



Measuring the effects of COPD on the patient

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Summary Evaluation of the effectiveness of treatment for chronic obstructive pulmonary disease (COPD) requires the assessment of both clinical and physiological measures. Parameters such as the forced expiratory volume in 1 s are well established in providing an indication of the degree of airflow limitation. However, additional measurements, such as dyspnoea, functional status and health status, are required to provide a complete picture of COPD. Indeed, dyspnoea is the predominant symptom of COPD experienced by the patient, which treatment is designed to reduce. Methods of assessing dyspnoea have developed over the previous five decades. The most widely used instruments for assessing the impact of dyspnoea are the baseline dyspnoea index, the transition dyspnoea index and the Medical Research Council Questionnaire.

A more comprehensive approach to the assessment of disability caused by dyspnoea and fatigue is provided by assessments of functional status, such as the pulmonary functional status and dyspnoea questionnaire. Respiratory-specific health status questionnaires, such as the St. George's Respiratory Questionnaire, attempt to capture the wide range of effects of COPD into a single score that reflects the overall impact of the disease.

Developing the means to measure the effects of COPD is important, both in terms of understanding disease pathophysiology for research purposes, and in terms of accurately assessing the effects of treatment on the patient. Future developments will include computerising these methodologies to permit faster and more individual patient-centred measurements.

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Abbreviations: AECB, acute exacerbation of chronic bronchitis; BDI, baseline dyspnoea index; CAT, computer adaptive testing; COPD, chronic obstructive respiratory disease; CRQ, chronic respiratory questionnaire; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HRQoL, health-related quality of life; ISOLDE, inhaled steroids in obstructive lung disease in Europe; LVRS, lung-volume-reduction surgery; MRC, Medical Research Council; PFSDQ, pulmonary functional status and dyspnoea questionnaire; QoL, quality of life; SAC, self-administered computerised; SGRQ, St. George's respiratory questionnaire; TDI, transition dyspnoea index

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Introduction

For some time, spirometric measurements such as forced expiratory volume in 1 s (FEV₁) have served as core measures in chronic obstructive pulmonary disease (COPD) research and in the assessment of treatment response. However, FEV₁ measures alone are not sufficient to define treatment response, as this marker does not fully reflect the pervasive nature of, and the burden associated with, COPD. Recent momentum in the field has increased the number of treatment options available, which in turn require adequate characterisation in terms of their benefit to the patient.

A number of clinical and physiological outcomes, such as dyspnoea, functional status and health status, are recognised as being important for characterising response to treatment. For instance, dyspnoea is the primary reason for patients seeking medical care. Measurements of dyspnoea provide an insight into the practical effects of treatment on everyday life, reflecting whether or not patients perceive an improvement in this primary symptom of COPD. Patients with COPD frequently decrease their activity in order to avoid the unpleasant sensation of breathlessness. Functional status measurement reveals the number of activities that a patient can perform—something not always reflected in measurements of FEV₁ or dyspnoea. Health status provides an overall assessment of patient quality of life (QoL), and is mainly evaluated using questionnaires such as the St. George's Respiratory Questionnaire (SGRQ).¹

This article examines the rationale for quantifying breathlessness, functional status and health status, and evaluates their application in COPD research, alongside more established parameters such as FEV₁ and exacerbation frequency. Challenges facing the use of these measures and the direction of their future development are also discussed.

Methods for measuring dyspnoea in COPD

Why is it important to measure dyspnoea?

Dyspnoea is the primary symptom experienced by patients with COPD, making the reduction of breathlessness a central goal of treatment.^{2–4} It is important to note that a patient's perception of dyspnoea does not necessarily increase with worsening lung function and therefore cannot be assumed to improve with FEV₁.⁵ Furthermore, there may be improvements in dyspnoea, exercise capacity and QoL with only minimal changes in FEV₁. Although measures such as FEV₁ reflect direct

changes in airflow limitation, it is important to measure dyspnoea to reveal the practical effects of treatment on a patient's everyday life.^{6,7} In order to address this requirement, questionnaires have been developed, which grade a patient's experience of his or her breathlessness.

Unidimensional scales measuring dyspnoea

Because dyspnoea plays a central role in COPD, methods have been developed to evaluate the patient's experience of breathlessness, either during daily activities (questionnaires) or exercise testing (the Borg scale). These measures have been produced in order to grade the severity of dyspnoea according to the degree of breathlessness associated with particular tasks. Unidimensional scales are useful for separating those who suffer from dyspnoea from those who do not. For example, in 1959 Fletcher et al.⁸ developed a scale as part of a survey of chronic bronchitis sufferers to establish which type of activity (of five graded options) subjects could complete before becoming hindered by breathlessness. The Medical Research Council's (MRC) five-point scale ranges from patients only being affected by dyspnoea during strenuous exercise (grade 1), to severe dyspnoea preventing patients from leaving the house or getting dressed comfortably (grade 5).⁹ This scale has been used for diagnostic evaluation and in clinical trials,^{2,10,11} and is still used to compare the categorisations of dyspnoea with the staging of disease severity.^{12,13}

Unidimensional scales tend to have the advantage of being easy to administer and score. A drawback, however, is the fact that patients may modify their behaviour to avoid dyspnoea, for example by using the lift instead of climbing the stairs. Thus, unidimensional scales may be unable to provide a completely accurate assessment of the type of tasks which are likely to cause dyspnoea. Furthermore, they do not take into account the variation in effort which patients may exert in completing certain activities. For example, climbing the stairs at speed is likely to cause more acute dyspnoea than slow climbing, which may cause none at all, but both may be graded as a similar activity. Lastly, scales which contain a relatively small number of grades, such as the MRC scale, may not be sensitive enough to reflect small changes within the grades.¹⁴

Multidimensional scales measuring dyspnoea

Multidimensional scales, such as the baseline dyspnoea index (BDI) and the transition dyspnoea

index (TDI), have been developed to provide a more comprehensive assessment of dyspnoea.¹⁴ These tools also had to be precise enough to enable comparison between patients in large clinical trials. Currently, the most widely used of these are the BDI and the TDI. Developed by Mahler and colleagues in 1984,¹⁴ the BDI rates the severity of dyspnoea at baseline and the TDI quantifies changes from baseline. These indices cover information on the individual components of dyspnoea: functional impairment, magnitude of task needed to evoke dyspnoea and magnitude of effort needed to evoke dyspnoea. Since their introduction, the BDI/TDI have been shown to be sufficiently responsive in measuring improvements in patients treated with a variety of therapeutic modalities.^{15–20}

To estimate the minimal clinically important difference of the TDI, Witek and Mahler²¹ analysed the validity and pattern of response of the BDI/TDI in a retrospective survey of 997 COPD patients who received tiotropium, salmeterol or placebo in addition to pre-existing treatment. Their analysis showed a significant association between two dyspnoea parameters (dyspnoea diary score and the BDI/TDI). The BDI/TDI were also significantly associated with spirometric (FEV₁) and health status outcomes. Moreover, the analysis demonstrated that a 1-unit change in the TDI total score was clinically relevant. These findings support a previous retrospective analysis of 921 COPD patients, in which responders (TDI ≥ 1 unit) to treatment also required significantly less supplemental albuterol ($P < 0.05$) and had significantly fewer exacerbations ($P < 0.01$) compared with non-responders (TDI ≤ 1 unit).²²

These collective studies show that the BDI/TDI are valid indices for use in clinical trials, and have the ability to identify clinically important differences in dyspnoea.

Interviewer-administered versus patient-reported questionnaires

Criticisms of the BDI/TDI and similar tools include their reliance upon open-ended questions and the potential bias of the interviewer. The interview process may also be time consuming. In order to address these issues, both the BDI/TDI and the chronic respiratory questionnaire (CRQ) can be self-administered.^{23,24}

In the self-administered computerised (SAC) version of the TDI, patients are reminded of their previous BDI grades, and then enter any changes in dyspnoea on a continuous bidirectional visual analogue scale (VAS).²³ In one study performed to

Table 1 Correlations (Pearson's coefficients) between changes in patient-reported dyspnoea and changes in lung function ($N = 27$).

Dyspnoea measures	Lung function parameters		
	Δ FEV ₁	Δ FVC	Δ IC
Δ MRC	−0.39*	−0.38	−0.25
SAC TDI	0.63*	0.58*	0.57*

Δ = difference between baseline and follow-up values; MRC = Medical Research Council scale; SAC TDI = self-administered computerized transition dyspnoea index; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity.

* $P < 0.05$.

assess the validity and responsiveness of the computerised versions, Mahler and colleagues found a high correlation between the BDI/TDI scores obtained from SAC and interviewer-administered versions, when conducted in 25 patients (BDI, $r = 0.83$, $P < 0.0001$; TDI, $r = 0.94$, $P < 0.0001$).²³ Furthermore, scores from SAC and interviewer-administered versions had similar correlations with FEV₁, forced vital capacity (FVC) and inspiratory capacity (IC) at baseline and at follow-up. In a preliminary study of 27 patients with COPD who received either inhaled medication or pulmonary rehabilitation, the SAC BDI/TDI, interview BDI/TDI and the MRC questionnaires were administered in a randomised order at baseline and follow-up.²⁵ Correlation coefficients for SAC versus interviewer-administered questionnaire were high (0.87 at baseline and 0.68 at follow-up), and the correlations for SAC TDI versus changes in lung function parameters were higher than for MRC versus lung function parameters (Table 1). Moreover, of the 16 patients who reported no change in dyspnoea on the MRC scale, 10 patients reported a change in the SAC TDI ≥ 1 unit (the clinically important difference). These data suggest firstly, that the SAC BDI/TDI can be used in clinical trials and secondly, that the SAC TDI is more sensitive to changes in dyspnoea than the MRC questionnaire.

Discrete versus continuous methods of measuring dyspnoea

Exercise testing is traditionally used to evaluate an individual's perception of dyspnoea, usually by asking them at timed intervals during exercise to choose a rating of their perceived exertion, on the Borg scale or a 'VAS', which best describes their breathlessness. Although discrete measurement of dyspnoea has proved useful in research settings for

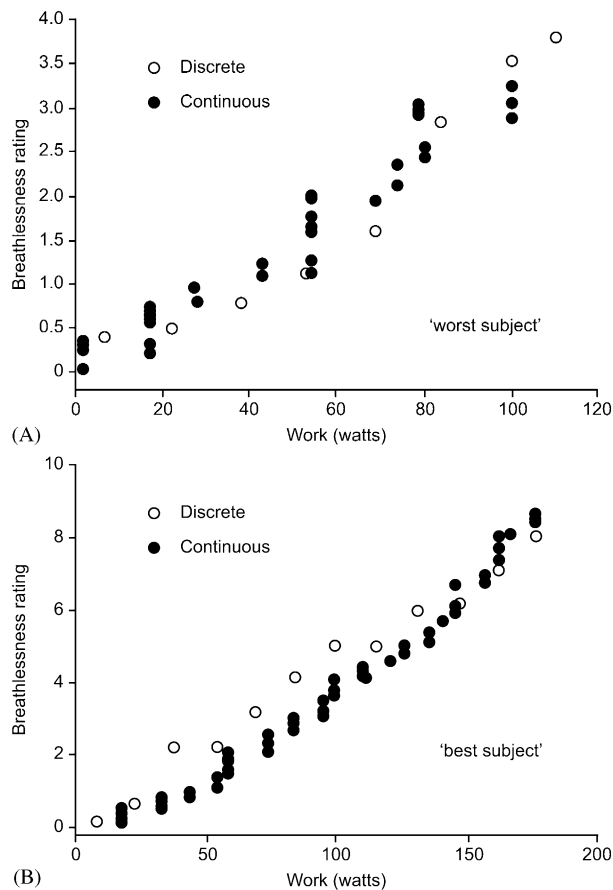


Figure 1 Comparison between 'discrete' and 'continuous' methods for evaluating dyspnoea during exercise (as measured by work in watts), showing data from subjects yielding (A) the 'worst' ($r = 0.94$) and (B) the 'best' ($r = 0.98$) mean correlation coefficient between results from the two methods.²⁷

the evaluation of effectiveness of therapeutic interventions in COPD, its wider application may have limitations. Firstly, a short test (for example 3–4 min) will only provide a small number of dyspnoea ratings, making it problematic to assign a function to the data. Secondly, discrete ratings may not accurately represent the continuous change in dyspnoea experienced by the patient.²⁶ Therefore, a continuous method of dyspnoea rating has been developed whereby the patient moves a computer mouse to indicate a change in dyspnoea during a cycle test. Mahler et al.²⁷ have established the validity and reliability of this method. Their data indicated no significant difference between discrete and continuous methods of assessing dyspnoea during exercise (Fig. 1), even when examining results from the subject yielding the 'worst' mean correlation coefficient between data obtained using the two methods. Furthermore, the continuous method proved more respon-

sive to changes in dyspnoea induced by respiratory load (i.e. transient changes) and yielded more ratings of breathlessness compared with the discrete method.²⁷

Measuring dyspnoea—established principles

Some general conclusions can be drawn about the requirements for instruments used to measure dyspnoea. In particular, they should rely on patient-reported outcomes, be multidimensional where possible, adhere to standardised methodology and ideally be computerised. These recommendations should be upheld if the evaluation of dyspnoea in COPD is to provide consistently reliable data in future clinical trials.

Functional status in COPD

Definitions and influencing factors

Functional status refers to a patient's ability to participate in everyday activities. This is not only influenced by lung function, indeed, comorbidities, conditioning and motivation are all contributing factors, as is the fact that some patients may choose to perform activities despite the associated dyspnoea. Measuring functional status should, therefore, not rely on physiological changes alone, and consequently is a complex parameter to assess.

Why is functional status so important?—A case study

The need to evaluate functional status can be illustrated by the following case study.²⁸ A male patient with COPD was monitored over 16 years, during which time he underwent pulmonary rehabilitation and lung-volume-reduction surgery (LVRS). During the first 13 years, the patient's dyspnoea and lung function ratings according to the pulmonary functional status and dyspnoea questionnaire (PFSDQ) remained severe but stable (Fig. 2). However, his functional status, defined as the number of activities which he could no longer perform from a specific set of 79 tasks, worsened considerably. This worsening was not reflected in his FEV₁ or dyspnoea levels. Crucially, after the patient underwent LVRS, his dyspnoea score fell from 7 to 1 (on a scale where 10 is the most severe), but his FEV₁ improvement was <0.5 L. However, after LVRS he resumed performing 33 activities which he had previously given up (Fig. 2). These data demonstrate the complexity of functional status and show how its evaluation adds to

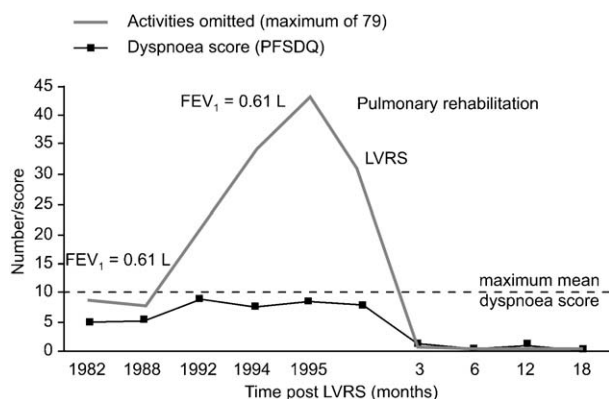


Figure 2 Case study data showing the functional status of the patient (number of activities no longer performed) and dyspnoea score (as measured by the pulmonary functional status and dyspnoea questionnaire [PFSDQ]), for the time before and after lung-volume-reduction surgery (LVRS) and pulmonary rehabilitation. Measurements of forced expiratory volume in 1 s (FEV_1) are also shown.²⁸

our understanding of the practical effects of COPD on individual patients. Determining functional status may also help assess which treatments are most effective in specific patient populations, where spirometric parameters provide insufficient differentiation.

Measurement of functional status

Methods of assessing functional status are still evolving. Reasons for this state of affairs are three-fold: daily activities are numerous, making it difficult to include all those that are relevant; different activities may be of different value to specific patients; and the degree of dyspnoea associated with activities may vary according to the amount of effort exerted. Thus, measurement tools need to comprise solutions for all of these problems, if possible. Currently available options include self reports, motion sensors and direct observation through videotaping.

Self reports

Self reports provide a patient's assessment of their activity, either by asking the patient about their activity levels regardless of symptoms²⁹ or by asking patients to rate their symptoms associated with specific activities.^{1,14,30} Although several of these tools have demonstrated strong reliability,^{1,29} the data collected are qualitatively different between tools and therefore cannot be compared easily. Therefore, other methods need to be examined.

Activity monitors

Motion sensors ranging from pedometers to accelerometers allow the precise evaluation of activity time and intensity. Although data collected this way correlate well with physiological measures, they do not appear to correlate with self reports and may actually measure a different aspect of patient activity. In support of this hypothesis, Belza et al.³¹ showed that accelerometer data did not correlate with most disease-specific self-reported measures, although accelerometer data did correlate with FEV_1 ($P < 0.01$), 6-min walk distance ($P < 0.01$), and self efficacy ($P < 0.05$). This consideration, along with practical limitations, means that the current role of motion sensors is mainly limited to evaluating the frequency, intensity and duration of walking activities during research. However, in the future they may play a complementary role to self report measures in assessing activity improvement after treatment.

Direct observation

Recently, methods of direct observation of activity levels have been explored. Activity recorded on video can be translated into units of motion or into a three-dimensional report. One clear advantage of direct observation is that, if used during rehabilitation, it can help patients understand how to perform activities more efficiently, for example by modifying their breathing technique. Disadvantages are mainly practical and include the enormous amount of storage capacity required to process the data, and potential issues of patient privacy. A further element which is lacking from direct observation is the capacity to monitor a patient's breathing pattern. However, the Life Shirt (VivoMetrics®; Ventura, CA, USA) may help to gain a more complete picture of ventilatory mechanics and dyspnoea.

Given the distinct but synergistic characteristics of these three options for assessing functional status, it is likely that the future gold standard will not consist of a single measure alone but rather be an optimal combination of different methods. Establishing this combination strategy and improving the technology required for these systems are therefore key goals in this area.

COPD and health status

What role does health status play in COPD research?

COPD has a substantial impact on patient overall health and QoL. Health is an abstract concept, but

it is possible to produce standardised health status measures that have true interval-scaling properties (i.e. the questionnaire behaves like a ruler). By contrast, QoL is personal to each individual. Whilst there is a relationship between reduced lung function and impaired health,³² this is not sufficiently strong for spirometric measures to provide a reliable estimate of health-related quality of life (HRQoL).³³ For that reason, measurements of health status must be made using specifically designed questionnaires.^{33,34} A large body of evidence now supports the use of these questionnaires to quantify the impact of COPD on the patient's daily life and well-being.³²

HRQoL in COPD progression

Several generic questionnaires are currently in use, for example the short form-36,³⁵ EuroQol-5D^{35,36} and CRQ.^{30,35,36} Perhaps the most widely used disease-specific health status questionnaire is the SGRQ,¹ which is a self-administered 50-item survey encompassing three components: symptoms, activity and social or psychological impacts. Scored from 0 (best score) to 100 (worst score), a change of 4 units is deemed clinically significant. The scores from this questionnaire are reproducible and sensitive to change over extended time periods. The ISOLDE trial (Inhaled Steroids in Obstructive Lung Disease in Europe)³⁷ showed that health status declines at a measurable rate, which is influenced by the rate of decline in FEV₁ and the frequency of exacerbations.³⁸ The decline was seen in all three components of the SGRQ showing that all aspects of COPD worsen progressively. Long-term treatment with fluticasone propionate reduced this rate of deterioration in all three SGRQ components and the overall score, showing for the first time that it is possible to ameliorate the rate of progression of loss of health in this disease.

HRQoL, mortality and exacerbations

Several studies have tested whether or not there is a relationship between health status (generic or disease-specific instruments) and mortality.^{39–42} These studies provide strong evidence that survival is reduced with higher (i.e. worse) SGRQ scores (Fig. 3).^{1,39–42} However, it is unclear whether or not all health status measures have the ability to predict mortality.

The relationship between health status and exacerbations is more precisely defined. Spencer and Jones⁴³ analysed data from the 26-week gemifloxacin long-term outcomes in bronchitis

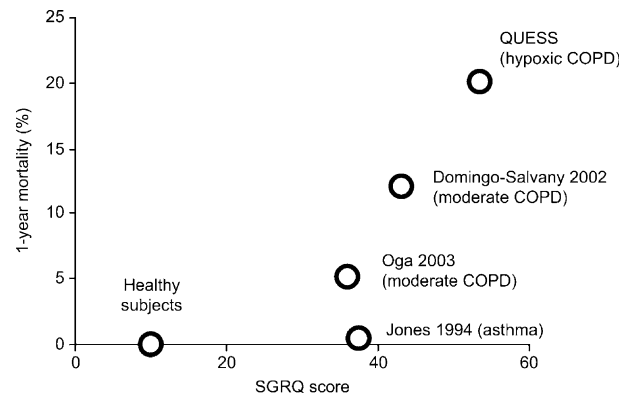


Figure 3 Collated data showing the association between mortality and St. George's Respiratory Questionnaire (SGRQ) score.^{1,39–42}

exacerbations study, which included 438 patients who had suffered from an acute exacerbation of chronic bronchitis (AECB). Patients who suffered repeated exacerbations during the study had a significantly worse SGRQ score at baseline than those who suffered no further AECB during the trial. Faster recovery from the initial AECB was also associated with a longer period to the next exacerbation. Furthermore, Spencer et al.³⁸ analysed data from the ISOLDE trial ($N = 613$) and showed that frequent exacerbations were independently associated with a worse baseline SGRQ score ($P < 0.0001$) and a more rapid rate of deterioration in health status ($P = 0.0003$). Statistical modelling suggested that the benefits from fluticasone propionate are largely the result of a reduction in exacerbation frequency. In conclusion, exacerbation frequency appears to have a marked effect on health status, making it all the more important to reduce exacerbations through treatment.

Measuring health status: consequences and inferences

Much has been learnt from the use of health status measurements in clinical studies; and it is now known that the SGRQ does have true interval scaling properties. A difference of 4 units (the threshold of clinical significance) at the mild end of the disease spectrum has the same meaning as 4 units at the severe end. By contrast, the implications for a patient of a 4-unit change may differ greatly between mild and severe disease. For example, a 4-unit deterioration with an infection may not even be enough to make a patient with mild disease visit their doctor for an antibiotic, but in the most severe patient a worsening of COPD sufficient to produce a 4-unit change may trigger a

hospital admission. More needs to be understood about the relationship between baseline health status, changes in health and their clinical consequences.

Future developments in health status measurement include refining and simplifying existing instruments and the development of computerised versions that can be used and scored in the clinic or using the internet. These developments will still not produce a major reduction in the time to complete a comprehensive health status questionnaire (typically 8–15 min currently), but the use of sophisticated mathematical algorithms in computer adaptive testing (CAT) could reduce this time to 1–2 min. Even more attractive is the potential power of CAT to make individual patient-tailored HRQoL questionnaires a reality.

Conclusions

Advances in measuring the effects of COPD may prove to be equally as important as the development of novel treatments for COPD. In this article, we have examined how parameters of dyspnoea, functional status and health status provide complementary information to more established physiological measures such as FEV₁. With improved treatment options in COPD, specific patient populations should be monitored accurately by applying these methods in order to gain a complete picture of their disease status. Only then will tailored treatment programmes become a reality.

References

1. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–7.
2. Rennard S, Decramer M, Calverley PM, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD international survey. *Eur Respir J* 2002;20:799–805.
3. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–12.
4. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med* 1999;159:321–40.
5. Lareau SC, Meek PM, Press D, Anholm JD, Roos PJ. Dyspnea in patients with chronic obstructive pulmonary disease: does dyspnea worsen longitudinally in the presence of declining lung function? *Heart Lung* 1999;28:65–73.
6. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–46.
7. Mahler DA, Tomlinson D, Olmstead EM, Tosteson AN, O'Connor GT. Changes in dyspnea, health status, and lung function in chronic airway disease. *Am J Respir Crit Care Med* 1995;151:61–5.
8. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J* 1959(5147):257–66.
9. Fletcher C. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). *BMJ* 1960;2:1665.
10. Morgan WK, Lapp NL, Seaton D. Respiratory disability in coal miners. *JAMA* 1980;243:2401–4.
11. Murphy JE, Donald JF, Molla AL. A single-blind comparative clinical trial of lymecycline and amoxycillin in the treatment of acute bronchitis in general practice. *J Int Med Res* 1976;4:64–8.
12. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnea vs. disease severity in indicating the health-related quality of life of patients with COPD. *Chest* 1999;116:1632–7.
13. Mahler DA, Rosiello RA, Harver A, Lentine T, McGovern JF, Daubenspeck JA. Comparison of clinical dyspnea ratings and psychophysical measurements of respiratory sensation in obstructive airway disease. *Am Rev Respir Dis* 1987;135:1229–33.
14. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85:751–8.
15. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217–24.
16. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest* 2003;124:834–43.
17. Mahler DA, Matthay RA, Snyder PE, Wells CK, Loke J. Sustained-release theophylline reduces dyspnea in nonreversible obstructive airway disease. *Am Rev Respir Dis* 1985;131:22–5.
18. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:1084–91.
19. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med* 1997;155:1984–90.
20. Reardon J, Awad E, Normandin E, Vale F, Clark B, ZuWallack RL. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. *Chest* 1994;105:1046–52.
21. Witek Jr. TJ, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003;21:267–72.
22. Witek Jr. TJ, Mahler DA. Meaningful effect size and patterns of response of the transition dyspnea index. *J Clin Epidemiol* 2003;56:248–55.
23. Mahler DA, Ward J, Fierro-Carrion G, et al. Development of self-administered versions of modified baseline and transition dyspnea indexes in COPD. *J COPD* 2004;1:165–72.
24. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD. Development of a self-reported chronic respiratory questionnaire (CRQ-SR). *Thorax* 2001;56:954–9.

25. Mahler DA, Waterman LA, Ward J. Validity and responsiveness of the self-administered computerized (SAC) versions of the baseline (BDI) and transition (TDI) dyspnea indexes in COPD. *Proc Am Thor Soc* 2005 Abstract A643.
26. Fierro-Carrion G, Mahler DA, Ward J, Baird JC. Comparison of continuous and discrete measurements of dyspnea during exercise in patients with COPD and normal subjects. *Chest* 2004;125:77–84.
27. Mahler DA, Mejia-Alfaro R, Ward J, Baird JC. Continuous measurement of breathlessness during exercise: validity, reliability, and responsiveness. *J Appl Physiol* 2001;90:2188–96.
28. Lareau SC, Meek PM, Wilhite C, Specht NL. Longitudinal evaluation of functional status and dyspnea following lung volume reduction surgery (LVR). *Am J Respir Crit Care Med* 1998;157:A867.
29. Lareau SC, Carrieri-Kohlman V, Janson-Bjerklie S, Roos PJ. Development and testing of the pulmonary functional status and dyspnea questionnaire (PFSDQ). *Heart Lung* 1994;23:242–50.
30. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–8.
31. Belza B, Steele BG, Hunziker J, Lakshminaryan S, Holt L, Buchner DM. Correlates of physical activity in chronic obstructive pulmonary disease. *Nurs Res* 2001;50:195–202.
32. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56:880–7.
33. Jones PW, Quirk FH, Baveystock CM. Why quality of life measures should be used in the treatment of patients with respiratory illness. *Monaldi Arch Chest Dis* 1994;49:79–82.
34. Harper R, Brazier JE, Waterhouse JC, Walters SJ, Jones NM, Howard P. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax* 1997;52:879–87.
35. Ware JJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
36. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
37. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:122–8.
38. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* 2004;23:698–702.
39. Carone M, Ambrosino N, Bertolotti G, et al. Quality of life evaluation and survival study: a 3-yr prospective multinational study on patients with chronic respiratory failure. *Monaldi Arch Chest Dis* 2001;56:17–22.
40. Jones PW. Quality of life, symptoms and pulmonary function in asthma: long-term treatment with nedocromil sodium examined in a controlled multicentre trial. Nedocromil sodium quality of life study group. *Eur Respir J* 1994;7:55–62.
41. Domingo-Salvany A, Lamarca R, Ferrer M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:680–5.
42. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003;167:544–9.
43. Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 2003;58:589–93.