item generation of a PROM (Cough Severity Index)
Sinha, 2018 ⁴⁷	223	United Kingdom	cough lasting >8 weeks	Qualitative study
Smith, 2006 ⁴⁸	26	United Kingdom	CSS daytime cough score ≥ 2	Cross-sectional study
Song, 2013 ⁴⁹	857	Korea	cough lasting >12 weeks	Cross-sectional analysis of a prospective cohort study
Ternesten-Hasseus, 2011 ⁵⁰	121	Sweden	cough lasting >8 weeks	Cross-sectional study
Van de Kerkhove, 2012 ⁵¹	51	Belgium	cough lasting >8 weeks	Prospective cohort study
Vazquez, 2018 ⁵²	1422	United States	cough lasting >2 years	Cross-sectional analysis of a prospective cohort study
Vernon, 2009 ⁵³	22	United States	cough lasting >8 weeks	Qualitative study
Vernon, 2010 ⁵⁴	39	United States	cough lasting >8 weeks	Study addressing item generation of a PROM (Cough Severity Diary)
Vertigan, 2014 ⁵⁵	38	Australia	cough lasting >8 weeks	Study addressing item generation of a PROM (Newcastle Laryngeal Hypersensitivity Questionnaire)
Vertigan, 2007 ⁵⁶	171	Australia	cough lasting >8 weeks	Cross-sectional study
Vertigan, 2007 ⁵⁷	171	Australia	cough lasting >8 weeks	Cross-sectional study
Vertigan, 2011 ⁵⁸	53	Australia	cough lasting >8 weeks	Cross-sectional study
Won, 2019 ⁵⁹	478	Korea	cough lasting >8 weeks	Cross-sectional study
Xu, 2015 ⁶⁰	87	China	cough lasting >8 weeks	Retrospective cohort study

Zhan, 2020 ⁶¹	237	China	cough lasting >8 weeks	Study addressing item generation of a PROM (Cough Evaluation Test)
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NR=not reported

Table 4-2: Characteristics of patients in included studies

Study	Total sample size	Sample size of patients with chronic cough	Type of care/sample type	Age	Female (%)	Never smoker (%)	Current smoker (%)	Former smoker (%)	Smoking pack history (pack-year)	Causes of chronic cough (%)	Duration of chronic cough
Adams, 2009 ¹	3960	812	other; general population	NR	NR	NR	NR	NR	NR	13.5 (asthma), 7.3 (CB), 1.3 (emphysema)	NR
Baiardini, 2005 ^{2§}	166	166	secondary/tertiary	53.9	56.0	34.3	39.8	25.9	NR	NR	25 months (SD: 9 months)
Birring, 2003 ^{3†}	104	104	secondary/tertiary	57.0	62.5	NR	NR	NR	NR	100 (UCC)	65 months (range: 2.6-650 months)
Campi, 2020 ⁴	1204	1204	secondary/tertiary	61.0	70.4	61.1	8.6	29.0	NR	1.74 (COPD)	39 months
Chamberlain, 2015 ⁵	1120	1120	other; general population	51.0	67.0	NR	16.5	NR	NR	11.88 (asthma), 7.14 (GERD), 3.57 (PND), 8.75 (bronchitis), 4.38 (COPD), 3.84 (viral infection), 2.41 (cough hypersensitivity syndrome), 0.89 (laryngitis), 1.96 (allergy), other	26-65 months (range: 2 months-10+ years)
Chan, 2010 ⁶	55	18	NR	53.0	32.7	100.0	0.0	0.0	NR	100 (sleep disordered breathing, no known respiratory cause of cough)	67% (≤8 weeks), 33% (>8 weeks)
Cheng, 2017 ⁷	176	NR	secondary/tertiary	64.3	56.8	NR	2.8	59.7	8.17	15.91 (ACEi), 76.70 (GERD), 11.93 (chronic sinus disease), 28.98 (chronic heart disease), 19.32 (non-ILD chronic lung disease)	36.5 months
Çolak, 2019 ⁸	14740	554	other; general population	58.2	54.5	45.6	10.4	43.1	14.87	12.64 (asthma), 87.36 (other)	NR
Çolak, 2017 ⁹	14669	554	other; general population	58.2	55.1	46.0	10.5	43.5	NR	2.53 (asthma), 0.18 (bronchiectasis), 2.89 (GERD), 1.26 (UACS)	NR
Cornford, 1998 ¹⁰	30	30	primary	48.0	NR	NR	NR	NR	NR	NR	NR
Crawford, 2008 ^{11**}	41	NR	NR	NR	NR	NR	NR	NR	NR	100 (CB)	NR
Decalmer, 2007 ¹²	62	62	secondary/tertiary	54.9	62.9	NR	0.0	37.1	NR	53.23 (GERD), 12.9 (PND), 9.68 (asthma), 3.23 (EB), 3.23 (bronchiectasis), 3.23 (tracheopathia osteochondroplastica)	71.5 months (range: 13-390 months)
Everett, 2007 ¹³	373	373	77.21 (primary), 60.58 (secondary/tertiary), 41.55 (secondary/tertiary)	65.3	73.0	NR	2.1	40.8	8	24 (asthma), 66 (no respiratory diagnosis other than cough)	84.5 months (range: 0.63-949 months)
Everett, 2007 ¹⁴	47	47	secondary/tertiary	54.3	55.3	NR	NR	NR	NR	100 (GERD)	NR

Faruqi, 2014 ¹⁵	86	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Faruqi, 2011 ¹⁶	25	25	secondary/tertiary	54.0	60.0	0.0	NR	NR	NR	NR	130 months
Ford, 2006 ¹⁷	3883	481	primary	40-49	56.1	NR	21.7	NR	NR	NR	NR
French, 2017 ¹⁸	80	80	secondary/tertiary	58.5	68.8	97.5	NR	NR	NR	86.3 (GERD), 72.5 (UACS), 27.5 (asthma), 5.0 (drug induced), 3.8 (bronchiectasis), 3.8 (postinfectious), 2.5 (NAEB), 2.5 (COPD), 2.5 (laryngeal sensory neuropathy), 1.3 (CHF), 1.3 (bronchiolitis), 1.3 (infiltrate), 1.3 (suppurative airway infection), 1.3 (vocal cord dysfunction), 1.3 (ILD)	86 months (SD: 123.7 months)
French, 1998 ¹⁹	39	39	secondary/tertiary	54.0	82.1	NR	NR	NR	NR	40 (PND), 36 (GERD) 15 (asthma), 3 (bronchiectasis), 3 (pertussis), 3 (other)	56 months (SD: 63 months)
Fujimura, 2012 ²⁰	1000	232	other; general population	55.3	38.2	41.6	22.2	36.1	566	10.1 (cold), 18.5 (asthma), 7.6 (CB), 6.7 (CVA), 5.9 (GERD), sinusitis, 6.7 (pulmonary emphysema), pneumonia, atopic cough, lung cancer, COPD, 17.6 (CB), 15.1 (unknown)	3.8 weeks
Hilton, 2015 ²¹	100	100	secondary/tertiary	60.0	71.0	NR	0.0	NR	NR	NR	91 (IQR: 52-195 months)
Hsu, 1994 ²²	47	14	secondary/tertiary	49.1	57.1	NR	NR	NR	NR	14.29 (GERD), 21.43 (PND due to paranasal sinusitis or rhinosinusitis), 4 (responsive to inhaled steroid therapy, no wheeze or shortness of breath), 5 (UCC)	81.65 months (SD: 79.3 months)
Hulme, 2019 ²³	14	14	secondary/tertiary	58.9	85.7	NR	NR	NR	NR	100 (CRC)	82.94 months (SD: 61.49 months)
Kang, 2019 ²⁴	447	447	secondary/tertiary	55.1	67.1	73.6	8.3	18.1	NR	8.72 (UCC)	46% (2-6 months), 14.09% (6-12 months), 21.72% (1-5 years), 18.19% (>5 years)
Kelsall, 2011 ²⁵	62	62	secondary/tertiary	56.8	69.4	NR	0.0	NR	NR	32.26 (GERD), 37.10 (rhinosinusitis), 6.45 (asthma), 8.06 (EB), 6.45 (bronchiectasis), 29.03 (UCC)	42.9 months (IQR: 26-130 months)
Kelsall, 2008 ²⁶	70	70	secondary/tertiary	55.0	72.9	100.0	0.0	0 (stopped <6 months)	NR	100 (UCC)	62.4 months (IQR: 32.5-131.3 months)

Koo, 2019 ^{27*}	401	401	secondary/tertiary	48.4	61.1	NR	NR	NR	NR	0 (ILD), 0 (COPD), 0 (asthma), 0 (severe bronchiectasis), 0 (lung cancer)	NR
Koskela, 2018 ²⁸	3697	976	other; general population	47.8	82.6	NR	6.9	31.4	6.38	NR	57% (>13 months), 26% (>65 months)
Koskela, 2019 ²⁹	3695	975	other; general population	47.8	82.6	NR	31.4	NR	NR	10.25 (asthma), 15.66 (chronic rhinosinusitis), 12.59 (GERD)	13.85% (2-12 months), 86.15% (3-8 weeks)
Kuznair, 2007 ³⁰	136	136	secondary/tertiary	63.0	65.4	63.2	3.7	33.1	NR	64.71 (rhinitis or sinusitis), 36.03 (GERD), 16.18 (asthma), 6.62 (bronchitis), 6.62 (ILD), 5.88 (postinfectious), 4.41 (bronchiectasis), 1.47 (ACEi), 6.62 (others)	18 months (IQR: 6-48 months)
Lai, 2020 ³¹	1162	1162	secondary/tertiary	42.6	55.4	100.0	0.0	0.0	NR	22.29 (EB), 19.10 (CVA), 12.48 (GERD), 7.31 (UACS), 38.81 (other)	27.07 months
Lan, 2020 ³²	164	118	secondary/tertiary	69.0	47.0	41.5	9.2	49.4	25.07	61.02 (GERD), 16.95 (ACEi), 12.71 (asthma), 12.71 (UACS), 9.32 (infection)	89.7 months (SD: 123.5 months)
Landt, 2020 ³³	41545	2381	other; general population	59.9	55.4	45.8	11.5	42.5	13.55	50.22 (COPD), 49.78 (other)	NR
Lätti, 2018 ³⁴	3673	957	other; general population	47.8	82.6	NR	6.9	31.4	6.41	15.51 (chronic rhinosinusitis), 11.69 (asthma), 12.59 (GERD)	5.42% (<3 weeks), 3.43% (3-8 weeks), 7.27% (>8 weeks)
Lee, 2015 ³⁵	49	28	secondary/tertiary	54.8	55.1	NR	0.0	NR	NR	21 (asthma), 14 (GERD), 7 (postinfectious disease), 4 (rhinitis), 4 (EB), 4 (OSA), 4 (bronchiectasis), 43 (UCC)	41.5 months
Lee, 2012 ³⁶	100	100	secondary/tertiary	54.0	57.0	80.0	5.0	15.0	NR	24 (asthma), 7 (EB), 9 (rhinitis), 3 (GERD), 29 (UCC), 7 (postviral cough), 6 (sarcoidosis), 8 (ILD), 2 (OSA), 2 (bronchiectasis), 1 (CB), 1 (ACEi), 1 (postinfective)	40 months
Lee, 2017 ³⁷	32	17	secondary/tertiary	51.3	59.4	100.0	0.0	0.0	NR	24 (asthma), 24 (GERD), 6 (EB), 6 (post-infectious), 6 (bronchiectasis), 35 (UCC)	34 months (range: 24-85 months)
Ma, 2009 ³⁸	200	110	secondary/tertiary	47.0	62.0	100.0	0.0	0.0	NR	9.09 (UACS), 49.09 (CVA), 5.45 (GERD), 9.09 (NAEB), 8.18 (post virus cough), 9.09 (two causes), 10 (other)	9 months (range: 2-360 months)

Mello, 1996 ³⁹	88	88	secondary/tertiary	53.1	72.7	99.4	NR	NR	NR	40 (GERD), 38 (PND), 14 (asthma), 4 (bronchiectasis), 4 (other)	85.8 months (SD: 127.4 months)
Morice, 2011 ^{40*}	255	185	secondary/tertiary	60.8	63.1	NR	NR	NR	NR	NR	NR
Murry, 2010 ⁴¹	16	16	NR	29-69	NR	NR	NR	NR	NR	100 (GERD, laryngopharyngeal reflux, and concurrent paradoxical vocal fold movement)	8.4 months (SD: 5.3 months)
Ojoo, 2013 ⁴²	112	112	secondary/tertiary	56.2	65.2	53.6	5.4	41.1	NR	29.35 (reflux related cough), 21.74 (asthma), 11.96 (rhinitis), 4.35 (post-infective), 11.96 (multiple causes), 7.61 (UCC), 13.04 (other)	39 months (range: 3.25-832 months)
Ozge, 2005 ⁴³	165	NR	secondary/tertiary	43.3	58.2	41.2	38.2	20.6	NR	25.6 (asthma), 18 (PND), 21 (sinusitis), 35.6 (CB)	46.5 months (SD: 9.6 months)
Sato, 2019 ⁴⁴	129	129	secondary/tertiary	68.5	40.9	NR	7.8	NR	23.0	54.26 (idiopathic interstitial pneumonias), 37.98 (connective tissue disease-associated ILD), 7.75 (chronic hypersensitivity pneumonitis)	NR
Shariat, 2009 ⁴⁵	360	263	secondary/tertiary	39.4	100.0	NR	NR	NR	NR	NR	260 months of chest symptoms (range: 6.5-793 months)
Shembel, 2013 ⁴⁶	365	345	secondary/tertiary	53.7	84.7	NR	NR	NR	NR	100 (UACS)	NR
Sinha, 2018 ⁴⁷	223	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith, 2006 ⁴⁸	26	26	secondary/tertiary	68.7	NR	NR	0.0	NR	42.4	100 (COPD)	117 months (range: 26-936 months)
Song, 2013 ⁴⁹	857	37	other; general population	76.8	57.0	62.2	12.2	25.5	NR	16.2 (asthma), 13.5 (allergic rhinitis), 2.8 (GERD)	NR
Ternesten-Hasseus, 2011 ⁵⁰	121	62	secondary/tertiary	53.6	64.5	61.3	0.0	38.7	NR	100 (UCC)	137.8 months (SD: 130 months)
Van de Kerkhove, 2012 ⁵¹	51	51	secondary/tertiary	NA	80.4	NR	NR	NR	NR	100 (UCC)	48 months (IQR: 2-192 months)
Vazquez, 2018 ⁵²	1422	552	NR	54.8	76.6	NR	61.7	NR	37.59	100 (COPD)	28.13% (3 months-2 years), 10.69% (>2 years)
Vernon, 2009 ⁵³	22	22	secondary/tertiary	66.1	72.7	NR	NR	NR	NR	31.82 (GERD), 22.73 (asthma), 18.18 (bronchitis), 18.18 (PND), irritant	100% (>8 weeks), 81.8% (>52 weeks)

exposure, post-infectious cough, mild COPD										
Vernon, 2010 ⁵⁴	39	24	primary	44.1	71.8	NR	0.0	NR	NR	38.46% (3 weeks-2 months), 17.95% (2-6 months), 10.26% (6-12 months), 30.77% (>1 year)
Vertigan, 2014 ^{55*}	38	11	secondary/tertiary	56.1	77.0	NR	11.0	NR	NR	49 (reflux), 29 (asthma), 17 (rhinitis)
Vertigan, 2007 ⁵⁶	171	111	secondary/tertiary	53.3	76.6	NR	NR	NR	NR	50.45 (CRC), 49.55 (CRC/paradoxical vocal fold movement)
Vertigan, 2007 ⁵⁷	171	111	secondary/tertiary	56.4	76.6	NR	3.5	NR	NR	55 (GERD), 18 (asthma), 49 (PND), 35 (allergies)
Vertigan, 2011 ⁵⁸	53	53	secondary/tertiary	60.0	66.0	100.0	0.0	0.0	NR	100 (CRC)
Won, 2019 ⁵⁹	478	478	secondary/tertiary	55.1	68.4	74.7	7.7	17.7	NR	12.97 (UCC), 87.03 (chronic cough with unspecified underlying condition)
Xu, 2015 ⁶⁰	87	87	secondary/tertiary	45.1	55.2	NR	NR	NR	NR	100 (GERD)
Zhan, 2020 ^{61†}	237	237	secondary/tertiary	40.4	54.0	NR	NR	NR	NR	NR

ACEi=ACE inhibitor use; CB=chronic bronchitis; CRC=chronic refractory cough; CVA=cough-variant asthma; EB=eosinophilic bronchitis; GERD=gastroesophageal reflux disease; ILD=interstitial lung disease; NAEB=non-asthmatic eosinophilic bronchitis; OSA=obstructive sleep apnea; PND=post-nasal drip; UACS=upper airway cough syndrome; UCC=unexplained chronic cough

§Item generation and reduction sample; *Validation sample; †Item reduction and validation sample; **Item generation sample

NR=not reported

NA=not applicable

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Table 4-3: Domains and items related to measurement of cough severity in adult patients with chronic cough

Domain, n	Subdomain, n	Item, n	Example phrases
Urge-to-cough (n=31)			“Although technically not a "cough" as defined medically, patients considered this sensation (urge) an inseparable part of the cough experience indicating it should be a component of an evaluation tool.”
Sensations (i.e. laryngeal, chest) that can lead to cough	Urge frequency (n=5)	Urge frequency (n=5)	“The most common descriptions were abnormal sensation in the throat, phlegm and mucous in the throat, tickle and irritation in the throat and a tickle in the throat. The median response for abnormal sensation, phlegm and irritation was 3.0 [on a scale of 1=all of the time to 7=none of the time] which indicates that the majority of patients rated that item occurring at least a good bit of the time.” “There was infrequent occurrence of pushing on the chest, pressing on the throat, food catching, itch and tingle. The majority of these participants rated these items between 4.0 and 7.0 ranging from some of the time to none of the time.” “How much warning do you get before you cough? 1=None, 2=Occasionally, 3=Frequently “Meanwhile, a study of urge to cough and associated somatic sensations in 100 unselected patients with chronic cough attending a specialist clinic in UK found that 91% always cough in response to urge to cough and that the urge to cough was frequently associated with abnormal throat sensations such as irritation (86%) and tickling (73%).”
	Urge intensity (n=6)	Urge intensity (n=6)	“Sometimes I can't sleep at all night. I have to get up and go get in a chair, because whatever is coming out of my head or my throat is sitting in this bronchial tube down there, and it's messing up everything.” “In the last 2 weeks...I have been annoyed by an irritation, such as a tickle or itch in my throat.” “Well I think the more you try and like think ‘Don’t let the tickle ... don’t let the tickle bother you and don’t cough’, sometimes the tickle comes like to a point where you just can’t stop it.”

			“People with CC may cough deliberately in response to a sensation in the throat even though referred for behavioral management of cough. The issue, in these cases, is the perception of a throat sensation rather than the actual cough.” “And that then trickles down here, and then I cough like the devil... I get-it sticks here, great big chunks of it will stick here-can't get it out.” “Congestion in throat (as though something "fuzzy" there that needs to be swallowed) and chest. Need to clear throat to get rid of it.”
Cough (n=58)	Cough control (n=10)	Cough control to prevent a cough from starting (n=3)	“People with CC may cough deliberately in response to a sensation in the throat even though referred for behavioral management of cough.” “It is hypothesized that warning before the cough characterized by irritation in the throat or a strangulating sensation is an important precursor to controlling the cough and that if people can anticipate that a cough is about to occur they can be taught strategies to inhibit the cough before it starts.” “Do you cough deliberately to clear something from your throat? 1=None, 2=Occasionally, 3=Frequently”
		Cough control once a cough has started (n=3)	“The majority of respondents (63%) were unable to suppress their cough.” “The final cough was absolutely – absolutely retched and, ugh, I think was XXXXX who mentioned embarrassed. Ugh, I had a lot of – I had a number of meetings that I – that I had to go to and, uh, I couldn't stop coughing in those things.” “An uncontrolled cough is very unpleasant for the patient.” “The cough controlled me, I had no control at all over when I coughed, how often I coughed, how strong the cough was ... it got to the point where ... I didn't even want to go out to get my shopping.”

	Cough frequency (n=33)	Overall frequency, defined as frequency of single coughs and fits/bouts (n=28)	“How often does the current cough bother you? 1. Every day more than once a day, 2. Every day at least once a day, 3. Four to six days a week, 4. Two to three days a week, 5. At least once a week, 6. Less than once a week” “The cough controlled me, I had no control at all over when I coughed, how often I coughed.” “I’m not coughing at all and, you know, it could be months before I get another cough, but when I get a cough, the frequency is close to ten and how bad it is can be a ten.” “Which of the following best describes the pattern of coughing? 1=cough occurs in bouts, 2=cough occurs continuously throughout the day, 3=other (please specify)”
		Daytime frequency (n=14)	“Counting the recordings in hourly segments allowed for a diurnal cough profile to be produced and this has been presented as three diurnal phases (Fig. 2). The mean cough scores for the nocturnal phase was significantly lower ($P < 0.001$) than the daytime or early evening phases.” “Numerical Cough Scoring System Day 0=no cough during the day, 1=cough for one short period, 2=cough for >two short periods, 3=frequent coughing that did not interfere with usual daytime activities, 4=frequent coughing that did interfere with usual daytime activities, 5=distressing cough most of the day”
		Nighttime frequency (n=21)	“Counting the recordings in hourly segments allowed for a diurnal cough profile to be produced and this has been presented as three diurnal phases. The mean cough scores for the nocturnal phase was significantly lower ($P < 0.001$) than the daytime or early evening phases.” “For me it's not being able to sleep, you know, just waking up coughing, coughing, and coughing.”

			“...I cough a lot when I go to bed. I lay down, and I find that makes me cough a lot.” “Has the cough disturbed your sleep in the previous 2 weeks? All the time, most of the time, part of the time, a small part of the time, almost never, never” “A cluster of factors developed as the most indicative for estimating the practical and emotional impact that chronic cough has on patients’ quality of life and included: high cough frequency, presence (and frequency) of nocturnal coughing, ...” “Uh, yes, uh, I wake up at least by midnight and have a series of coughs and then about 3:00.” “Numerical Cough Scoring System Night 0=no cough during the night, 1=cough on waking only, 2=wake once or early because of cough, 3=frequent waking because of cough, 4=frequent cough most of the night, 5=distressing cough most of the night”
		Morning frequency (n=6)	“Cough symptoms: how much did you cough in the morning? (in the past 7 days, range from never to always)” “Some of the participants reported that they experience more frequent coughing in the morning...”
		Prandial/postprandial frequency (n=8)	“I cough after I drink or eat.” “Cough on eating Percentage of patients with the symptom: 74.4”
		Fit/bout frequency (n=12)	“Cough bout frequency (median, range) Participants without repetitive doctor's consultations due to cough, n=840: daily (less than weekly to several times a day) Participants with repetitive doctor's consultations due to cough, n=135: several times a day (less than weekly to several times a day)

			P value: <0.001” “In the last 2 weeks...I have had coughing bouts.” “In the last 2 weeks, how many times a day have you had coughing bouts? 1=all the time (continuously), 2=most times during the day, 3=several times during the day, 4=some times during the day, 5=occasionally through the day, 6=rarely, 7=none”
	Fit/bout duration (n=4)	Fit/bout duration (n=4)	“Paroxysms of coughing, which were extended bouts of individual coughs and that were described as less controllable than a single cough, were also a component of frequency.” “Quantification in terms of epochs (frequency) effectively ignored epoch length; the poorer correlations with cough quality of life and VAS imply that epoch length was important to patients.”
	Intensity (n=17)		“Patients’ perceptions of the severity of their cough remain important and may not correlate [with cough frequency] for a number of reasons, including changes in cough intensity.”
		Effort to cough (n=6)	“It sticks here, great big chunks of it will stick here-can't get it out. And I cough, and cough, and cough, and then if you go to a restaurant and start coughing, they throw you out.” “Difficulty to expectorate.” “Sputum symptoms: how difficult was it for you to bring up phlegm? (in the past 7 days, ranging from "ot at all" to “a lot/extremely”)” “In the last 2 weeks...I have found it difficult to cough up phlegm (sputum)” “This physical effort [of coughing] was associated with a range of [adverse] symptoms.”

			“Patients described the physicality of the cough and described the sheer effort a ‘fit’ took.”
		Harshness of cough (n=2)	“Intensity of coughing was described in terms of how 'deep,' 'hard,' or 'harsh,' the coughing was.”
		Deepness of cough (n=2)	"...it was a really deep hacking, not just an ordinary sort of cough, very deep, you know, from your chest."
		Hacking due to cough (n=2)	“Mine is very hacking, and it's not intense or deep, and nothing comes up. It's not productive.... It's dry hacking.”
		Barking due to cough (n=1)	“Character of cough: Barking - having a sound quality similar to that of a dog's bark.”
		Honking due to cough (n=1)	“Character of cough: Honking - sounding like the honk of a Canadian wild goose.”
		Strong cough (n=2)	“I had no control at all over when I coughed, how often I coughed, how strong the cough was.”
		Intense cough (n=1)	“Mine is very hacking, and it's not intense or deep.” “I have it under control with the medication, but I still get some fits that usually last five minutes, and they're rather intense, uh, in coughing.”
	Associated features/sequelae (n=44)	<i>Experiences while coughing that are associated with intensity</i>	
		Dizziness due to cough (n=4)	“To me that strikes me as always a very serious bout of coughing, because obviously, oxygen wasn't getting where it was supposed to be getting. Um, and I find this is freaky, especially if you're driving, you know, and your coughing, and all of a sudden you're dizzy.”
		Syncope due to cough (n=6)	“I feel I may pass out because of my coughing.”
		Wheeze due to cough (n=13)	“Cough was commonly associated with other symptoms such as [...] wheeze (37%)...”
		Dyspnea/shortness of breath due to cough (n=15)	“Cough was commonly associated with other symptoms such as breathlessness (55%)...”

			“This physical effort was associated with a range of symptoms [...]: "It's retching, it's struggling for breath [...] It's like sometimes it's working its way up to a crescendo until I am sick.”
		Incontinence due to cough (n=15)	“In addition, cough resulted in disturbed sleep in 70%, sore throat in 45% and caused incontinence in 55% of women and 5% of men.” “Incontinence No problem: 77 (57% of chronic cough patients) Small problem: 41 (30% of chronic cough patients) Major problem: 18 (13% of chronic cough patients)” “In the last 2 weeks...I have been incontinent of urine (wet my underwear) during coughing.” “Sometimes I wet on myself I cough so hard and it makes my head hurt.” “[He] coughed so hard that [...] now, I have incontinence [sic] so bad, that I have to urinate every hour.” “[Cough] was the most important symptom in 31% of patients and up to 36% had reached the stage of retching, vomiting or being incontinent during cough episodes.”
		Tightness of throat due to cough (n=4)	“I feel tightness in my throat when I am having a coughing problem.”
		Tightness of chest due to cough (n=5)	“Within the last month, how did the following problems affect you? (0 = no problem and 5 = severe/frequent problem) Chest tightness when coughing”
		Distress due to cough (n=3)	“Finally, several studies reviewed included measures that assessed intensity of cough (e.g., distressing cough; chest/abdominal pain).”
		<i>Immediate experiences after coughing that are associated with intensity depending on susceptibility</i>	

		General pain due to cough (n=6)	“I’ve gotten to that point where I’m coughing, I mean, the diaphragm, the rib cage, umm, is painful.”
		Rib pain or fracture due to cough (n=6)	“Have you had chest or stomach pain due to cough in the last 2 weeks? All the time, most of the time, part of the time, a small part of the time, almost never, never.”
		Chest pain due to cough (n=13)	“What are the following symptoms or ailments have you had in the last month? Chest pain during exertion, [...] back pain, ...”
		Abdominal pain due to cough (n=6)	“Broken ribs, retching, chest pains, or hoarseness No problem: 64 (47% of CC patients) Small problem: 47 (35% of CC patients) Major problem: 25 (18% of CC patients)”
		Back pain due to cough (n=2)	“In the last 2 weeks...I have had chest pain during coughing.” “[He] coughed so hard that I have developed costochondritis [sic] (cracked rib cartilage) twice and ended up in the emergency room, adding that now, I have incontinence [sic] so bad, that I have to urinate every hour.” “Last year the cough was so severe I fractured two ribs.” “I am at my wits end,” adding “my ribs and my back are very sore from all the coughing.”
		Aches due to cough (n=1)	“Spectrum and frequency of adverse occurrences before and after treatment in patients whose cough was eliminated Achiness Before treatment (%): 21 After treatment (%): 0”
		Headache due to cough (n=8)	“Have you had stomach pain or headache as a result of cough? (not at all to extremely)”

			"Sometimes I throw up a lot of mucous and I really cough a lot at night...Sometimes I wet on myself I cough so hard and it makes my head hurt." "However transient, severe headache upon coughing [...] is defined as "cough headache" (CH). CH [is] considered to be a form of exertional headache."
		Sore throat due to cough (n=3)	"In addition, cough resulted in [...] sore throat in 45% [of patients]." "...I keep coughing, and that's when your throat starts to hurt."
		Tiredness/exhaustion due to cough effort (n=15)	"Cough was commonly associated with other symptoms such as feeling tired or drained (72%)..." "Do you feel drained or tired due to your cough? Never, seldom, sometimes, often, always, NA" "... one of those (coughs) that goes on and on and on and I think 'I can't do with that, it's tired me out' ... you know drained."
		Voice change/hoarseness due to cough (n=15)	I had one on a job interview, and by the time I was done trying to speak, I sounded like Minnie Mouse on speed. I was so squeaky. But it (the cough) wouldn't stop, just would not stop." "In the last 2 weeks, have you suffered from hoarseness due to coughing? All the time, most of the time, part of the time, a small part of the time, almost never, never" "My coughing problem affects my voice*." "I am often hoarse because of my cough." "In the last 2 weeks, have you suffered from hoarseness due to coughing? 1. All the time, 2. Most of the time, 3. Most of the time, 4. Part of the time, 5. A small part of the time, 6. Almost never, 7. Never"

		Retching/vomiting due to cough (n=12)	"I will cough, and cough, and cough, and cough until I basically have triggered, you know, trying to vomit in my stomach kind of thing." "Intense coughing sometimes had broader physical affects including pain, discomfort, and vomiting." "...the minute he gets up he coughs until he vomits many times." "[Cough] was the most important symptom in 31% of patients and up to 36% had reached the stage of retching, vomiting or being incontinent during cough episodes."
		Expectoration of phlegm, sputum, or mucous (n=19)	"I stopped going to church because people look at me like I have something really bad. Sometimes I throw up a lot of mucous..." "During the previous 2 weeks, have you been disturbed by the increase in sputum during coughing? 1. Every time, 2. Most often, 3. Often, 4. Sometimes, 5. From time to time, 6. Rarely, 7. Never"
		Umbilical hernia due to cough (n=1)	"Other cough complications were encountered in 25 patients. These were [...] umbilical hernia (6 patients, 3.6%)..."
		Excessive sweating due to cough (n=1)	"Spectrum and frequency of adverse occurrences before and after treatment in patients whose cough was eliminated Excessive sweating Before treatment (%): 29 After treatment (%): 7"
		Watery eyes due to cough (n=1)	"This physical effort [of coughing] was associated with a range of symptoms including headache, eyes watering, pain, syncope and incontinence"
		Runny nose due to cough (n=1)	"It's retching, it's struggling for breath ... it's vomiting ... Nose running, headaches with just the coughing."

n = number of studies endorsing the item or domain

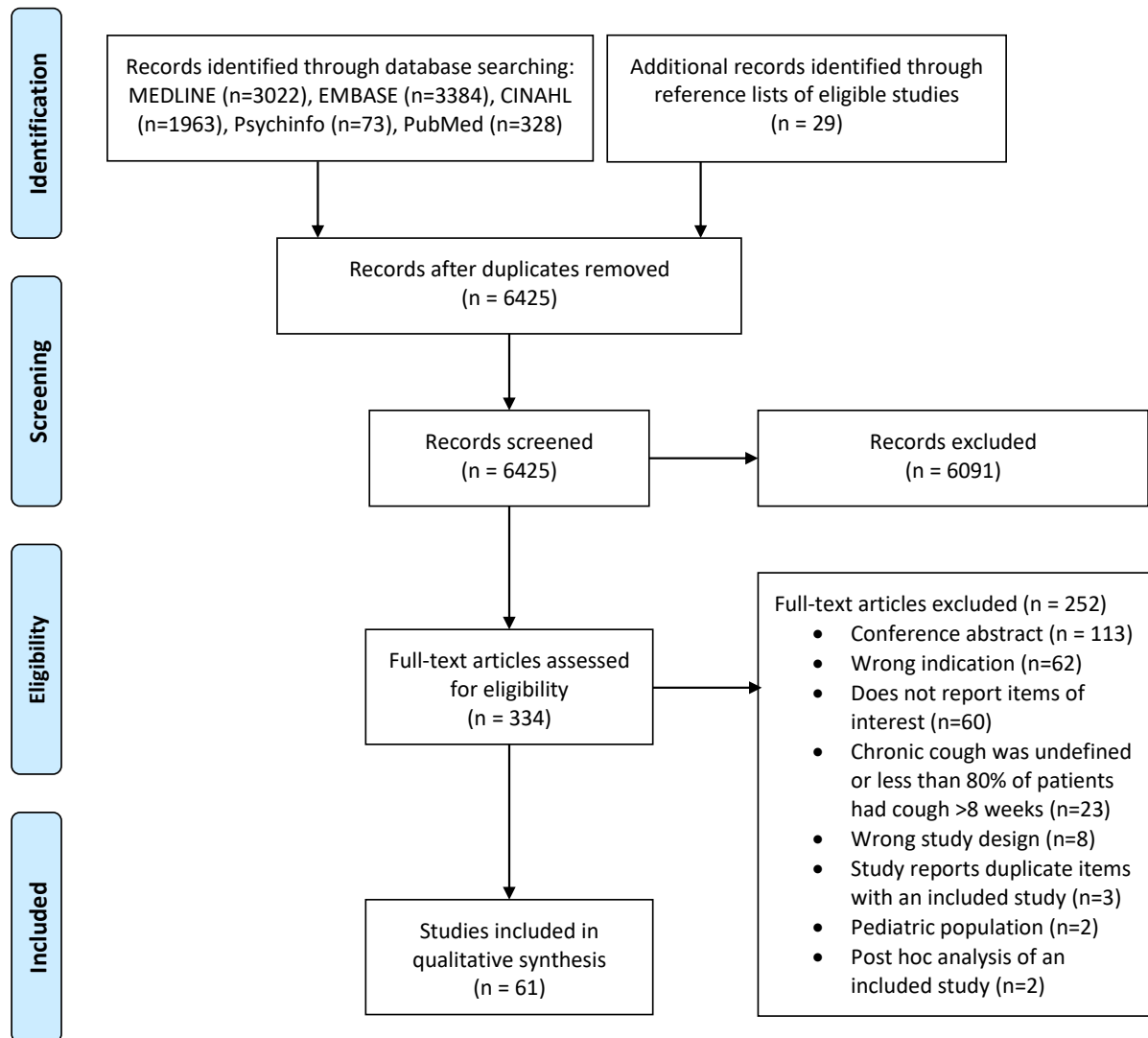


Figure 4-1: Study selection flow chart

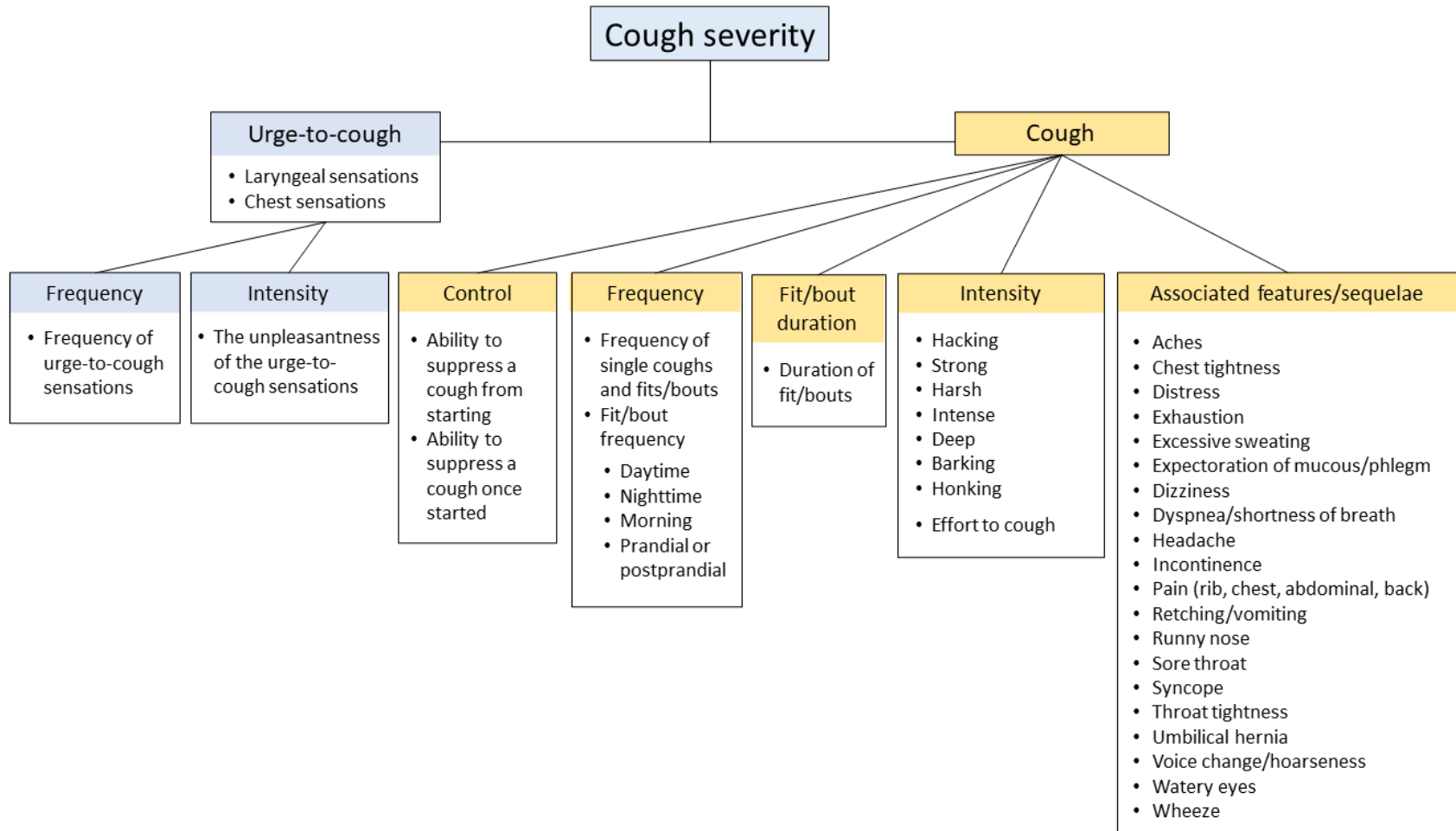


Figure 4-2: Conceptual framework of cough severity in patients with chronic cough

eTable 4-1: Search strategy

MEDLINE	
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Search Strategy:	

1	(measure or measurement).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1132643)
2	"Quality of Life"/ (195719)
3	(QALY or HRQOL or HRQL).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (28959)
4	patient reported outcome measures/ (6171)
5	Patient reported outcome*.mp. (21964)
6	PROMS.mp. (2015)
7	Self Report/ (32811)
8	questionnaire*.mp. or exp "Surveys and Questionnaires"/ (1288591)
9	(scale or scales).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (879118)
10	measures.mp. (752006)
11	assessment.mp. (1381428)
12	index.mp. (1064192)
13	(diary or diaries).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (24177)
14	or/1-13 (4809120)
15	Cough/ (15928)
16	(cough adj5 (chronic* or persistent* or refractory)).mp. (6331)
17	15 or 16 (19484)
18	14 and 17 (4874)
19	COPD.mp. or exp Pulmonary Disease, Chronic Obstructive/ (73349)
20	exp Asthma/ or asthma.mp. (176455)
21	bronchiectasis.mp. or Bronchiectasis/ (12627)
22	Gastroesophageal Reflux/ (25909)
23	GERD.mp. (8747)
24	Respiratory Tract Diseases/ (22194)
25	or/19-24 (295030)
26	25 and cough.ti. (1904)
27	14 and 26 (575)
28	18 or 27 (4902)
29	limit 28 to yr="2007 -Current" (3022)
EMBASE (OVID)	

Database: Embase <1974 to 2020 August 20>

Search Strategy:

-
- 1 (measure or measurement).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1585118)
 - 2 "quality of life"/ (473877)
 - 3 (QALY or HRQOL or HRQL).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (49704)
 - 4 patient-reported outcome/ (23682)
 - 5 Patient reported outcome*.mp. (40876)
 - 6 PROMS.mp. (3172)
 - 7 self report/ (121253)
 - 8 questionnaire*.mp. (967340)
 - 9 questionnaire/ (698105)
 - 10 (scale or scales).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1266774)
 - 11 measures.mp. (917402)
 - 12 assessment.mp. (2729948)
 - 13 index.mp. (1225948)
 - 14 (diary or diaries).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (38577)
 - 15 or/1-14 (6762480)
 - 16 (cough adj5 (chronic* or persistent* or refractory)).mp. (11599)
 - 17 chronic cough/ (4133)
 - 18 16 or 17 (11599)
 - 19 15 and 18 (3898)
 - 20 COPD.mp. or chronic obstructive lung disease/ (153682)
 - 21 exp asthma/ or asthma.mp. (290806)
 - 22 bronchiectasis.mp. or bronchiectasis/ (21916)
 - 23 Gastroesophageal Reflux.mp. or gastroesophageal reflux/ (60147)
 - 24 GERD.mp. (18388)
 - 25 respiratory tract disease/ (57958)
 - 26 or/20-25 (532230)
 - 27 26 and cough.ti. (3389)
 - 28 15 and 27 (1299)
 - 29 19 or 28 (4341)
 - 30 limit 29 to yr="2007 -Current" (3384)

CINAHL (Ebsco)

#	Query	Results
S28	S18 OR S27	1,963
S27	S14 AND S26	176
S26	S24 AND S25	555
S25	TI cough*	3,418
S24	S19 OR S20 OR S21 OR S22 OR S23	79,446
S23	(MH "Respiratory Tract Diseases")	4,219
S22	(MH "Gastroesophageal Reflux") OR "GERD"	7,802

S21	(MH "Bronchiectasis") OR "bronchiectasis"	1,971
S20	(MH "Asthma+") OR "asthma"	44,584
S19	(MH "Pulmonary Disease, Chronic Obstructive") OR "COPD"	25,710
S18	S14 AND S17	1,960
S17	S15 OR S16	6,586
S16	TX (cough N5 (chronic* or persistent* or refractory))	1,753
S15	(MH "Cough")	5,737
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR	
S13	1,814,773	
S13	TX diary or diaries	19,561
S12	"index"	276,816
S11	"assessment"	653,257
S10	"measures"	343,398
S9	TX scale or scales	557,780
S8	(MH "Questionnaires") OR "questionnaire"	501,631
S7	(MH "Self Report")	69,370
S6	"PROMS"	1,000
S5	TX Patient reported outcome*	11,096
S4	(MH "Patient-Reported Outcomes")	2,540
S3	TX QALY or HRQOL or HRQL	13,599
S2	(MH "Quality of Life")	111,854
S1	measure or measurement	646,905
PsycInfo (OVID)		
Database: APA PsycInfo <1806 to August Week 3 2020>		
Search Strategy:		

1	(measure or measurement).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]	(396852)
2	exp "quality of life"/	(43380)
3	(QALY or HRQOL or HRQL).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]	(6651)
4	patient reported outcome measures/	(312)
5	Patient reported outcome*.mp.	(3027)
6	PROMS.mp.	(213)
7	self-report/	(17610)
8	exp Questionnaires/ or questionnaire*.mp.	(414670)
9	(scale or scales).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]	(688234)
10	measures.mp.	(385967)
11	exp Measurement/	(439807)
12	assessment.mp.	(397089)
13	index.mp.	(198172)
14	(diary or diaries).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]	(13544)
15	or/1-14	(1676130)
16	(cough adj5 (chronic* or persistent* or refractory)).mp.	(117)
17	COPD.mp. or exp Chronic Obstructive Pulmonary Disease/	(2129)
18	asthma.mp. or exp Asthma/	(8076)
19	bronchiectasis.mp.	(33)
20	GERD.mp.	(304)

21	Gastroesophageal Reflux.mp. (409)
22	exp Respiratory Tract Disorders/ (14824)
23	or/17-22 (18802)
24	23 and cough.ti. (69)
25	15 and 24 (30)
26	15 and 16 (48)
27	25 or 26 (73)
PubMed	
Query (measure or scale or index or or assessment or questionnaire) AND (((("publisher"[Filter] OR "inprocess"[Filter]) OR "pubmednotmedline"[Filter]) OR "pubstatusaheadofprint"[All Fields])) AND (cough[Title]))	
Sort By Publication Date	
Search Details ((((((((((((((((("measurability"[All Fields] OR "measurable"[All Fields]) OR "measurably"[All Fields]) OR "measure s"[All Fields]) OR "measureable"[All Fields]) OR "measured"[All Fields]) OR "measurement"[All Fields]) OR "measurement s"[All Fields]) OR "measurements"[All Fields]) OR "measurer"[All Fields]) OR "measurers"[All Fields]) OR "measuring"[All Fields]) OR "measurings"[All Fields]) OR "measurment"[All Fields]) OR "measurments"[All Fields]) OR "weights and measures"[MeSH Terms]) OR ("weights"[All Fields] AND "measures"[All Fields])) OR "weights and measures"[All Fields]) OR "measure"[All Fields]) OR "measures"[All Fields]) OR (((((((("scale s"[All Fields] OR "scaled"[All Fields]) OR "scaling"[All Fields]) OR "scalings"[All Fields]) OR "weights and measures"[MeSH Terms]) OR ("weights"[All Fields] AND "measures"[All Fields])) OR "weights and measures"[All Fields]) OR "scale"[All Fields]) OR "scales"[All Fields])) OR (((((((((((("abstracting and indexing"[MeSH Terms] OR ("abstracting"[All Fields] AND "indexing"[All Fields])) OR "abstracting and indexing"[All Fields]) OR "index"[All Fields]) OR "indexed"[All Fields]) OR "indexes"[All Fields]) OR "indexing"[All Fields]) OR "indexation"[All Fields]) OR "indexations"[All Fields]) OR "indexe"[All Fields]) OR "indexer"[All Fields]) OR "indexers"[All Fields]) OR "indexs"[All Fields])) OR (((((((("assess"[All Fields] OR "assessed"[All Fields]) OR "assessment"[All Fields]) OR "assesses"[All Fields]) OR "assessing"[All Fields]) OR "assessment s"[All Fields]) OR "assessments"[All Fields])) OR (((("questionnaire"[All Fields] OR "questionnaire s"[All Fields]) OR "surveys and questionnaires"[MeSH Terms]) OR ("surveys"[All Fields] AND "questionnaires"[All Fields])) OR "surveys and questionnaires"[All Fields]) OR "questionnaire"[All Fields]) OR "questionnaires"[All Fields])) AND (((("publisher"[Filter] OR "inprocess"[Filter]) OR "pubmednotmedline"[Filter]) OR "pubstatusaheadofprint"[All Fields]) AND "cough"[Title]))	
Results 328	
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eTable 4-2: Characteristics of cough-specific PROMs included in the review

Patient reported outcome measurement	Target conditions	Construct(s) assessed	Number of items	Number of domains	Domains/items assessed	Recall period	Score range
Chronic Cough Impact Questionnaire (CCIQ)¹	Chronic cough	Cough impact on QoL	21	4	Impact on daily life Impact on relationships Impact on mood Impact on sleep	2 weeks	21-105
Cough and Sputum Assessment Questionnaire (CASA-Q)²	Cough in patients with chronic obstructive pulmonary disease and chronic bronchitis	Frequency and severity of cough and sputum, impact on QoL	20	4	Cough symptom Cough impact Sputum symptom Sputum impact	1 week	0-100
Cough Assessment Test (COAT)³	Chronic cough	Cough impact on QoL	5	0	Frequency Impact on daily life Impact on sleep Fatigue Cough hypersensitivity	3 days	0-20

Cough Evaluation Test (CET)⁴	Chronic cough	Cough severity, cough impact on QoL	5	0	Frequency Intensity Impact on sleep Impact on daily life Impact on psychological health	Not specified	5-25
Cough Severity Diary (CSD)⁵	Chronic and subacute cough	Cough severity, cough impact on QoL	7	3	Frequency Intensity Disruption	1 day	0-10
Cough Severity Index (CSI)⁶	Chronic cough related to the upper airway	Cough severity, cough impact on QoL	10	0	Cough hypersensitivity Impact on daily life Impact on social life Impact on mood	1 month	0-40
Cough Specific Quality of Life (CQLQ)⁷	Chronic and acute cough	Cough impact on QoL	28	6	Physical complaints Psychosocial issues Functional abilities Emotional well-being Extreme physical complaints Personal safety fears	Not specified	28-112

Cough Symptom Score (CSS) ⁸	Chronic cough	Cough severity, cough impact on QoL	2	0	Frequency Intensity Impact on daily activities Impact on sleep	Not specified	0-5
Hull Airway Reflux Questionnaire (HARQ) ⁹	Chronic cough	Cough hypersensitivity	14	0	Cough hypersensitivity Cough symptom	1 month	0-70
Leicester Cough Questionnaire (LCQ) ¹⁰	Chronic cough	Cough impact on QoL	19	3	Physical Psychological Social	2 weeks	3-21
Newcastle Laryngeal Hypersensitivity Questionnaire (LHQ) ¹¹	Laryngeal dysfunction syndromes	Laryngeal sensory disturbance	14	3	Obstruction Pain/thermal Irritation	Not specified	score ≤ 17 taken as abnormal
Punum Ladder ¹²	Chronic cough	Cough severity, cough impact on QoL	2	0	Cough severity Overall quality of life	1 week	0-10 (two subscales)

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Chapter 5 Assessing cough symptom severity in refractory or unexplained chronic cough: findings from patient focus groups and an international expert panel

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Abstract

Background: Cough symptom severity represents an important subjective endpoint to assess the impact of therapies for patients with refractory or unexplained chronic cough (RCC/UCC). As existing instruments assessing the severity of cough are neither widely available nor tested for measurement properties, we aim to develop a new patient-reported outcome measure addressing cough severity.

Objective: To establish items and domains that would inform development of a new cough severity instrument.

Methods: Three focus groups involving 16 adult patients with RCC/UCC provided data that we analyzed using directed content analysis. Discussions led to consensus among an international panel of 15 experts on candidate items and domains to assess cough severity.

Results: The patient focus group provided 48 unique items arranged under broad domains of urge-to-cough sensations and cough symptom. Feedback from expert panel members confirmed the appropriateness of items and domains, and provided an additional subdomain related to cough triggers. The final conceptual framework comprised 51 items in the following domains: urge-to-cough sensations (subdomains: frequency and intensity) and cough symptom (subdomains: triggers, control, frequency, fit/bout duration, intensity, quality, and associated features/sequelae).

Conclusions: Consensus findings from patients and international experts established domains of urge-to-cough and cough symptom with associated subdomains and relevant items. The results support item generation and content validity for a novel patient-reported outcome measure for use in health research and clinical practice.

Introduction

Chronic cough lasting >8 weeks is a common health problem that affects 2-18% of adults worldwide.¹ Although clinicians can often identify and effectively treat known causes of cough—including asthma, chronic obstructive pulmonary disease, bronchiectasis, gastro-esophageal reflux disease, and upper airway cough syndromes—many patients, despite treatment targeting these underlying conditions, experience refractory chronic cough (RCC).^{2,3} In others, clinical assessment fails to identify a cause and patients are classified with unexplained chronic cough (UCC).^{2,3} Patients with RCC/UCC often exhibit cough hypersensitivity syndrome, defined as a troublesome cough triggered by low levels of thermal, mechanical, or chemical irritants.⁴

RCC/UCC can lead to significant impairment in quality of life (QoL); thus, QoL serves as an important endpoint in establishing treatment impact. Cough-specific QoL measures, including the Leicester Cough Questionnaire (LCQ),⁵ Cough Quality of Life Questionnaire (CQLQ),⁶ and Chronic Cough Impact Questionnaire (CCIQ),⁷ address the impact of cough symptoms on patients' physical, social, and psychological health. Such assessments, although crucial in addressing treatment impact, are limited in that they capture domains influenced by factors aside from cough symptom severity (i.e., psychosocial context). The same degree of cough in two patients can thus lead to substantially different responses regarding cough QoL. Neuromodulatory agents, such as pregabalin⁸ and experimental neurokinin receptor antagonists,⁹ can improve cough QoL independent of cough suppression. Thus, full insight into therapeutic efficacy must, alongside cough QoL, include assessment of cough symptom severity.

Objective cough frequency using the VitaloJAK monitor represents the most common primary endpoint in antitussive clinical trials.¹⁰ Cough monitors provide direct insight into whether treatment improves cough frequency by quantifying spontaneous coughs over a defined period.

Existing monitors are limited, however, in that they are typically only used over a 24-hour period, they can pose burden for patients to wear repeatedly, and they are expensive to administer.¹¹ Furthermore, they cannot assess whether other dimensions of cough (i.e., intensity) may be improved with treatment. A measure that directly assesses patients' experience of cough and sequelae (herein referred to as "symptom severity") might address the limitations of currently available instruments.

The visual analogue scale (VAS)¹² and Cough Severity Diary (CSD)¹³ represent existing instruments to assess cough severity. Limitations of the cough severity VAS include lack of evidence supporting its measurement properties and limitations of single-item instruments in fully capturing complex patient experiences.¹⁴ While the CSD has undergone psychometric testing,¹⁵ it is currently a proprietary questionnaire with restrictions on use for clinical and research purposes. Furthermore, the CSD lacks conceptual clarity in that the domain "disruption" measures cough impact on daytime activities and sleep. A widely available instrument with established measurement properties that measures cough symptom severity rather than cough QoL remains unavailable.

We aim to develop a cough symptom severity instrument—the McMaster Cough Severity Questionnaire—for use in patients with RCC/UCC. To inform item generation for the instrument, we conducted a systematic survey in which we identified 43 items addressing the following domains: urge-to-cough sensations (subdomains: frequency and intensity) and cough symptom (subdomains: frequency, control, bout duration, intensity, and associated features/sequelae).¹⁶ To assess the comprehensiveness and appropriateness of items, domains, and subdomains identified in our systematic survey, we conducted patient focus groups and consultation with clinical experts, and report here our findings.

Methods

Patient focus groups

We conducted focus groups with patients with RCC/UCC to explore (1) attributes of their cough and its severity; and (2) issues important to patients in relation to their cough severity. This report adheres to consolidated criteria for reporting qualitative research standards.¹⁷

Patient recruitment

We recruited 16 adult (≥ 18 years old) patients with RCC/UCC from a tertiary care clinic at the McMaster University Medical Centre (Hamilton, Ontario, Canada). Eligible patients experienced cough lasting >8 weeks. We excluded patients who currently smoked or had a smoking history of >10 pack-years; whose English was limited; or who presented with memory, cognitive, or psychiatric issues preventing optimal participation. Patients provided written informed consent and received \$50 for participating. The Hamilton Integrated Research Ethics Board provided ethics approval (No. 12-881).

Sample

We employed purposive sampling to obtain experiences among a diversity of patients with RCC/UCC.¹⁸ Our sample size was based on the anticipated number of patients required to reach thematic saturation on the concept of cough symptom severity.¹⁹

Group configuration and data collection

Following informed consent, a study coordinator (EK) contacted patients over the telephone to establish their age, sex, smoking history, and co-morbidities. The coordinator convened three focus groups, each with 5–6 patients.

Following a semi-structured guide (**eMethods 5-1**), a trained interview facilitator (EK) led the focus group discussions over Zoom videoconferencing, each for 60–90 minutes. A prior systematic survey¹⁶ informed an initial draft of the interview guide that was subsequently revised based on input from the steering group (GHG, IS). The facilitator asked open-ended questions, followed by directed questions on themes identified from the systematic survey. As patients discussed, the facilitator identified emerging themes for further discussion. To ensure full exploration of themes, we provided patients with the opportunity to add comments at the end. Focus groups were audio-recorded, transcribed verbatim, and de-identified.

Data analysis

We used directed content analysis, informed by a prior conceptual framework,¹⁶ to identify related themes.²⁰ Two researchers (EK, CM) independently coded transcripts by assigning statements to items or domains in the framework. The two researchers discussed statements that could not be categorized within existing items or domains, and if relevant, created a new code. Researchers then summarized these codes as a new item or domain contributing to our evolving conceptual framework. The study team, comprised of clinical experts, methodologists, and patient partners, reviewed the results of the analysis, and resolved disagreements through discussion leading to consensus.

Expert consensus study

We elicited feedback from an international panel of chronic cough experts on the comprehensiveness and appropriateness of items and domains identified from the systematic survey and patient focus groups. Using purposive sampling, we invited 14 key opinion leaders in chronic cough, all of whom agreed to participate. The final group consisted of 18 members (the steering group: EK, GHG, PMOB, IS, and 14 experts: RA, HB, LPB, RC, PD, LD, SKF, CLF,

PGG, RSI, PM, LM, JAS, WJS). Experts came from the UK, USA, Canada, and one each from Australia, Belgium, China, Ireland, Saudi Arabia, and South Korea.

Pre-meeting survey and feedback

Without having seen our conceptual framework, expert panel members provided 3–10 questions to assess patients' severity of cough. Once returned, the steering group then sent a draft conceptual framework, from which experts could provide written suggestions to either drop, merge, and/or add items or domains.

Consensus meeting

The steering group and expert panel participated in a 1-hour videoconference to reach consensus on the items and domains for a cough symptom severity instrument. The steering group presented the results of the systematic survey, patient focus groups, and pre-meeting feedback. Following presentation of the results, experts participated in discussions addressing the proposed items and domains. After the conference, the steering group sent expert panel members a report of the discussion and a modified list of items and domains based on their feedback. Experts had the opportunity, if desired, to provide additional written feedback.

Results

The 16 focus group patients had a median age of 61 years. Most identified as female (68.8%), reported no history of smoking (81.3%), and coughed for a median duration of 13.5 years (**Table 5-1**).

Statements from patients provided 48 items that we categorized under two broad domains of cough symptom severity: urge-to-cough sensations (subdomains: frequency and intensity) and

cough symptom (subdomains: control, frequency, fit/bout duration, intensity, quality, and associated features/sequelae) (Figure 5-1; Table 5-2).

Urge-to-cough sensations

Patients described sensations, including “tickle”, “chest pressure”, “chest tightness”, “something in the back of the throat”, and “hoarseness”, as antecedents to coughing. These sensations could vary in terms of intensity: *“Most of the severe ones start with that karate chop effect in my throat. [...] Another time, I will feel pressure in my chest... like someone’s pushing with their hand down on my chest”* (#15). The frequency with which patients experienced these sensations ranged considerably, some reporting a constant sensation and others reporting that it occurs less consistently or not at all:

“I’m constantly feeling as though I want to clear the back of my throat” (#3).

“So there’s not always any sensation or sign that it’s going to come on. I do get sometimes that dry tickle [but] it’s not consistent” (#1).

When asked to compare the severity of their urge-to-cough sensations in relation to their cough, patients reported different experiences:

“When I said my urge-to-cough is severe, it’s just as severe as the cough... one is not worse than the other” (#12).

“My urge-to-cough, is it more severe than the cough itself? Not necessarily” (#6).

Cough control

Patients perceived an ability to suppress the start of their cough as a less severe cough: *“At the beginning, I know I could take a cough drop, and it would make it less severe or I could drink water and it may control it a bit, but I mean those possibilities are long gone way in the past”* (#14). The lack of control was often attributed to an urge sensation: *“It just seems that, as the*

phlegm builds up it just gets to a point where you just have no choice. I mean you're going to cough" (#3). Patients also described cough severity in terms of control once a cough had started: *"There's no ability to stop it or control it; it's like it takes over, it just takes over your body and until that cough is out"* (#10). Some patients shared that, once started, their ability to bring a cough under control was dependent upon bringing up phlegm.

Cough frequency and fit/bout duration

Patients assessed cough severity in terms of the number of coughs (single or episodes) that they experience in a day: *"I judge severity by frequency, so some days I may only have three to four episodes which I would classify as a good day, other days I may have 12 to 15 episodes which obviously, is not so good of a day, so I kind of throw that in there with severity- how many episodes I have"* (#1). When describing cough frequency, patients noted that periods of the day (i.e., morning, daytime, and/or nighttime) may be more or less problematic: *"Whether at any time of day or night I'm worse in the morning [and] worse at night, but I do cough all day long"* (#11). In addition to variation within a day, patients noted that each day could differ in terms of frequency: *"It's not really a daily thing, like the milds would be daily, sometimes like anywhere from 10–20 times in a day I'll have a mild cough. The severe ones, it all depends upon when somebody tells a good joke or somebody makes me laugh is when I get my more severe coughs so it varies right? It could be once a week, some maybe once a month"* (#16). When asked to recall cough frequency, some patients struggled to provide an estimate and alluded to preoccupation with their coughing or the fact it had become inured to them: *"I don't keep track of how many times I cough a day, I just know I cough constantly"* (#10). The number of fits/bouts of coughing seemed easier to recall: *"I have it mostly everyday, some days I may have 1 or maximum 2 of what I would call the severe*

cough” (#6). The duration of coughing fits/bouts was seen as a factor to their overall perception of cough severity: “Many times, my cough gets so bad that I will go for 5-10 minutes” (#15).

Cough quality and intensity

Patients provided descriptions about the sensory experience of coughing, including “hacking”, “harsh”, “strong”, “deep”, and “barking”. The study team classified these terms separately from intensity, which patients conveyed in terms of the physical effort required to cough and the difficulty expectorating:

“It can get so severe that I literally have to go to the sink just to hold on just to keep my body” (#9).

“It’s just sometimes, the phlegm comes up very easily, very quickly. Other times I’ll have to really start to expel it and pressure it” (#6).

Associated features/sequelae

Patients described symptoms during or immediately after an episode of coughing, including headache and pain around their chest, ribs, abdomen, or back: *“It just seems to be like every part of your chest and all around there ache, like really ache, when it’s really bad” (#5).* Patients described feeling breathless, dizzy, wheezy, and/or on the verge of fainting after a fit of coughing: *“At times it’ll get bad enough, where I blackout, or I feel like I’m going to blackout, like I can’t get my breath, I’m choking constantly” (#4).* Coughing drove some patients to vomit or retch, and many felt exhausted: *“You just feel very weak, like you just feel sick and helpless. It takes a lot out of you, a lot of energy” (#15).* Female patients described stress incontinence following a severe cough. Less common symptoms included hernia, rib fracture, voice loss, hoarseness, chest and head pressure, throat and chest tightness, and feeling overly heated (**Figure 5-1; Table 5-2**).

Conceptual difference between cough symptom severity and impact

Although cough symptom severity is related to cough impact on QoL, patients reported differences in the extent to which the same symptom could be viewed as bothersome: *“I feel like my cough is very minimal, because I do not have these violent coughs. I do not choke, my heart rate is always normal and my cough, as I said, I do not get violent coughs. But still it’s bothering me a lot, especially during the night”* (#8). The study team therefore classified impact on QoL as a separate concept from symptom severity.

Expert consensus

An open-ended survey to members of the expert panel identified 32 potential items/domains considered relevant to cough symptom severity (**Table 5-3**). During the consensus meeting, experts agreed that severity should be conceptualized as an overarching term encompassing domains of frequency, intensity, duration, quality, and associated features/sequelae. Experts also agreed that urge-to-cough is an important symptom to capture in a cough severity instrument. A small minority viewed the impact of cough symptoms on QoL (i.e., daily activities, ability to speak, social life) as a necessary aspect of symptom severity. Experts raised cough hypersensitivity as a potentially missing concept from the framework. Thus, the steering group added “triggers” as an additional subdomain (**Figure 5-1**).

Discussion

We report consensus findings from patient focus groups and expert panel discussions regarding items and domains to assess cough symptom severity in patients with RCC/UCC. The study confirms findings from a prior systematic survey and identifies 8 additional items/domains. The final conceptual framework includes 51 items arranged under two broad domains of urge-to-

cough (subdomains: frequency and intensity) and cough symptom (subdomains: triggers, control, frequency, fit/bout duration, intensity, quality, and associated features/sequelae) (**Figure 5-1**).

Although experts and patients agreed on the appropriateness of items and domains, a small minority of experts viewed the impact of cough on QoL as a necessary component of symptom severity. Evaluation of symptom severity and impact on QoL provides a complete assessment of cough (**Figure 5-2**). An instrument addressing symptom severity alone may, however, be important for several reasons.

First, there is substantial variation in the extent to which patients find the same symptoms bothersome. Impact on QoL can be influenced by factors other than cough symptom severity, including co-morbid anxiety and depression.²¹ As this study focused solely on symptom severity, rather than impact, the domains identified are less likely to be influenced by distal factors.

Second, the experience of chronic cough over years can have cumulative impact on QoL that may not be responsive to change in symptom severity over short periods of treatment. Current patient-reported outcome measures primarily assess cough impact on QoL and demonstrate modest association with objective measures,²²⁻²⁴ cough symptom severity requires directed and targeted measurement that responds well to treatment effects.

Third, neuromodulatory agents can improve cough QoL with little to no effect on underlying objective cough frequency.^{8,9} A subjective instrument assessing change in cough severity, rather than impact, is therefore needed to establish whether treatment is targeting the intended symptom. For this reason, regulatory agencies often require that primary endpoints measure on-target effects to establish effectiveness for claimed indications.

Fourth, although cough frequency monitors are ideal to objectively assess cough, their limited feasibility in clinical practice suggests potential utility in developing a symptom severity

instrument for better longitudinal assessment. The cough severity VAS, although widely used in clinical practice, has limitations as a single-item instrument and with lack of evidence supporting its measurement properties.

Finally, a cough symptom severity instrument that assesses domains of cough and urge-to-cough sensations may identify subgroups of patients who share cough pathophysiology.²⁵ Although current guidelines recommend treatment with centrally-acting neuromodulatory agents and speech therapy, there is currently limited evidence to inform patients who may benefit more from a specific treatment. As new therapies, including peripherally-acting P2X3 antagonists,²⁶⁻³¹ that target specific pathophysiology are introduced, stratification of patients with chronic cough based on domains of cough symptom severity may be useful for precision medicine.

A qualitative study informed development of the CSD and identified three concepts under cough severity: intensity, frequency, and disruption.³² Although our results are consistent with themes identified in their study, our work differs in that we involved patient partners and experts to optimally define the measurement construct of a cough symptom severity instrument,³³⁻³⁵ and strove for conceptual clarity by excluding items/domains related to cough impact on QoL.

Other strengths of this study include strict inclusion of patients who would qualify for phase 2/3 antitussive clinical trials;^{28,29} and triangulation of focus groups with an existing framework, patient partners, and clinical experts.

Limitations include recruitment of English-speaking patients from a single tertiary clinic; potential selection bias of experts; potential response bias among focus group patients; and subjectivity in interpretation of themes leading to consensus.

Conclusion

We outline a conceptual framework for measuring cough symptom severity in patients with RCC/UCC. The results support content validity of a patient-reported outcome measure. Future studies should address items and domains that are most important to patients for item reduction of a cough symptom severity questionnaire.

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Figure 5-1: Conceptual framework of cough symptom severity in patients with RCC/UCC

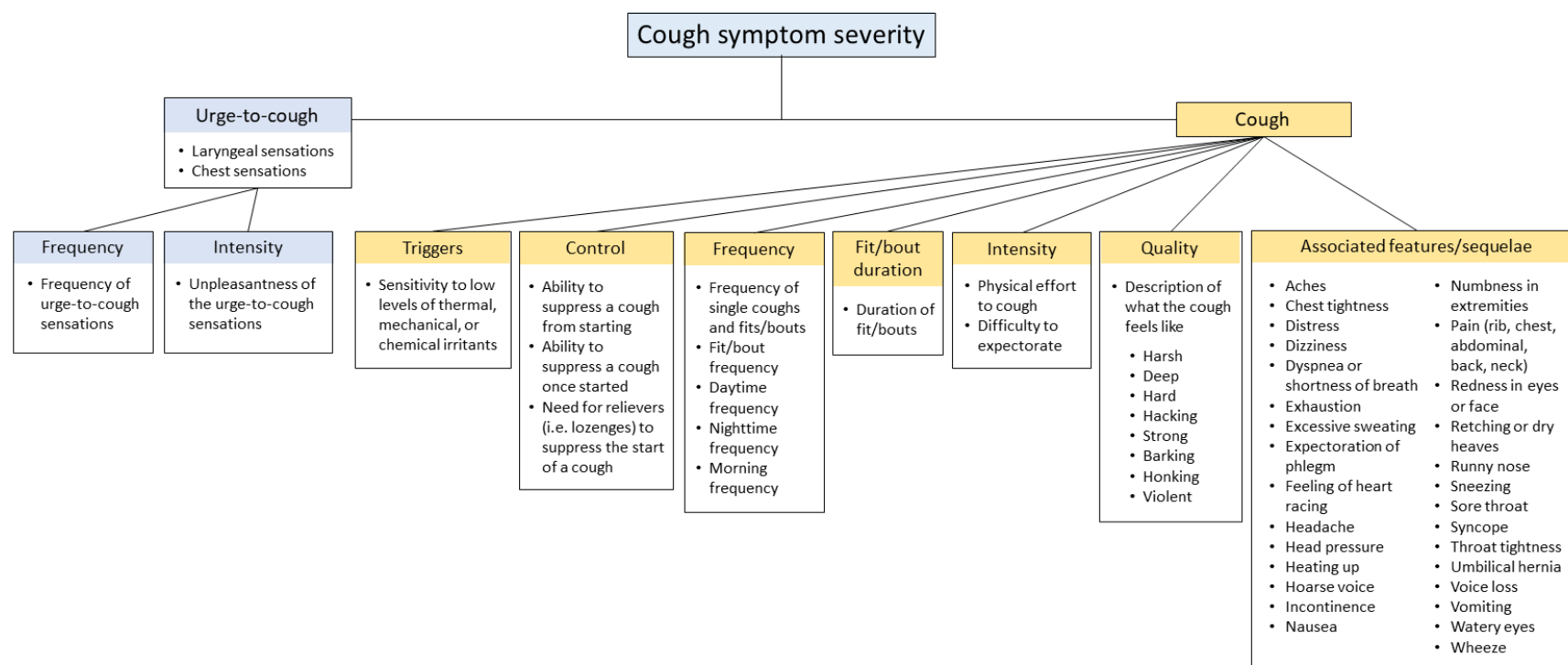


Figure 5-2: Assessing cough in patients with RCC/UCC

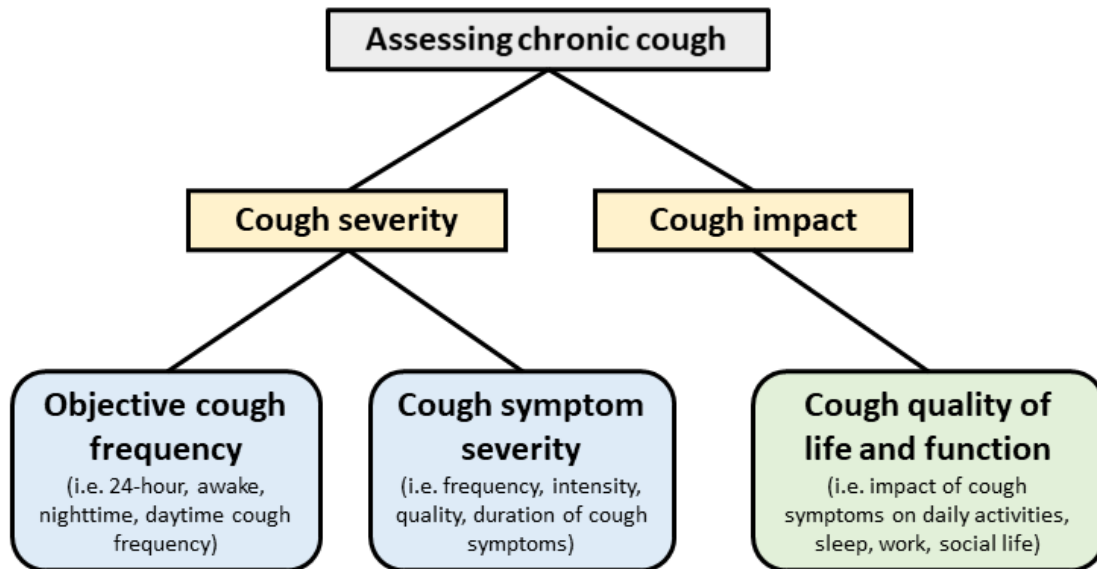


Table 5-1: Characteristics of 16 focus group patients

Category	
Sex, n (%)	
Male	5 (31.3%)
Female	11 (68.8%)
Age, years	
Median (range)	61 (50-79)
Smoking status, n (%)	
Never	13 (81.3%)
Former	3 (18.8%)
Duration of cough, years	
Median (range)	13.5 (2-44)
Co-morbidities, n (%)	
Asthma	1 (6.3%)
Gastroesophageal reflux disease	2 (12.5%)
Chronic bronchitis	1 (6.3%)

Table 5-2: Domains and items related to measurement of cough symptom severity in patients with RCC/UCC

Domain	Subdomain	Item	Example phrases
1. Urge-to-cough Sensations (i.e. laryngeal, chest) that can lead to cough	1.1 Urge frequency	1.1.1 Urge frequency	“I’m constantly feeling as though I want to clear the back of my throat and that’s where the cough comes in and it’s almost like... If I’ve cleared my throat for maybe just a moment or two it’s almost like there’s a sense of, ‘okay, I’m good.’ But then almost as quickly as it’s cleared, I feel like it’s starting again so it’s mostly in the background. I’m constantly feeling like I’ve got something in the back of my throat. And then, once it builds up to a certain point, I’m feeling like I just I am coughing” (#3, male, age 53 years). “Okay, so there’s not always, like I mentioned, any sensation or sign that it’s going to come on. I do get sometimes that dry tickle [but] it’s not consistent” (#1, male, 44). “It’s kind of like a constant tickle that I try to get rid of [and] if I don’t, then I wind up coughing to try to get rid of it” (#13, female, age 62 years). “The urge comes and then there’s no stopping it once that urge is there. And the urge is there a lot” (#12, female, age 75 years).
	1.2 Urge intensity	1.2.1 Urge intensity	“For me, it would be definitely the tickle as a sensation that I get. That’s the most common with my mild [coughs]. When I get into my severe [coughs] it could be a hostile tickle because of the laughing getting that tickle started. Even it’s like a little bit of a pressure build up at the larynx or like I don’t know... a little bit below Adam’s apple there’s a little bit of pressure builds up there just to start the hack attack or severe cough” (#16, male, age 48 years). “Most of my severe coughs start with that karate chop effect, I was talking about... It can be just... boom it hits me, most of the severe ones start with that karate chop effect in my throat [...] Another time I will feel pressure in my chest... like something... I feel just like someone’s pushing with their hand down on my chest, and then that will start a cough as well. You know the pressure in my chest, next thing you know it goes more into my throat, and then I start coughing” (#15, female, age 57 years). “I almost feel like my throat is closing by the time I get up in the morning, it feels kind of like where your trachea is that, it’s almost like, full? Like the passageway, whether it’s

			mucus or whatever it is, I went to the doctor and they said there's nothing there, but the same sensation is there, that it's closed" (#9, female, age 50 years).
2. Cough	2.1 Cough control		"I don't think I've got the ability anymore to stop my cough" (#12, female, age 75 years). "I cough more than I say I do because I said it, it's part of your life, whether you like it or not, you can't control it, or I can't control it, it just comes" (#7, female, age 72 years). "I mean if I could control the cough, it would be great. I've been using- I've been seeing a speech therapist to try to help me control the cough and she's heard me cough a couple of times and she'll say to me, 'Oh, you can control that just swallow it down,' [and] it's like no I can't swallow it down, because then I'll start to choke so it's a no-win situation for me" (#4, female, age 62 years).
		2.1.1 Cough control to prevent a cough from starting	"It just seems that, as the phlegm builds up it just gets to a point where you just have no choice. I mean you're going to cough or you're going to try and clear it or get it out" (#3, male, age 53 years). "The less severe cough they all start with a trickle - with a tickle rather - and or, as I said, sort of that mind over matter where I'm going into a theater I think, "I'm gonna cough here now", but typically it's a tickle that begins. The less severe cough happens when I very quickly produce a phlegm and that's it. The less severe cough can be controlled with a lozenge" (#6, male, age 70 years). "Sometimes when I can feel it coming I try to hold my breath to stop it, which I shouldn't do because it just makes it worse. But like the other two, there's no ability to stop it or control it, it's like it takes over, it just takes over your body and until that cough is out... there's no way to stop it or control it" (#10, female, age 57 years). "At the beginning, I know I could take cough drop, and it would make it less severe or I could drink water and it my control a bit, but I mean those possibilities are long gone way in the past, nothing controls it" (#14, female, age 66 years). "And I when to get into that stage, I am the one who is initiating the severe cough, I'm trying to cough up phlegm and nothing is coming up, although I can feel it there. [...] So I

			am the one who instigates that severe cough as opposed to it just happening on its own” (#6, male, age 70 years).
	2.1.2 Cough control once a cough has started		“Yeah, I think if you can control it, it would be a less severe cough. I have no control once I start” (#11, female, age 60 years). “I don't have an ability to control it once it starts coughing that's it until it stops... and yeah so there's no ability to control it, and it does get more severe as I'm coughing” (#9, female, 50 years). “All you can do [is] cough... you can't control it [during an episode]” (#1, male, age 44 years).
	2.2 Cough frequency	2.2.1 Overall frequency, defined as frequency of single coughs and fits/bouts	“I also judge severity by frequency, so some days I may only have three to four episodes, which I would classify as a good day. Other days I may have 12 to 15 episodes, which obviously, is not so good of a day. So I kind of throw that in there with severity- how many episodes I have” (#1, male, age 44 years). “I would say in my case that it's less about violent frequencies and more of a constant throughout the day. I must cough at least 200 plus times a day. And I don't seem to go through a period of not coughing. It's become just a part [of me]” (#3, male, age 53 years). “I'll have a severe attack at least once a day, sometimes two and three times a day with my short coughs, the easy coughs happen, some days 10 times some days maybe 50 times, I can't seem to pinpoint what makes it cough, what makes it more frequent. I'll have good days when I feel like, “wow I only coughed 10 times today”, but I will still have a good day without having a really severe cough” (#15, female, age 57 years). “Yeah I agree mines all day long, sometimes it's just little coughs sometimes it's big ones...” (#4, female, age 62 years). “Mine doesn't last a long time, but it happens a lot” (#11, female, age 60 years).

		2.2.2 Daytime frequency	“So for me I don’t think I cough much at night at all. But crazy during the day” (#9, female, age 50 years). “For me personally [my cough frequency] during the day is worse because that’s when I’ll have more triggers. If I use my voice too much that can be a trigger. Could even be a certain way the wind blows on my face or by my ear that will trigger a sort of spasm or episode” (#1, male, 44 years). “During the day there’s more frequency” (#12, female, 75 years). “[My cough] is very rare at night, mostly during the day - actually always during the day” (#6, male, age 70 years).
		2.2.3 Nighttime frequency	“So basically when I’m sleeping I don’t have a lot of cough” (#9, female, age 50 years). “I am very lucky when I go to sleep, I do not cough. I feel like I should stay in bed” (#14, female, age 66 years). “Yes, I find at night, like most nights, my nights are just as bad as my days, just out of the blue I’ll start coughing. Doesn't matter if I’m on my back, my side, sometimes I have to sit up and just cough it out, or I leave the room and go sit somewhere just because I can't catch my breath” (#10, female, age 57 years). “And I do cough throughout the night. I have a bedtime medication that I take with a sip of water before I go to bed, but as soon as I put my head down, I cough for the next 5-10 minutes, and then I fall asleep, but then I do wake myself up periodically throughout the night with a dry cough” (#13, female, age 62 years).
		2.2.4 Morning frequency	“When I do get up in the morning, as soon as I stand up and as soon as I wake up that’s when It all starts happening” (#9, female, 50 years). “My cough is worse in the morning” (#2, male, age 51 years).
		2.2.5 Fit/bout frequency	“I’ll have a severe attack at least once a day, sometimes, two and three times a day” (#15,

			“I would go a month because I think I have one every month. So somebody would be able to relate, I’ve had seven severe [bouts] in that month period. But like for me it’d be at least once a month, but it seems like everybody else has them more regularly than what I’ve got right now” (#16, male, age 48 years). “And it’s a lot more than what I’m hearing from 6, where he said he could have 2 [severe bouts], like I could have 20” (#9, female, age 50 years). “I have it mostly everyday, some days I may have 1 or maximum 2 of what I would call the severe cough” (#6, male, age 70 years).
	2.3 Fit/bout duration	2.3.1 Fit/bout duration	“I definitely have spasms and they can go on for 15-20 minutes” (#7, female, age 72 years). “But when I cough it can go up to two to three seconds, and I cough very hard” (#8, female, age 79 years). “Yeah, the duration is probably anywhere from one to three minutes ... it's pretty violent, it's more like- almost like a seizure type event” (#1, male, age 44 years). “I cough like probably 30 times a day and it lasts for 15-20 minutes” (#12, female, age 75 years). “I can have coughs that [...] it’s just like it could be a couple of seconds, and it could be several minutes” (#9, female, age 50 years). “Many times, my cough gets so bad that I will go for 5-10 minutes” (#15, female, age 57 years).
	2.4 Intensity	2.4.1 Physical effort to cough	“... It's nonstop and very deep where you literally hold your chest in your stomach when you cough and it can go on all night long for hours and hours so” (#7, female, age 72 years). “It could be very cloudy in the morning, like the phlegm that comes out of your system, and it’s to the point where I have to go to the counter or the sink and I’m almost holding

			on to the counter because it's so hard on your body... so that's what's happening during" (#9, female, age 50 years).
		2.4.2 Difficulty expectorating	"The funny thing is as much as I'm trying to clear something at the back, I would say, if this makes sense, it's more of a dry cough that is very, very difficult to clear anything" (#3, male, age 53 years). "A more severe cough is one that which I think is brought on by...that I just can't get the phlegm to come up. [...] Like when the cough comes on and I have to cough... and until I get that phlegm up, I will continue to cough. It's just sometimes, the phlegm comes up very easily, very quickly. Other times I'll have to really start to expel it and pressure it" (#6, male, age 70 years). "During the cough, I have to cough and cough and cough and usually there's phlegm that I have to expel in some way. And I basically won't stop coughing until I get rid of it" (#14, female, age 66 years). "During the day it's more of just a cough and it doesn't stop until my throats clear or something I don't know" (#11, female, age 60 years).
	2.5 Quality	2.5.1 Harshness of cough	"[My cough is] harsh" (#7, female, age 72 years).
		2.5.2 Deepness of cough	"I cough from my feet. So it's deep and it's loud" (#7, female, age 72 years). "Maybe deep, [...] it comes from your feet... it can definitely be deep when it's severe" (#1, male, age 44 years). "The cough comes from my gut, it comes from way down, and then sometimes it comes from my chest" (#12, female, age 75 years). "For me it may be a deeper cough like we're having a conversation just like this [inaudible]... there is just a mild cough right? Just in mid conversation, you can have a mild cough, but when we're getting into the severe coughs as we're referring to them as, I find it's a lot deeper cough there's a lot more...I don't want to say thought put into it, but

			there's a lot more pressure like there's a lot... it's a lot deeper so like a very it's a deep cough I guess" (#16, male, age 48 years).
		2.5.3 Hacking due to cough	"Yeah mine, it's a hacking. I just got a cough...really force it up" (#6, male, age 70 years). "So somebody tells a good joke I started laughing and then I end up into a hack attack, (is what I refer to it as) where it's multiple coughs and usually I feel like a pressure in the top of my head, almost like my head's going to explode when I have those hack attacks" (#16, male, age 48 years).
		2.5.4 Hardness of cough	"When cough it can go up to two to three seconds and I cough very hard" (#8, female, age 79 years). "I consider a severe with me, is when I cough so hard, I actually throw up" (#11, female, age 60 years).
		2.5.5 Barking due to cough	"Oh, I think I sound like a walrus - like a bark. [...] A loud bark" (#12, female, age 75 years).
		2.5.6 Strong cough	"I think you have to hear it to describe it. It's just very strong." (#9, female, age 50 years). "I have to make a point [and say], 'okay breathe, take a break and breathe' because sometimes you're exhaling so much and it's such a strong and violent exhale that I have trouble getting air to breathe in." (#15, female, age 57 years).
		2.5.7 Violent cough	"It can be very violent and it doesn't last very long these spasms" (#1, male, age 44 years). "It's the violence of the cough" (#4, female, age 62 years). "It's such a strong and violent exhale" (#15, female, age 57 years).
	2.6 Associated features/sequences	<i>Experiences while coughing that are associated with intensity</i>	
		2.6.1 Dizziness due to cough	"Afterwards, I sometimes get dizziness like severe dizziness" (#1, male, age 44 years).

			“Occasionally, I have had some coughing fits that have left me dizzy whether it’s my blood pressure changing or what have you, but the dizziness definitely does play a part in it at certain points” (#3, male, age 53 years). “And it does leave you with some dizziness” (#7, female, age 72 years). “I’m coughing my brains out, let’s put it that way. My head is spinning after” (#12, female, age 75 years). “When I finish it one of my bad sessions, I feel extremely exhausted, lightheaded” (#15, female, age 57 years).
		2.6.2 Syncope due to cough	“At times it’ll get bad enough, where I blackout, or I feel like I’m going to blackout” (#4, female, age 62 years). “You’re coughing hard enough that you’re passing out” (#16, male, age 48 years). “I start coughing. I get to the point where I’m turning red, feel like I’m going to pass out” (#15, female, age 57 years). “You’re just coughing and coughing and coughing and you get all heated up, lightheaded, feel like you want to pass out because the severity of the cough has taken so much out of you” (#13, female, age 62 years).
		2.6.3 Wheeze due to cough	“I’d say the sound is almost like you’re wheezing” (#9, female, age 50 years). “Almost feels like I would go into a wheeze and sometimes I have, but not all the time” (#11, female, age 60 years).
		2.6.4 Dyspnea/sh ortness of breath due to cough	“My husband was sitting staring at me waiting for me to- I felt like he was waiting for me to die, and it was like, ‘is she ever going to get her breath back?’, and I finally got it calmed down enough to get my breath back and then I’m sitting and I’m deep breathing.” (#4, female, age 62 years). “I find that I can lose my air and what I mean by that is I’ve got to breath in to speak out after a bad session” (#7, female, age 72 years).

			“And after, I have a lot of spells [...] I also lose my breath, so it takes a bit to catch my breath again after coughing” (#10, female, age 57 years). “At my cough I get coughing really, really bad and shortness of breath. Sometimes, it can’t breathe properly. But it calms down on its own, after a while” (#2, male, age 51 years). “So it gets to the point where you’re coughing, so much, so severe and so badly that you almost feel like you’re losing your breath because you’re gasping” (#9, female, age 50 years). “I have to make a point [and say], ‘okay breathe, take a break and breathe’ because sometimes you’re exhaling so much and it’s such a strong and violent exhale that I have trouble getting air to breathe in” (#15, female, age 57 years).
		2.6.5 Incontinence due to cough	“[Incontinence] can be bad” (#4, female, age 62 years). “I literally have to go to the bathroom or I might go in my pants type thing. And it’s not pee, it’s the opposite - it’s diarrhea. It’s not always, it’s just when I have those really severe ones and if it’s morning” (#9, female, age 50 years). “Unfortunately, I’m incontinent when it happens, sometimes. [That’s when] it’s really terrible” (#12, female, age 75 years).
		2.6.6 Pressure in head due to cough	“I end up into a hack attack (is what I refer to it as), where it’s multiple coughs and usually I feel like a pressure in the top of my head, almost like my head’s going to explode when I have those hack attacks” (#16, male, age 48 years). “I had the head pressure, everything like you said, I felt like I was going to pass out” (#15, female, age 57 years). “I’m all heated up and my head feels it’s going to explode” (#13, female, age 62 years).

			“It puts a lot of pressure on your face, you know from the coughing and everything” (#14, female, age 66 years).
		2.6.7 Tightness of throat due to cough	“And then I feel the pain in my temples but also that’s true the neck pain I feel it afterwards, like that tightness just like I have tight scarf or something around my neck” (#15, female, age 57 years).
		2.6.8 Tightness of chest due to cough	“I cough from my feet. [...] Your muscles all tighten up in your chest” (#7, female, age 72 years). “For myself, for the severe coughs, again it’s the pressure. It’s very... I can relate to the struggle to breathing... it’s just a lot of pressure. A lot of pressure in the head and the chest. But the mild ones, nothing to it really it’s just. Just a mild, like the common cough. No pressure” (#16, male, age 48 years).
		<i>Immediate experiences after coughing that are associated with intensity depending on susceptibility</i>	
		2.6.9 General pain due to cough	“I cough from my feet. So it’s deep and it’s loud and it hurts, your muscles all tighten up in your chest” (#7, female, age 72 years). “I have severe pains, like in my chest and in my back, in my abdomen. I had a muscle or something popped out just on my chest, like the size of the bb finger overnight from the coughing. I’m just really sore and tender because I cough so much. Like my back, my ribs, my abdomen and things like that” (#15, female, age 57 years).
		2.6.10 Rib pain or fracture due to cough	“I think coughing so badly that you feel it in your ribs almost and in back pain” (#9, female, age 50 years). “And it does hurt my ribs and my stomach, like when I caught so bad, and they just come out of the blue” (#10, female, age 57 years). “I have actually coughed so bad that I have popped the rib in my back” (#13, female, age 62 years). “It puts a lot of pressure on your face, you know from the coughing and everything, and I do pop ribs frequently” (#14, female, age 66 years).

	2.6.11 Chest pain due to cough	“My cough is worse in the mornings, sometimes I get chest pains, but they go away after a while when I try to settle it down” (#2, male, age 51 years).
	2.6.12 Abdominal pain due to cough	“[After I cough] [...] my stomach is sore...” (#12, female, age 75 years). “And it does hurt my ribs and my stomach, like when I caught so bad, and they just come out of the blue” (#10, female, age 57 years).
	2.6.13 Back pain due to cough	“And during [the cough] sometimes it can be very severe where it feels almost like you’re coughing so badly that you feel it in your back” (#9, female, age 50 years).
	2.6.14 Neck pain due to cough	“My neck as well, I can feel pain in my neck when I have the severe cough as well” (#11, female, age 60 years). “It’s almost like someone is squeezing your neck from both sides, like that hard pressure and pain” (#15, female, age 57 years).
	2.6.15 Aches due to cough	“I would remember yesterday, too - I had a session, where I coughed all night, and I was really sore” (#7, female, age 72 years). “I find it very agonizing – that’s the word I was looking for, agonizing. It just seems to be like every part of your chest and all around there ache, like really ache, when it’s really really bad” (#5, female, age 70 years).
	2.6.16 Headache due to cough	“[After I cough] my head aches” (#5, female, age 70 years). “Sometimes I’ll get a headache after my cough” (#16, male, age 48 years). “I find that when I have the cough attack the actual headache is in my temples, like it actually hurts to touch my temple sometime” (#15, female, age 57 years).
	2.6.17 Exhaustion due to cough effort	“It (my cough) is very draining.” (#13, female, age 62 years). “It can be physically exhausting” (#1, male, age 44 years).

		“Just from coughing so much that it takes so much energy out of you” (#9, female, age 50 years). “When I finish the cough, to be honest with you, I don’t feel better I’m just really exhausted” (#12, female, age 75 years). “I feel the same way, I’m exhausted and I’d like to lay down for a bit” (#10, female, age 57 years). “And it sometimes can make me feel very worn out” (#14, female, age 66 years). “When I finish it one of my bad sessions, I feel extremely exhausted” (#15, female, age 57 years).
	2.6.18 Voice loss due to cough	“One of the after effects as well that I get sometimes [is that] it’ll really weaken my voice if I have a couple of really bad episodes, my voice [will be] next to gone for a few hours” (#1, male, age 44 years). “I lost my voice for three weeks because of the coughing... [the coughing was] so severe” (#5, female, age 70 years). “Something I want to mention is when I went to ear, nose and throat specialist a year and a half or two years ago, because I lost my voice from the coughing” (#14, female, age 66 years).
	2.6.19 Retching/dry heaving/gag ging/chokin g due to cough	“I get dry heaving sometimes too like its associated with choking, I don’t always throw up, but definitely some dry heaving. Sometimes that’s even a worse symptom than the coughing itself” (#1, male, age 44 years). “But it’s almost like you’re almost like – you’re not throwing up but it feels like the same thing of throwing up” (#9, female, age 50 years). “Yeah, I almost feel at times [that] when I get the phlegm and I can make it come up that it’s a successful cough, as stupid as that sounds, because most of them are just a dry heave” (#4, female, age 62 years).

		2.6.20 Vomiting due to cough	“[I can] cough like crazy... to the point where I’m almost like vomiting” (#9, female, age 50 years). “I consider a severe with me, is when I cough so hard, I actually throw up” (#11, female, age 60 years). “And after, I have a lot of spells when I cough where I vomit” (#10, female, age 57 years). “A lot of times with a severe cough I have to cough until I expel all this phlegm. If it’s after eating I’ll throw up food” (#14, female, age 66 years).
		2.6.21 Nausea due to cough	“It (my cough) can cause nausea sometimes too” (#1, male, age 44 years). “I was going through this same thing where [if I was] nauseated, [bad] stomach, anything you know, and I just never, never, never stopped [coughing]” (#5, female, age 70 years).
		2.6.22 Expectorati on of phlegm, sputum, or mucous	“The only time I find relief, believe it or not- if the phlegm is really bad, is if I throw up... it seems to clear everything right out, and I feel relief” (#5, female, age 70 years). “Okay, with my cough like I cough so much where I vomit a lot of mucus” (#10, female, age 57 years). “I consider a severe with me, is when I cough so hard, I actually throw up. Now, sometimes throw up, but sometimes it is literally, sorry I don’t mean to be gross, literally a mouth full of phlegm. So that’s my most severe” (#11, female, age 60 years). “Sometimes I have a coughing spell and then I burp and then sort of throw up the phlegm. This would possibly happen after drinking, for example, water” (#14, female, age 66 years).
		2.6.23 Feeling of heart racing due to cough	“It’s a constant fight to try to get my breath to bring my heart rate back down” (#4, female, age 62 years).

		“Afterwards, I sometimes get dizziness like severe dizziness or I could feel my heart rate slow, slow and then speed up after the event is over. So it’s like my heart rebounding from slowing down” (#1, male, age 44 years). “But I find every time I have a really strong one, which happens many times a day, it’s almost like your heart is racing. So I just put my hand on my heart, I want to make sure that I’m calming it down. So I think it’s tough on our internal organs” (#9, female, age 50 years). “And one thing I noticed after a cough, is that it raises my blood pressure” (#14, female, age 66 years). “And my pulse rate, as I’m sure all of yours, goes extremely high. And oxygen level goes low, I have one of those, you know the oxygen levels dropped significantly as well” (#15, female, age 57 years).
	2.6.24 Feeling of body heating up due to cough	“You’re just coughing and coughing and coughing and you get all heated up” (#13, female, age 62 years). “You’ve got during the cough your body temperature goes up” (#9, female, age 50 years). “Many times, my cough gets so bad [...] and then the rest of my body breaks out into a sweat” (#15, male, age 48 years).
	2.6.25 Umbilical hernia due to cough	“I had a muscle or something popped out just on my chest, like the size of the bb finger overnight from the coughing” (#15, male, age 48 years).
	2.6.26 Watery eyes due to cough	“You’ve got during the cough [...] your eyes are watering, and that to me is the description of the more severe” (#9, female, age 50 years). “It almost looked like I was crying when I have the bad attacks” (#10, female, age 57 years). “But it was so bad was so bad, I was in tears” (#16, male, age 48 years).

		2.6.27 Sneezing due to cough	“I experience like coughing low from the gut, coughing loud, sneezing - like I can sneeze up to 20 times. And my cough is usually dry. Actually, I don't usually produce anything. Although this is the sneezing is wet and yeah it's just severe coughing sneezing and coughing and sneezing” (#12, female, age 75 years). “And often at the end of my cough sessions, I will end with the sneezes as the finale” (#15, female, age 57 years).
		2.6.28 Numbness in extremities due to cough	“And I sometimes get some numbness in my extremities like if I'm having a really bad episode I'll feel numbness in my hands and my feet” (#1, male, age 44 years). “[I get numbness] down my arms, yeah” (#4, female, age 62 years). “[I get like] like pins and needles” (#7, female, age 72 years). “Many times, my cough gets so bad that [...] I feel my legs going numb and burning” (#15, female, age 57 years).
		2.6.29 Redness in eyes and face due to cough	“[After I cough] my head aches and I think like 9 said, my eyes are beet red” (#12, female, age 75 years). “And then afterwards as I've mentioned about the eyes [getting red and tearing up] and that sort of thing” (#9, female, age 50 years). “During a severe cough my face may become red” (#6, male, age 70 years). “Many times, my cough gets so bad that [...] I'm turning the red during my cough sessions” (#15, male, age 48 years).

Table 5-3: Open-ended responses among 11 experts regarding items/domains to assess of cough symptom severity

Items/domains	n
Global score of cough severity (0-10)	1
Urge-to-cough	2
Allotussia/hypersensitivity	3
Control/suppressibility	1
Intensity	6
Physical discomfort	1
Pain (chest/abdominal)	3
Headache	1
Dizziness	1
Rib fractures	1
Hernia	1
Sore throat	1
Throat tightness	1
Dyspnea	1
Syncope	2
Urinary incontinence	3
Retching	1
Vomiting	1
Timing	2
Frequency	4
Bout frequency	1
Duration of bouts	1
Quality	2
Distress	2
Impact on depression or anxiety	2
Impact on daily activities	6
Impact on sleep	3
Impact on ability to speak	1
Impact of social life	1
Worry that cough represents a serious illness	1
Perceived impact on family/co-workers	2
Number of previous investigations for cough	1

n = number of endorsements

eMethods 5-1: Focus group interview guide
Patient perspectives on cough symptom severity

1) Welcome, consent process, and introduction

a. Welcome

Good morning/afternoon/evening and welcome to our session.

Thanks for taking the time to join us and to talk about chronic cough symptoms. My name is _____ and assisting me is _____. The goal of this study is to develop a patient-reported outcome measurement of cough severity that can be used in clinical trials and potentially in clinical practice to assess the effectiveness of therapies for patients with chronic cough. We are meeting with patients with chronic cough to better understand what items, domains, and concepts are relevant to assess cough severity. We would like to talk to you today to explore any attributes about your cough. We also would like to identify and discuss, in your view, what issues, concerns, and short-term impacts are important and related to your chronic cough severity. Finally, we would like to identify what language and terminology you use to describe your cough.

b. Consent Process

As a group, we are going to go over the informed consent form before we start our focus group to be sure that you understand why we are having this focus group and to be sure that you voluntarily want to participate.

c. About the focus group

- Ask the group if anyone has participated in a focus group before. Explain that focus groups are being used more and more to gain information to further inform future trials, study planning, etc.
- You are the experts
- We are not trying to get everyone to agree or achieve consensus

2) Focus group logistics and ground rules

a) Logistics

- Focus group will last 60-90 minutes
- Feel free to move around
- If the Internet connection is poor, please re-join the Zoom focus group with the provided link to the meeting

b) Ground Rules

- Everyone should participate and only one person talks at a time
- It is important for us to hear everyone's ideas and opinions
- There are no right or wrong answers to questions – just ideas, experiences and opinions, which are all valuable

• The session will be audio recorded to help us gather more detailed information about your responses, and it will allow us to double check our data for accuracy. All videos should remain off. Stay with the group, please don't have side conversations, and speak clearly to increase recording quality

- Turn off or silence cell phones
- Please refrain from recording the focus group session
- Enjoy the discussions

Ask the group if there are any questions before starting.

Turn on Recorder

Focus Group Questions

1. Please describe what happens before, during and immediately after your cough.
2. What symptoms, sensations, and/or triggers do you experience that lead up to a cough?
 - a. Do you find the urge-to-cough sensation more severe than the cough itself?
 - b. How would you describe the intensity of your urge-to-cough sensation?
3. What symptoms do you experience during a severe cough?
 - a. What are sound terms that you use to describe a more severe cough?
 - b. Do you perceive a wet, productive cough to have different severity from a dry, non-productive cough?
4. What are the symptoms that occur immediately (within minutes) of experiencing a severe cough?
 - a. How long does it take for you to recover from a severe cough episode? Do you consider the time to recover from a cough a measure of cough severity?
5. How would you describe a less severe cough from a more severe cough?
6. How would you describe the intensity of your cough?
7. Which is easier to recall: the number of coughs within an episode or the duration of that episode?
8. Do you perceive the number of bursts of cough throughout the day to be more important than the number of individual coughs?
9. Does coughing at night while sleeping versus coughing during the day have different importance to you? If so, please elaborate.
10. Do you consider the ability to control your coughing a feature of less severe cough? If so, please elaborate.
11. Over what time period are you able to recall your cough severity (ex. over the last day, week, 2 weeks, month)?
12. Do your family members mention that you cough more often than you think you do? If so, please elaborate.
13. Is there anything further you would like to tell us that would help us to characterize or understand cough severity?

Chapter 6 The McMaster Cough Severity Questionnaire (MCSQ): a cough severity instrument for patients with refractory chronic cough

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Abstract

Background: Cough severity represents an important endpoint to assess the impact of therapies for patients with refractory chronic cough (RCC).

Objective: To develop a new patient-reported outcome measure addressing cough severity in patients with RCC.

Methods: Phase 1 (item generation): A systematic survey, focus groups, and expert consultation generated 51 items. Phase 2 (item reduction): From a list of 51 items, 100 patients identified those they had experienced in the previous year and rated their importance on a 5-point scale. The MCSQ included items reported to occur most frequently and that had the highest importance scores. Patient feedback on the MCSQ led to elimination of redundant items. Another 100 patients completed the MCSQ, from which we performed an exploratory factor analysis and a Rasch analysis to further refine items on the MCSQ.

Results: Phase 2 led to selection of 15 items from the initial 51. Patient feedback on the 15 items led to elimination of 5 redundant items. An exploratory factor analysis of the 10-item MCSQ led to selection of two domains, elimination of one item that demonstrated cross-loading, and another that had high inter-item correlations. A Rasch analysis of the 8-item MCSQ confirmed that the response options functioned in a logically progressive manner and that no items exhibited differential item functioning. The final 8-item MCSQ has a one-week recall period and includes two domains (intensity and frequency). The 8-item MCSQ had high internal consistency (Cronbach's alpha, 0.89), proved able to distinguish different levels of cough severity (Pearson separation index, 0.89), and demonstrated high cross-sectional convergent validity (Pearson's correlation, 0.76 [95% CI 0.66 to 0.83]) with the 100-mm cough severity visual analogue scale.

Conclusion: Initial evidence supports the validity of the MCSQ, an 8-item instrument measuring cough severity in patients with RCC. Future studies should evaluate its properties in measuring change over time.

Background

Chronic cough is a common health problem that affects 5-10% of adults worldwide.¹ Although clinicians can often identify and effectively treat known causes of cough—including asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, gastro-esophageal reflux disease (GERD), and upper airway disease—around 30% of patients experience persistent cough despite treatment targeting these underlying conditions or have no identifiable cause (refractory chronic cough, RCC).²

Objective measurement of cough frequency represents the current gold standard to assess the efficacy of novel therapies for RCC. Although cough frequency is an important endpoint, and a dominant aspect of severity, there remain other patient-important factors that contribute to patients' overall perception of cough severity (i.e., intensity). Patient-reported outcome (PRO) measures that capture patients' experience of cough are thus an additional important strategy for assessing the efficacy and harms of interventions.

PROs including the Leicester Cough Questionnaire (LCQ),³ Cough Specific Quality of Life Questionnaire (CQLQ),⁴ and Punum Ladder^{5,6} measure the impact of cough on distal concepts including physical, psychological, and social domains of health. They do not, however, provide a direct measure of the cough symptom itself and its severity, which is recommended in the clinical practice for patients with chronic cough.⁷ The cough severity visual analogue scale (VAS) in which patients use a 100-mm scale ranging from “no cough” to the “worst possible cough” provides a measure of patients' experience of cough severity.⁸ Limitations of the cough severity VAS include its failure to fully capture complex patient experiences as a single-item instrument, its modest test-retest reliability (ICC 0.45-0.51),⁹ and its reliance on subjective self-anchoring that precludes between-patient comparisons.

The Cough Severity Diary (CSD), a 7-item daily diary including domains of frequency, intensity, and disruption, represents another instrument assessing cough severity.¹⁰ Although it has undergone psychometric testing,^{10,11} it remains a proprietary questionnaire with restrictions on its use for clinical and research purposes.

Thus, a widely available instrument with established measurement properties that subjectively measures cough severity rather than cough impact on quality of life remains unavailable. To address this need, we have developed the McMaster Cough Severity Questionnaire (MCSQ), an instrument for use in both clinical trials and clinical practice to assess the efficacy of therapies for patients with RCC.

Methods

Phase 1: Item generation

Development of the MCSQ followed established methodology and guidance for optimal PRO development (**Figure 6-1**).^{12,13} To generate items for our instrument, we identified 51 candidate items from a systematic survey of the literature (Study 1), concept elicitation interviews with 16 patients (Study 2), and consultation with 15 clinical experts in chronic cough (Study 3). Previous publications provide details on each of these phases.^{14,15}

Phase 2: Item reduction

Study 4: Cross-sectional administration of the 51-item reduction questionnaire

To achieve optimal efficiency and feasibility in completing the MCSQ, we reduced the number of items using the clinical impact method.¹⁶ This method involves an item reduction

questionnaire that identifies items that patients perceive as most frequently occurring and most important.

One-hundred adults (≥ 18 years old) with RCC lasting >8 weeks participated in this phase. Excluded participants included current smokers or ex-smokers with >10 pack/year history; non-English speakers; and those with language, memory, cognitive, or psychiatric issues that prevented optimal participation. The study recruited patients from the McMaster University Medical Centre (Canada), Foothills Medical Centre (Canada), and UMass Memorial Medical Center (USA). The Hamilton Integrated Research Ethics Board (REB) provided study approval, and the other REBs waived their own reviews based on this approval.

Following informed consent, a trained interviewer administered an item reduction questionnaire (**eMethods 6-1**) to patients either in person or over the telephone. Patients indicated which of the items on the questionnaire had been problematic to them (occurred sometimes, often, or all the time) over the past year. For each problematic item, patients rated its importance on a 5-point scale ranging from “1=not very bothersome” to “5=extremely bothersome”.

To generate an impact score for each item, we calculated the proportion of patients who labelled an item as problematic (frequency), the mean importance score among those patients labelling an item problematic (mean importance), and the product of the frequency and the mean importance (overall importance). The maximum possible impact score if all 100 patients chose an item and rated it at 5 was 5.0.

We retained the 15 highest rated items for the MCSQ, excluding those that addressed a concept redundant with another item that patients found clearer. Once items were chosen, to ensure adequate responsiveness to change,¹⁷ we developed 7-point Likert scales. To ensure accurate recall with representative sampling of cough, each item has a one-week recall period. Patient partners

reviewed the draft MCSQ and confirmed its clarity, recall period, ease of completion, and comprehensiveness.

To achieve sufficiently precise confidence intervals (± 0.1) around the proportion of patients who endorse an item as problematic and important (a score of ≥ 2 on a scale of 0 [not very bothersome] to 5 [extremely bothersome]), we calculated a sample size of 100 patients for this phase. Assuming a conservative proportion of 0.5, we needed 100 patients to achieve a confidence interval of 0.4 to 0.6. For proportions greater or less than 0.5, the confidence interval would be narrower.

Study 5: Cross-sectional administration of the 10-item MCSQ and exploratory factor analysis

Once we reduced items using the clinical impact method, we administered the 10-item MCSQ to another 100 adults (≥ 18 years old) from the McMaster University Medical Centre with RCC. The inclusion and exclusion criteria did not differ from the previous phase. Because we planned an exploratory factor analysis, a sample size of 100 was chosen to provide at least 10 responses per item.¹⁸

The exploratory factor analysis identified potential factors (domains) within the items. Using principal component analysis, we extracted factors with an eigenvalue ≥ 1 . We used a scree plot to help decide on the possible numbers of factors. Once we chose the optimal number of factors, a varimax rotation facilitated separation of factors with an optimal balance of variance explained by each factor. Items that had factor loadings < 0.4 on all factors or that had substantial cross-loading were removed.

We subsequently examined for inter-item correlations suggesting possible redundancy ($r \geq 0.8$) and substantial ceiling or flooring effects (defined as >15% of patients selecting either the highest or lowest response option). Analyses were performed using SPSS (version 26).

Study 6: Cognitive debriefing of the 10-item MCSQ

To gather qualitative feedback on the clarity, comprehensiveness, and ease of completing the 10-item MCSQ, we performed cognitive debriefing interviews with a purposive sample of 12 patients. We based this sample size on studies addressing optimal sample sizes for qualitative interviews.¹⁸ Purposive sampling ensured a variety of perspectives and experiences among a diversity of patients with RCC.¹⁹

Patients who underwent cognitive debriefing received instructions on both the think-aloud and probing procedures (**eMethods 6-2**). The interviewer explained to patients that the purpose of these procedures was to elicit feedback on the MCSQ.

Using the think-aloud approach, the interviewer asked the patient to actively share what he or she is thinking while completing each item on the MCSQ. While the patient was thinking aloud, the interviewer recorded all conversations with the patient. Once the patient completed the MCSQ, the interviewer used the probing approach to gather further feedback on the clarity, appropriateness, and ease of completing the MCSQ. Using a pre-scripted, semi-structured interview guide, the interviewer asked, if not already addressed, targeted questions to the patient (**eMethods 6-3**). At the end of the interview, the interviewer and patient discussed suggestions for item modification(s). All audio recorded interviews were transcribed verbatim and de-identified.

We analyzed transcripts from both the think-aloud and verbal probing interviews. Conventional content analysis informed data analysis. Two study researchers examined and coded

the transcripts. The steering group and patient partners reviewed the results of the analysis and modified or eliminated items as appropriate.

Rasch analysis of the 8-item MCSQ

The exploratory factor analysis and cognitive debriefing led to elimination of two items, after which we performed a Rasch analysis on the 8-item MCSQ using the partial credit model. We used Rasch analysis to evaluate the unidimensionality of the MCSQ. Analyses were performed on the two domains and with all items combined to evaluate the overall instrument using the Test Analysis Modules (TAM) and extended Rasch modelling (eRm) packages in R (version 2023.06.0+421). Infit and outfit statistics informed model fit. Category probability curves for each item informed the presence of disordered thresholds. We examined items for differential item functioning based on gender. Person separation indices (PSI), which represent the degree to which items distinguish differences in cough severity among participants, were calculated for domains and the overall instrument. PSI values between 0.70 and 0.95 provided evidence of high reliability.

Internal consistency

Internal consistency represents the extent to which items are correlated and measuring the same concept. To measure internal consistency, we calculated Cronbach's alpha values for each MCSQ domain and the overall instrument. A Cronbach's alpha between 0.70 and 0.95 provided evidence of high internal consistency.²⁰

Cross-sectional convergent validity

Construct validity refers to the extent to which scores on an instrument relate to other measures in a manner that is consistent with theoretically-derived hypotheses concerning the concepts being measured.²¹ To assess cross-sectional convergent validity, we calculated Pearson's correlations between scores on the 100-mm cough severity VAS and the 8-item MCSQ. Based on our theoretical understanding of the constructs each instrument is measuring, we anticipated that scores on the MCSQ would demonstrate moderate to high (≥ 0.5) correlations with scores on the cough severity VAS.

Results

Item reduction using the clinical impact method

One-hundred patients completed the item reduction questionnaire. Most identified as female (74%), reported a median age of 63, had no history of smoking (61%), and coughed for a median duration of 6 years (**Table 6-1**) – characteristics that are similar to those enrolled into clinical trials investigating antitussives for RCC.

Table 6-2 presents the highest scoring items among all participants. The top 15 highest scoring items addressed the number of coughing bouts, the bout duration, the ability to control coughing, the urge-to-cough sensations, the daytime frequency of coughing, the nighttime frequency of coughing, and its harshness. Among the top 15 ranked items, patients completing this phase informed that 5 items may have conceptual redundancy with other items (see **eTable 6-1** for the item tracking matrix). This led to selection of 10 items for which we constructed item stems and 7-point Likert scales.

Item level analysis, exploratory factor analysis, and inter-item correlations of the 10-item MCSQ

We administered the 10-item MCSQ to another 100 patients with RCC. These patients mainly identified as female (66%), reported a median age of 58.5 years, had no history of smoking (68%), and coughed for a median duration of 5.25 years (**Table 6-1**). Administration of the 10-item MCSQ revealed no missing data. Three items (items 3, 4, and 6) exhibited substantial ceiling or floor effects with >15% of participants selecting either the minimum or maximum response option. All items had sufficient response variation with endorsement of response options across the 7-point Likert scale. Only one item about frequency of daytime coughing did not have any responses to the lowest possible response option (“None”).

An exploratory factor analysis of the 10-item MCSQ suggested a two-factor (domain) solution for the MCSQ: frequency and intensity. **Table 6-3** presents the factor loadings on the rotated component matrix. Review of item content demonstrated that most fitted intuitively either as measures of frequency or intensity. Item 3 (ability to prevent cough) exhibited substantial cross-loading (<.30) between domains and was removed. Item 6 (disruption of nighttime sleep) exhibited borderline cross-loading; nonetheless, we retained this item as its impact score demonstrated its importance to patients and its contribution to content validity.

Inter-item correlations ranged acceptably between 0.29 to 0.82. Item 9 (harshness) and item 10 (physical effort to cough) had the highest inter-item correlation. This led to removal of item 10, which from cognitive debriefing interviews was noted to have further issues related to comprehension (**eTable 6-2**).

Cognitive debriefing interviews of the 10-item MCSQ

Cognitive debriefing interviews revealed that most items were well understood. Patient feedback led to minor wording modifications to Items 2 and 7 (**eTable 6-2**). Patients frequently

considered the content of Item 4 (ability to stop cough once started) while responding to Item 3 (ability to prevent cough from starting) so we combined these items into one about the control of coughing. Patients had considerable difficulty understanding Item 10 (physical exertion due to cough) and often considered the content of Item 9 (harshness of cough) in answering this question. We therefore merged Items 3 and 4 removed Item 10 by the end of the exploratory factor analysis and cognitive debriefing stages. Patients confirmed that the length of the MCSQ, recall period, and content of items were appropriate.

Rasch analysis of the 8-item MCSQ

A Rasch analysis of the 8-item MCSQ and its domains revealed that all items had acceptable infit statistics suggesting a good overall fit to the Rasch model (**Table 6-4**). Three items (items 1, 2, and 5) had poor outfit mean square statistics suggesting unexpected responses according to the Rasch model. Outfit statistics for these items could be explained by few patients with high overall cough severity selecting “never” or “hardly ever” to experiencing urge-to-cough sensations; coughing in response to triggers; and coughing disrupting sleep at night. Despite their suboptimal outfit to the Rasch model, we retained these items due to their high impact scores suggesting they capture patient-important aspects of cough severity.

The item-person threshold distribution demonstrated that MCSQ items and their response options capture a wide range of cough severities (**Figure 6-2**). None of the items exhibited disordered thresholds, which confirmed that the response options function in a logically progressive manner. The overall MCSQ had a high Pearson separation index of 0.89 indicating a strong ability to distinguish different levels of cough severity (**Table 6-4**). No items exhibited differential item functioning by gender.

Internal consistency and cross-sectional convergent validity with the cough severity visual analogue scale

The 8-item MCSQ demonstrated high internal consistency overall (Cronbach's alpha, 0.89) and within its frequency (Cronbach's alpha, 0.81) and intensity (Cronbach's alpha, 0.89) domains. The MCSQ also showed moderate to high cross-sectional convergent validity with the 100-mm cough severity visual analogue scale, with Pearson's correlations of 0.76 (95% CI: 0.66 to 0.83) for the overall MCSQ, 0.74 (95% CI: 0.64 to 0.82) for the intensity domain, and 0.57 (95% CI: 0.42 to 0.69) for the frequency domain (**Figure 6-3; Table 6-4**).

Discussion

The MCSQ represents a valid 8-item instrument with domains of frequency (3 items) and intensity (5 items) (**Figure 6-4; eTable 6-3**). Each item has a 7-point Likert scale with a one-week recall period. The total and domain scores range from 0 to 6, with higher scores indicating worse severity (**eTable 6-4**). To support the convergent validity of the MCSQ, our study found moderate to high correlations between the total and domain scores on the MCSQ with the 100-mm cough severity VAS. The overall MCSQ and its domains proved to be internally consistent and able to distinguish different levels of cough severity. Cognitive debriefing interviews confirmed the appropriateness and clarity of the MCSQ for assessing cough severity.

Strengths and limitations

Strengths of the development of the MCSQ include adherence to best practices and rigorous methodology outlined by regulatory agencies for PRO development.¹³ A comprehensive

systematic survey of the literature,¹⁴ concept elicitation interviews with patients with RCC,¹⁵ and consultation with an international panel of cough experts¹⁵ informed an initial item bank. To reduce and evaluate items, we used a combination of classical test theory and item response theory approaches (i.e., the clinical impact method, exploratory factor analysis, and Rasch analysis). These steps ensured the most efficient instrument while retaining optimal measurement properties and preserving its content validity.

Possible limitations of the work arise from the Rasch analysis. While Rasch analysis confirmed the MCSQ's overall fit to the model, three items (Items 1, 2, and 5) exhibited poor outfit statistics. These findings resulted from individuals who had high overall cough severity but reported minimal nighttime cough, few perceptible triggers, and few urge-to-cough sensations. These results are not surprising given studies showing that patients with RCC have considerably lower cough at nighttime compared to daytime,²² that urge-to-cough ratings do not always correspond with cough severity VAS ratings;²² that triggers only weakly correlate with subjective cough scores (i.e., the LCQ);²³ and that there is wide inter-individual variability in the experience of urge-to-cough sensations and cough triggers.²⁴ Cluster analyses of triggers in patients with RCC have suggested phenotypes of patients, some of whom are more likely to be male with fewer triggers and better LCQ scores.^{25,26} Although retaining these items may compromise the unidimensionality of the overall instrument, patients consistently emphasized their importance in assessing cough severity, and researchers may wish to characterize phenotypes of patients with RCC. We therefore retained these items to preserve the MCSQ's content validity, its ability to capture complex experiences by patients, and to capture different phenotypes of RCC.

While Rasch scoring offers advantages in calibration and standardization of item difficulty, we opted to use raw scoring for the MCSQ. This decision was driven by our focus on preserving

the instrument's content validity and interpretability for clinical use. Raw scoring maintains the intuitive interpretation of item scores and total scores such that it directly reflects patient experiences without transformation into a standardized metric. This approach ensures that the MCSQ remains accessible and meaningful to clinicians and researchers who may wish to integrate the MCSQ into routine clinical practice and research studies.

Final limitations of the study include recruitment of English-speaking patients primarily from a single tertiary clinic, only cross-sectional evaluation of the MCSQ, and inclusion of only patients with RCC who have minimal smoking history. Future prospective studies should further examine the MCSQ's longitudinal validity, test-retest reliability, responsiveness, and minimal important difference. Additionally, while the MCSQ may serve useful in assessing cough severity in other patients with chronic cough, future research must establish its content validity and measurement properties in these groups.

Relation to prior work

The MCSQ has advantages over existing instruments that assess cough severity. Unlike the 100-mm cough severity VAS, which is a single-item measure with modest test-retest reliability that fails to capture cough severity as a multi-dimensional construct, the MCSQ captures cough severity across two domains. While the current data does not confirm whether the MCSQ has improved test-retest reliability over the cough severity VAS, we anticipate better performance demonstrated in future studies due to descriptive words associated with each Likert scale option that allow for more consistent and interpretable responses.

The Cough Severity Diary, a 7-item daily diary with domains of frequency, intensity, and disruption, is a proprietary instrument with restricted access. In contrast, the MCSQ will be widely available for use in industry and academic studies, as well as in routine clinical practice.

Instruments including the Leicester Cough Questionnaire (LCQ) and the Cough Specific Quality of Life Questionnaire (CQLQ) capture the impact of cough on quality of life (QoL). While these instruments serve important uses in evaluating the impact of treatments, cough severity and impact on QoL should remain separate constructs. Reasons for keeping the constructs separate include patients' variability in how disruptive they find the same symptom. By focusing solely on cough severity, the MCSQ's items and domains are less likely to be influenced by factors unrelated to cough that influence QoL.

A second reason for keeping these constructs separate is that chronic cough over years can have a cumulative impact on QoL that may not respond to changes in cough severity over short treatment periods. The MCSQ, which provides directed and targeted measurement of cough severity, should respond well to treatment effects.

Third, neuromodulatory agents with antidepressant activity can improve cough QoL with little to no effect on underlying objective cough frequency.^{27,28} A subjective instrument assessing change in cough severity, rather than impact, is needed to establish whether treatment targets the intended symptom. For this reason, regulatory agencies often require that primary endpoints measure on-target effects to establish the effectiveness for claimed indications.

Finally, an instrument with items related to urge-to-cough sensations, triggers, frequency, and intensity may identify patient subgroups who share cough pathophysiology. Although current guidelines recommend treatment with centrally-acting neuromodulatory agents and speech therapy, limited evidence informs patients who may benefit more from a specific treatment. As

new therapies including peripheral²⁹⁻³¹ and central antagonists³² emerge, stratification of patients with chronic cough based on domains of cough severity may be useful for precision medicine.

Implications for practice and research

The MCSQ represents a valid 8-item instrument with a one-week recall period, 7-point Likert scales, and domains of frequency and intensity. The MCSQ addresses an unmet need for a valid, reliable, and widely accessible PRO measure that captures cough severity – a common subjective endpoint in clinical trials evaluating novel antitussives for patients with RCC. While the instrument in its current form may be used in clinical practice and clinical trials, future studies that address its properties in measuring change over time will serve crucial in establishing its role in cough severity assessment.

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Conflicts of interest

G.H. Guyatt, R. Abdulqawi, L. Dupont, F. Johnston, R. Newman, and N. Popovic report no conflicts of interest. E. Kum reports receiving personal fees from Respiplus and that she is supported by a Canadian Institutes of Health Research (CIHR) Canada Graduate Scholarships Doctoral Award (CGS-D). P. Dicpinigaitis reports consulting fees from Merck, Bellus, Bayer, Shionogi and Chiesi, outside the submitted work. S.K. Field has served on advisory boards for GSK and Merck, has given sponsored talks for Boehringer Ingelheim, GlaxoSmithKline and Novartis, and has received research funding from AstraZeneca, CIHR, InsMed and Novartis, outside of the submitted work. C.L. French and R.S. Irwin disclose that they are co-developers of the Punum Ladder and the CQLQ, and that they hold the copyright of the CQLQ. They have each received less than \$700 in fees over the past 3 years for its use in studies. P.G. Gibson reports grants from GlaxoSmithKline, and personal fees from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, outside the submitted work. L. McGarvey reports honoraria from Chiesi, Bellus Health, GSK, Merck, NeRRe Therapeutics, Nocion, Trevi, Shionogi Inc and Reckitt Benckiser; grant support from Merck and Bellus Health. J.A. Smith reports grants from Merck, Ario Pharma,

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Table 6-1: Patient baseline characteristics

	Study 4: Administration of 51-item questionnaire (n=100)	Study 5: Administration of 10-item MCSQ (n=100)	Study 6: Cognitive debriefing interviews (n=12)
Sex, n (%)			
Male	26	34	6
Female	74	66	6
Age, years			
Median (range)	63 (26-86)	58.5 (19-85)	57.5 (19-78)
Smoking status, n (%)			
Never	61	68	10
Former	39	32	2
Primary diagnosis, n (%)			
Refractory chronic cough	47	64	7
Unexplained chronic cough	53	36	5
Comorbid conditions, n (%)*			
Asthma	21	30	3
Chronic bronchitis	2	21	2
Gastroesophageal reflux disease	30	26	2
Upper airway disease	4	10	2
Other	4	3	1
Duration of cough, years			
Median (range)	6 (0.5-46)	5.25 (0.33-61)	6 (2-40)
Education level, n (%)			
High school or less		25	1
College, vocational training, or university		67	11
Master's or doctoral training		8	0
Cough severity visual analogue scale (mm)†			
Mean (SD)		55.2 (25.4)	47.25 (22.2)
McMaster Cough Severity Questionnaire			

Total score, mean (SD)‡		3.3 (1.2)	2.9 (1.1)
Frequency score, mean (SD)¶		3.8 (1.2)	3.8 (1.1)
Intensity score, mean (SD)¶¶		3.0 (1.4)	2.4 (1.3)

*Patients could have more than one comorbid condition

†Score ranges from 0 (no cough) to 100 (worst cough)

‡Score ranges from 0 (not severe) to 6 (very severe)

¶Score ranges from 0 (not frequent) to 6 (very frequent)

¶¶Score ranges from 0 (not intense) to 6 (very intense)

Table 6-2: Impact scores of items

Rank	Item	Frequency*	Mean importance†	Overall impact score‡
1	Bouts of cough	0.92	4.58	4.21
2	Long duration of coughing bouts	0.87	4.70	4.09
3	Inability to suppress a cough from starting	0.96	4.24	4.07
4	Intense urge-to-cough sensations	0.96	4.16	3.99
5	Sensitive to low levels of thermal, mechanical or chemical irritants	0.89	4.19	3.73
6	Daytime coughs	0.99	3.76	3.72
7	Inability to suppress a cough once started	0.84	4.38	3.68
8	Frequent urge-to-cough sensations	0.90	4.08	3.67
9	Strong cough	0.80	4.38	3.50
10	Morning coughs	0.84	3.89	3.27
11	Harsh cough	0.69	4.54	3.13
12	Physical effort to cough	0.66	4.48	2.96
13	Exhaustion due to cough	0.68	4.31	2.93
14	Shortness of breath due to cough	0.68	4.29	2.92
15	Nighttime coughs	0.70	4.10	2.87
16	Distress due to cough	0.66	4.32	2.85
17	Hacking cough	0.65	4.23	2.75
18	Retching or gagging (dry heaves) due to cough	0.62	4.32	2.68
19	Aches due to cough	0.63	4.19	2.64
20	Expectoration of phlegm due to cough	0.70	3.76	2.63
21	Hoarse voice due to cough	0.71	3.69	2.62
22	Difficulty expectorating	0.61	4.27	2.61
23	Need for relievers to suppress the start of a cough	0.75	3.43	2.57
24	Deep cough	0.57	4.46	2.54
25	Hard cough	0.56	4.50	2.52
26	Incontinence due to cough	0.55	4.58	2.52
27	Pain due to cough	0.53	4.23	2.24
28	Chest tightness due to cough	0.53	3.75	1.99
29	Watery eyes due to cough	0.63	3.08	1.94

30	Violent cough	0.41	4.59	1.88
31	Sore throat due to cough	0.51	3.63	1.85
32	Runny nose due to cough	0.51	3.53	1.80
33	Headache due to cough	0.46	3.87	1.78
34	Dizziness due to cough	0.45	3.76	1.69
35	Wheeze due to cough	0.48	3.50	1.68
36	Vomiting due to cough	0.35	4.60	1.61
37	Head pressure due to cough	0.42	3.81	1.60
38	Voice loss due to cough	0.39	3.87	1.51
39	Feeling of heart racing due to cough	0.40	3.75	1.50
40	Heating up due to cough	0.39	3.72	1.45
41	Sweating due to cough	0.40	3.58	1.43
42	Redness in eyes or face due to cough	0.42	3.29	1.38
43	Throat tightness due to cough	0.39	3.46	1.35
44	Nausea due to cough	0.34	3.88	1.32
45	Barking cough	0.28	4.39	1.23
46	Individual coughs	0.55	2.05	1.13
47	Sneezing due to cough	0.25	2.68	0.67
48	Honking cough	0.10	4.70	0.47
49	Fainting/blackout (syncope) due to cough	0.11	4.27	0.47
50	Numbness in extremities due to cough	0.08	4.13	0.33
51	Hernia due to cough	0.08	3.63	0.29

*Proportion of patients reporting the item as problematic

†Mean importance score in patients who report the item as problematic (maximum=5.0)

‡Overall impact score is calculated as the proportion of patients endorsing an item as problematic (frequency), multiplied by the mean importance score. Items could have an overall impact score between 0 (least impact) to 5 (most impact).

Table 6-3: Rotated component matrix of the loading factors for the 10-item MCSQ

Item	Factor 1	Factor 2
	Intensity	Frequency
Item 1 – Frequency of urge-to-cough sensations		.861
Item 2 – Frequency of cough in response to triggers		.750
Item 3 – Ability to prevent cough	.536	.504
Item 4 – Control of cough once started	.698	
Item 5 – Awake cough frequency		.803
Item 6 – Disruption of nighttime sleep	.595	.349
Item 7 – Frequency of episodes/bouts of cough	.860	
Item 8 – Duration of episodes/bouts of cough	.802	
Item 9 – Harshness of cough	.884	
Item 10 – Physical exertion due to cough	.862	

Extraction method: Principal component analysis

Rotation method: Varimax

Factor loadings of 10 items under two factors. Factor 1 (intensity) had strong positive loadings for Items 4, 7, 8, 9, and 10. Factor 2 (frequency) had strong positive loadings for Items 1, 2, and 5. Item 3 exhibited substantial cross-loading ($<.30$) and was subsequently eliminated. Item 6 had borderline cross-loading but was retained within Factor 1 due to its importance to patients.

Table 6-4: Summary statistics of the 8-item MCSQ

	MCSQ domains		Total score
	Frequency	Intensity	
Items	3	5	8
Mean score (SD)	11.43 (3.67)	15.09 (7.01)	26.52 (9.68)
Rasch analysis			
Mean fit residual (SD)*	0.05 (0.80)	-0.00 (0.89)	0.00 (0.92)
Range of infit mean squares (MNSQ)†	0.96 to 1.10	0.83 to 1.23	0.82 to 1.14
Range of outfit mean squares (MNSQ)†	0.92 to 3.50	0.51 to 2.60	0.55 to 6.47
Person Separation Index (PSI)‡	0.79	0.88	0.89
Internal consistency			
Cronbach's alpha¶	0.81	0.89	0.89
Cross-sectional convergent validity			
Pearson's correlation with the 100-mm cough severity visual analogue scale (95% CI)¶¶	0.57 (0.42 to 0.69)	0.74 (0.64 to 0.82)	0.76 (0.66 to 0.83)

*A good fit to the Rasch model typically results in mean item fit residuals close to 0 (indicating little deviation from model expectations) with a standard deviation (SD) close to 1. This suggests that items are functioning as expected under the Rasch model.

†Infit Mean Squares (MNSQ) and Outfit Mean Squares (MNSQ) represent additional statistics to evaluate the fit of individual items to the Rasch model. Infit MNSQ measures how well items fit the model relative to the expected variance of their residuals, while Outfit MNSQ assesses fit without regard to the expected variance. Infit MNSQ is sensitive to less extreme unexpected responses whereas Outfit MNSQ is sensitive to extreme departures from model expectations. Ideally, Infit and Outfit MNSQ values close to 1 indicate a good fit to the Rasch model (i.e., observed responses match with model expectations).

‡The Person Separation Index (PSI) assesses how well the MCSQ and its domains discriminate patients with different levels of cough severity. PSI values between 0.70 and 0.95 provide evidence that the instrument and its domains can distinguish different levels of cough severity. ¶Cronbach's

alpha provides a measure of internal consistency. Cronbach alpha values between 0.70 and 0.95 provide evidence that the instrument and its domains have high internal consistency.

¶¶Based on our theoretical understanding of the constructs each instrument and domain measures, we anticipate that scores on the MCSQ would demonstrate a moderate to high (≥ 0.5) correlation with scores on the 100-mm cough severity visual analogue scale.

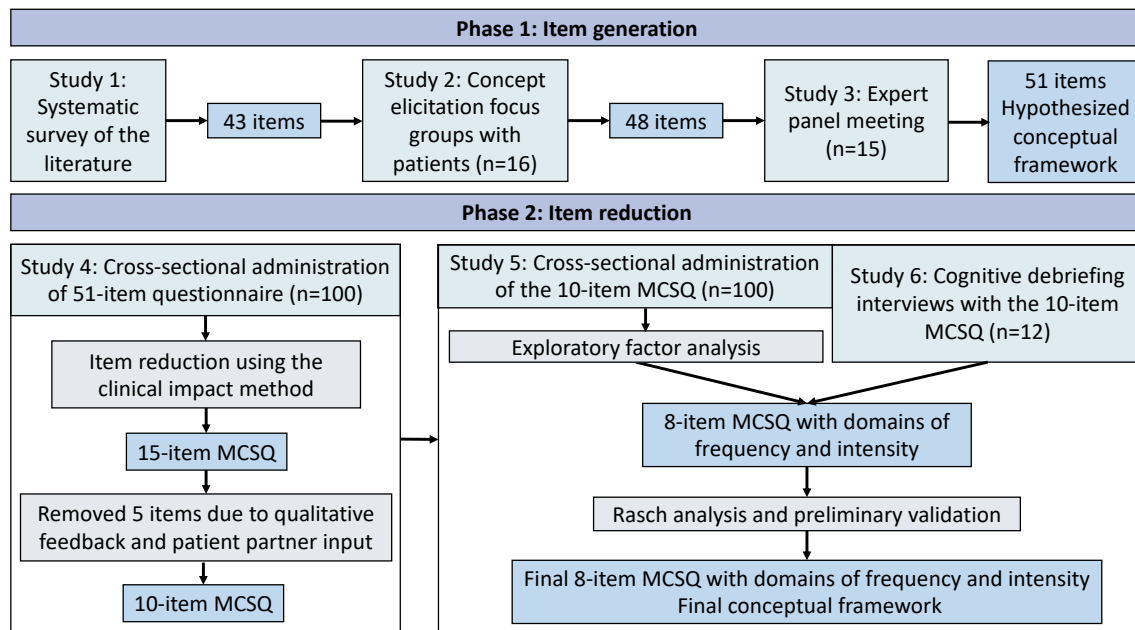


Figure 6-1: Overview of the steps involved in the development of the MCSQ

This paper focuses on Studies 4, 5, and 6. Previous publications report on the details of the preceding studies (Studies 1-3).^{1,2}

1. 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**(161).
2. 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 Research* 2022.

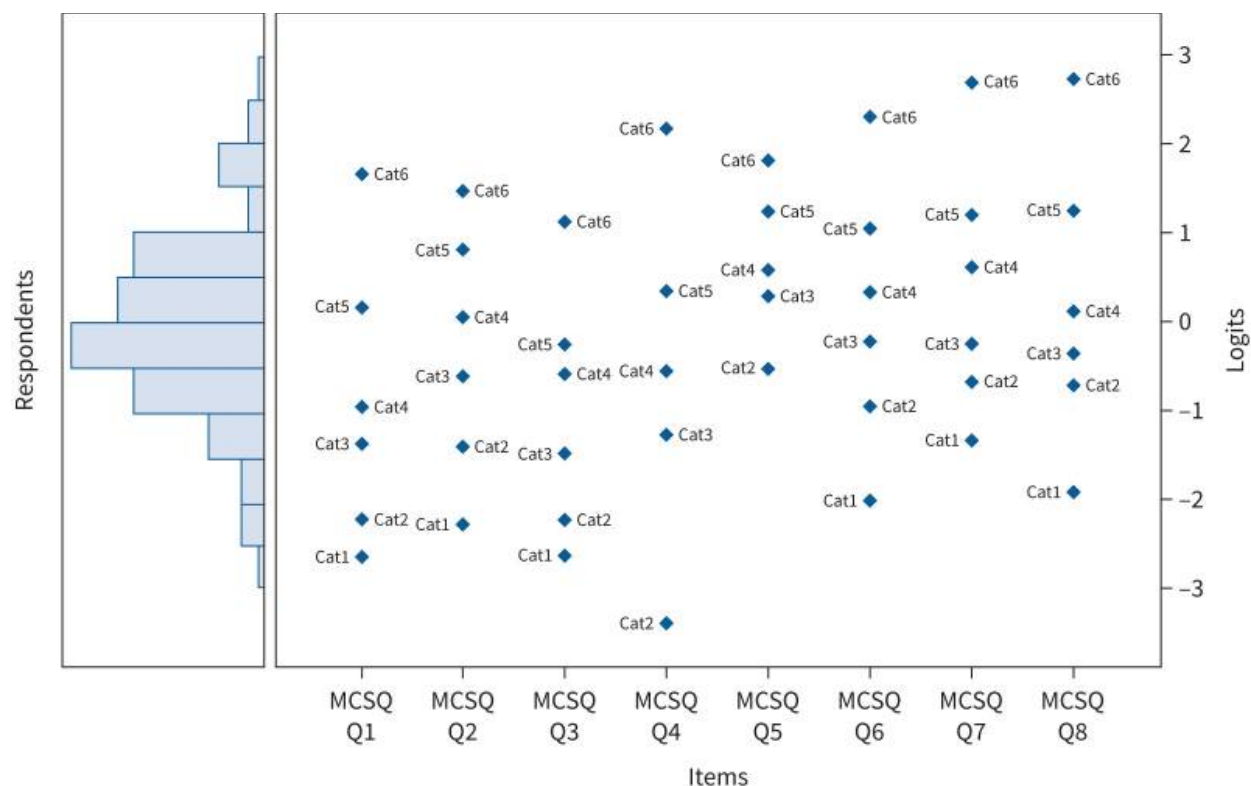


Figure 6-2: Item person map.

The left displays a histogram of the cough severity levels among participants. The right shows the MCSQ item thresholds in logits for each item and response option. These thresholds indicate the cough severity level at which respondents are equally likely to endorse adjacent response options for each item. In Rasch analysis, logits calibrate item difficulties (thresholds) and person abilities (cough severity levels) on the same scale, with more positive logits indicating higher levels of cough severity. The item-person map demonstrates that the MCSQ items and their response options align with the distribution of cough severities in the studied population. This suggests that the MCSQ adequately captures variation in cough severity among patients with RCC.

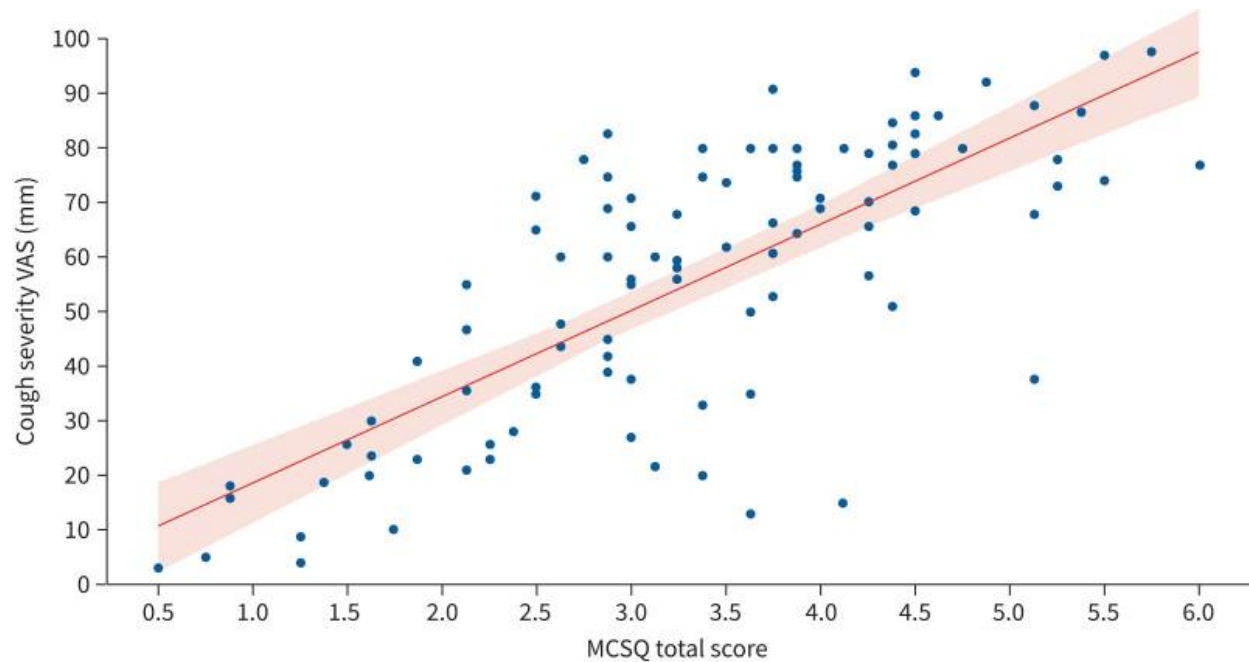


Figure 6-3: Convergent validity of the MCSQ total score

Scatter plot illustrates the relationship between total scores on the MCSQ and the 100-mm cough severity visual analogue scale. Each data point represents an individual participant's score on both measures. The red regression line and its 95% confidence interval indicates the linear trend fitted to the data points. The overall MCSQ has high cross-sectional convergent validity with the 100-mm cough severity visual analogue scale (Pearson's correlation, 0.76 [95% CI 0.66 to 0.83]).

McMaster Cough Severity Questionnaire

Please answer Questions 1-8.

Select the response that best describes how you have been in the past week.

1. On average, in the past week, how often did you experience urge-to-cough sensations (e.g., throat irritation, tickle, feeling of something stuck)?

 - 0 Never
 - 1 Hardly ever
 - 2 A few times
 - 3 Several times
 - 4 Many times
 - 5 A great many times
 - 6 All the time

2. On average, in the past week, how often did you cough in response to triggers (e.g., smoke, talking, changes in temperature, exercise, etc.)?

 - 0 Never
 - 1 Hardly ever
 - 2 A few times
 - 3 Several times
 - 4 Many times
 - 5 A great many times
 - 6 All the time

3. On average, in the past week, how often were you able to control your cough?

 - 0 All the time
 - 1 Almost all the time
 - 2 Most of the time
 - 3 Some of the time
 - 4 A little of the time
 - 5 Hardly ever
 - 6 Never

4. On average, in the past week, how often did you cough during the day while awake?

 - 0 Never
 - 1 Hardly ever
 - 2 A few times
 - 3 Several times
 - 4 Many times
 - 5 A great many times
 - 6 All the time

5. On average, in the past week, how often did coughing disturb your sleep at night?
- 0 Never
 - 1 Hardly ever
 - 2 A few times
 - 3 Several times
 - 4 Many times
 - 5 A great many times
 - 6 All the time
6. On average, in the past week, how often did you experience prolonged episodes/bouts of coughing?
- 0 Never
 - 1 Hardly ever
 - 2 A few times
 - 3 Several times
 - 4 Many times
 - 5 A great many times
 - 6 All the time
7. In the past week, how long, on average, have your episodes/bouts of cough lasted?
- 0 Not at all long
 - 1 A little long
 - 2 Somewhat long
 - 3 Moderately long
 - 4 Quite long
 - 5 Very long
 - 6 Extremely long
8. On average, in the past week, how harsh was your cough?
- 0 Not at all harsh
 - 1 A little harsh
 - 2 Somewhat harsh
 - 3 Moderately harsh
 - 4 Quite harsh
 - 5 Very harsh
 - 6 Extremely harsh

Thank you for completing the questionnaire.

Figure 6-4: McMaster Cough Severity Questionnaire

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eTable 6-1: Item tracking matrix

Item/concept	Stage of removal/modification	Modified or removed	Rationale
Intensity urge-to-cough sensations (concept)	Feedback during administration of 51-item questionnaire	Removed	Patients felt this was redundant with asking about the frequency of urge-to-cough sensations.
Strong cough (concept)	Feedback during administration of 51-item questionnaire	Removed	Patients felt this was redundant with asking about the harshness of cough.
Morning cough (concept)	Feedback during administration of 51-item questionnaire	Removed	Patients felt this was redundant and encompassed within daytime cough frequency.
Exhaustion due to cough (concept)	Feedback during administration of 51-item questionnaire	Removed	Patients felt this was redundant and encompassed within physical effort to cough.
Shortness of breath due to cough (concept)	Feedback during administration of 51-item questionnaire	Removed	Patients felt this was redundant and encompassed within physical effort to cough.
MCSQ-Q2: On average, in the past week, how often did you cough in response to triggers (e.g., smoke, talking, changes in temperature, etc.)?	Cognitive debriefing interviews	Modified	Patient suggested adding exercise as an example trigger to the item stem. The item now reads: On average, in the past week, how often did you cough in response to triggers (e.g., smoke, changes in temperature, exercise, etc.)?
MCSQ-Q3: On average, in the past week, how often were you able to prevent your cough	Exploratory factor analysis, cognitive debriefing interviews	Removed	Patients felt this item had redundancy with MCSQ-Q4. Item had substantial cross-loading (<0.30) across domains. Item exhibited substantial ceiling effect (>15% of respondents selecting the maximum response option).

from starting? (item)			This item merged with MCSQ-Q4 to form one item: On average, in the past week, how often were you able to control your cough?
MCSQ-Q4: On average, in the past week, how often were you able to immediately stop your cough once started? (item)	Cognitive debriefing interviews	Modified	Patients felt this item had redundancy with MCSQ-Q3. This item merged with MCSQ-Q3 to form one, which now reads: On average, in the past week, how often were you able to control your cough?
MCSQ-Q7: On average, in the past week, how often did you experience prolonged episodes/bouts of cough?	Cognitive debriefing interviews	Modified	Patient suggested changing “cough” to “coughing” in the word stem for improved comprehension. The item now reads: On average, in the past week, how often did you experience prolonged episodes/bouts of coughing?
MCSQ-Q10: On average, in the past week, how much physical effort did you exert while coughing?	Inter-item correlation matrix, cognitive debriefing interviews	Removed	Item had high inter-item correlations with MCSQ-Q9 addressing harshness of cough. Patients had difficulty understanding this question.

eTable 6-2: Cognitive debriefing interview summary

Item presented in cognitive interviews	Participant responses to what item means	Participant responses to inquiry about difficulty with item	Comments and discussion	Suggestion for changes to item
Item 1: On average, in the past week, how often did you experience urge-to-cough sensations (e.g., throat irritation, tickle, feeling of something stuck)?	ID-007: The whole tickle. Tickles. I rarely get tickles. ID-047: So in terms of experiencing urge to cough sensations, like the throat irritation, feeling if something's stuck, I would say it's gonna be many times. ID-068: I kind of think about just the feeling in my throat while I'm sitting at work. Yeah, happens quite a lot.	ID-005: No difficulty. ID-007: No difficulty. ID-050: No difficulty. ID-068: No difficulty.	Patients generally understood the question to be asking about the urge-to-cough sensations related to their chronic cough.	None.
Item 2: On average, in the past week, how often did you cough in response to triggers (e.g., smoke, talking, changes in temperature, etc.)?	ID-030: So I would probably say many times there. You know, the triggers primarily, I would be speaking. Right now, because of the weather, I have also found, sometimes humidity, sometimes air conditioning, changes in temperature and what not can sort of provoke that as well. ID-047: I don't usually get into situations where I have smoke or anything like that and the change of temperature has been off and on. ID-059: I would say a few times maybe. When I'm out in	ID-033: No difficulty. ID-047: Suggests adding exercise as an example. ID-049: No difficulty.	Patients generally understood the question to be asking about how often their cough is provoked by perceptible triggers. One patient (ID-049) noted that the item is highly relevant to the construct of cough severity.	Suggested change: On average, in the past week, how often did you cough in response to triggers (e.g., smoke, changes in temperature, exercise, etc.)?

	the cold, walking I get sometimes. But other times I'm in the cold and it doesn't bother me.			
Item 3: On average, in the past week, how often were you able to prevent your cough from starting?	ID-006: I can't prevent it, so I would say never, or yeah, I would say never because if it starts I can't stop. ID-049: To prevent my cough from starting, I've been, I've been really trying to do that. [...] I was trying to deep breathe when I had the urge and also take water. And I, I really want to do that more often. In terms of how often was I able to prevent the cough from starting, I would say, um, some of the time. ID-050: Probably hardly ever for me because I can't really get it to stop.	ID-005: No difficulty. ID-050: It's a bit hard for me to answer compared to the first two. ID-068: No difficulty.	Patients generally understood the question to be asking about how often they can prevent their cough from starting. When asked about the meaning of the question, however, many patients considered how often they could stop the cough once started. This suggests redundancy with Item 4.	Suggested change: Eliminated and merged with Item 4. Item now reads: On average, in the past week, how often were you able to control your cough?
Item 4: On average, in the past week, how often were you able to immediately stop your cough once started?	ID-005: I'm not really trying to immediately stop my cough. I'm not really having coughing fits where I'm trying to stop coughing. ID-033: Some of the time. Like sometimes a couple of coughs will do it. ID-068: I just think of, once I start coughing, I can't stop.	ID-007: No difficulty. ID-045: No difficulty. ID-046: Prefers control over immediately stop. ID-048: Prefers control over immediately stop.	Patients generally understood the question to be asking about how often they can stop their cough from continuing on and on. Patients suggested use of the word "control" rather than immediately stop.	Suggested change: Eliminated and merged with Item 3. Item now reads: On average, in the past week, how often were you able to

				control your cough?
Item 5: On average, in the past week, how often did you cough during the day while awake?	ID-033: A great many. Um, just because it is constant through the day. ID-059: Okay, many times, but a lot of them aren't *big coughs*, they're just *small coughs*. ID-068: I just think of, I cough all the time, every day.	ID-005: People might be able to associate well, it's one or two versus a hundred as opposed to you know, hardly and very often. Like that's sometimes hard to quantify. I'm more like of a technical person so I'm trying to quantify. Maybe [other] people will [be] like, I don't count, but I definitely know it's many, many times. ID-030: No difficulty. ID-073: No difficulty.	Patients generally understood the question to be asking about how often they cough during the daytime while awake. Some patients had difficulty with the subjective response options and preferred numbers. However, not all patients can remember the number of times they cough. We decided to keep the scale subjective for this reason.	None.
Item 6: On average, in the past week, how often did coughing disturb your sleep at night?	ID-007: Oh, that's really interesting. Hardly ever. Because one I'm asleep, I don't cough. ID-033: Sometimes I'll wake up like when it's dry, and that will trigger a cough. ID-068: It doesn't really disturb my sleep. Maybe when I'm going first to bed. Mm hmm. So, a little bit, a few times.	ID-005: No difficulty. ID-006: No difficulty. ID-050: No difficulty.	Patients generally understood the question to be asking about how often coughing disturbs their sleep at night.	None.

Item 7: On average, in the past week, how often did you experience prolonged episodes/bouts of cough?	ID-005: Prolonged, so, uh, prolonged coughing. Um, I'm starting to cough. I can't stop coughing. [...] That never happens to me. ID-030: Uh, again, throughout the day, not so much, there are more almost singular events that occur. But in the evenings before bed, it was probably a few, a few times, so a few evenings over the past week where I have that little cough that's just persistent.	ID-047: Suggests rewording "cough" to "coughing". ID-050: No difficulty. ID-073: No difficulty.	Patients generally understood the question to be asking about how often they experience episodes/bouts of coughing.	Suggested change: On average, in the past week, how often did you experience prolonged episodes/bouts of coughing?
Item 8: In the past week, how long, on average, have your episodes/bouts of cough lasted?	ID-050: I'm going to say, I mean, they're 10 minutes, so I'm going to say somewhat long. That feels like somewhat to me on average in the past week. ID-068: I haven't really had many in the last week, so not too long, maybe somewhat long.	ID-005: No difficulty. ID-006: No difficulty. ID-073: No difficulty.	Patients generally understood the question to be asking about how often their episodes/bouts of coughing last.	None.
Item 9: On average, in the past week, how harsh was your cough?	ID-005: So, like, how violent is this cough? My coughs are very mild coughs, so I would say they're not harsh. It's almost like people would interpret me on coughing to clear my throat. Right. Not quite, but more like, and that's the end. Is that a	ID-007: No difficulty. ID-030: No difficulty. ID-049: No difficulty.	Patients generally understood the question to be asking about how harsh is their cough on average in the last week.	None.

	severe cough? Well, I'm not hacking. ID-006: Uh, like harsh, I would say, moderately harsh. Prior to that, I was actually vomiting, so I would say quite harsh. But, I'm gonna say I'm answering for the last week, moderately.			
Item 10: On average, in the past week, how much physical effort did you exert while coughing?	ID-006: Oh, yeah. Friggin exhausting. ID-049: In terms of physical, except when I have those bouts [which] I find it's more physical, I say very little or a little. I would say very little. ID-050: It's probably. I mean, similar to number [item] nine, so I'm going to say quite a bit.	ID-003: Physical effort is hard to understand. ID-082: As it is currently worded, I started to think about coughing while exercising (exerting).	Patients had a difficult time understanding this question. For many, they felt that this question was very similar to Item 9 except worded less clearly.	Suggested change: Eliminated item.

eTable 6-3: Final conceptual framework

Items	Domains	Construct
• Frequency of urge-to-cough sensations	Frequency	Cough severity
• Frequency of cough in response to triggers		
• Awake cough frequency		
• Control of cough	Intensity	
• Disruption of nighttime sleep		
• Frequency of episodes/bouts of cough		
• Duration of episodes/bouts of cough		
• Harshness of cough		

eMethods 6-1: Item reduction questionnaire

In considering the severity of your cough over the past year, which of the following items have been a problem for you?" The options will then be read aloud to the patient ("pain", "vomiting", "bouts of cough", etc.), and the interviewer will pause after each item to allow the patient to respond. At the end of each domain, the interviewer will then ask the patient to rate the importance of each problematic item using a scale of 1-5, indicating "1, not at all bothersome" to "5, extremely bothersome."

	Indicate whether the patient says the item is problematic.	For problematic items, indicate the degree of importance on a scale of 1 (not at all bothersome) to 5 (extremely bothersome).
Urge-to-cough sensations intensity		
Unpleasant tickle		
Unpleasant irritation		
Unpleasant sensation of "something stuck"		
Urge-to-cough frequency		
Frequent urge-to-cough sensations		
Cough control		
Inability to suppress a cough from starting		
Inability to suppress a cough once started		
Cough frequency		
Bouts of cough		
Individual coughs		

Daytime coughs		
Nighttime coughs		
Morning coughs		
Duration of coughs		
Long duration of coughing bouts		
Intensity		
Harsh cough		
Deep cough		
Hacking cough		
Hard cough		
Honking cough		
Barking cough		
Strong cough		
Violent cough		
Physical effort to cough		
Difficulty expectorating an urge		
Associated features/sequelae		
Aches due to cough		
Chest tightness due to cough		
Distress due to cough		
Dizziness due to cough		
Exhaustion due to cough		
Expectoration of phlegm due to cough		
Headache due to cough		
Incontinence due to cough		
Abdominal pain due to cough		

Back pain due to cough		
Chest pain due to cough		
Fainting/blackout (syncope) due to cough		
Feeling of heart racing due to cough		
Heating up due to cough		
Hoarseness due to cough		
Nausea due to cough		
Neck pain due to cough		
Numbness in extremities due to cough		
Pressure in head due to cough		
Redness in eyes or face due to cough		
Retching or gagging (dry heaves) due to cough		
Rib pain due to cough		
Runny nose due to cough		
Shortness of breath due to cough		
Sneezing due to cough		
Sore throat due to cough		
Sweating due to cough		
Throat tightness due to cough		
Hernia due to cough		
Voice loss due to cough		
Vomiting due to cough		
Watery eyes due to cough		
Wheeze due to cough		

eMethods 6-2: Instructions for the think-aloud and verbal probing procedures

Now that you have provided your demographic information, I would like to discuss with you the format for the interview. There are two ways in which we will elicit feedback on the MCSQ. First, we will ask you to “think aloud” while completing the MCSQ. During this procedure, we will go through each item on the MCSQ one-by-one. As you are answering the item, I want you to tell me what you are thinking when you are both reading and answering the question. Keep in mind, there are no right or wrong answers when verbalizing your thoughts.

[Pause and see if the patient understands. If so, continue.]

To encourage you to think aloud, I will also stop you after each question and ask you what you were thinking when you were answering the question. Our objective is to get a better understanding of how a patient comprehends and responds to the question.

[Pause and see if the patient has questions. If no, continue.]

While you are completing the MCSQ, I will also record the time in which it takes you to complete the questionnaire. However, do not feel the need to rush through the MCSQ. Our main objective is to understand your thought processes while completing the MCSQ.

[Pause and see if the patient has questions. If no, continue.]

Once you complete all items on the MCSQ, we will move onto the second stage of the interview called the “verbal probing” stage. During this phase, I will ask you targeted questions related to the MCSQ (i.e., are the response options easy to understand?). Similarly, you will provide your honest responses to the questions.

[Pause and see if the patient has questions. If no, proceed to provide the patient with the MCSQ, then start the recorder and the interview.]

eMethods 6-3: Verbal probing interview questions

1. Are questions and sections on the MCSQ appropriate for assessment of cough severity?
2. Are there questions or sections that should be eliminated?
3. Are there questions or sections that are missing?
4. Are questions easy to understand?
5. Are response options easy to understand?
6. Are the response options comprehensive?
7. Is the chosen recall period optimal?
8. Did you find the MCSQ easy to complete?
9. Would you like to share any further feedback on the MCSQ?

eTable 6-4: MCSQ Scoring Sheet

MCSQ Scoring Sheet

Frequency		Intensity	
Item	Score (range 0-6)	Item	Score (range 0-6)
Q1		Q3	
Q2		Q5	
Q4		Q6	
		Q7	
		Q8	
Total		Total	
Frequency Domain Score = (Total)/(Number of Items in the Domain)		Intensity Domain Score = (Total)/(Number of Items in the Domain)	
Frequency Domain Score (range 0-6)		Intensity Domain Score (range 0-6)	
Total MCSQ Score			
Total MCSQ Score = (Q1 + Q2 + Q3 + Q4 + Q5 + Q6 + Q7 + Q8)/(Number of Items in Total)			
Total MCSQ Score (range 0-6)			

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Chapter 7 Test-Retest Reliability of the McMaster Cough Severity Questionnaire in patients with refractory or unexplained chronic cough

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Abstract

Background: The McMaster Cough Severity Questionnaire (MCSQ) is a newly developed 8-item instrument assessing cough severity in patients with refractory or unexplained chronic cough (RCC/UCC). Although prior work supports its content validity, internal consistency, and cross-sectional convergent validity, its test-retest reliability remains untested.

Objective: To assess the test-retest reliability of the MCSQ in patients with RCC/UCC.

Methods: Adult patients (≥ 18 years) with stable RCC/UCC completed the MCSQ at two visits separated by 1 week. Eligible patients reported “no change” on the Patient Global Impression of Change—Cough Severity Instrument over the 4 weeks prior to enrolment and thus anticipated to remain stable over the subsequent week. We assessed test-retest reliability by calculating two-way random-effects intraclass correlation coefficients (ICC) for absolute agreement with 95% confidence intervals (CI) for the MCSQ total score and the frequency and intensity domain scores.

Results: The study enrolled 75 patients (mean age [SD], 57.8 years [13.0]; 65.3% female; median cough duration [range], 7 years [1-35]). The MCSQ total score demonstrated strong test-retest reliability (ICC = 0.89, 95% CI 0.80-0.93). Reliability was also high for both domains, with ICCs of 0.78 (95% CI 0.63-0.87) for cough frequency and 0.90 (95% CI 0.84-0.94) for cough intensity.

Conclusions: The MCSQ total and domain scores have strong test-retest reliability, indicating low measurement error and observed score differences largely reflecting true variation between individuals.

Introduction

Evaluation of new therapies for refractory or unexplained chronic cough (RCC/UCC) relies on subjective outcome measures that capture the impact of treatment on how patients feel. This is particularly important in RCC/UCC where treatment is largely symptomatic. In response to the need for appropriate measurement instruments, we developed the McMaster Cough Severity Questionnaire (MCSQ) for adult patients with RCC/UCC.¹ Prior work has established its content validity, internal consistency, and cross-sectional convergent validity.¹⁻³ However, its stability over time in clinically unchanged patients remains untested.

For instruments intended to discriminate between patients and assess change within patients, observed score differences must reflect true clinical differences rather than measurement error.⁴ Demonstrating test-retest reliability in clinically stable patients is therefore necessary to provide an estimate of measurement error.

This study evaluates the test-retest reliability of the MCSQ over a 1-week interval in adults with stable RCC/UCC, and compares these estimates to those with the commonly used Cough Severity Visual Analogue Scale (CS-VAS).

Methods

Study setting

The study recruited consecutive patients with RCC/UCC from tertiary cough clinics at the McMaster University Medical Centre (Hamilton, ON, Canada) and St. Joseph's Healthcare Hospital (Hamilton, ON, Canada). All participants provided written informed consent. The study received ethics approval from the Hamilton Integrated Research Ethics Board (Project No. 19082).

Eligibility criteria

Eligible patients included adults (≥ 18 years old) with RCC/UCC lasting for more than 8 weeks who reported “no change” on the Patient Global Impression of Change—Cough Severity Instrument over the 4 weeks preceding enrolment and thus anticipated to remain stable over the subsequent week.

Excluded patients included current or ex-smokers with a < 20 pack/year history; those with cough due to angiotensin converting enzyme inhibitor use; those with symptoms of an upper respiratory infection within the last month that have not resolved; those with an asthma exacerbation within the last month that required the start of an oral corticosteroid; those with other primary pulmonary disorders, including pulmonary embolism, pulmonary hypertension, lung cancer, cystic fibrosis, radiologically proven emphysema, or interstitial lung disease, or severe bronchiectasis; those with language, memory, cognitive, or psychiatric issues that may prevent optimal participation; and non-English speakers.

Study procedures

All patient-reported outcome measures were administered electronically on Research Electronic Data Capture (REDCap). A research coordinator collected demographics, smoking history, medical comorbidities, and a detailed cough history at Visit 1.

Patients completed the MCSQ, CS-VAS, and Patient Global Impression of Change (PGIC) instruments at Visits 1 and 2. Separate PGIC instruments assessed perceived change in cough severity, cough frequency, and cough intensity using a 7-point Likert scale.

Statistical analysis

Descriptive statistics summarized baseline characteristics. For test-retest reliability, we calculated a two-way random-effects intraclass correlation coefficient for absolute agreement and single measurements (ICC[2,1]) with 95% confidence intervals (CI) for the MCSQ Total Score, MCSQ Frequency Score, MCSQ Intensity Score, and the CS-VAS. In addition, Bland-Altman plots assessed agreement between test and retest scores by plotting the differences against the mean of the two measurements. We examined these plots for systematic bias, limits of agreement, and evidence of proportional bias across the score range.

The primary analysis included all patients who reported “no change” on the PGIC—Cough Severity instrument at Visit 1 over the preceding 4 weeks. A sensitivity analysis restricted the sample to those who reported “no change” on the corresponding PGIC at Visit 2 over the 1-week interval.

Pearson’s correlation coefficients with 95% CIs assessed cross-sectional convergent validity between the MCSQ and the CS-VAS at Visit 1. All analyses were performed in R studio version 2023.06.0+421 using the *irr* and *ggplot2* packages.

Sample size

We calculated a sample size of 75 patients to achieve sufficiently precise confidence intervals (± 0.1) around an acceptable ICC of 0.75.⁵

Results

Seventy-five patients enrolled and completed the study with no missing data. Patients had a mean age of 57.8 years, mainly identified as female (65.3%), reported no history of smoking

(70.7%), and coughed for a median duration of 7 years. On average, patients experienced high cough burden evidenced by their baseline MCSQ and CS-VAS scores (**Table 7-1**).

The MCSQ Total Score demonstrated strong test-retest reliability (ICC = 0.89, 95% CI 0.80-0.93). Reliability was also high for both domains, with ICCs of 0.78 (95% CI 0.63-0.87) for cough frequency and 0.90 (95% CI 0.84-0.94) for cough intensity. Reliability estimates for the MCSQ total and domain scores were higher than estimates for the CS-VAS (ICC = 0.66, 95% CI 0.51 to 0.77; **Table 7-2**). Bland-Altman plots confirmed good agreement between the test-retest scores, with most differences falling within the 95% limits of agreement. A small systematic increase in scores from Visit 1 to Visit 2 occurred; however, the absence of proportional bias confirmed consistent test-retest measurements across the full score range (**Figure 7-1**).

Most patients (>73.3%) reported “no change” on the PGIC at the 1-week follow up. **Table 7-3** shows the mean change scores on the MCSQ and CS-VAS according to PGIC categories.

In a sensitivity analysis restricted to patients reporting “no change” at Visit 2, reliability estimates for the MCSQ remained similar, while the CS-VAS demonstrated higher reliability (ICC = 0.74, 95% CI 0.59 to 0.83; **Table 7-2**).

The MCSQ Total Score ($r = 0.81$, 95% CI 0.72 to 0.88) and MCSQ Intensity Score ($r = 0.81$, 95% CI 0.72 to 0.88) showed stronger correlations with the CS-VAS than the MCSQ Frequency Score ($r = 0.62$, 95% CI 0.72 to 0.88).

Discussion

The MCSQ total and domain scores demonstrated good to excellent test-retest reliability, with ICCs meeting conventional thresholds for strong reliability. The ICC quantifies the proportion of total variance in observed scores attributable to between-person differences rather than

measurement error. In a two-way random-effects model for absolute agreement, the ICC represents the ratio of between-participant variance to the total variance, which includes between-participant variance, between-occasion variance, and residual error variance. The high ICCs observed in this study therefore indicate that repeated measurements yield consistent scores that predominantly reflect stable differences in cough severity between patients rather than random error or systematic time effects. Compared with the widely used CS-VAS, the MCSQ demonstrated superior test-retest reliability, suggesting that a multi-item instrument may provide more stable measurements than a single-item instrument in this patient population.

While we strove to include patients who would typically enrol into clinical trials of RCC/UCC, we did not require a minimum baseline CS-VAS score (e.g., ≥ 40 mm) for enrolment. Reliability is a ratio of between-patient variability over total variability (calculated as within- and between-patient variability). Restricting enrolment to only the most severe patients would yield reliability estimates applicable solely to that subgroup. By including patients with varying baseline cough severities, we generated reliability estimates applicable to the broader RCC/UCC population.

Test-retest reliability assumes that the underlying construct remains stable between measurements. However, even in clinically stable individuals, observed scores may fluctuate. This variation arises not only from measurement error inherent to the instrument itself, but also from random within-person fluctuations (i.e., natural variability of disease, environmental influences, behavioural factors) that occur independent of true clinical change. In classical test theory, each observed score reflects the sum of a true score plus error; therefore, small differences between timepoints may occur despite no real change in cough severity.

Because test-retest reliability requires identification of patients whose underlying condition is likely to remain stable, the method used to define clinical stability warrants careful consideration. In this study, we used a baseline PGIC (referencing the prior 4 weeks) to operationalize likely stability over the subsequent week. However, the PGIC itself has sources of measurement error. First, it requires patients to recall their prior symptom state and compare it with their current condition, introducing recall bias if patients do not accurately remember their baseline severity. Second, response shift may occur when patients recalibrate their internal standards or reinterpret symptom severity over time; for example, patients with RCC/UCC may adjust what they consider “severe”, thereby altering their perception of change even when the underlying symptom burden remains similar. Third, patients with RCC/UCC frequently experience day-to-day symptom fluctuation due to natural variability of disease, environmental influences, and/or behavioural factors. These random within-patient fluctuations may influence how patients respond to a PGIC anchor at a given timepoint, even when the underlying disease state has not meaningfully changed. Consequently, PGIC responses may reflect not only true clinical change but also other sources of variability, meaning the anchor itself is not free from measurement error.

Despite the limitations of the PGIC, the more fundamental methodological issue concerns when stability is defined for test-retest reliability. In our study, we defined patients as clinically stable *a priori* using baseline PGIC scores, anticipating that this sample would likely remain stable in the subsequent week. By contrast, most studies assessing test-retest reliability retrospectively identify “stable” patients based on a minimally observed change (e.g., using a PGIC anchor at follow-up). While this approach preferentially selects individuals whose scores happened to vary little, and are therefore assumed to be “clinically stable”, it has two limitations. First, it treats the PGIC as a reference standard with no measurement error. Second, it may inadvertently exclude

truly stable individuals whose scores fluctuate due to random variation. In RCC/UCC, symptoms can fluctuate day-to-day even when underlying cough severity remains stable. Retrospectively selecting patients based on minimal change reduces within-patient variance by design, thereby increasing the proportion of between-patient variance and artificially inflating ICC estimates. By defining stability *a priori* and including patients with natural day-to-day fluctuation, our approach ensures that test-retest estimates reflect reliability under true clinical stability and in the population for whom the instrument is intended to differentiate varying cough severities. This potential bias may explain the discrepancy in reliability estimates for the CS-VAS between the primary and sensitivity analyses, underscoring the importance of prespecified stability criteria. This bias did not affect reliability estimates for the MCSQ.

The study had a 1-week follow-up interval to balance two competing methodological considerations: minimize the likelihood of clinical change beyond natural fluctuation in patients considered stable, and reduce recall bias that may artificially increase score agreement if the retest interval is too short. Patients with RCC/UCC typically have persistent cough severity over short intervals, making a 1-week interval appropriate for assessing score stability.

The reliability of the MCSQ domains differed modestly, with the cough intensity domain demonstrating higher reliability than the cough frequency domain. This may reflect greater day-to-day fluctuation in perceived frequency of coughing compared with intensity, which may be more consistent day-to-day. Nonetheless, both domains demonstrated acceptable reliability.

The MCSQ has comparable test-retest reliability to the Leicester Cough Questionnaire assessing cough impact on quality of life (ICCs = 0.80-0.89, total score; 0.75-0.85),^{6,7} and other proprietary instruments including the Cough Severity Diary (ICCs = 0.90, total score; 0.89-0.93 for domain scores),⁸ and Severity of Chronic Cough Diary (ICCs = 0.89, item 1 on frequency of

cough; 0.92, item 5 on severity of cough).⁷ These findings demonstrate MCSQ's similar reliability with instruments previously used in clinical trials of RCC/UCC.

Strengths and limitations

Strengths of this study include the prospective identification of clinically stable patients, complete follow-up without attrition, and the use of construct-specific anchors to define stability. The study also evaluated reliability at both total and domain levels, providing a nuanced understanding of the instrument's performance.

Several limitations should be acknowledged. First, participants' recruitment from tertiary care centers limits generalizability of reliability estimates to community populations or patients with milder disease. Second, although the 1-week interval was chosen to minimize true clinical change, we cannot exclude the possibility of some true change over time. Finally, to fully support the MCSQ's use for evaluating change within patients, one must also evaluate its responsiveness. Responsiveness refers to the instrument's ability to detect true clinical change in patients who genuinely change relative to those who remain stable.⁹ Test-retest reliability alone, which quantifies measurement error in stable patients, is insufficient to establish this evaluative property. Future studies must examine responsiveness to ensure that the MCSQ can detect meaningful changes in cough severity over time.

Conclusions

The MCSQ demonstrates strong test-retest reliability over a 1-week interval in adults with RCC/UCC, indicating that most score variability reflects true differences between patients rather than measurement error. The findings provide essential foundation for evaluating MCSQ's

responsiveness, which refers to its ability to detect true clinical change beyond variability in stable individuals. Establishing test-retest reliability and, subsequently, responsiveness will strengthen confidence that changes in MCSQ scores in clinical trials reflect true clinical change rather than measurement error.

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Table 7-1: Baseline demographics of participants (n=75)

Age (years), mean (SD)	57.8 (13.0)
Female, n (%)	49 (65.3)
Smoking history	
Never smoker, n (%)	53 (70.7)
Former smoker, n (%)	22 (29.3)
Cough duration (years), median (range)	7 (1-35)
Primary diagnosis	
Refractory chronic cough, n (%)	54 (72.0)
Unexplained chronic cough, n (%)	21 (28.0)
Comorbidities	
Asthma, n (%)	25 (33.3)
Chronic bronchitis, n (%)	4 (5.3)
Gastroesophageal reflux disease, n (%)	36 (48.0)
Upper airway disease, n (%)	19 (25.3)
Other, n (%)	5 (6.7)
McMaster Cough Severity Questionnaire	
Total score ¹ , mean (SD)	3.4 (1.1)
Frequency score ² , mean (SD)	4.2 (1.1)
Intensity score ³ , mean (SD)	2.9 (1.3)
Cough Severity Visual Analogue Scale (mm) ⁴ , mean (SD)	63.8 (19.3)

¹ MCSQ—Total Score ranges from 0 to 6, with higher scores reflecting worse cough severity.

² MCSQ—Frequency Score ranges from 0 to 6, with higher scores reflecting worse cough frequency.

³ MCSQ—Intensity Score ranges from 0 to 6, with higher scores reflecting worse cough intensity.

⁴ Cough Severity Visual Analogue Scale ranges from 0 mm (no cough) to 100 mm (worst possible cough).

Table 7-2: Test-retest reliability

	All participants		Sensitivity analysis including only participants reporting “no change” on the corresponding PGIC at Visit 2	
	ICC (95% CI)	n	ICC (95% CI)	n
MCSQ-Total Score	0.885 (0.801 to 0.931)	75	0.883 (0.792 to 0.933)	58
MCSQ Frequency Score	0.784 (0.634 to 0.870)	75	0.753 (0.578 to 0.856)	55
MCSQ-Intensity Score	0.898 (0.84 to 0.935)	75	0.909 (0.849 to 0.945)	56
CS-VAS	0.662 (0.514 to 0.772)	75	0.735 (0.590 to 0.834)	58

Table 7-3: Change scores by Patient Global Impression of Change responses at visit 2

Cough Severity				Cough Frequency				Cough Intensity			
Patient Global Impression of Change–Cough Severity	n (%)	Change in MCSQ-Total Score, mean (SD)	Change in CS-VAS, mean (SD)	Patient Global Impression of Change–Cough Frequency	n (%)	Change in MCSQ-Frequency Score, mean (SD)	Change in CS-VAS, mean (SD)	Patient Global Impression of Change–Cough Intensity	n (%)	Change in MCSQ-Intensity Score, mean (SD)	Change in CS-VAS, mean (SD)
Very much better	0 (0.0)	--	--	Very much less	0	--	--	Very much less	--	--	--
Much better	2 (2.7)	-0.31 (0.27)	-30.00 (36.77)	Much less	1 (1.3)	-0.33	-56.00	Much less	1 (1.3)	-0.60	-56.00
A little better	6 (8.0)	-0.46 (0.38)	1.33 (4.63)	A little less	9 (12.0)	-0.37 (0.59)	-1.33 (5.63)	A little less	9 (12.0)	-0.53 (0.44)	-4.78 (9.54)
No change	58 (77.3)	-0.20 (0.52)	-2.71 (13.79)	No change	55 (73.3)	-0.31 (0.73)	-2.29 (14.05)	No change	56 (74.7)	-0.11 (0.56)	-2.50 (13.82)
A little worse	7 (9.3)	-0.27 (0.26)	-2.43 (8.66)	A little more	7 (9.3)	-0.48 (0.38)	-5.00 (9.09)	A little more	8 (10.7)	0.05 (0.67)	5.13 (9.86)
Much worse	2 (2.7)	0.81 (0.62)	34.50 (9.19)	Much more	3 (4.0)	0.44 (0.51)	24.00 (19.31)	Much more	1 (1.3)	0.40	41.00
Very much worse	0 (0.0)	--	--	Very much more	0	--	--	Very much more	--	--	--

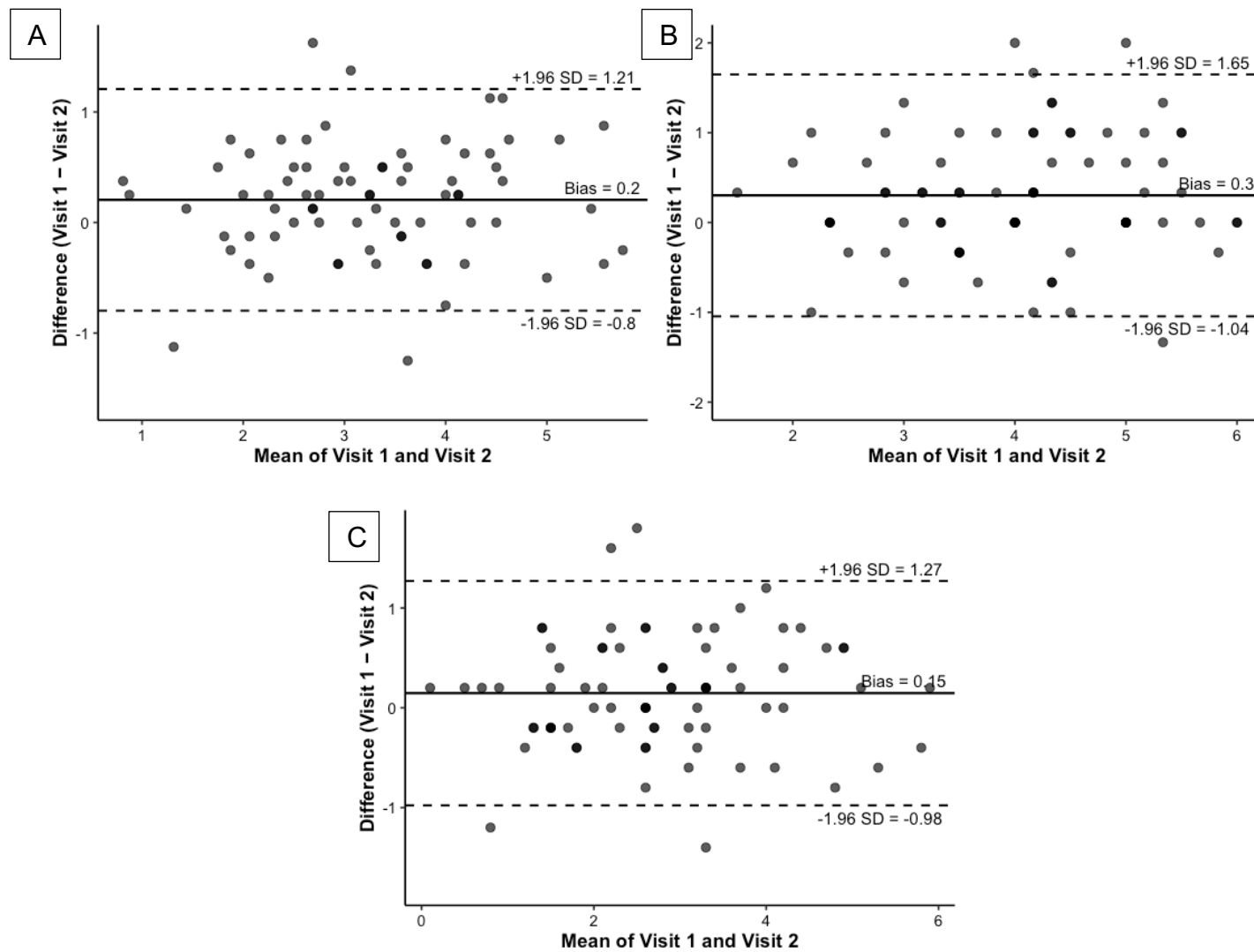


Figure 7-1: Bland-Altman plots demonstrating test-retest agreement for (A) MCSQ Total Score, (B) MCSQ Frequency Score, and (C) MCSQ Intensity Score.

Each point represents an individual patient. The solid horizontal line represents the mean difference (systematic bias), and dashed lines indicate the 95% limits of agreement (mean difference ± 1.96 SD). Across the total score and both domains, a small systematic bias occurred, as reflected by a mean difference slightly above zero. However, the scatter of points suggests random measurement variability without increasing dispersion at higher or lower scores, suggesting no proportional bias across the range of scores.

Chapter 8 A 2x2 factorial, randomized, open-label trial to evaluate neuromodulators and cough control therapy in patients with refractory or unexplained chronic cough: the FORTITUDE trial protocol

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The work presented in this chapter is in preparation for submission to BMJ Open.

Trial Structured Summary

Primary Registry and Trial Identifying Number NCT07288528
Date of Registration in Primary Registry 2025-Dec-17
Secondary Identifying Numbers None
Sources of Monetary or Material Support Canadian Institutes of Health Research
Primary Sponsor Respiratory Research Lab, McMaster University
Secondary Sponsor(s) None
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Public Title Randomized trial to evaluate neuromodulators and cough control therapy in patients with refractory or unexplained chronic cough
Scientific Title A 2x2 factorial, randomized, open-label trial to evaluate neuromodulators and cough control therapy in patients with refractory or unexplained chronic cough: the FORTITUDE trial
Countries of Recruitment Canada
Health Condition(s) or Problem(s) Studied Refractory or unexplained chronic cough
Interventions (1) Morphine sulphate (up to 5 mg twice daily) (2) Pregabalin (up to 150 mg twice daily) (3) Morphine sulphate (up to 5 mg twice daily) plus cough control therapy (4) Pregabalin (up to 150 mg twice daily) plus cough control therapy
Key Inclusion and Exclusion Criteria Eligible patients will include adults (≥ 18 years old) with either: (1) Refractory chronic cough (RCC), defined as having one or more identifiable causes of cough (asthma, upper airway disease, and/or GERD), but with previous trials of treatment targeting the underlying condition leading to no cough resolution; OR (2) Unexplained chronic cough (UCC), defined as having a cough lasting >8 weeks with (i) a normal chest X-ray/CT in the last 5 years and since the onset of chronic cough; (ii) FEV ₁ and FVC $\geq 80\%$ predicted or $>$ lower limit of normal (LLN); (iii) FEV ₁ /FVC ≥ 0.7

or >LLN; (iv) no evidence of asthma; and (vi) no regular symptoms of nasal/reflux disease.

We will exclude patients meeting any of the following criteria:

- (1) Those who, in the opinion of the investigator, have previously tried low-dose morphine, pregabalin, and/or a CCT with full intervention fidelity for the treatment of RCC/UCC;
- (2) Are currently taking morphine or pregabalin for the treatment of any indication (i.e., RCC/UCC or chronic pain);*
- (3) Are currently taking other centrally-acting medication (i.e., gabapentin, amitriptyline, dextromethorphan) for the treatment of any indication (i.e., RCC/UCC, seizures, or depression);*
- (4) Have a history of opioid or substance abuse that, in the opinion of the investigator, may interfere with the conduct of the study;
- (5) Are a current or ex-smoker with a >20 pack-year history or abstinence <6 months;
- (6) Have cough due to angiotensin-converting enzyme inhibitor use;
- (7) Have symptoms of an upper respiratory infection within the last month that have not resolved;
- (8) Had an asthma exacerbation within the last month that requires an increase or start of an oral corticosteroid;
- (9) Have other primary pulmonary disorders, including pulmonary embolism, pulmonary hypertension, lung cancer, cystic fibrosis, radiologically-proven emphysema, interstitial lung disease, or severe bronchiectasis;
- (10) Have language, memory, cognitive, or psychiatric issues that may prevent optimal participation;
- (11) Have creatinine clearance <15 mL/min, including individuals with end-stage renal disease who require hemodialysis or peritoneal dialysis;
- (12) Have any other condition that, in the opinion of the qualified investigator, may adversely affect the participant's ability to complete the study or its measures or pose significant risk to the participant;
- (13) Have participated in another clinical trial of an investigational medicinal product within 30 days;
- (14) Pregnant or breastfeeding; or
- (15) Females of child-bearing potential who:
 - a. Do not agree to use a medically approved method of birth control for the duration of the study. All hormonal birth control must have been in use for a minimum of 3 months.
 - b. Acceptable methods of birth control include oral contraceptives, hormone birth control patch, vaginal contraceptive ring, injectable contraceptives, or hormone implant, double-barrier method, intrauterine devices, non-heterosexual lifestyle or agrees to use contraception if planning on changing to heterosexual partner(s), vasectomy of partner at least 6 months prior to screening.
 - c. Females who are not of child-bearing potential will be defined as females who have undergone a sterilization procedure (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, complete endometrial ablation) or have been post-menopausal for at least 1 year prior to screening.

* Participants taking any of the above medications at baseline will only be eligible if they are willing and medically able to safely discontinue them at least 2 weeks prior to the first study visit. Eligibility will be confirmed by the local study investigator prior to enrolment.
Study Type Type of study: Interventional Method of allocation: Randomized Masking: Open-label Assignment: Factorial Phase: 4
Date of First Enrollment TBD
Sample Size 124
Recruitment Status Pending: participants are not yet being recruited or enrolled at any site
Primary Outcome(s) The change from baseline in 24-hour cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks.
Key Secondary Outcome(s) (1) The change from baseline in awake cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks. (2) The change from baseline in sleep cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks. (3) The change from baseline in cough bouts (defined by inter-cough intervals) measured by the VitaloJAK ambulatory cough monitor at 6 weeks. (4) The change from baseline in cough severity on the McMaster Cough Severity Questionnaire at 6 weeks. (5) The change from baseline in cough severity on the 100-mm visual analogue scale at 6 weeks. (6) The change from baseline in cough-specific quality of life on the Leicester Cough Questionnaire at 6 weeks. (7) Proportion of patients achieving a $\geq 30\%$ reduction in 24-hour cough frequency at 6 weeks. (8) Proportion of patients achieving a ≥ 30-mm reduction on the 100-mm cough severity visual analogue scale at 6 weeks. (9) Proportion of patients achieving a ≥ 1.3-point improvement on the Leicester Cough Questionnaire at 6 weeks. (10) The change from week 6 (end of randomized phase) in cough severity on the McMaster Cough Severity Questionnaire at 6 and 12 months. (11) The change from week 6 (end of randomized phase) in cough severity on the 100-mm visual analogue scale at 6 and 12 months. (12) The change from week 6 (end of randomized phase) in cough-specific quality of life on the Leicester Cough Questionnaire at 6 and 12 months.
Safety outcomes

(1) The proportion of patients with any adverse event for each intervention at 6 weeks, 6 months, and 12 months. (2) The proportion of patients with treatment-related adverse events for each intervention at 6 weeks, 6 months, and 12 months. (3) The proportion of patients with serious adverse events for each intervention at 6 weeks, 6 months, and 12 months. (4) The proportion of patients with adverse events leading to discontinuation for each intervention at 6 weeks, 6 months, and 12 months.
Ethics Review Provisional approval by the Hamilton Integrated Research Ethics Board. Ethical approval pending at other participating sites.
Completion Date TBD
Summary Results TBD

Abstract

Introduction: While clinicians commonly prescribe neuromodulators for the treatment of refractory or unexplained chronic cough, no trials have directly compared these treatments. Furthermore, although guidelines recommend non-pharmacologic management involving physiotherapy and speech therapy, few trials have evaluated its effectiveness.

Methods and analysis: FORTITUDE (*FactOrial Randomized TrIal To evalUate neuromoDulators and cough control thErapy*) is a 6-week, 2x2 factorial, randomized, open-label trial with an observational extension up to 1 year. The trial will include Canadian hospital sites enrolling 124 patients. Patients ≥ 18 years old with either refractory or unexplained chronic cough will undergo 1:1:1:1 randomization to receive either low-dose morphine (up to 5 mg twice daily) or pregabalin (up to 150 mg twice daily) with or without cough control therapy. The cough control therapy will consist of five virtual sessions delivered over 6 weeks by a trained physiotherapist and speech-language pathologist. Change from baseline in 24-hour cough frequency at 6 weeks represents the primary outcome. Secondary outcomes include change from baseline in awake, sleep, and cough bout frequencies; cough severity on the McMaster Cough Severity Questionnaire and the 100-mm visual analogue scale; and cough quality of life on the Leicester Cough Questionnaire at 6 weeks. We will analyze safety and tolerability at 6 weeks and explore potential interactions between neuromodulators and cough control therapy. Follow-up in an observational extension of up to 12 months post-randomization will assess long-term treatment patterns, adherence, and safety in a real-world setting.

Ethics and dissemination: Health Canada's Pharmaceutical Drugs Directorate has provided approval to conduct this study. We have ethics approval from the local research ethics board of the Main Coordinating Site (McMaster University, Hamilton), with ethics pending at other

participating sites. Results of the main trial and the observational extension will be published as manuscripts in peer-reviewed journals.

Keywords: Cough, chronic cough, morphine, pregabalin, non-pharmacologic

Protocol version: 1.3 (04FEB2026)

Article summary

Strengths and limitations of this study

- Guidelines recommend centrally-acting neuromodulators, such as low-dose morphine and pregabalin, for the treatment of refractory or unexplained chronic cough, yet no trials have directly compared these treatments.
- Guidelines also endorse non-pharmacologic management involving physiotherapy and speech therapy, but there is limited randomized trial evidence on the effectiveness of a virtual program and its long-term outcomes.
- FORTITUDE is a 6-week, 2x2 factorial, randomized, open-label trial with a 1-year observational extension in Canadian hospital sites that evaluates low-dose morphine (up to 5 mg twice daily) and pregabalin (up to 150 mg twice daily), with or without virtual cough control therapy (CCT).
- This trial represents the first to compare the effectiveness, safety, and tolerability of two widely prescribed neuromodulators and assess a virtual non-pharmacologic cough intervention.
- While the study is powered to compare morphine versus pregabalin and CCT versus no CCT, it is underpowered to detect interactions between these treatments.

Introduction

What is the problem to be addressed?

Chronic cough lasting >8 weeks is a common health problem. In Canada, it affects 16% of adults aged >45 years, representing one of the highest prevalence rates globally.¹ Although some patients respond to treatments addressing known causes of cough, approximately 26% have, despite optimal therapy, refractory or unexplained chronic cough (RCC/UCC).²

RCC/UCC can lead to substantial physical and psychosocial burden.³ Patients frequently experience chest pain, urinary incontinence, syncope, headaches, depression, and sleep disturbance.^{4,5} Improving quality of life in these patients requires administration of effective therapies.

Current management of RCC/UCC

In Canada and many countries globally, there remains no licensed treatments for RCC/UCC. Clinical practice guidelines^{6,7} therefore recommend behavioural cough suppression⁸⁻¹⁰ or off-label use of neuromodulators, including low-dose morphine,¹¹ pregabalin,⁸ or gabapentin.¹²

Two randomized trials have evaluated low-dose morphine given at 5-10 mg twice daily for 2-4 weeks in adults with RCC/UCC.^{11,13} The first trial in 27 patients found that, compared to placebo, morphine reduced cough severity by 2 points (95% CI 1.1 to 2.1) on a 10-point scale.¹¹ The second trial in 22 known responders found that it improved 24-hour cough frequency by 71.8% and cough severity on the 100-mm visual analogue scale (CS-VAS) by 27.2 mm compared to placebo.¹³ In both trials, patients generally tolerated morphine, and the most common side effects included constipation and drowsiness.^{11,13}

Another neuromodulator, pregabalin, has shown benefit when combined with speech therapy. In a randomized trial of pregabalin (150 mg twice daily) plus speech therapy, the combination improved cough quality of life on the Leicester Cough Questionnaire (LCQ) by 3.5 points (95% CI 1.1 to 5.8) and the CS-VAS by 25.1 mm (95% CI 10.6 to 39.6 mm) compared to speech therapy alone.⁸ Treatment discontinuation occurred in 5% of patients due to drowsiness, nausea, or weight gain.

Non-pharmacologic interventions that often combine education, cough suppression, and behavioral modification have also shown benefit.^{8-10,14} In one randomized trial of 87 patients, speech pathology improved cough scores by 2.8 points (95% CI 1.3 to 4.0) on a 5-point scale compared to placebo.⁹ Another randomized trial of 75 patients evaluating physiotherapy with a speech and language therapy intervention (PSALTI) found that, compared to healthy lifestyle advice, PSALTI reduced cough frequency by 41% (95% CI 36% to 95%) and improved LCQ scores by 1.53 points (95% CI 0.21 to 2.85), with effects sustained up to 3 months.¹⁰ Together, these trials informed a conditional recommendation in favour of non-pharmacologic interventions.⁶

Gaps in the literature

Although current evidence supports the individual efficacy of low-dose morphine^{11,13} and pregabalin⁸, no head-to-head trials have compared these treatments. The routine use of these agents highlights the need for a large randomized trial directly comparing their benefits and harms.

Furthermore, while guidelines recommend non-pharmacologic interventions, randomized trial evidence remains limited to two small studies, with uncertainty regarding durability beyond 3 months,¹⁰ the specific intervention components that drive benefit, and the factors influencing

scalability and broader implementation. This highlights the need for a rigorous evaluation of the effectiveness of a scalable virtual intervention, as well as its fidelity and implementation considerations.

Why is this trial needed now?

Our trial is the first to evaluate two commonly prescribed neuromodulators—low-dose morphine and pregabalin—and a virtual non-pharmacologic intervention called “cough control therapy” (CCT).

We selected low-dose morphine based on evidence from two trials^{11,13} demonstrating cough improvements with doses between 5-10 mg twice daily. Although guidelines recommend both pregabalin and gabapentin,⁶ we selected pregabalin due to its more predictable pharmacokinetics and twice daily dosing,¹⁵ which may improve tolerability and adherence¹⁶ compared to gabapentin’s three times daily dosing.

Building on work from other groups^{8,9,14} and our own,^{17,18} we developed a structured CCT program that can be delivered virtually. In a small observational cohort study of patients with RCC/UCC, our group demonstrated the feasibility of virtual CCT and observed a 59.3% reduction in 24-hour cough frequency following the intervention.¹⁸ We now propose to evaluate virtual CCT in a randomized trial alongside neuromodulators to clarify its independent and additive effects, and comprehensively assess its acceptability, the components that drive benefit, intervention fidelity, and implementation considerations.

Objectives

The co-primary objectives of FORTITUDE are to compare the effectiveness of (1) low-dose morphine versus pregabalin and (2) virtual CCT versus no CCT in adults with RCC/UCC. Secondary and exploratory objectives include assessment of the safety and tolerability of neuromodulators and CCT, exploration of potential interactions between them, and evaluation of treatment adherence.

Methods

Patient and public involvement

Patient partners were involved in the design of the trial and will be involved in the interpretation and reporting of the trial results.

Trial design

FORTITUDE is a multicentre, superiority, 2x2 factorial, randomized, open-label trial in adults with RCC/UCC (**Figure 8-1**). Participants will undergo 1:1:1:1 randomization to receive low-dose morphine, pregabalin, low-dose morphine and CCT, or pregabalin and CCT. Primary outcome assessment will occur at 6 weeks.

Following the 6-week randomized period, participants will enter a 1-year observational extension with assessments at 6- and 12-months. Participants will not be required to remain on their randomized treatment, allowing us to examine real-world long-term effectiveness, treatment trajectories, tolerability, and CCT uptake.

This trial will adhere to the 2025 Consolidated Standards of Reporting Trials (CONSORT),¹⁹ the Factorial Randomized Trials Extension,²⁰ and the 2025 Standard Protocol

Items: Recommendations for Interventional Trials (SPIRIT) guidelines.²¹ The trial is registered on ClinicalTrials.gov: NCT07288528.

Study setting

FORTITUDE will include 5 Canadian academic hospital clinics providing secondary or tertiary care to patients with RCC/UCC.

Screening and informed consent

The study team will approach patients consecutively. Interested patients will receive a study information letter and consent form. Consent discussions may occur in person or by telephone. A research coordinator will obtain written informed consent at an in-person visit.

Eligibility criteria

Eligible patients will include adults (≥ 18 years old) with either: (1) refractory chronic cough (RCC), defined as having one or more identifiable causes of cough (asthma, upper airway disease, and/or GERD), but with previous trials of treatment targeting the underlying condition leading to no cough resolution; OR (2) unexplained chronic cough (UCC), defined as having a cough lasting >8 weeks with (i) a normal chest X-ray/CT in the last 5 years and since the onset of chronic cough; (ii) FEV_1 and FVC $\geq 80\%$ predicted or $>$ lower limit of normal (LLN); (iii) $FEV_1/FVC \geq 0.7$ or $>$ LLN; (iv) no evidence of asthma; and (v) no regular symptoms of nasal/reflux disease.

Key exclusions include patients who (1) have previously tried low-dose morphine, pregabalin, and/or a CCT with full intervention fidelity for the treatment of RCC/UCC; (2) are

currently taking morphine or pregabalin for treatment of any indication (i.e., RCC/UCC or chronic pain); (3) are currently taking other centrally-acting medication (i.e., gabapentin, amitriptyline, dextromethorphan) for the treatment of any indication; (4) have a history of opioid or substance abuse; (5) are a current or ex-smoker with a >20 pack-year history or abstinence <6 months; (6) have cough due to angiotensin-converting enzyme inhibitor use; (7) have symptoms of an upper respiratory infection within the last month that have not resolved; (8) have had an asthma exacerbation within the last month that requires an increase or start of an oral corticosteroid; (9) have other primary pulmonary disorders, including pulmonary embolism, pulmonary hypertension, lung cancer, cystic fibrosis, radiologically-proven emphysema, interstitial lung disease, or severe bronchiectasis; (10) have creatinine clearance <15 mL/min, including individuals with end-stage renal disease who require hemodialysis or peritoneal dialysis; (11) have participated in another clinical trial of an investigational medicinal product within 30 days; or (12) are pregnant or breastfeeding.

Randomization, allocation concealment, and blinding

Authorized research staff will use an automated centralized randomization system on REDCap to ensure concealed allocation stratified by site and with variable block sizes. The REDCap randomization module will generate and conceal the allocation sequence, and research staff enrolling participants will not have access to the sequence prior to assignment. This is an open-label trial in which participants, study staff, investigators, and treating clinicians will be aware of treatment assignment after allocation.

Study interventions

Low-dose morphine

Patients will take oral morphine sulphate 5 mg twice daily (BID) until as tolerated or until the end of the study (1 year). Two trials suggest that this dose optimally balances efficacy and tolerability.^{11,13} It is also the lowest effective dose to mitigate the risk of dependency and addiction. Participants randomized to morphine will also receive a bowel regimen (polyethylene glycol 3350 17 grams once daily) to be taken as needed (PRN) for the prevention and management of constipation.

Pregabalin

Patients will orally titrate to their maximum tolerated dose up to 150 mg BID over 2 weeks using 25 or 50 mg tablets. Similar dosing occurred in a previous trial except their schedule involved quicker up-titration within 6 days.⁸ To mitigate adverse effects due to rapid up-titration, we will allow for a similar maximum tolerated dose, but with up-titration within 2 weeks. Renal-adjusted dosing will follow **Table 8-1** based on creatinine clearance.

Patients will have a telephone visit at 2 weeks with their local study physician to determine their maintenance dose until the end of the study (1 year). If the patient requires stopping of pregabalin for any reason or they reach the end of the study, they should taper their dose over 2 weeks.

Cough control therapy (CCT)

Patients assigned to CCT will attend five 45-60-minute virtual sessions delivered by a trained physiotherapist or speech-language pathologist. The structure, based on prior literature^{8,9,14}

and our group's work,^{17,18} includes education, cough suppression strategies, breathing/laryngeal exercises, and goal setting (**Table 8-2**).

Participants will complete a weekly CCT diary asking them to reflect on the past 7 days and report: (i) how often they used cough control strategies (e.g., urge suppression, breathing techniques); (ii) in what contexts they applied these strategies (e.g., at work, in public, while talking); (iii) what barriers or facilitators influenced their ability to use the techniques; and (iv) the perceived effectiveness of the strategies scored on a 0-10 scale.

We will assess treatment fidelity and therapist adherence using a modified version of the Intervention Fidelity Monitoring Checklist for Trials in Chronic Cough.^{22,23} We will further evaluate participant engagement session-by-session through structured self-report checklists that assess perceived usefulness, understanding, and confidence in applying each session's content.²³

Concomitant therapy

Sites will follow the 2020 European Respiratory Society guidelines for the treatment of chronic cough.⁶ During the 6-week randomized phase, use of morphine, pregabalin, and non-pharmacologic cough interventions outside of the allocated treatment will generally not be permitted to avoid confounding. During this phase, patients will also not be allowed to co-enrol in other clinical trials involving investigational medicinal products for the treatment of RCC/UCC.

Patients who do not respond to their allocated treatment (morphine or pregabalin) will not be permitted to switch to the other neuromodulator or alternative antitussives (e.g., gabapentin, amitriptyline, codeine, dextromethorphan) during the 6-week randomization period. This is to preserve the integrity of treatment allocation and minimize treatment contamination.

Once patients complete the 6-week randomized phase and enter the observational extension, patients can take any concomitant treatments, including switching neuromodulators, engaging in adjunctive therapies, or enrolling in other clinical trials of RCC/UCC. We will closely monitor and document therapies taken during the observational extension for up to 1 year.

Study treatment adherence

We will assess adherence to morphine and pregabalin by self-report and tablet count. The physiotherapist and speech-language pathologist will evaluate adherence to CCT via the number of attended sessions and through weekly adherence diaries.²⁴ For participants receiving the PRN bowel regimen, we will record the number of doses taken since the previous visit.

Study outcomes

Primary effectiveness outcome (randomized phase)

For the comparison between morphine versus pregabalin, and CCT versus no CCT, we will evaluate:

- (1) The change from baseline in 24-hour cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks.

Secondary effectiveness outcomes (randomized phase)

For the comparison between morphine versus pregabalin, and CCT versus no CCT, we will evaluate:

- (1) The change from baseline in awake cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks.

- (2) The change from baseline in sleep cough frequency (coughs/hour) measured by the VitaloJAK ambulatory cough monitor at 6 weeks.
- (3) The change from baseline in cough bouts (defined by inter-cough intervals) measured by the VitaloJAK ambulatory cough monitor at 6 weeks.
- (4) The change from baseline in cough severity on the McMaster Cough Severity Questionnaire at 6 weeks.
- (5) The change from baseline in cough severity on the 100-mm visual analogue scale at 6 weeks.
- (6) The change from baseline in cough-specific quality of life on the Leicester Cough Questionnaire at 6 weeks.
- (7) The proportion of patients achieving a $\geq 30\%$ reduction in 24-hour cough frequency at 6 weeks.
- (8) The proportion of patients achieving a ≥ 30 -mm reduction on the 100-mm cough severity visual analogue scale at 6 weeks.
- (9) The proportion of patients achieving a ≥ 1.3 -point improvement on the Leicester Cough Questionnaire at 6 weeks.

Secondary effectiveness outcomes (observational extension phase)

- (1) The change from week 6 (end of randomized phase) in cough severity on the McMaster Cough Severity Questionnaire at 6 and 12 months.
- (2) The change from week 6 (end of randomized phase) in cough severity on the 100-mm visual analogue scale at 6 and 12 months.

- (3) The change from week 6 (end of randomized phase) in cough-specific quality of life on the Leicester Cough Questionnaire at 6 and 12 months.

Safety outcomes

- (1) The proportion of patients with any adverse event for each intervention at 6 weeks, 6 months, and 12 months.
- (2) The proportion of patients with treatment-related adverse events for each intervention at 6 weeks, 6 months, and 12 months.
- (3) The proportion of patients with serious adverse events for each intervention at 6 weeks, 6 months, and 12 months.
- (4) The proportion of patients with adverse events leading to treatment discontinuation for each intervention at 6 weeks, 6 months, and 12 months.

Visit schedule

Trained research staff will perform all study visits. The study has in person and telephone visits, with electronic administration of all patient-reported outcome measures on REDCap in English and French. **Table 8-3** provides a summary of the visits.

Outcome measures

24-hour cough monitoring with VitaloJAK

An ambulatory cough monitor (VitaloJAK™, Vitalograph, UK) will quantify the number coughs over a 24-hour period. The VitaloJAK cough monitor consists of an air microphone on the lapel, a chest sensor on the sternum, and a battery-operated device around the waist.

The monitor captures audio at 8 kHz and 16-bit WAV. A study coordinator will transfer recordings to a password-protected and encrypted institutional server, where validated, custom-written software will remove silence and background noises. Outputs include 24-hour, awake, and sleep cough frequency expressed as coughs/hour. Cough bouts, defined as more than one cough occurring with inter-cough intervals of 3-10 seconds,²⁵ will be explored as a secondary endpoint.

Patient-reported outcome measures

McMaster Cough Severity Questionnaire (MCSQ)

The MCSQ is an 8-item instrument that assesses patients' perception of cough severity.²⁶ The MCSQ has a 1-week recall period and items with 7-point Likert scales. It has 2 domains (frequency and intensity), and its domain and total scores range from 0 to 6, with higher scores indicating worse cough severity. The MCSQ will serve as a secondary outcome measure and be assessed for its measurement properties.

Cough Severity Visual Analogue Scale (CS-VAS)

The CS-VAS asks patients to mark their cough severity over the last week on a 100-mm VAS ranging from 0 (no cough) to 100 (worst possible cough).²⁷ The CS-VAS will serve as a secondary outcome measure and support construct validation of the MCSQ.

Leicester Cough Questionnaire (LCQ)

The LCQ is a valid and reliable 19-item instrument that assesses cough impact on quality of life.²⁸ The LCQ has a 2-week recall period and items with 7-point Likert scales. It has 3 domains (physical, psychological, and social), and its domain scores range from 1 to 7, with higher scores

indicating better cough quality of life. Its total score ranges from 3 (maximal impairment) to 21 (no impairment). Its minimal important differences are 1.3 (LCQ total), 0.8 (physical domain), 0.9 (psychological domain), and 0.8 (social domain).²⁹ The LCQ will serve as a secondary outcome measure and support construct validation of the MCSQ.

Patient Global Impression of Change (PGIC) Instruments

The PGIC assesses patient-reported change at follow-up visits. We will have separate PGIC Instruments for cough severity, cough intensity, and cough frequency. The PGIC scores changes using a 7-point scale (i.e., cough severity: +3 = very much better, +2 = much better, +1 = a little better, 0 = no change, -1 = a little worse, -2 = much worse, -3 = very much worse). The PGIC will support construct validation and estimation of the minimal important difference of the MCSQ.

Patient Global Impression of Severity (PGIS) Instrument

The PGIS assesses patient-reported severity over the past week on a 5-point scale (i.e., cough severity: 0 = no cough to +4 = very severe). Three separate instruments will assess cough severity, cough frequency, and cough intensity. The PGIS will support construct validation and estimation of the minimal important difference of the MCSQ.

EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L represents a generic health-related quality of life measure that assess how a person's health impacts their quality of life.³⁰ The "5-Dimension" refers to the five key areas of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The "5-Level" indicates that each dimension has five levels of severity, ranging from no problems to

extreme problems. The ED-5D-5L will support a cost-effectiveness analysis of the study interventions.

Data collection

Source documents/electronic case report forms (eCRFs) in REDCap will record all data collected during study visits.

Withdrawal of study participant

Participants can withdraw from the study at any given time. If a participant stops study treatment, we will strongly encourage participants to attend follow-up visits for collection of outcome data. They will remain eligible for financial compensation based on their continued participation in follow-up assessments, regardless of treatment discontinuation or adherence. If they do not wish to participate in outcome data collection and wish to withdraw from all parts of the study, their anonymized data recorded up to the point of withdrawal will be included in the study analysis. All patient data will be anonymized.

Sample size

We will enrol 124 patients and randomize them in a two-stage process. First, a 1:1 randomization will assign patients to low-dose morphine or pregabalin (62 per group). Within each arm, a second independent 1:1 randomization will assign patients to CCT or no CCT. This will result in four groups of 31 patients each. We powered the study on the 62-patient comparisons (i.e., morphine versus pregabalin; CCT versus no CCT) rather than on individual groups. Because we

anticipate a smaller effect size for the morphine versus pregabalin contrast, we conservatively based our sample size on this comparison.

The primary outcome is the change from baseline in natural log-transformed 24-hour cough frequency at 6 weeks. Assuming a 30% relative reduction in 24-hour cough frequency³¹ (corresponding to a mean difference of -0.357 units on the log scale), a standard deviation in log coughs/hour of 0.6,³² and a 10% dropout, a total sample size of 124 participants (62 per intervention comparison) will provide 80% power at a two-sided alpha of 0.025. To maintain a family-wise type I error rate of 5% across our two co-primary hypotheses (morphine versus pregabalin and CCT versus no CCT), we applied a Bonferroni correction and set the significance level at $\alpha=0.025$ for each comparison. We performed these calculations using the `pwr.t.test` function in the `pwr` package in R (version 4.3.1).

While our primary interest lies in estimating main effects, the factorial design also permits exploration of potential interactions between treatments. For the sample size calculation, we assumed no significant interaction—i.e., that the effect of one intervention is consistent across levels of the other. Under this assumption, we will estimate the effect of morphine versus pregabalin by averaging across CCT and no CCT arms, and the effect of CCT versus no CCT by averaging across morphine and pregabalin arms.

To ensure sufficient participant enrollment, we will monitor recruitment at each site monthly and enact strategies (e.g., additional sites) as needed to achieve the target sample size.

Statistical analysis

General considerations

A statistician will conduct all analyses. Descriptive statistics (count and percentage for categorical variables and mean or median with standard deviation or interquartile range for continuous variables, as appropriate) will describe baseline characteristics of enrolled patients.

Main efficacy analysis at 6 weeks

The primary and responder analyses of all primary and secondary outcomes will occur in the intention-to-treat (ITT) population, which includes all participants in the group to which they were randomized. **Table 8-4** summarizes the statistical analysis plan.

Primary analysis of the primary outcome at 6 weeks

For the primary outcome at 6 weeks, we will use a linear model to estimate changes from baseline in log-transformed 24-hour coughs per hour. The model will include treatment group, site, and baseline log-transformed 24-hour cough frequency as fixed effects. Each primary hypothesis (morphine versus pregabalin; CCT versus no CCT) will be tested at a two-sided alpha of 0.025.

We will handle missing data under a missing-at-random assumption using multiple imputation. If $\geq 15\%$ of outcome data are missing, we will perform a missing-not-at-random (MNAR) sensitivity analysis using a pattern-mixture model. Missing outcomes will be assumed to differ by a fixed offset (e.g., 10%) from observed values, and the impact on treatment effects will be examined. Model assumptions (i.e., normality, homoscedasticity) will be checked.

Mean changes from baseline in log-transformed 24-hour coughs per hour will be estimated as marginal means with their 95% confidence intervals (95% CI), and between-group differences (95% CI) will be calculated. To present geometric means of 24-hour coughs per hour for treatment groups at each time point, we will back transform the log-transformed estimates. The percent

difference in the change from baseline and 6 weeks between treatment groups will be calculated as $100*(e^{\text{diff}}-1)$, where diff represents the between-group difference on the log scale. P-values for treatment effects at 6 weeks will be reported.

Primary analysis of the secondary outcomes at 6 weeks

For continuous secondary outcomes at 6 weeks, we will use linear models or linear mixed-effects models. All models will include site and treatment group as fixed effects. For the MCSQ, CS-VAS, and LCQ measured at three timepoints (baseline, 2 weeks, and 6 weeks), we will include participant-level intercept as a random effect, and time and the interaction between treatment and time as fixed effects.

We will estimate marginal means (95% CI) at each timepoint. Between-group differences in mean changes from baseline at 6 weeks (95% CI) will be calculated using post hoc contrasts based on the model. Handling of missing data will follow the same approach as the primary outcome.

For secondary outcomes, p-values for the treatment effect at week 6 will be reported at the conventional two-sided 0.05 level without adjustment for multiple comparisons. While the trial is powered for and will focus on inferential testing of the primary outcome of 24-hour cough frequency, we recognize that some secondary outcomes may better reflect patient-important benefits. Accordingly, interpretation of the trial findings will consider the overall pattern and consistency of effects across primary and secondary outcomes at 6 weeks.

Secondary responder analyses at 6 weeks

We will conduct responder analyses to support clinical interpretation of treatment effects analyzed on a continuous scale. Responders will include those who achieve a (1) $\geq 30\%$ reduction from baseline in 24-hour cough frequency;³¹ (2) ≥ 30 -mm reduction from baseline on the CS-VAS;³³ and (3) ≥ 1.3 -point improvement from baseline on the LCQ.²⁹ We will analyze each responder outcome separately.

For each responder definition, we will report the proportion of responders by treatment group. Generalized linear models with an identity link will estimate between-group absolute risk differences and corresponding 95% CIs. These models will include treatment group and site as fixed effects. Where models fail to converge, risk differences will be estimated using alternative appropriate methods. Handling of missing data will follow the same approach as for the primary outcome.

Sensitivity analyses

Testing the impact of protocol adherence

Anticipating that patients may discontinue treatment due to adverse events, we will assess the robustness of the primary analysis at 6 weeks to deviations from the intervention protocol. This sensitivity analysis will occur with the primary outcome and select secondary outcomes in the per-protocol population.

For the morphine versus pregabalin comparison, the per-protocol population will include patients who received $\geq 80\%$ of the intended study drug over the 6-week period. For the CCT versus no CCT comparison, the per-protocol population will include patients who (1) completed at least four out of the five weekly adherence diaries and (2) reported using at least one cough control strategy in three of those diary entries.

The same linear model or linear mixed-effects model described in the primary analysis will be applied to the per-protocol population.

Testing the impact of including site as a random effect

To assess potential clustering by site, we will repeat analyses for the primary and key secondary outcomes using a model that treats site as a random effect. As site represents a stratification variable in the randomization, we do not anticipate that site-level variation will meaningfully impact treatment effect estimates. However, this sensitivity analysis will account for any unmeasured heterogeneity across sites that may influence outcomes. We will compare estimates with those from the fixed effect model to assess any meaningful differences.

Subgroup analysis

Testing whether the effect of CCT differs depending on neuromodulator treatment

Although not powered to detect interactions, we will conduct an exploratory subgroup analysis evaluating whether the effect of CCT differs depending on the neuromodulator treatment and vice versa.

Linear models will include fixed effects for site, CCT, neuromodulator treatment, their interaction, and baseline log 24-hour cough frequency. Secondary outcomes with repeated measures will use mixed-effects models with participant-level intercepts and interaction terms as appropriate. If we observe evidence of a clinically meaningful interaction, treatment effects will be presented stratified by the interacting factor and conclusions will be interpreted accordingly. Interaction effects will be interpreted cautiously as exploratory.

Testing whether baseline self-efficacy impacts the effectiveness of CCT

Among participants receiving CCT, we will evaluate whether treatment effectiveness differs by baseline self-efficacy measured with the New General Self-Efficacy Scale (median split). Linear models for the primary outcome will include fixed effects for site, self-efficacy group (low versus high), and baseline log cough frequency. Secondary outcomes with repeated measures will use mixed-effects models with participant-level intercepts and interaction terms.

Post hoc contrasts will estimate the effect of CCT within each self-efficacy group (low versus high) at 6 weeks. These analyses will be exploratory with p-values interpreted cautiously.

Testing the effect of CCT on self-efficacy

Among participants receiving CCT, a linear model including fixed effects for site, time, and baseline self-efficacy will assess changes on the New General Self-Efficacy Scale and the Cough Self-Efficacy Scale.

Main analyses for observational extension phase

Descriptive analyses at 6 and 12 months

We will report the frequency and proportion of patients who continue on their assigned treatment, switch to an alternative treatment, discontinue all treatment (i.e., are on no treatment), enrol in another clinical trial, and continue to use techniques learned during the CCT program. Among those who switch, we will describe the treatments they switch to (e.g., morphine, pregabalin, gabapentin, amitriptyline, codeine). For those who switch treatments, discontinue all treatment, or enrol in another clinical trial, we will descriptively summarize the reasons (e.g., adverse effects, lack of benefit) by initial randomized group and by treatment exposure at the time

of the switch or discontinuation. For CCT participants, reasons for not continuing techniques will be documented.

Analysis of patient-reported outcomes at 6 and 12 months

Linear mixed-effects models will estimate changes from week 6 (baseline for the extension phase) to 6 and 12 months for the MCSQ, CS-VAS, and LCQ. Models will include time, treatment group (time-varying), site, and baseline score as fixed effects, and participant-level random intercepts.

Treatment group will be defined as a time-varying categorical fixed effect based on the patient's self-reported treatment at each follow-up visit. The categories will be: (1) on morphine, (2) on pregabalin, (3) on another antitussive, (4) in a clinical trial, or (5) not on any treatment.

The primary analysis will be conducted under a missing-at-random assumption using maximum likelihood estimation. If missing outcome data is $\geq 15\%$, an MNAR sensitivity analysis will be performed. Marginal means (95% CI) at each timepoint will be estimated. Between-group differences in mean changes from baseline at 6 and 12 months (95% CI) will be calculated using post hoc contrasts. P-values for the treatment effect at months 6 and 12 will be reported at the conventional two-sided 0.05 level without adjustment for multiple comparisons. These p-values will be interpreted cautiously given the observational and exploratory nature of these analyses.

Analysis of safety outcomes

We will report all safety outcomes descriptively according to the as-treated population. The as-treated population will include analyzing those based on the treatment received, regardless of their initial randomization. During the randomized phase, adverse event categories—including

participants with any adverse event, treatment-related adverse events, serious adverse events, and discontinuation due to adverse events—will be reported descriptively at 6 weeks. Adverse events occurring in $\geq 10\%$ of participants in a single group at 6 weeks will be highlighted. In addition, we will specifically monitor and report the incidence of the most common side effects of each study drug. For morphine, this includes constipation and drowsiness/sedation. For pregabalin, this includes dizziness, somnolence, and peripheral edema. Safety outcomes during the observational extension will be similarly reported based on participants' treatment exposure at 6 and 12 months.

Study monitoring

Trial management

The Respiratory Research Lab at McMaster University will act as Study Sponsor, Main Coordinating, and Methods Centre, overseeing contracts, ethics submissions, site initiation, training, data quality, and finances. It will prepare study materials (SOPs, manuals, eCRFs), be the point of contact for queries, and communicate protocol amendments. The sponsor will oversee study analysis, interpretation, reporting, and publication decisions.

Data management

To protect participant confidentiality, all study data will be anonymized using unique identifiers. Secure files will store personal identifiers separately. Delegated local staff will enter data into REDCap, a secure, web-based, password-protected, encrypted system with role-based access. Validation rules, consistent coding, audits, query resolution, and backups will ensure data quality.

Steering committee and data monitoring committee

The FORTITUDE Trial Steering Committee, comprised of the Principal Investigator, site leads, and Coordinating Centre research coordinator, will advise on protocol revisions and provide clinical guidance.

A formal Data Monitoring Committee (DMC) will provide independent oversight of participant safety and trial conduct in accordance with a pre-specified DMC charter. The DMC will consist of one independent statistician and two independent physicians with relevant clinical and trial experience. Given the established safety profiles of the study interventions (morphine, pregabalin, and CCT) and the absence of planned interim efficacy analyses, the primary role of the DMC will be to review safety data, protocol adherence, and overall trial conduct.

The DMC will review accumulating safety data at regular intervals and may recommend protocol modifications or additional safeguards if safety concerns arise. Monitoring frequency will depend on recruitment rates, unresolved issues, and findings from prior reviews, and is expected to occur once or twice annually. The Sponsor and Steering Committee will remain responsible for day-to-day trial oversight and implementation of any DMC recommendations.

Adverse events (AEs) and serious adverse events (SAEs)

AEs include any adverse health changes during the study and will require documentation in source documents/eCRFs. Local investigators will assess severity, causality, and expectedness, following centralized guidance. SAEs include death, life-threatening events, hospitalization/prolongation, significant disability, congenital anomalies, or other medically significant events. SAEs will be recorded in patient hospital notes and source documents/eCRFs and reported to the Sponsor and local research ethics board.

Ethics and dissemination

Health Canada's Pharmaceutical Drugs Directorate and the Hamilton Integrated Research Ethics Board has provided study approval. We will also obtain ethical approval from the local research ethics boards of all participating sites before study initiation.

Protocol amendments will be documented with rationale and communicated to the Sponsor, investigators, and sites. If participation or rights change, participants will re-consent.

We will disseminate study findings at international conferences (ATS, ERS) and through open-access published manuscripts in peer-reviewed journals regardless of results. Authorship will follow ICMJE guidelines, acknowledging all sites and personnel. Funders will not influence data handling, analysis, or reporting. Reports will adhere to the 2025 CONSORT¹⁹ and the Factorial Randomized Trials Extension guidelines.²⁰

Data sharing and data access

The Principal Investigator and Steering Committee will review requests for data sharing on an individual basis. After the main publication of the FORTITUDE trial, there may be opportunities to conduct additional analyses on the data collected. Formal requests for additional analyses with a submitted rationale and analysis plan will be made to the Principal Investigator and reviewed with the Steering Committee.

Ancillary and post-trial care

We do not plan specific provisions for ancillary or post-trial care, as all studied interventions are routinely available in clinical practice.

Discussion

Despite guidelines recommending neuromodulators for the treatment of RCC/UCC and their frequent prescription among clinicians, there remains no head-to-head evidence on the comparative benefits and potential long-term harms of these treatments. FORTITUDE will provide important evidence to guide clinicians on which neuromodulator to prescribe for their patients.

FORTITUDE will also represent the largest trial to robustly evaluate the effectiveness of a virtual CCT program. Data from utility scores, diaries, attendance, checklists, and interviews capturing intervention intensity and patient experience will support cost-effectiveness and acceptability analyses.

A 2×2 factorial design allows simultaneous evaluation of two interventions. Since our objective is to compare low-dose morphine versus pregabalin and virtual CCT versus no CCT, this design provides efficient estimation of main effects with fewer participants than two separate trials. In addition, this trial will study these interventions in combination. While one trial has evaluated pregabalin in combination with speech therapy,⁸ no trials have evaluated non-pharmacologic interventions with low-dose morphine.

Although we propose a 2x2 factorial trial with combined interventions, our primary analysis assumes no interaction between neuromodulators and CCT. For separate estimation of main effects, we will assume no interaction between neuromodulators and CCT. As neuromodulators and CCT act through distinct mechanisms—neurobiological versus behavioural modulation of the cough reflex—we believe this assumption may be biologically plausible. The main analysis will independently estimate the effects of neuromodulator treatment (morphine versus pregabalin) and CCT (virtual CCT versus no CCT), with the trial powered accordingly.

While we considered a 3x2 factorial design including a placebo group, we opted against this design to keep the study pragmatic and to not withhold active treatment.

Acknowledging that potential synergistic or antagonistic interactions between these treatments may exist, we will perform exploratory subgroup analyses to assess whether the effect of one treatment differs depending on the other. Our study will have limited power, however, to detect statistically significant interactions, and this represents a study limitation. All exploratory analyses investigating interactions will be interpreted with caution and considered hypothesis-generating.

Finally, the observational extension phase may introduce confounding and selection bias, limiting causal inferences for long-term outcomes.

Conclusions

The FORTITUDE trial will provide important head-to-head evidence on the comparative effectiveness and harms of two commonly prescribed neuromodulators, the effectiveness of a virtual CCT, and the long-term outcomes of these treatments. These findings will inform clinical guidelines and personalized treatment for patients with RCC/UCC.

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et services sociaux (INESSS) for an update of the asthma general practice information booklet for general practitioners as well as therapeutic indications for Enerzair, and is a member of the asthma steering committee of the Canadian Thoracic Society. SKF reports grants from GSK, advises on the CTS Chronic Cough Working Group, and previously advised on the ACCP Cough Guidelines. AK has received consulting fees from ALK, Amgen, AstraZeneca, DIA, GSK, Pfizer, Roche, Sanofi, Trudel, and Valeo; personal fees for speaking or advisory boards from ALK, Amgen, AstraZeneca, DIA, GSK, Pfizer, Roche, Sanofi, Trudel, and Valeo; and holds leadership within the Family Physician Airways Group of Canada and Respiratory Effectiveness Group. POB reports grants from AstraZeneca, Merck, Biohaven and Jasper, consultancy fees from AstraZeneca, GSK, Sage, Teva and Affibody, payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, GSK and Covis and is a Section Editor for the European Respiratory Journal. IS is supported by the Canada Research Chair program, reports grants from Merck, MITACS, GSK, Bellus, Trevi Therapeutics, Bayer, Genentech, Nocion; personal speaker fees from Merck, GSK, AstraZeneca, Sanofi-Regeneron, Nocion; consulting fees from Merck, GSK, Bellus, Sanofi-Regeneron, Methapharm, and Vitalograph outside the submitted work.

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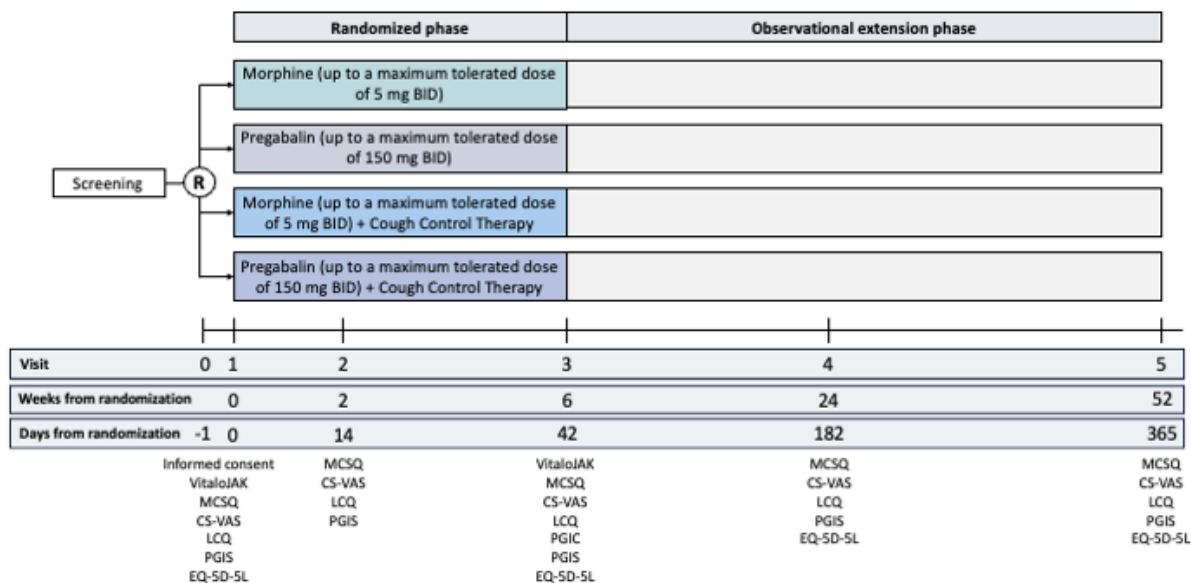


Figure 8-1: FORTITUDE study design

Abbreviations: BID: twice daily; MCSQ: McMaster Cough Severity Questionnaire; CS-VAS: Cough Severity Visual Analogue Scale; LCQ: Leicester Cough Questionnaire; PGIC: Patient Global Impression of Change Instrument; PGIS: Patient Global Impression of Severity Instrument; EQ-5D-5L: EuroQol-5 Dimensions-5 Instrument.

Table 8-1: Dosing schedule of pregabalin

Phase	Days	CLcr $\geq$ 60 mL/min	CLcr 30-60 mL/min	CLcr 15-30 mL/min
Titration	1-7	50 mg AM + 50 mg PM	50 mg AM + 50 mg PM	25 mg AM + 25 mg PM
	8-14	100 mg AM + 100 mg PM	100 mg AM + 100 mg PM	50 mg AM + 50 mg PM
Maintenance	15-21	150 mg AM + 150 mg PM	150 mg AM + 150 mg PM	75 mg AM + 75 mg PM

CLcr: Creatinine clearance estimated by the Cockcroft-Gault equation.

Table 8-2: Summary of cough control therapy

Session	Week	Content
1	1	This session will focus on general education about chronic cough (i.e., definitions, anatomy, and mechanisms), introduction to cough suppression, and goal setting. Participants will complete a baseline self-efficacy assessment using a combined measure consisting of the New General Self-Efficacy Scale ¹ and a brief, cough-specific self-efficacy scale developed for this study. ² Additionally, an entry interview will explore participants' lived experiences with chronic cough and their expectations of the program.
2	2	This session will focus on educating participants about cough triggers, behavioural sensitization mechanisms, and the benefits of non-pharmacological strategies. This session will also include the training and practice of 1-2 cough suppression techniques, with reinforcement of goal-oriented behaviour.
3	3	This session will cover the role of hydration, laryngeal hygiene, and breathing exercises to control chronic cough.
4	4	This session will serve as a consolidation session, reviewing all aspects of cough control therapy and exploring the sustainability of the cough control strategies after the intervention.
5	6	This session will evaluate participants' implementation of cough control strategies in daily life and their progress toward previously established goals. A final self-efficacy reassessment will be conducted, along with an exit interview to qualitatively explore participants' experiences, barriers to maintenance, and perceived impact of the therapy. Interview data will be analyzed following a pre-specified protocol using reflexive thematic analysis. ³

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Table 8-3: Study visits and procedures

Phase	Screening		Randomized phase		Observational extension	
Visit	0	1*	2	3	4	5
Week	0	0	2	6	24	52
Day	-1	0	14	42	182	365
Visit Window (days)	±5	±5	±5	±5	±5	±5
In-Person/Telephone	In-Person	In-Person	Telephone	In-Person	Telephone	Telephone
Informed consent	X					
Eligibility criteria	X					
Review of chest X-ray/CT from the past 5 years [†]	X					
Review of spirometry with post-bronchodilator reversibility from the past 6 months	X					
Review of methacholine challenge from the past 6 months [‡]	X					
Review of sputum induction with differential cell count from the past 6 months [†]	X					
Review of complete blood count (CBC) from the past 6 months	X					
Review of serum creatinine from the past 3 months	X					
Physical examination	X					
Medical history	X					
Cough history	X					
Urine pregnancy test or serum beta-hCG ^{††}	X					
Randomization	X	X [§]				
Initiate treatment	X	X [§]				
Neuromodulator therapy**	-----					
Virtual cough control therapy	-----					
Adverse events	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X

Treatment discontinuation			X	X	X	X
Treatment adherence			X	X	X	X
Vital signs	X			X		
24-hour cough monitoring (VitaloJAK)	X [¶]			X ^{‡‡}		
McMaster Cough Severity Questionnaire (MCSQ)	X		X	X	X	X
Cough Severity Visual Analogue Scale (CS-VAS)	X		X	X	X	X
Leicester Cough Questionnaire (LCQ)	X		X	X	X	X
Patient Global Impression of Change (PGIC)—Cough Severity Instrument				X		
Patient Global Impression of Change (PGIC)—Cough Frequency Instrument				X		
Patient Global Impression of Change (PGIC)—Cough Intensity Instrument				X		
Patient Global Impression of Severity (PGIS)—Cough Severity Instrument	X		X	X	X	X
Patient Global Impression of Severity (PGIS)—Cough Frequency Instrument	X		X	X	X	X
Patient Global Impression of Severity (PGIS)—Cough Intensity Instrument	X		X	X	X	X
EuroQol-5 Dimensions-5 Levels (EQ- 5D-5L)	X			X	X	X
Weekly adherence diary ^{§§}	-----					
Therapist treatment fidelity checklist at each session***	-----					
Participant treatment fidelity checklist at each session ^{§§}	-----					
New General Self-Efficacy Scale ^{§§}	X			X		
Cough Self-Efficacy Scale ^{§§}	X			X		
CCT interviews ^{§§}	X			X		

* Visit 1 only done if eligibility assessment, informed consent, randomization, and baseline assessments cannot occur on the same day as Visit 0.

¶ If not performed within the 5 years before Visit 1 and following the onset of chronic cough, a chest X-ray/CT may be obtained prior to Visit 1. Chest X-ray/CT can be repeated as clinically warranted at the discretion of the investigator.

‡ Only if clinically warranted.

† Only if clinically warranted and where available.

§ Only done at Visit 1 if cannot be done at Visit 0.

** Continue for as long as tolerated or until the end of study (Visit 5).

¶¶ If Visit 0 and 1 are combined, patients will receive instructions to mail back the VitaloJAK cough monitor to their local study site. If Visit 0 and 1 are separate, patients will have the VitaloJAK cough monitor fitted on them at Visit 0 and returned by the patient to their local study site at Visit 1.

‡‡ Patients will receive instructions to mail back the VitaloJAK cough monitor to their local study site.

†† Only in females of child-bearing potential.

§§ Only in individuals receiving virtual cough control therapy.

*** Completed by therapists delivering virtual cough control therapy.

Table 8-4: Summary of statistical analysis plan for the 6-week randomized phase

Objective	Outcome	Research hypothesis	Analysis method
Primary analysis of the primary outcome			
To determine the effect of morphine versus pregabalin on the outcome	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Morphine will reduce 24-hour cough frequency compared to pregabalin	Linear model including fixed effects for treatment, site, and baseline log 24-hour cough frequency
To determine the effect of virtual CCT versus no CCT on the outcome		Virtual CCT will reduce 24-hour cough frequency compared to no CCT	
Primary analysis of the secondary outcomes			
To determine the effect of morphine versus pregabalin on the outcome	Change in awake cough frequency (log-transformed) at 6 weeks	Morphine will reduce awake cough frequency compared to pregabalin	Linear model including fixed effects for treatment, site, and baseline log awake cough frequency
	Change in sleep cough frequency (log-transformed) at 6 weeks	Morphine will have no effect on sleep cough frequency compared to pregabalin	Linear model including fixed effects for treatment, site, and baseline log sleep cough frequency
	Change in cough bouts (log-transformed) at 6 weeks	Morphine will reduce cough bouts compared to pregabalin	Linear model including fixed effects for treatment, site, and baseline log cough bout frequency
	Change in the McMaster Cough Severity Questionnaire (MCSQ)—Total Score at 6 weeks	Morphine will improve cough severity on the MCSQ compared to pregabalin	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the 100-mm cough severity visual analogue scale (CS-VAS) at 6 weeks	Morphine will improve cough severity on the CS-VAS compared to pregabalin	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline CS-VAS score, with participant-level intercept specified as a random effect
	Change in the Leicester Cough Questionnaire (LCQ)—Total Score at 6 weeks	Morphine will improve cough quality of life on the LCQ compared to pregabalin	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect

To determine the effect of virtual CCT versus no CCT on the outcome	Change in awake cough frequency (log-transformed) at 6 weeks	CCT will reduce awake cough frequency compared to no CCT	Linear model including fixed effects for treatment, site, and baseline log awake cough frequency
	Change in sleep cough frequency (log-transformed) at 6 weeks	CCT will have no effect on sleep cough frequency compared to no CCT	Linear model including fixed effects for treatment, site, and baseline log sleep cough frequency
	Change in cough bouts (log-transformed) at 6 weeks	CCT will reduce cough bouts compared to no CCT	Linear model including fixed effects for treatment, site, and baseline log cough bout frequency
	Change in the MCSQ—Total Score at 6 weeks	CCT will improve cough severity on the MCSQ compared to no CCT	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the CS-VAS at 6 weeks	CCT will improve cough severity on the CS-VAS compared to no CCT	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline CS-VAS score, with participant-level intercept specified as a random effect
	Change in the LCQ—Total Score at 6 weeks	CCT will improve cough quality of life on the LCQ compared to no CCT	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect
Responder analyses			
To determine the effect of morphine versus pregabalin on the outcome	Risk difference for achieving a $\geq 30\%$ reduction in 24-hour cough frequency (log-transformed) at 6 weeks	A greater proportion of participants receiving morphine will achieve a response in 24-hour cough frequency compared with those receiving pregabalin	Linear model with identity link including fixed effects for treatment and site
	Risk difference for achieving a ≥ 30 -mm reduction on the CS-VAS at 6 weeks	A greater proportion of participants receiving morphine will achieve a response on the CS-VAS compared with those receiving pregabalin	
	Risk difference for achieving a ≥ 1.3 -point improvement on the LCQ at 6 weeks	A greater proportion of participants receiving morphine will achieve a response on the	

		LCQ compared with those receiving pregabalin	
To determine the effect of virtual CCT versus no CCT on the outcome	Risk difference for achieving a $\geq 30\%$ reduction in 24-hour cough frequency (log-transformed) at 6 weeks	A greater proportion of participants receiving CCT will achieve a response in 24-hour cough frequency compared with those receiving no CCT	
	Risk difference for achieving a ≥ 30 -mm reduction on the CS-VAS at 6 weeks	A greater proportion of participants receiving CCT will achieve a response on the CS-VAS compared with those receiving no CCT	
	Risk difference for achieving a ≥ 1.3 -point improvement on the LCQ at 6 weeks	A greater proportion of participants receiving CCT will achieve a response on the LCQ compared with those receiving no CCT	
Sensitivity analyses			
To determine the effect of morphine versus pregabalin under optimal protocol adherence (those who received $\geq 80\%$ of the intended study drug over the 6-week period, regardless of CCT adherence)	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Protocol adherence will change the effect of morphine versus pregabalin on 24-hour cough frequency	Linear model including fixed effects for treatment, site, and baseline log 24-hour cough frequency
	Change in the MCSQ—Total Score at 6 weeks	Protocol adherence will change the effect of morphine versus pregabalin on the MCSQ	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the LCQ—Total Score at 6 weeks	Protocol adherence will change the effect of morphine versus pregabalin on the LCQ	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect
To determine the effect of virtual CCT vs no CCT under	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Protocol adherence will change the effect of CCT versus no CCT on 24-hour cough frequency	Linear model including fixed effects for treatment, site, and baseline log 24-hour cough frequency

optimal protocol adherence (those who (1) complete at least four out of the five weekly adherence diaries and (2) report using at least one cough control strategy in three of those diary entries)	Change in the MCSQ— Total Score at 6 weeks	Protocol adherence will change the effect of CCT versus no CCT on the MCSQ	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the LCQ— Total Score at 6 weeks	Protocol adherence will change the effect of CCT versus no CCT on the LCQ	Linear mixed-effects model including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect
If $\geq 15\%$ of outcome data is missing, to determine the effect of morphine versus pregabalin under a missing not at random (MNAR) assumption	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Missing data will change the effect of morphine versus pregabalin on 24-hour cough frequency	Pattern-mixture linear model with delta adjustment, including fixed effects for treatment, site, and baseline log 24-hour cough frequency
	Change in the MCSQ— Total Score at 6 weeks	Missing data will change the effect of morphine versus pregabalin on the MCSQ	Pattern-mixture linear mixed-effects model with delta adjustment, including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the LCQ— Total Score at 6 weeks	Missing data will change the effect of morphine versus pregabalin on the LCQ	Pattern-mixture linear mixed-effects model with delta adjustment, including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect
If $\geq 15\%$ of outcome data is missing, to determine the effect of virtual CCT versus no CCT under a missing not at random (MNAR) assumption	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Missing data will change the effect of CCT versus no CCT on 24-hour cough frequency	Pattern-mixture linear model with delta adjustment, including fixed effects for treatment, site, and baseline log 24-hour cough frequency
	Change in the MCSQ— Total Score at 6 weeks	Missing data will change the effect of CCT versus no CCT on the MCSQ	Pattern-mixture linear mixed-effects model with delta adjustment, including fixed effects for site, treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept specified as a random effect
	Change in the LCQ— Total Score at 6 weeks	Missing data will change the effect of CCT versus no CCT on the LCQ	Pattern-mixture linear mixed-effects model with delta adjustment, including fixed effects for site, treatment, time, their interaction, and baseline LCQ score, with participant-level intercept specified as a random effect

To determine whether including site as a random effect impacts the effect of morphine versus pregabalin	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Site as a random effect will not change the effect of morphine versus pregabalin on 24-hour cough frequency	Linear model including fixed effects for treatment and baseline log 24-hour cough frequency, and site as a random effect
	Change in the MCSQ—Total Score at 6 weeks	Site as a random effect will not change the effect of morphine versus pregabalin on the MCSQ	Linear mixed-effects model including fixed effects for treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept and site specified as random effects
	Change in the LCQ—Total Score at 6 weeks	Site as a random effect will not change the effect of morphine versus pregabalin on the LCQ	Linear mixed-effects model including fixed effects for treatment, time, their interaction, and baseline LCQ score, with participant-level intercept and site specified as random effects
To determine whether including site as a random effect impacts the effect of virtual CCT versus no CCT	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Site as a random effect will not change the effect of CCT versus no CCT on 24-hour cough frequency	Linear model including fixed effects for treatment and baseline log 24-hour cough frequency, and site as a random effect
	Change in the MCSQ—Total Score at 6 weeks	Site as a random effect will not change the effect of CCT versus no CCT on the MCSQ	Linear mixed-effects model including fixed effects for treatment, time, their interaction, and baseline MCSQ score, with participant-level intercept and site specified as random effects
	Change in the LCQ—Total Score at 6 weeks	Site as a random effect will not change the effect of CCT versus no CCT on the LCQ	Linear mixed-effects model including fixed effects for treatment, time, their interaction, and baseline LCQ score, with participant-level intercept and site specified as random effects
Subgroup analyses			
To determine whether the effect of CCT differs depending on neuromodulator treatment (morphine versus pregabalin)	Change in 24-hour cough frequency (log-transformed) at 6 weeks	There may be a synergistic effect between CCT and morphine or CCT and pregabalin in terms of 24-hour cough frequency	Linear model including site, treatment, baseline log 24-hour cough frequency, and a CCT x neuromodulator interaction term; post hoc contrasts to estimate the effect of CCT within each neuromodulator group
	Change in the MCSQ—Total Score at 6 weeks	There may be a synergistic effect between CCT and morphine or CCT and pregabalin in terms of cough severity on the MCSQ	Linear mixed-effects model including time, site, treatment, neuromodulator group, baseline MCSQ score, and all two- and three-way interactions among time, treatment, and neuromodulator, with a participant-level random intercept; post hoc contrasts

			will estimate the effect of CCT within each neuromodulator group
	Change in the LCQ— Total Score at 6 weeks	There may be a synergistic effect between CCT and morphine or CCT and pregabalin in terms of cough quality of life on the LCQ	Linear mixed-effects model including time, site, treatment, neuromodulator group, baseline LCQ score, and all two- and three-way interactions among time, treatment, and neuromodulator, with a participant-level random intercept; post hoc contrasts will estimate the effect of CCT within each neuromodulator group
To determine whether response to CCT differs by baseline self-efficacy measured on the New General Self-Efficacy Scale	Change in 24-hour cough frequency (log-transformed) at 6 weeks	Patients with greater self-efficacy at baseline are more likely to benefit from CCT in terms of 24-hour cough frequency	Linear model including site, baseline log 24-hour cough frequency, and baseline self-efficacy group (low vs high); post hoc contrasts to estimate the effect of CCT within each self-efficacy group
	Change in the MCSQ— Total Score at 6 weeks	Patients with greater self-efficacy at baseline are more likely to benefit from CCT in terms of cough severity on the MCSQ	Linear mixed-effects model including time, site, baseline self-efficacy group (low vs high), baseline MCSQ score, and the interaction between time and self-efficacy group, with a participant-level random intercept; post hoc contrasts will estimate the effect of CCT within each self-efficacy group
	Change in the LCQ— Total Score at 6 weeks	Patients with greater self-efficacy at baseline are more likely to benefit from CCT in terms of cough quality of life on the LCQ	Linear mixed-effects model including time, site, self-efficacy group (low vs high), baseline LCQ score, and the interaction between time and self-efficacy group, with a participant-level random intercept; post hoc contrasts will estimate the effect of CCT within each self-efficacy group
To determine the effect of CCT on self-efficacy	Change in the New General Self-Efficacy Scale (NGSES)—Total Scale at 6 weeks	CCT will improve self-efficacy on the NGSES at 6 weeks compared to baseline	Linear model including site, time, and baseline NGSES score
	Change in the Cough Self-Efficacy Scale (CSES) at 6 weeks	CCT will improve self-efficacy on the CSES at 6 weeks compared to baseline	Linear model including site, time, and baseline CSES score

Chapter 9 Discussion and Conclusions

Overview of Thesis Contributions

Drug development programs in refractory or unexplained chronic cough (RCC/UCC) face several challenges, including suboptimal clinical trial endpoints and large placebo responses. Together, these issues complicate interpretation of treatment effects and may hinder appropriate evaluation of new treatments. This thesis addresses these challenges through four key contributions.

First, we provide an evidence-based synthesis of the clinical development program for gefapixant, the first therapy in RCC/UCC to reach phase 3 trials. Our dose-response meta-analysis quantified gefapixant's modest treatment effects, substantial taste-related adverse effects, and large placebo responses. These results contextualize the clinical significance of observed findings and provide insight into why the drug received regulatory approval in some jurisdictions but not others.

Second, we identify potential mechanistic and methodological reasons for the placebo response in trials of RCC/UCC. Potential mechanisms for true placebo effects may involve activation of descending inhibitory pathways and release of endogenous opioids within the central nervous system. In addition, we highlight methodological contributors to the placebo response such as regression-to-the-mean, which may occur when trials recruit patients during periods of heightened cough burden. Together, these insights help explain the placebo response and may inform future study designs aimed at improving signal detection.

Third, we describe the development and preliminary evaluation of the McMaster Cough Severity Questionnaire (MCSQ), an instrument capturing patient-important aspects of cough severity. Development of the MCSQ occurred through item generation from a systematic survey, patient focus groups, and expert panel input, followed by item reduction through patient surveys,

exploratory factor analysis, cognitive debriefing interviews, and Rasch modelling. This process resulted in an 8-item instrument consisting of two domains (cough frequency and cough intensity) and a one-week recall period. The final MCSQ demonstrated high internal consistency, strong cross-sectional convergent validity with the 100-mm cough severity visual analogue scale, and excellent test-retest reliability. The findings support the MCSQ as a promising patient-important outcome measure for use in clinical trials and clinical practice.

Finally, we establish a protocol for the FORTITUDE trial, a multicentre, pragmatic, 2x2 factorial randomized trial evaluating commonly prescribed treatments for RCC/UCC. FORTITUDE will also provide the first head-to-head comparison of two guideline-recommended neuromodulators, low-dose morphine and pregabalin, while also evaluating the effectiveness of virtual cough control therapy (CCT). The trial's 2x2 factorial design enables estimation of the independent and potential interactive effects of pharmacologic and non-pharmacologic therapies, including the first evaluation of combined low-dose morphine and CCT. In addition, the study represents the largest evaluation to date of a virtual CCT, addressing an urgent need for accessible non-pharmacologic management. As the first pan-Canadian academic randomized trial in RCC/UCC, FORTITUDE will generate important evidence to inform international clinical guidelines, policy decisions, and day-to-day treatment decisions for patients. The trial will also provide an opportunity to further evaluate the longitudinal validity, responsiveness, and minimal important differences (MIDs) of the MCSQ.

Future Research Directions

Several future research directions could build on this thesis to further strengthen outcome measurement, improve the evidence base for treatments, and advance precision medicine in RCC/UCC.

Further Evaluation of the MCSQ

While existing studies support the content validity, internal consistency, cross-sectional convergent validity, and test-retest reliability of the MCSQ, additional work should evaluate its ability to detect meaningful within-patient change over time. This includes evaluating responsiveness¹ and estimating the MID,² defined as the smallest change in an instrument's score that patients perceive as important.

These investigations will occur as part of the FORTITUDE trial, which includes repeated longitudinal assessments with the MCSQ along with objective cough frequency, the Leicester Cough Questionnaire, and the Cough Severity Visual Analogue Scale. We will assess responsiveness by examining the MCSQ's ability to detect change over time relative to variability observed in clinically stable patients.¹ To estimate MIDs for the MCSQ total and domain scores, we will apply both anchor- and distribution-based approaches, with greater emphasis on anchor-based methods.³ Anchor-based approaches link changes in MCSQ scores to independent measures of patient-perceived change, such as the Patient Global Impression of Change and the Patient Global Impression of Severity instruments.⁴ In contrast, distribution-based approaches rely on statistical properties of the score distribution, such as standard deviation or standard error of measurement, to define a threshold for meaningful change.⁴ Applying multiple anchors and using both methods will generate precise estimates of the MID for the MCSQ.

Several academic and industry-sponsored trials evaluating emerging treatments for chronic cough and RCC/UCC have already incorporated the MCSQ as an endpoint. These studies will enable further evaluation across diverse patient populations (i.e., RCC/UCC and chronic cough in asthma, bronchiectasis, and interstitial lung disease) and across multiple languages. Our group has already completed forward and back translations of the MCSQ for several languages, followed by cognitive debriefing to ensure clarity, cultural relevance, and conceptual equivalence. Together, these efforts will help establish the MCSQ as a widely applicable, patient-centered outcome measure for both clinical trials and clinical practice.

Optimizing Guideline-Based Treatments

In addition to evaluating the effectiveness of guideline-based treatments, the FORTITUDE trial will include several secondary analyses informing clinical decision-making and policy. A health economic evaluation will quantify the cost-effectiveness of pharmacologic therapy and virtual CCT, providing actionable evidence for healthcare payers and policymakers. Mixed-methods analyses will examine patients' experiences with virtual CCT and identify perceived beneficial components and factors influencing adherence and implementation. Insights from these analyses will inform strategies to optimize delivery, accessibility, and integration of CCT into routine clinical practice.

Identifying Predictors of Treatment Response

A key priority for future research is identifying predictors of treatment response in RCC/UCC. At present, clinicians have limited ability to determine which patients will most likely benefit from specific therapies, resulting in a trial-and-error approach.

A potential sub-study within the FORTITUDE trial could examine genetic predictors of response to therapies. Specifically, this would involve examining whether polymorphisms in genes involved in opioid signalling—such as catechol-O-methyltransferase (COMT),⁵ the μ -opioid receptor gene (OPRM1),⁶ and other related pathways—associate with response to low-dose morphine. Such analyses would require baseline blood collection for genotyping and may require combining samples with a larger cohort to ensure adequate statistical power. Pharmacogenetic studies in the field of chronic pain have similarly sought to identify predictors of response to opioid analgesics.⁶ An analogous approach in RCC/UCC could support more personalized treatment strategies and improved patient selection for therapy.

Another FORTITUDE sub-study that would improve understanding of the mechanisms of centrally acting neuromodulators would involve assessing descending inhibitory control. In neuropathic pain, researchers have studied poor descending inhibitory control in the central nervous system using conditioned pain modulation (CPM).⁷ In CPM, a nociceptive stimulus activates diffuse noxious inhibitory pathways; for example, a noxious stimulus applied to the left hand can reduce pain experienced from a second stimulus applied to the right hand.

One study in RCC/UCC applied a similar technique called conditioned cough modulation (CCM) to evaluate descending inhibition.⁸ During CCM, participants underwent cough challenge testing before and after a conditioning stimulus of hand immersion in cold water. This stimulus activated endogenous inhibitory pathways, enabling quantification of descending modulation of the cough reflex. The study showed that patients with RCC/UCC exhibited impaired descending inhibitory control during capsaicin cough challenge compared with healthy individuals.⁸

Building on this principle, a FORTITUDE sub-study could incorporate CCM assessments with cough challenge testing at baseline to evaluate whether impaired descending inhibition

predicts response to neuromodulator therapy. Repeating CCM and cough challenge after treatment could also reveal whether low-dose morphine, pregabalin, or CCT restore inhibitory control over cough pathways. Together, these investigations may clarify mechanisms underlying treatment response while also supporting the development of predictive tools to guide treatment selection.

Advancing Diagnosis and Phenotyping of Cough Hypersensitivity Syndrome

Another unmet need involves tools for diagnosing and phenotyping patients with RCC/UCC. Currently, RCC/UCC remains a diagnosis of exclusion, with no widely available diagnostic test to objectively assess underlying cough hypersensitivity syndrome.

Cough challenge testing using inhaled tussive agents may help address this gap.⁹ Several studies have examined challenges using capsaicin,¹⁰ mannitol,¹¹ citric acid,¹² adenosine 5'-triphosphate (ATP),¹³ and other tussive agents.⁹ However, clinicians have not adopted these tests into clinical practice. Limited uptake reflects the absence of a standardized, simple methodology using equipment that is broadly accessible. Additionally, traditional endpoints, such as the concentrations evoking two or five coughs (C_2 and C_5), capture a single-point on the dose-response curve and correlate poorly with patient-important outcomes, including cough frequency,¹⁴ cough severity, and quality of life.¹⁵ Alternative approaches, such as calculating the area under the cough dose-response curve, may provide a more comprehensive measure of cough reflex sensitivity and responsiveness.

To address these challenges, our lab has developed a standardized methodology for ATP cough challenge testing. The protocol mimics methacholine challenge testing that is performed routinely for the diagnosis of airway hyperresponsiveness in asthma. During testing, participants inhale increasing doubling doses of ATP via tidal breathing through the Aerogen Solo Vibrating

Mesh Nebulizer. After each dose, a researcher systematically records coughs, FEV₁, and patient-reported symptoms. Using this approach, we have demonstrated the safety and feasibility of ATP cough challenges, as well as the high reliability of novel endpoints including area under the dose-response curve. We have also shown that ATP cough challenge may differentiate cough due to cough hypersensitivity syndrome from cough related to bronchoconstriction.¹⁶

Future studies must confirm these findings in larger cohorts, but these results suggest that ATP cough challenge could help diagnose patients with cough hypersensitivity syndrome. In addition, ATP cough challenge may serve as a predictive tool to identify patients most likely to respond to targeted therapies (i.e., P2X3 antagonists), thereby supporting more precise phenotyping and individualized treatment selection.

Conclusions

This thesis advances the understanding and measurement of RCC/UCC by addressing key challenges in clinical trials and patient-centered assessment. First, it provides a rigorous synthesis of gefapixant trials, quantifying modest treatment effects and clarifying drivers of substantial placebo responses. Second, it describes mechanistic and methodological contributors to placebo responses, including central inhibitory pathways, endogenous opioids, and trial factors such as regression-to-the-mean. Third, it introduces the MCSQ, a brief patient-reported outcome measure that captures cough frequency and intensity with strong reliability and convergent validity. Finally, it establishes the FORTITUDE trial as a national platform to evaluate pharmacologic and non-pharmacologic therapies. Within the FORTITUDE trial, further assessment of the MCSQ's responsiveness and MID will occur.

Collectively, these contributions strengthen the methodological foundation for research in RCC/UCC by enabling improved interpretation of treatment effects and more patient-centered evaluation of new therapies. This thesis also establishes a framework for future studies focused on improving diagnosis, phenotyping, prediction of treatment response, and understanding central mechanisms of RCC/UCC.

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