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REVIEW

A review of the most common patient-reported outcomes in COPD – revisiting current knowledge and estimating future challenges

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Abstract: Patient-reported outcome (PRO) measures that quantify disease impact have become important measures of outcome in COPD research and treatment. The objective of this literature review was to comprehensively evaluate psychometric properties of available PRO instruments and the ability of each of them to characterize pharmaceutical treatment effects from published clinical trial evidence. Identified in this study were several PRO measures, both those that have been used extensively in COPD clinical trials (St George's Respiratory Questionnaire and Chronic Respiratory Questionnaire) and new instruments whose full value is still to be determined. This suggests a great need for more information about the patient experience of treatment benefit, but this also may pose challenges to researchers, clinicians, and other important stakeholders (eg, regulatory agencies, pharmaceutical companies) who develop new treatment entities and payers (including but not limited to health technology assessment agencies such as the National Institute for Health and Care Excellence and the Canadian Agency for Drugs and Technologies in Health). The purpose of this review is to enable researchers and clinicians to gain a broad overview of PRO measures in COPD by summarizing the value and purpose of these measures and by providing sufficient detail for interested audiences to determine which instrument may be the most suitable for evaluating a particular research purpose.

Keywords: COPD, patient reported outcome, health related quality of life, quality of life, psychometric properties

Introduction

COPD is a complex, multicomponent, chronic condition that is characterized by progressive airflow limitation that is not fully reversible.[1] Progressive deterioration of lung function together with other comorbidities imposes various impacts on the patients' physical condition, functioning, and health related quality of life (HRQoL).[1,2] Patients with COPD show progressive decline in lung function, and they show the exacerbations that the condition brings with it: breathlessness (dyspnea) on exertion; cough and sputum production; and reduced exercise capacity.[2] Because measurement of forced expiratory volume in 1 second (FEV_1) is the most repeatable lung function parameter, it is usually the primary parameter used to assess patient outcome, to classify patients by severity, and to measure disease progression both in clinical trials and in clinical practice.[1,2] Therefore, changes in FEV_1 are often used to adapt treatment strategies and to test the effectiveness of various treatments in COPD patients. However, this strategy falls short, as it has been well documented that changes in FEV_1 do not correlate well with changes in COPD symptoms and correlate only modestly with health status or other patient-reported outcome (PRO) measures.[3–6] In addition to

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pulmonary manifestations, patients with COPD may develop other systemic problems and comorbidities[1,2] that contribute significantly to reduced exercise capacity and HRQoL, but none of these are reflected in changes in FEV_1.[7] Therefore, recent treatment guidelines for COPD have recommended the inclusion of symptom assessments such as the COPD Assessment Test[8] (CAT) and the modified Medical Research Council (m-MRC)[9] dyspnea scale to fully assess patients.[1] In clinical practice, it is important that spirometry be accompanied by other assessments that use relevant PRO measures to evaluate the response to treatment.[10,11]

PROs

The use of a PRO as a primary or a secondary endpoint in clinical trials has become more widespread in recent years, and guidance on the use of PROs in clinical trials has been recently published.[12] Typically, PROs present the patient perspective of treatment benefit and can be used to assess and monitor disease progression, exacerbation of symptoms, or adverse effects of treatment.[13–17] Key concepts in COPD that have significant impact on a patient's HRQoL include breathlessness/dyspnea, fatigue, cough and sputum production, physical functioning, social functioning, and exacerbations.[2,18] In order to evaluate the effects of treatment that are relevant to patients with COPD, PRO instruments need to be fit for the purpose: they should be valid, reliable, and responsive to clinically meaningful treatment effects in COPD. This review provides an overview of the most commonly used PROs that are condition-specific to COPD. We evaluated the role of PROs in assessing treatment benefit, as well as their abilities to evaluate health status and well- being of patients. This study differs from a systematic review of PRO instruments published by Weldam et al in 2013, which evaluated the psychometric criteria of the instruments with each other and concluded that there is too little evidence to recommend generic HRQoL instruments for use in COPD care.[19] In this article, we describe the characteristics of the most commonly used COPD instruments in more detail so that individuals who are looking to use PRO instruments in studies can get a reasonable insight into the benefits and characteristics of each instrument. Furthermore, instruments that were not available in 2012, such as the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and the Exacerbations of Chronic Pulmonary Disease Respiratory Symptoms (E-RS), are detailed in this study.

Methods

A literature search was conducted to retrieve articles describing tools for measuring COPD PROs (symptoms, health status, functioning, and HRQoL) and their development. References for this review were identified through searches in PubMed for articles published with the terms "chronic obstructive pulmonary disease", "COPD", "patient reported outcomes", "health related quality of life", "health status questionnaires", "exacerbation measures", or "breathlessness measures". Relevant published articles found through searches in the author's personal files and in Google Scholar were also included. Articles resulting from these searches and relevant references and citations were also included in the review. No date was set for inclusion of articles; included were those publications that were in English and based on some information of psychometric validation to ensure the validity of the instrument development. Excluded were articles about generic HRQoL instruments such as the SF-36 and articles about functioning measures that were not specific to COPD or used in clinical trials of studies that compared treatment benefit.

Results

Frequently used PRO measures in COPD

High level psychometric information (including minimal important difference) about the commonly used PRO instruments is presented in Tables 1 and 2. The paper will further provide a short instrument-by-instrument description as a quick reference guide.

Health status and HRQoL measures

St George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item, self-administered measure that evaluates HRQoL in individuals with chronic airflow limitation.[20–22] This tool has been developed with patient input and with the response to each of its items weighted by using patient derived-weights. This strategy of empirical determination of different item weights overcomes the methodological challenge of obtaining an overall measure of the symptomatic impact of the disease. The SGRQ has well documented content validity and has shown good reliability and validity.[23,24] The SGRQ has been recommended as a suitable HRQoL instrument that can be used in drug development programs and clinical trials in a UK report to the department of health, European Medicines Agency,[25] as well as mentioned as a suitable endpoint in the COPD draft guidance by the US Food and Drug Administration (FDA).[14] The SGRQ has also been widely used in clinical trials, including many pivotal trials in COPD, because its discriminative and evaluative properties and predictive validity have been established and its responsiveness to pharmacological

Table 1 Overview of patient-reported outcome measures in COPD

PRO	Developers	Purpose of tool	Domains	Number of items	Recall period	Mode of administration	Response scale	Scoring	MCID
Frequently used PRO measures in COPD									
St George's Respiratory Questionnaire (SGRQ)	Jones et al[21,22]	To assess health impairment in chronic airflow limitation	Symptoms; activity; impacts on daily life	50	Last 4 weeks Last 3 months Last year	Self-administered Telephone-administered Electronic version	3–5 point Likert scales Yes/no	Total subscale scores calculated from the summed weights for questions 1–8 in symptoms; 11–15 in activity; and 9–10, 12–14 and 16–27 in impact. Total score sums all positive responses and expresses these as a percentage of the total weight of the questionnaire.	Improvement of 4 points on the separate domains and the total score is most commonly used, although changes of 2 to 8 are also sometimes considered.
St George's Respiratory Questionnaire for COPD (SGRQ-C)	Meguro et al[31]	To assess COPD in a way that allows scores to be directly compared to the SGRQ but with the weakest items removed	Symptoms; activity; impacts on daily life	40	No standard recall	Self-administered Telephone-administered Electronic version	3–5-point Likert scales Yes/no	Specific scoring algorithm was developed to make sure that the revised scoring is equivalent to the original scale.	Improvement of 4 points on the separate domains and the total score is most commonly used, although changes of 2 to 8 are also sometimes considered.
Chronic Respiratory Disease Questionnaire (CRQ)	Guyatt et al[33]	To measure health-related quality of life in patients with chronic respiratory disease	Mastery; fatigue; emotional function; dyspnea	20	Last 2 weeks	Self-administered Telephone-administered Interviewer-administered	7-point Likert scale Yes/no	Total score and subscores can be calculated; higher scores indicate better health-related quality of life. A score of 1–7 can be calculated, or a score of 20–140.	0.5 on 7-point scale, 10 on the scale of 140
Short Form Chronic Respiratory Disease Questionnaire (SF-CRQ)	Tsai et al[38]	To measure health-related quality of life in patients with chronic respiratory disease	Mastery; fatigue; emotional function; dyspnea	8	No standard recall period	Self-administered Telephone-administered	7-point Likert scale	Total score and subscores can be calculated; higher scores indicate better health-related quality of life.	0.5 on 7-point scale
Clinical COPD Questionnaire (CCQ)	van der Molen et al[39]	To assess health status in a primary setting	Symptoms; functional state; mental state	10	Last 7 days Last 24 hours	Self-administered	7-point Likert scale	The final score is the mean of all ten items, and domain-specific scores can be calculated separately if required.	0.4
COPD Assessment Test (CAT)	Jones et al[8]	To quantify the symptom burden of COPD in a short, simple measure	Energy; sleep; confidence; activities; breathlessness; chest tightness; phlegm; cough	8	Not specified	Self-administered; pen and paper	6-point numeric rating scale	There is a total score of 40; scores of 0–10, 11–20, 21–30, and 31–40 represent mild, moderate, severe, or very severe clinical impact, respectively.	Estimated at 1–3 points, but unclear.

(*Continued*)

Table 1 (*Continued*)

PRO	Developers	Purpose of tool	Domains	Number of items	Recall period	Mode of administration	Response scale	Scoring	MCID
Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)	Leidy et al[46]	To evaluate the frequency, severity, and duration of acute exacerbations of COPD and chronic bronchitis	Breathlessness; cough and sputum; chest symptoms	14	Today	Self-administered Electronic	5- and 6-point Likert scales	Items are scored according to the 5-6 point scales and summed to find a total score; the total score then is converted to a 0–100 scale, with higher scores indicating more severe health state or exacerbation.	Yet to be established.
Exacerbations of Chronic Pulmonary Disease Respiratory Symptoms (E-RS)	Leidy et al[50]	To assess the effect of treatment on the severity of respiratory symptoms of COPD	Breathlessness; cough and sputum; chest symptoms	11	Today	Self-administered Electronic	5- and 6-point Likert scales	Total score ranges from 0–40, with score ranges of 0–17 for breathlessness, 0–12 for chest symptoms, and 0–11 for cough and sputum.	3-point change in E-RS total score. 2-point change in E-RS breathlessness domain. 1-point change in E-RS cough domain. 1-point change in E-RS chest symptom domain.
The Breathlessness Cough and Sputum Scale (BCSS)	Leidy et al[52]	To track the severity of respiratory symptoms and evaluate the efficacy of treatment in clinical trials of patients with COPD	Breathlessness; cough; sputum	3	Daily diary	Self-administered	5-point Likert scale	A daily total is expressed as the sum of three item scores, with a range of 0–12 for which a higher score indicates a more severe manifestation of symptoms.	A mean ΔBCSS total score >1.0 represents substantial symptomatic improvement; changes of approximately 0.6 can be interpreted as moderate, and changes of 0.3 can be considered small.
Baseline and Transition Dyspnea Indexes (BDI-TDI)	Mahler et al[54–56]	To provide a multidimensional measurement of dyspnea based on activities of daily living in symptomatic individuals	BDI: functional impairment; magnitude of task; magnitude of effort TDI: functional impairment; magnitude of task; magnitude of effort	BDI: 3 TDI: 3	Last 2 weeks	Self-administered Physician-administered Electronic version (self-administered)	Grades are based on patient responses	Score range in BDI is 0–12, score range in TDI is –9 to 9.	1 unit change in TDI.
Medical Research Council (MRC) Dyspnea Scale	Medical Research Council[9]	To categorize disability in COPD	Not applicable; unidimensional	1	Not specified	Originally physician-administered Self-administered; pen and paper	5-point numeric rating scale	Patients are classified into one of the 5 MRC grades on the basis of their perceived level of disability.	Yet to be established.

Modified Medical Research Council (m-MRC) Dyspnea Scale	Aaron et al[62]	To categorize disability in COPD	Not applicable; unidimensional	1	Not specified	Self-administered; pen and paper	5-point numeric rating scale	Patients are classified into one of the 5 MRC grades on the basis of their perceived level of disability.	Changes in the CRQ dyspnea score and TDI correlated with each other (r=0.78; P=0.0001) and with changes in FEV_1 (CRQ, r=0.48 and P=0.0001; TDI, r=0.46 and P=0.0002).
McGill COPD Quality of Life Questionnaire	Pakhale et al[63,64]	To combine generic health status with disease-specific modules for COPD health status	Physical function; feelings; and symptoms	29	Last 4 weeks	Self-administered pen and paper	5-point numeric rating scale	Feelings, physical function, and three separate subscale symptoms.	Yet to be established.
The Visual Simplified Respiratory Questionnaire (VSRQ)	Perez et al[65]	To evaluate quality of life in COPD patients	Dyspnea; anxiety; depressed mood; sleep; energy; daily activities; social activities; sexual life	8		Physician-administered	Unidimensional scale	Good level of consistency between the concepts measured by VSRQ and those by SGRQ, but no redundancy (correlations of –0.70 between VSRQ global score and SGRQ total score). The VSRQ global score was found to be more strongly correlated with the SGRQ activities and impacts subscores than with the symptoms subscore.	3.4
Dyspnea-12	Yorke et al[66,67]	To measure the current level of a patient's breathlessness severity	Not applicable; unidimensional	12	These days	Self-administered pen and paper	4-point numeric rating scale	A total score is calculated from 12 items (although 3 items may be missing) and then a weighted scoring is applied.	Yet to be established.
Dyspnea Management Questionnaire Computer Adaptive Test (DMQ-CAT)	Norweg et al[69]	To compare dyspnea scores obtained before and after treatment of individual patients and of groups of patients	Dyspnea intensity; dyspnea-related anxiety; activity avoidance; activity self-efficacy	71	Last 2 weeks	Self-administered	Variable (1–6-point scale with separate category for not relevant)	Uses CAT so that only the most informative items are used.	Using CAT simulation analyses, the DMQ-CAT showed higher measurement accuracy compared to the total item pool (r=0.83–0.97, P<0.0001), and it showed evidence of good to excellent concurrent (r=–0.61 to –0.80, P<0.0001) validity
Shortness of Breath with Daily Activities Questionnaire (SOBDA)	Wilcox et al[70]	To measure dyspnea during daily activities	Not applicable; unidimensional	13	Daily	Self-administered electronic diary	Slightly, moderately, severely, and so severe that I could not do the activity	Weekly mean score ranging from 1–4, with higher scores indicating more severe breathlessness.	Yet to be established

(*Continued*)

Table 1 (*Continued*)

PRO	Developers	Purpose of tool	Domains	Number of items	Recall period	Mode of administration	Response scale	Scoring	MCID
Global Chest Symptoms Questionnaire (GCSQ) Capacity of Daily Living during the Morning questionnaire (CDLM)	Partridge et al[71]	To assess the burden and extent of morning symptoms and the ability of patients to perform morning activities	The patient's ability to carry out morning activities; shortness of breath; chest tightness	GCSQ – 2 CDLM – 6	Daily	Self-administered	5-point numeric rating scale	A total score can be calculated as an average of the questions on each questionnaire.	Estimated to be 0.20 for CDLM and 0.15 for GCSQ
Living with COPD (LCOPD)	McKenna et al[77]	To assess the overall impact of COPD from a patient's perspective	Not applicable unidimensional	22	Not mentioned	Self-administered	True/not true	A total score can be calculated.	Yet to be established

Abbreviations: MCID, minimal clinically important difference; PRO, patient-reported outcome; FEV_1, forced expiratory volume in 1 second.

Table 2 Psychometric properties of patient reported outcomes in COPD

PRO instrument	Reliability[a]	Validity
Frequently used PRO measures in COPD		
St George's Respiratory Questionnaire (SGRQ)	Acceptable internal consistency reliability; Cronbach's alpha >0.7 test–retest reliability: ICC =0.8–0.9	Convergent validity SGRQ scores correlated with appropriate comparison measures. For example, symptom score versus frequency of wheeze, r^2=0.32, $P<0.0001$; activity versus 6-MWD, r^2=0.50, $P<0.0001$; impact versus anxiety, r^2=0.38, $P<0.0001$
St George's Respiratory Questionnaire for COPD (SGRQ-C)	Excellent internal consistency reliability; ICC =0.96–0.99	Correlations with other measures of disease were very similar to those obtained with the SGRQ.
Chronic Respiratory Disease Questionnaire (CRQ)	Good internal consistency reliability; Cronbach's alpha =0.80 test–retest reliability: ICC =0.83–0.95 (short-term) and ICC =0.83–0.90 (long-term)	Convergent validity[b] a) Moderate correlation of CRQ dyspnea domain with the global rating of dyspnea (r=0.61) and CRQ fatigue domain with the global rating of emotions (r=0.53) b) Strong correlation of CRQ and SGRQ (r=0.72–0.88) c) Strong correlation of CRQ with BPQ (r=0.75)
Short Form-Chronic Respiratory Disease Questionnaire (SF-CRQ)	Good internal consistency reliability; Cronbach's alpha =0.82	Significant convergent validity with dimension-specific instruments, such as the SAS and VAS for dyspnea

Clinical COPD Questionnaire (CCQ)	Excellent internal consistency reliability; Cronbach's alpha =0.91 test–retest reliability: ICC =0.94	Discriminant validity[c] a) Significant differences in CCQ scores for healthy (ex) smokers and for patients with or at risk for COPD b) Significant differences in CCQ scores between different disease-severity stages of COPD Convergent validity: Significant correlations ($P<0.01$) between the CCQ total score and domains of the SF-36 ($\rho=0.48–0.69$) and the SGRQ ($\rho=0.72$) Divergent validity: CCQ scores and FEV_1 %predicted correlated significantly in patients with COPD (stages I–III), with the highest correlation between the total score and FEV_1 %predicted ($\rho=–0.49$: $P<0.01$)
Chronic obstructive pulmonary disease (COPD) Assessment Test (CAT)	Good internal consistency; Cronbach's alpha =0.88 test–retest reliability: ICC =0.8	Correlates well with the SGRQ (across seven European countries $r=0.84$) and in the US ($r=0.80$)
Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)	Excellent internal consistency reliability; Pearson separation index =0.92 test–retest reliability: ICC =0.77	EXACT scores correlated with SGRQ-C ($r=0.64$; $P<0.0001$) and differentiated acute and stable patients ($P<0.0001$)
The Breathlessness Cough and Sputum Scale (BCSS)	Acceptable internal consistency reliability; Cronbach's alpha =0.70 daily, 0.95–0.99 over time test–retest reliability: ICC =0.77–0.788	Correlations with pulmonary function (FEV_1 %predicted) were –0.01 (ns) to –0.36 ($P<0.001$). Correlations with the SGRQ total and SF-36 Physical Functioning subscale were 0.44–0.59 ($P<0.0001$)
Baseline and Transition Dyspnea Indexes (BDI-TDI)	Good internal consistency reliability; Cronbach's alpha =0.80 test–retest reliability: ICC =0.76	Baseline focal score had the highest correlation ($r=0.60$; $P<0.001$) with the 12-MWD and significant but lower correlations for lung function. For the transition focal score, there was a significant correlation with the 12-MWD ($r=0.33$; $P=0.04$)
Medical Research Council (MRC) Dyspnea Scale		Significant association between MRC grade and shuttle distance, SGRQ and CRQ scores, mood state and EADL. FEV_1 was not associated with MRC grade.
McGill COPD Quality of Life Questionnaire	Internal consistency reliability; Cronbach's alpha =0.68–0.82 test–retest reliability: ICC =0.74–0.96 for the subscales and 0.95 for the total score	Convergent validity (correlation with the SGRQ was moderately high, $r=–0.88$ [95% CI, –0.84 to 0.91])
The Visual Simplified Respiratory Questionnaire (VSRQ)	Good internal consistency reliability; Cronbach's alpha =0.84 test–retest reliability: ICC =0.77	Good concurrent validity with SGRQ (Spearman's coefficient =–0.70)
Exacerbations of COPD Respiratory Symptoms (E-RS)	Good internal consistency reliability: Cronbach's alpha =0.88 test–retest reliability: ICC =0.90	Total scores correlated significantly ($P<0.0001$) with SGRQ: total ($r=0.75$), symptoms ($r=0.66$), activity ($r=0.57$), impact ($r=0.70$) scores; subscale correlations were also significant ($r=0.26$, $P<0.05$ [RS-Chest Symptoms with Activity] and $r=0.69$, $P<0.0001$ [E-RS-Cough and Sputum with Symptoms]). RS-Breathlessness correlated with rescue medication use ($r=0.32$, $P<0.0001$), clinician-reported mMRC ($r=0.33$, $P<0.0001$), and FEV_1 %predicted ($r=–0.17$, $P<0.05$)
Dyspnea-12	Good internal consistency reliability; Cronbach's alpha =0.93 test–retest reliability: ICC =0.94	Its scores were significantly associated with MRC grade ($r=0.59$; $P=0.001$), SGRQ (symptoms, $r=0.57$; activities, $r=0.78$; impacts, $r=0.75$; total, $r=0.79$; $P<0.001$)

(*Continued*)

Table 2 (*Continued*)

PRO instrument	Reliability[a]	Validity
Dyspnea Management Questionnaire Computer Adaptive Test (DMQ-CAT)	Good internal consistency reliability; Cronbach's alpha =0.92–0.98 test–retest reliability: ICC =0.58–0.82	Good to high concurrent validity with comparative questionnaires (UCSD, SOBQ, CRQ, CSES, and HADS) (r=−0.80 to −0.61)
Shortness of Breath with Daily Activities Questionnaire (SOBDA)	Good internal consistency reliability; Cronbach's alpha =0.87 test–retest reliability: ICC =0.91	Convergent validity was demonstrated by moderate[c] correlation with CRQ-SAS (0.60) and SGRQ-C (0.61)
Global Chest Symptoms Questionnaire (GCSQ) Capacity of Daily Living during the Morning Questionnaire (CDLM)	Good to high reliability: Cronbach's alpha =0.75–0.93	Validity was found to be significant $P<0.001$
Living with COPD (LCOPD)	Good and high reliability; Cronbach's alpha =0.92 test–retest reliability was also 0.83	Convergent validity was demonstrated by moderate correlations with SGRQ (Symptoms) 0.66; SGRQ (Activity) 0.79; and SGRQ (Impact) 0.85 All the values were found to be significant P=0.01

Notes: [a]Characterization of Cronbach's alpha: $\alpha \geq 0.9$= excellent; $0.9 > \alpha \geq 0.8$= good; $0.8 > \alpha \geq 0.7$= acceptable; $0.7 > \alpha \geq 0.6$= questionable; $0.6 > \alpha \geq 0.5$= poor; $0.5 > \alpha$= unacceptable. [b]Characterization of Pearson correlation r: 0.9–1= very high, 0.7–0.9= high, 0.5–0.7= moderate, 0.3–0.5= low, and 0–0.3= little or no correlation. [c]Spearman-rank correlation used to assess discriminant, convergent, and divergent validity.

Abbreviations: BPQ, Breathing Problems Questionnaire; CCQ, Clinical COPD Questionnaire; CI, confidence interval; CRQ, Chronic Respiratory Disease Questionnaire; CSES, COPD self-efficacy scale; EADL, Nottingham Extended Activity of Daily Living Questionnaire; FEV_1, forced expiratory volume in 1 second; HADS, Hospital Anxiety and Depression Score; ICC, intraclass coefficient correlation; MWD, minute walking distance; ns, not significant; PRO, patient-reported outcome; SAS, Symptom and Activity Scale; VAS, visual analog scale; UCSD SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

treatment over 6–8 weeks has been demonstrated.[26,27] The SGRQ is also appropriate to measure the subdomains of Subjective Symptoms and Subjective Impairment. The SGRQ can therefore facilitate the guidance of disease management in COPD.[28] A four-unit change in score is considered as the minimal clinically important difference for this instrument. However, some have argued that the SGRQ has been insufficient at determining the treatment effect of a drug narrowly targeted to a specific aspect of COPD.[29] Furthermore, others had noted that the SGRQ has some limitations, in particular that it is time-consuming to complete and therefore adds to the respondent burden.[30]

SGRQ for COPD (SGRQ-C)

The SGRQ-C is a 40-item version of the original 50-item SGRQ.[31] It was derived from the original version after a detailed analysis of data from large studies in COPD. The intention was to remove the items with the weakest measurement properties from the original instrument but at the same time ensure that its scores were directly comparable with the original SGRQ.[31] Rasch modeling (a powerful tool for examining the performance of individual items)[32] was applied to the SGRQ; this permitted the removal of several weaker items and thereby improved the measurement properties of SGRQ-C. The instrument has the same domains (symptoms, activity, and impact) as the SGRQ and has the capability to calculate a total score. Like the SGRQ, the SGRQ-C has demonstrated good reliability and has showed significant convergent validity with measures of both respiratory function (such as FEV_1, 6-minute walking distance) and other PRO measures (such as the Hospital Anxiety and Depression Scale and the Sickness Impact Profile).[31] Overall, the SGRQ-C is shorter, contains the best of the original items, and produces scores equivalent to the original instrument.

Chronic Respiratory Disease Questionnaire (CRQ)

The CRQ is a 20-item instrument which aims to measure HRQoL in COPD patients by assessing four domains: a patient's perception of mastery, fatigue, emotional function, and dyspnea experienced during certain activities in the 2 weeks prior to its administration.[33] The selection of important items was determined through a process that included reviewing current literature, consulting with clinical respiratory specialists, and interviewing patients. The CRQ was developed by using classical test theory and appears to be sensitive to treatment. However, as has been noted, only the standardized version of the CRQ is suitable for group comparisons; the individualised CRQ is less suitable

for interindividual comparisons because it only documents individual patient limitations.[23] The CRQ is also one of the most widely used disease-specific questionnaires that provides an overall measure of health status and has been used in many pharmaceutical trials. In addition, the CRQ has been recommended by the European Medicines Agency as a suitable HRQoL instrument that can be used in COPD drug development programs and clinical trials.[25] The CRQ has demonstrated good psychometric properties of high internal consistency[34] and good convergent validity. The emotional function domain of the CRQ showed a high correlation with the feelings domain of the generic Dartmouth Co-operative Functional Assessment Charts measure of functional status in patients receiving ambulatory oxygen.[35,36] The minimal clinically important difference of the CRQ has been consistently reported to be around 0.5 per question with a 0.43 for the dyspnea domain, 0.64 for fatigue, and 0.49 for emotional function. Jaeschke et al in 1989 stated that a CRQ change of 0.81 to 0.96 indicates a moderate effect and that a large effect is indicated by a change of 0.86 to 1.47.[37]

Short Form Chronic Respiratory Disease Questionnaire (SF-CRQ)

The SF-CRQ contains only eight items of the original 20-item CRQ. Item selection was based on previous research and in consultation with the developer of the original CRQ (Gordon Guyatt). The instrument was pilot tested with consecutive emergency department patients with COPD (number of subjects =301). Like the CRQ, the SF-CRQ has demonstrated good reliability, validity, and responsiveness for the assessment of short-term HRQoL change in patients with COPD exacerbations.[38]

Clinical COPD Questionnaire (CCQ)

The Clinical COPD questionnaire is a ten-item, self-administered tool. It was originally called the COPD Control Questionnaire but was later renamed. The CCQ was developed primarily to assess health status in a primary care setting, but it is also useful for measuring the response to intervention in clinical trials and for assessing clinical improvement after smoking cessation.[39] The CCQ has three domains: symptoms, functional state, and mental state. The scale has two versions, a 7-day recall of COPD status and a 24-hour recall of COPD status.[39] The CCQ's development suggests strong content validity, and the questionnaire has been used in many pharmaceutical trials.[40] The CCQ has good psychometric properties, test–retest reliability, responsiveness, and validity.[40,41] The CCQ has strong discriminative measurement properties; it can be used in all patients with COPD and in patients at risk of COPD.[39] The CCQ is able to identify patients with poor clinical COPD control and can be used to evaluate the effects of interventions in a standardized way.[39] Unfortunately, the CCQ has not been widely used to evaluate drugs in pharmaceutical trials. However, the CCQ total score has been shown to have value as a prognostic instrument for mortality in COPD, and the instrument was suggested to indicate which patients are most at risk for clinical interventions.[41]

CAT

The CAT was developed by Jones et al[8] in 2009 to FDA standards, is based on patient interviews, and the content has been reinforced by interviews with community physicians and pulmonologists. It uses Rasch modeling to identify items with the best fit to the unidimensional model. The instrument was developed with the purpose of quantifying the symptom burden of COPD with a concise, simple, and rigorously validated assessment tool.[42] The CAT has been shown to be reliable and to be sensitive to changes in health status after an exacerbation. The test also has been shown to be responsive to pulmonary rehabilitation in a manner similar to more complex COPD health status measures.[43–45] The instrument assesses the impact of the disease and, in the current Global Initiative of Chronic Obstructive Lung Disease (GOLD) strategy, it is used to assign appropriate treatments to patients.[1] Its usefulness as an outcome measure is currently under evaluation in randomized control trials.

Symptom diary measures

As defined in the recent GOLD strategy document, "An exacerbation is an acute event characterized by the worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to a change in medication".[1] Despite the efforts to understand the effect of treatment on exacerbations in COPD, until recently there was not a standardized PRO measure to evaluate this outcome.

The EXACT-PRO and the E-RS diaries

The EXACT-PRO is a 14-item PRO measure that evaluates the frequency, severity, and duration of acute exacerbations of COPD.[46,47] The EXACT-PRO was developed in collaboration with experts in instrument development and validation, specialists in clinical practice and research, and experts from the FDA.[47,48] The EXACT-PRO daily diary is designed to be completed by the patients before bedtime. Initial testing of the EXACT-PRO in an observational study

of patients with COPD indicated that the scale has scores that are internally consistent and reproducible in stable patients and that the scale correlates with clinical variables (eg, SGRQ-C).[46,47] Furthermore, this instrument has the ability to differentiate acute and stable patients, to measure change over time in exacerbations, and to differentiate physician- and patient-rated exacerbation severity.[46,47] The minimum changes that represent onset of and recovery from an exacerbation are under investigation.

The E-RS has been developed from the EXACT-PRO tool by using eleven of the 14 EXACT items to measure the cardinal symptoms of COPD (cough, chest symptoms, and breathlessness). The E-RS is described to have been developed consistently with good PRO research practices and FDA PRO requirements. The E-RS is a reliable and valid measure for evaluating the severity of respiratory symptoms in patients with COPD. [49–51]

The Breathlessness Cough and Sputum Scale (BCSS)

The BCSS is a brief, three-item, easy-to-use instrument that can be used for tracking the severity of respiratory symptoms and for evaluating efficacy of treatment in clinical trials of patients with COPD.[52,53] Designed as part of a daily diary, subjects are asked to assess and record the severity of three symptoms of COPD: breathlessness, cough, and sputum.[52,53] The BCSS is a reliable and valid measure of symptom severity.[52,53] A mean change in BCSS total score of >1.0 represents substantial symptomatic improvement. Changes of approximately 0.6 can be interpreted as moderate, and changes of 0.3 can be considered small.[51]

Breathlessness/dyspnea measures

Breathlessness is a commonly reported symptom in patients with COPD.[1] Persistent breathlessness can impair a patient's HRQoL; therefore, alleviating breathlessness among COPD patients is also an important goal.[1]

Baseline Dyspnea Index and Transition Dyspnea Index

The Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) were developed in 1984 by using data from patients with COPD, asthma, and interstitial fibrosis.[54] The BDI is a discriminative instrument used to quantify the severity of dyspnea in clinically stable patients. The TDI is an instrument used to quantify the changes in dyspnea from the baseline state with the purpose of providing a multidimensional assessment of dyspnea. The BDI and the TDI are both three-item instruments that assess COPD on the bases of functional impairment and the magnitude of task and effort of daily activities in the 2 weeks prior to administration.[55] When used together, the indices are referred to as one measure, the BDI-TDI. The BDI-TDI has been widely used together as a clinician-reported measure rather than a PRO instrument.

The BDI-TDI is a validated tool that is sensitive to intervention and that was originally designed as a physician interview with the patient.[55] In an observational study, the BDI and the TDI were shown to be responsive to changes in dyspnea associated with a COPD exacerbation.[51] A self-administered computerized version of the TDI became available in 2004 and avoids any interviewer interpretation.[56] Results using the self-administered computerized version of the TDI can be collected and analyzed electronically on a continuous scale. In a comparison with the CRQ, both the self administered and computerised measures were reported as having good construct and concurrent validity. No clear superiority of either measure has been shown. However, as the patient has to recall baseline state (BDI) in order to answer questions regarding the TDI, there is a high probability of recall bias in the assessment.[57]

The Medical Research Council (MRC) Dyspnea Scale

The MRC breathlessness scale was developed in 1960[9] and comprises five statements that describe the range of respiratory disability due to breathlessness from none (Grade 1) to almost complete incapacity (Grade 5). The MRC breathlessness scale does not quantify breathlessness itself; rather, it quantifies the disability associated with breathlessness by identifying whether breathlessness occurs when it should not (Grades 1 and 2) or by quantifying the associated exercise limitation (Grades 3–5). The MRC dyspnea scale is widely used to describe patient cohorts and stratify them for interventions, such as pulmonary rehabilitation.[9] It is advocated as a complementary measure to FEV_1 in COPD patients to describe disability.[58,59] Originally rated by the clinician, it can also be self-administered. All the questions relate to everyday activities and are generally easily understood by patients. The score correlates well with other breathlessness scales, lung function measurements, and direct measures of disability such as walking distance.[58,59] Its main disadvantage over other more complex scales is its poorer responsiveness to interventions.

The m-MRC

The m-MRC has a revised response scale from 0–4 (instead of 1–5 in the MRC scale) and is mostly self-administered.[60] A comparison study found that the m-MRC and the BDI were moderately correlated and thus demonstrated concurrent

validity.[61] In the same study, the BDI showed association with physiological measures, whereas the m-MRC was not significantly related with physiological measures.[62] It was not clear from the publication whether the m-MRC was completed independently by the patient or administered by the physician, a variable which may explain the difference in the outcome because the clinician may be unblinded to the spirometry findings. The current GOLD classification uses the m-MRC and CAT along with exacerbation history and airflow limitation to classify patients into four COPD categories grades (A–D).[1] The modification from the 1–5 scale to the 0–4 scale has not changed the measure's fundamental structure, and hence the tool has inherited the problems from the original MRC scale; these include low responsiveness and therefore infrequent use as an outcome measure in pharmaceutical trials.

Emerging PRO measures in COPD

In addition to the commonly used PRO measures, a number of new measures have been developed over the past few years: the McGill COPD Quality of Life Questionnaire,[63,64] the Visual Simplified Respiratory Questionnaire,[65] the Dyspnea-12,[66,67] the Dyspnea Management Questionnaire Computer Adaptive Test,[68,69] the Shortness of Breath with Daily Activities questionnaire,[70] the Global Chest Symptoms Questionnaire,[71] the Capacity of Daily Living during the Morning questionnaire,[71] and Living with COPD Questionnaire.[72] However, their use and value are still to be determined; as more knowledge about their reliability and validity, and their responsiveness to treatment need to be further evaluated. These instruments are described in detail along with their psychometric properties in Tables 1 and 2.

Discussion

The COPD patient population is heterogeneous in terms of clinical presentation, disease severity, and rate of disease progression; therefore, there is currently no agreement on what constitutes a desirable response to pharmacological interventions. The absence of a clear biomarker of disease progression also complicates how clinicians evaluate treatment efficacy. PRO measurements of dyspnea or functional status provide insights into the effects of treatment on everyday life by reflecting whether or not patients perceive improvement in their symptoms or their abilities to perform daily activities, regardless of whether FEV_1 has improved or not. This feature may be particularly useful when a treatment has multiple beneficial effects, which individually may be too small to register as a change on an assessment of an individual parameter but collectively may produce improvement.

Therefore, it appears useful to include PRO instruments in the evaluation of pharmaceutical interventions as well as other health care interventions (such as pulmonary rehabilitation). Our article summarized the benefits and characteristics of the main instruments.

We have neither compared nor recommended specific instruments for the reader as it is difficult to recommend a specific instrument without a solid understanding of the research question of the study and the situation in which the instruments will be used. In a scenario in which someone may have limited time to administer an instrument, a quick instrument such as the CCQ, SF-CRQ, or CAT tool has more merit than a longer instrument such as the SGRQ or the CRQ. If a researcher is interested in the assessment of control or mastery that the patient feels over their COPD, then the CRQ may be advisable, whereas if the intent is to explore the variability of symptomatology during an exacerbation, the EXACT or the E-RS may offer more value.

To ensure the comprehensiveness of this review, we would like to include a few references of studies that directly compare the psychometric criteria of these instruments,[27,73,74] but again would like to stress that we were not directly involved in those research studies and the conclusions drawn.

Conclusion

In order to completely understand the effects of therapies that are relevant to patients with COPD, PRO instruments need to be valid, reliable, responsive to clinically meaningful treatment effects, adaptable across various populations, and ideally understandable to patients and physicians by using easy to interpret scoring systems that are relevant to health care providers and acceptable to regulatory authorities.[15] Some of the instruments reviewed in this paper address multidimensional aspects of HRQoL. Most of them are included in the assessments of symptoms, physical functioning, and psychosocial well-being. A further concern with old PRO measures was their low responsiveness to pharmaceutical interventions, a factor that could reflect ineffective treatments but could also reflect the insensitivity of older tools to detect change. Recently, COPD field has progressed much more in assessing patients' daily living activities but published information needs to be established.[75] It would be very useful for the clinical community to update this review in 3–5 years, when more information around the value of these instruments is available. One of the most promising instruments

is probably the physical activity assessment in the European Innovative Medicines Initiative PRO-active project.[76]

Of these instruments, the CCQ, EXACT/E-RS, and the CAT appear to be the most promising because compared to the others, these are shorter and pose lower respondent burdens and, therefore, may be preferable to patients. The CCQ, EXACT/E-RS, and CAT seem to have demonstrated some validity and responsiveness to treatment in various studies. However, data on the development and validation of these new and promising COPD-specific instruments are still emerging. Future challenges for regulatory authorities such as the FDA and the European Medicines Agency, as well as health technology assessment agencies and clinicians, will be to keep up to date with the development of comprehensive COPD PRO instruments that may be used in drug development, therapeutic interventions, research, and clinical practice.

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