Health-related quality of life among patients with chronic obstructive pulmonary disease

J Randall Curtis, Richard A Deyo, Leonard D Hudson

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in industrialised nations. It is essentially incurable and, for many, inexorably progressive; health care providers spend much effort trying to minimise patients' symptoms and to improve their ability to function in day-to-day life. While improved survival time is an important aim of treatment, there is growing recognition that improving the quantity of an individual's life may not be the only goal; for some, improving the quality of life may be far more important. Since reducing symptoms, increasing function, and improving the quality of life are central therapeutic goals for patients with COPD, as for many chronic diseases, it is important for researchers and clinicians to develop a common understanding of what is meant by these phrases and how these concepts can be measured.

In the past 10 years there has been an increasing body of literature on measurement of quality of life in patients with COPD and, more recently, on the efficacy of therapeutic agents based on quality of life measures. Studies measuring the quality of life in these patients appeared in the mid 1980s[1-6] when quality of life measures were used to assess continuous oxygen therapy,[5] intermittent positive pressure breathing,[6] and, more recently, in the assessment of theophylline,[7] inhaled bronchodilators,[8] home respiratory nursing care,[9] and pulmonary rehabilitation programmes.[10] As this trend continues it is important for clinicians to understand and assess these measures to help decide whether a new treatment is valuable.

We will review quality of life measures in patients with COPD with the emphasis on issues important to the clinician who seeks an understanding of quality of life measures as they are used in therapeutic trials.

Definition and relevance of health related quality of life

TERMS AND DEFINITIONS

The term "quality of life" is widely used in clinical research and clinical care, but rarely defined. In its broadest definition the quality of an individual's life is strongly influenced by factors that health care does not directly affect, including financial status, housing, employment, and social support. Consequently many researchers favour the more restrictive terms "health-related quality of life" (HRQL) or "functional status" to mean the quality of life as it is affected by health status. Functional status connotes a stronger basis in ability to perform the tasks of daily life, while HRQL connotes a more subjective experience of the impact of health on the quality of one's life. Since COPD is a disease often affecting older, retired persons, the mechanics of task performance may be less important than the ability to enjoy life. We have therefore chosen to use the term HRQL.

In general HRQL measures the impact of an individual's health on his or her ability to perform and enjoy the activities of daily life. HRQL instruments vary from disease-specific measures of a single (usually crucial) symptom such as dyspnoea,[3] to a generic global assessment of many facets which may include emotional functioning (mood changes and other psychiatric symptoms), social role functioning (employment, home management, and social or family relationships), activities of daily living (self-care skills and mobility), and the ability to enjoy activities (hobbies and recreation).[1]

The operational definition of HRQL also varies somewhat depending on its use. In general, outcome measures can have at least three purposes: discriminating between subjects at a single point in time, predicting prognosis, or evaluating changes within a given subject over time. While the purpose does not alter development and application of many physiological measures, the design of HRQL measures may vary substantially depending on the intended purpose.[11] To discriminate between a group of subjects, questionnaire items are selected to represent important components of HRQL which are applicable to as many individuals as possible. In contrast, for use in a therapeutic trial the instrument should detect change over time in an individual. Thus, questionnaire items are chosen only if they reflect features amenable to change. An example from the sickness impact profile was chosen by Deyo in a recent review to illustrate this point.[12] A positive response to the statement "I have attempted suicide" would indicate a high level of emotional distress and help discriminate among individuals. However, the response would remain positive at subsequent testing and consequently would not help to

Department of
Medicine
J R Curtis
L D Hudson

Departments of
Medicine and Health
Services
R A Deyo

University of
Washington, 3747 15th
Avenue NE, Room 203,
Seattle, Washington
98105, USA

Reprint requests to:
Dr J Randall Curtis.

distinguish change over time. In contrast, the number of stairs an individual can climb would be an effective gauge of change over time, but might not be a useful discriminative tool in a group of older adults who have made environmental changes to avoid stairs.

RELEVANCE AND USEFULNESS OF HRQL

A common criticism of HRQL is that it is highly subjective and therefore inherently immeasurable or, at best, "soft" data. It is axiomatic that HRQL is subjective, since it is the individual patient's perspective that is the most important measure of HRQL. Is this subjective quality necessarily immeasurable or "soft"? As Feinstein argues, the crucial attribute of "hardness" is the reproducibility of a measure.[13] HRQL measures *are* able to provide adequate and often excellent reproducibility. If "hard" physiological measures accurately reflected HRQL, it could be argued that HRQL measures are unnecessary. However, physiological measures such as pulmonary function and exercise tolerance do not correlate strongly with measures of HRQL.[12 14]

HRQL should not be measured in every therapeutic trial or longitudinal survey. There are circumstances where survival is the paramount outcome measure and HRQL is irrelevant. An example would be a randomised controlled trial of corticosteroids in COPD patients with acute respiratory failure. This short term treatment is designed to improve survival or shorten the course of the acute illness: HRQL is less important in judging efficacy. In other instances treatment may be applied to asymptomatic adults to prevent progressive disease, such as a trial of smoking cessation techniques. In this case HRQL would not be expected to vary and the benefit would be more appropriately shown in terms of smoking cessation success rates.

The phase of treatment development should also be considered before assessing HRQL as an outcome measure. Phase I trials are primarily concerned with pharmacokinetics and dose finding, and HRQL measures would not be appropriate. In small, early phase II trials HRQL would be unlikely convincingly to show either benefit or lack of benefit. It is the large phase III trials, especially those designed to mimic clinical practice, where HRQL can add the patient's view to other, more traditional, outcome measures.

Finally, HRQL measures can be especially useful in trials designed to assess treatments which differ dramatically in cost, side effects, or degree of invasiveness. For instance, in trials of extensive pulmonary rehabilitation or even lung transplantation, HRQL would be an important component to factor into cost effectiveness analyses.

Measurement issues

GENERIC *V* DISEASE-SPECIFIC MEASURES

HRQL instruments may be designed to assess overall quality of life, or only those aspects directly related to a particular disease. For instance, COPD-specific instruments can assess a single symptom such as dyspnoea.[3] They could also measure a series of symptoms – for example, dyspnoea, cough, and sputum production – plus those components of life particularly affected by COPD – for example, exercise tolerance and mood.[4] Generic instruments also represent a spectrum of questions and symptoms and are often divided into sections devoted to several parameters such as physical discomfort, role functioning, emotional well being, and social interactions. In addition, generic HRQL instruments may include a summary score allowing investigators to assign a single number to overall HRQL and use this score for cost-effectiveness analyses.

Disease-specific and generic instruments each have their advantages and disadvantages.[15] The choice of the type of instrument depends on the question being asked. Disease-specific instruments are likely to be more sensitive to small changes in a therapeutic trial (an evaluative study) of an agent targeted at the specific symptoms of COPD. For instance, an instrument to measure dyspnoea is more likely to show a benefit of bronchodilators than a generic HRQL instrument. In addition, disease-specific instruments relate closely to the clinical history and, consequently, may be more readily understandable to the clinician.

Generic instruments have the advantage of being thoroughly tested in various clinical settings and populations. The breadth of HRQL issues that they cover may reveal important, but unexpected, impacts of the treatment. In addition, they are more likely appropriately to weigh diverse side effects of treatment and establish an overall assessment of treatment on the patient's life. Finally, generic instruments are necessary if one wishes to compare the HRQL benefits of interventions for widely disparate conditions – for example, is lung transplantation as effective as kidney transplantation?

REPRODUCIBILITY, VALIDITY, AND RESPONSIVENESS

Three features of a questionnaire are important for clinicians to understand before assessing evidence based on HRQL instruments. The first is the reproducibility (or reliability) of the instrument – that is, whether it is resilient to confounding variations in the environment. There are various components to reproducibility, including test-retest reproducibility (how vulnerable the instrument is to unimportant day-to-day variations in the subject's response), interobserver reproducibility (whether different administrators of the instrument get the same results from the same individual), and internal consistency (whether different parts of the instrument give consistent results). These issues are not necessarily re-examined with each study using the instrument, but a reader should be convinced that this assessment has been done and that the instrument fulfils the basic measurement expectations.

Validity is a more difficult issue to assess in HRQL. Validity asks whether the instrument is really measuring the impact of health on an individual's quality of life. For HRQL there is no reference standard to measure the instrument against and consequently correlations with biological indicators of disease such as FEV$_1$ and exercise tolerance, and other HRQL instruments must be used as proxies for a "gold standard." Very high correlations would not be expected as the intention is not to duplicate these other measures, but the instrument should correlate in the expected direction with markers of disease severity and with other HRQL instruments. This process is known as "construct validation" and is an ongoing process as no single critical observation can definitively establish validity, which contrasts with "criterion validity" in which a true "gold standard" exists. Some of these correlations should be provided with the use of an instrument in a clinical trial to confirm that it is valid for the population under study.

For clinical trials or other longitudinal studies responsiveness is a key feature of HRQL instruments as it needs to identify small, but clinically important, changes over time. This sensitivity is central to the use of HRQL instruments in clinical trials to show a benefit (or lack of benefit). Investigators should therefore define the minimal clinically important difference that can be detected by the instrument.[16] Conversely, a large controlled trial might easily be able to identify statistically significant differences in HRQL which are clinically irrelevant – for example, a statistically significant improvement in FEV$_1$ of 10 ml from a large study may be interpreted as clinically unimportant. With HRQL measures, however, it is usually the responsibility of the researchers to identify the minimal clinically important difference.

STATISTICAL ISSUES

It is important to identify the key hypotheses before data collection and to report when hypotheses were generated by analysis of associations in the data. This is particularly important in HRQL because these instruments often have multiple components and are conducive to "data dredging." If post hoc analyses are performed, the level of statistical significance should be adjusted appropriately to compensate for the problems of multiple comparisons.[17]

Sample size and power calculations are important variables in trials using HRQL instruments because the relative inexperience of using these measures may make it difficult to estimate a clinically important difference, a central component of these calculations. The difficulty with power calculations is usually considered to be the problem of the researcher, not the clinician. In a trial showing no benefit of treatment, however, the power of the trial to identify a benefit becomes of foremost interest to the clinician trying to decide whether to abandon this treatment. If power calculations are unreliable, it becomes difficult to judge the value of the trial.

Selected HRQL instruments

There are four generic HRQL instruments and four disease-specific instruments that have been used extensively in patients with COPD. Some important features of each of these instruments are shown in the table.

GENERIC HRQL INSTRUMENTS

The generic HRQL instrument which has been used most extensively in patients with COPD is the sickness impact profile (SIP). This comprehensive, 136 item, self-adminis-

Selected HRQL instruments used in patients with chronic obstructive pulmonary disease (COPD)

Instrument	Domains and dimensions examined	Length	Administration	Reproducible, valid and responsive
Generic:				
Sickness impact profile (SIP)	Physical: ambulation, mobility, body care Social: general well being, work/social role performance, social support and participation, global social function, personal relationships, and global emotional functioning	136 items (30 min)	Self-administered	Reproducibility, validity and responsiveness well demonstrated
Medical outcomes study (MOS)	Functioning: physical, role, and social Well being: mental health, health perceptions, and bodily pain	20 items (3 min)	Self-administered	Reproducibility and validity well demonstrated; responsiveness in COPD not well studied
Quality of well being (QWB)	Mobility: access to modes of transportation Physical: limits to activity Social: limits to activity Symptoms: review of systems	50 items (12 min)	Trained interviewer administered	Reproducible and valid; responsiveness in COPD not well demonstrated
Nottingham health profile (NHP)	Health: energy, pain, emotional reactions, sleep, social isolation, physical mobility Life functioning: employment, relationships, personal life, sex, hobbies, vacations, housework	45 items (10 min)	Self-administered	Reproducible and valid; responsiveness in COPD not well demonstrated
COPD specific:				
Chronic respiratory disease questionnaire (CRDQ)	Dyspnoea, fatigue, mastery over disease, emotional dysfunction	20 items (20 min)	Trained interviewer administered	Reproducibility, validity and responsiveness well demonstrated
St George's respiratory questionnaire (SGRQ)	Symptoms: cough, sputum, wheeze, breathlessness Activity: physical functioning, housework, hobbies Impact on daily life: social and emotional impact	76 items (? min)	Self-administered	Reproducibility, validity and responsiveness well demonstrated
Oxygen cost diagram (OCD)	Single vertical line to be marked in location to indicate degree of disability caused by dyspnoea	1 item (<5 min)	Self-administered	Intermediate reproducibility and validity. Not as responsive as SGRQ
Baseline dyspnoea index (BDI)	Functional impairment, magnitude of task evoking dyspnoea, magnitude of effort evoking dyspnoea	3 indices with four grades (<5 min)	Trained interviewer administered	Reproducibility, validity and responsiveness well demonstrated

tered questionnaire was developed to measure HRQL in a wide variety of chronic diseases. The instrument assesses a broad range of areas including ambulation, body care, mobility, emotional behaviour, social behaviour, work, sleep, eating, home management, and recreational activities. It is one of the longest instruments, requiring 20–30 minutes to complete. It has undergone extensive testing to establish its reproducibility and validity,[18] although its responsiveness has not been studied in patients with COPD. The SIP has been used extensively to document descriptively the HRQL in patients with COPD.[12 19 20] It has also been used in patients with COPD to assess the value of continuous oxygen therapy,[5] antidepressant therapy,[21] home respiratory nursing care,[9] and intermittent positive pressure breathing.[6]

A similar generic instrument was developed for the medical outcome study (MOS), a physicians' office based cross sectional study of 9385 adults.[22] An initially large number of questions was reduced to a 20 item, self-administered instrument divided into two parts. The first examines physical functioning, role functioning, and social functioning, and the second examines mental health, health perceptions, and bodily pain. This instrument requires approximately three minutes to complete and was shown to be reproducible and valid.[22] COPD was one of the diseases examined in this survey, and, although a new instrument, it has been used to assess the HRQL of patients with COPD.[23] The MOS has the advantage of brevity but, like the SIP, responsiveness in patients with COPD has not yet been thoroughly examined. Recently the authors of the MOS instrument have prepared a 36 item "short form" known as the MOS SF-36.[24] This generic health status instrument is being widely used and has been adopted by a number of researchers and health care organisations. Its validity has been well described,[25] but studies among patients with COPD are limited to those noted above for the 20 item version.

The quality of well being (QWB) is a 50 item interviewer administered questionnaire developed as a subcomponent of a larger health outcomes measure, the health status index.[26] The QWB is divided into three scales – mobility, physical activity, and social activity. The QWB score is expressed as the value that subjects associate with a particular combination of function and symptoms, so it can be used for quantitative assessment and cost-effectiveness analysis. It has been shown to be reproducible and valid[27 28] and has been used to describe HRQL in patients with COPD.[29] In addition, the QWB has been used to assess home respiratory nursing care[9] and pulmonary rehabilitation programmes[10] for individuals with COPD. Although the QWB does not assess as many domains as the SIP or the MOS, it has the unique advantage of being applicable to cost-effectiveness analysis.

Finally, the Nottingham health profile (NHP) is a 45 item, self-administered questionnaire composed of two parts. The first contains 38 items assessing energy, pain, emo-

tional reactions, sleep, social isolation, and physical mobility, and the second part contains seven items covering the areas of life functioning most often affected by health problems. This self-administered instrument takes 10 minutes to complete. It is reproducible and valid in the assessment of chronic diseases[30] and has been used to describe HRQL in patients with COPD.[31] The NHP has recently been used to assess inhaled bronchodilators in patients with COPD.[32]

Several other instruments which measure mood, depression, anxiety, and other psychiatric symptoms have been used to assess patients with COPD. These include the Minnesota multiphasic personality inventory (MMPI), the profile of mood states (POMS), and the Beck depression inventory.[12 21 33] While these instruments have provided insights into the HRQL of persons with COPD and may provide important information in the assessment of treatment for COPD, they are not strictly measures of HRQL and will not be discussed in detail in this review.

DISEASE-SPECIFIC HRQL INSTRUMENTS

The chronic respiratory disease questionnaire (CRDQ) was developed by Guyatt and colleagues through in-depth, unstructured interviews in 100 patients with COPD. The result was a 20 item questionnaire dealing with dimensions of dyspnoea, fatigue, patients' sense of control over the disease (mastery), and emotional dysfunction. This interviewer administered questionnaire takes 20 minutes to complete and has been shown to be reproducible, valid, and responsive.[34 35] In a head to head comparison the CRDQ was shown to be more valid and more responsive than two other measures of dyspnoea – the oxygen cost diagram and the Medical Research Council dyspnoea questionnaire.[35] The CRDQ has been used to assess inhaled bronchodilators,[8] theophylline,[8] and nocturnal nasal intermittent positive pressure.[36]

The St George's respiratory questionnaire (SGRQ) is a 76 item instrument divided into three components: symptoms, activity, and impact on daily life. This self-administered questionnaire has been shown to be reproducible, valid, and responsive.[14] In a comparison with SIP, SGRQ was shown to be twice as responsive as the generic instrument. Of note, Jones and colleagues excluded questions explicitly designed to assess anxiety and depression, since other questionnaires are available for this purpose.[14]

The oxygen cost diagram (OCD) represents a single vertical line with common activities listed beside it ascending in order of increasing exertional requirements. The activities range from sleeping at the bottom to brisk walking uphill at the top. Patients are asked to indicate the point above which they think their dyspnoea would limit activity. The instrument is moderately reproducible and, as already mentioned, less responsive than the CRDQ.[34]

The baseline dyspnoea index (BDI) was designed by Mahler and colleagues to measure

degree of dyspnoea as well as the impact of dyspnoea on an individual's life. The instrument obtains a rating from the patient on three scales: functional impairment, magnitude of task needed to evoke dyspnoea, and magnitude of effort needed to evoke dyspnoea. These are combined into a baseline score. In addition, Mahler and colleagues developed a transition dyspnoea index specifically to measure changes from the baseline condition.[3] These indices have been shown to be reproducible and valid in patients with COPD,[3 23 33 37] and are more responsive than the OCD.[37] While this instrument concentrates on a single symptom of COPD, it is an important symptom and often the target of therapeutic agents. The BDI has been used to assess the value of theophylline.[7]

Features of the HRQL of patients with COPD

DESCRIPTION OF HRQL IN PATIENTS WITH COPD
There have been many studies describing the HRQL of patients with COPD. These studies vary in their inclusion criteria and consequently examine the HRQL of patients with varying severity of disease. The severity of disease examined has ranged from patients eligible for continuous oxygen therapy having a mean FEV_1 of 0·75 l (30% of predicted)[1] to patients seen in a family practice with a mean FEV_1 of 1·86 (70% predicted).[38] Despite this heterogeneity of disease severity, a clear picture emerges showing that patients with COPD have significant decrements in their HRQL. Stewart and colleagues, using the MOS, showed that patients with COPD had decreased HRQL in all five domains of the MOS: physical functioning, role functioning, social functioning, mental health, health perceptions, and bodily pain.[22] Furthermore, patients with COPD consistently scored worse on all domains than patients with hypertension, arthritis, and diabetes, and worse than those with chronic back pain on all domains except bodily pain. Similarly, McSweeny and colleagues showed that patients with severe COPD had diminished HRQL in all domains of the SIP except employment.[1] Employment is not a sensitive marker of HRQL in patients with COPD because such a large proportion of patients with COPD are retired. In the study by McSweeny *et al* patients with COPD showed the largest decrements of HRQL in the domains of emotional disturbances (primarily depression), recreational activities, home management, and sleep and rest. Likewise, Prigatano and colleagues found wide ranging decrements of HRQL in a group of patients with COPD with moderate disease having a mean FEV_1 of 1·02 l.[2] It is interesting to compare the HRQL of patients from these two large studies. The patients studied by Prigatano and colleagues had a mean FEV_1 0·25 l higher and a mean PaO_2 at rest 20 mm Hg higher than those in the study by McSweeny and colleagues. Although the patients with less severe disease had significantly less impairment on the physical domains of the SIP, they

had very similar impairment in psychosocial domains. This suggests that while degree of physical limitation is associated with severity of disease, the degree of psychosocial limitation may not be as strongly influenced by severity of disease once some threshold of COPD is reached.

An interesting feature of these studies describing the HRQL in patients with COPD is that, regardless of the instrument used or the severity of disease studied, sleep and rest are significantly disturbed.[1 2 43 31 38]

DEPRESSION, EMOTIONAL DYSFUNCTION, AND HRQL

A striking finding is the prominent role that depression and emotional dysfunction play in COPD. In one study patients with COPD scored lower on the mental health domain than patients with hypertension, diabetes, congestive heart failure, myocardial infarction, angina, arthritis, and chronic back pain; only patients with chronic gastrointestinal disorders scored lower in mental health.[22]

The influence of depression on the overall HRQL of a group of patients with COPD depends on its prevalence in these patients and its effect on HRQL. McSweeny and colleagues, using the MMPI, found that 42% of patients fit the category of reactive depression compared with 9% of age matched controls.[1] Light and colleagues used a questionnaire designed to detect depression (the Beck depression inventory) and found the same prevalence in a group of patients with less severe COPD.[33] Prigatano and colleagues used POMS to quantify depression and anxiety and found that both strongly correlated with the HRQL as measured by the SIP.[2] In fact, both anxiety and depression predicted the overall SIP score substantially better than the physiological parameters FEV_1, PaO_2, $PaCO_2$, and exercise tolerance.

PHYSIOLOGICAL MEASUREMENTS AND HRQL
Intuitively we would expect HRQL to correlate with physiological measures of the severity of COPD. Most studies that have compared physiological measures with HRQL measures have shown correlations for the generic HRQL instruments including the SIP,[12 14] the QWB,[29] as well as disease-specific instruments such as the BDI[3] and the SGRQ.[14] However, not all studies show such correlations[1 31] and these correlations, when present, are not strong.

The most widely used measure of the severity of COPD is the FEV_1 which has been shown to be an accurate predictor of prognosis and survival.[39] While most studies show that FEV_1 is statistically correlated with HRQL,[2 3 14 29 38] others have shown no significant correlation.[1 31] Even studies demonstrating a correlation have found that FEV_1 is less well correlated with HRQL than are emotional dysfunction[2 14] and dyspnoea.[14 23] Similarly, measures of oxygenation such as PaO_2 and SaO_2 are either weakly correlated with HRQL[29] or not significantly correlated.[1 2 31]

Exercise tolerance is a physiological measure which is not well predicted by ventilatory capacity or pulmonary function parameters,[40][41] but correlates with HRQL better than either FEV_1 or oxygenation correlate with HRQL.[12][14][29][31] Exercise tolerance also correlates with dyspnoea measures better than other parameters of pulmonary function.[3][42][43] In a study by Jones and colleagues all the correlation between pulmonary function and HRQL could be accounted for entirely by exercise tolerance.[14]

Since dyspnoea is used as a measure of HRQL, one would expect it to correlate fairly well with other HRQL instruments; in fact, dyspnoea correlates better and is a better predictor of HRQL than either pulmonary function or oxygenation.[14][23][31][38]

In general, summary statistics of correlation from different studies should be compared with caution, since studies have different entry criteria, measure different outcome measures, and use different statistical techniques. Nevertheless the squared correlation coefficients (R^2) between different variables in HRQL studies of patients with COPD have shown some homogeneity. The squared correlation coefficient between HRQL, dyspnoea and several physiological, psychological, and descriptive variables are shown in the figure. HRQL and the dyspnoea scale correlate better with one another than the physiological parameters and descriptive variables. Depression and anxiety have an intermediate correlation with HRQL and the dyspnoea scale.

In summary, several studies have shown that HRQL does correlate in the expected direction with physiological measures of COPD severity, but that the correlation is not strong or universal to all studies which suggests that the physiological parameters do not predict HRQL well but still provide additional information in the assessment of patients with COPD.

COMORBIDITY AND HRQL
COPD frequently occurs in association with other diseases. Intuitively it makes sense that

persons with multiple conditions would have a worse HRQL than those with just one chronic condition. Stewart and colleagues have documented the impact of comorbidity.[22] However, it is important to realise that most clinical trials and descriptive studies of HRQL in patients with COPD have excluded significant comorbid illnesses. Consequently, the impact of comorbidity on the HRQL of patients with COPD is not well understood.

SMOKING AND HRQL
Another feature of HRQL is its association with continued smoking. Prigatano and colleagues found that those who continued to smoke had a significantly lower HRQL than those who had given up despite the fact that the smokers were younger and had a higher mean FEV_1.[2] While this does not prove a causal relation between continued smoking and HRQL, it is intriguing and worthy of further study.

Impact of treatment on HRQL in patients with COPD

IMPACT OF SPECIFIC TREATMENTS ON HRQL IN PATIENTS WITH COPD
Although descriptive data on the HRQL of patients with COPD are useful, the main concern of clinicians caring for patients with COPD is whether therapeutic interventions will improve HRQL. The instruments described in this review have been used to evaluate a number of specific treatments, and these studies provide insight into both specific treatments and the role of HRQL instruments in clinical practice.

Guyatt and colleagues used the CRDQ to assess inhaled salbutamol and oral theophylline in 19 patients and showed that both agents individually improved HRQL as well as FEV_1, exercise tolerance, and peak flow. Although some patients had additional benefit from the two agents used together, this was not statistically significant for the group.[8] Mahler and colleagues used the BDI in a crossover double
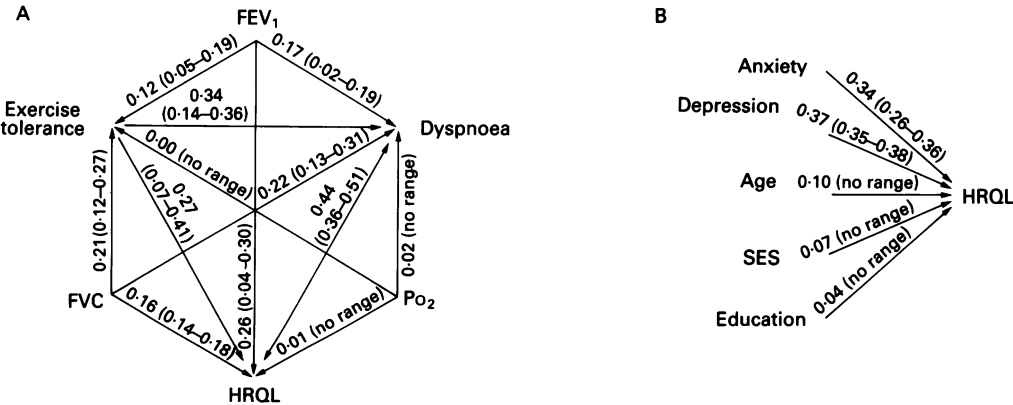
Squared correlation coefficients (R^2) between health related quality of life (HRQL), dyspnoea scale, pulmonary physiological parameters, demographic characteristics, and psychological states. The numbers represent the median of the R^2 values found with the ranges in parentheses.[1-3][14][20][29][31][33][35][42][43] R^2 can be viewed as an estimate of the proportion of the variability in HRQL or dyspnoea that is explained by a given parameter. The arrows do not imply demonstrated causality, but represent the direction of the relation of interest in understanding the role of HRQL measures. Panel A shows correlations of HRQL and dyspnoea with each other and with measures of pulmonary function, oxygenation, and exercise tolerance. Panel B shows correlations of HRQL with psychological states and demographic variables.

blind trial of theophylline. In this study the dyspnoea scale showed a benefit of theophylline while spirometric values, arterial blood gases, and exercise tolerance showed no advantage.[7]

A recent study by van Schayck and colleagues examined the impact of routine versus symptomatic inhaled salbutamol and ipratropium treatment on HRQL (using the NHP) and on spirometric indices.[32] Although they found no difference between salbutamol and ipratropium on either HRQL or spirometric parameters, there was a significantly greater decline in FEV_1 in the group receiving continuous therapy than in those receiving symptomatic treatment. The more rapid decline in FEV_1 was not associated with a decline in HRQL. Since changes in FEV_1 and HRQL did not move in the same direction, this trial emphasises the importance of measuring HRQL and not assuming it follows FEV_1.

Borson and colleagues examined the impact of antidepressant treatment on depression, HRQL, spirometric indices, and exercise tolerance in 36 patients with COPD and depression.[21] They found that treatment improved not only anxiety and depression, but also HRQL. There was no significant change in FEV_1, arterial blood gas tensions, or exercise tolerance.

The Nocturnal Oxygen Therapy Trial (NOTT) group examined the impact of nocturnal versus continuous oxygen therapy in patients with COPD and hypoxaemia[5] and found a significant decrease in mortality associated with continuous oxygen. Interestingly, despite decreased mortality with continuous oxygen, there was no benefit in HRQL. The absence of benefit should not, and did not, prevent continuous oxygen therapy from becoming the standard of care since it does confer a survival advantage. Nonetheless, the information that continuous oxygen therapy does not improve HRQL over nocturnal oxygen therapy is useful for clinicians counselling patients about what to expect from continuous oxygen therapy.

HRQL has been used to assess intermittent positive pressure ventilation in two separate trials. In the intermittent positive pressure breathing (IPPB) trial 985 patients used either IPPB or a routine compressor nebuliser to receive inhaled bronchodilators.[6] The authors found no benefit of IPPB in HRQL, survival, duration of stay in hospital, or lung function. In the second trial Elliott and colleagues used nocturnal nasal intermittent positive pressure in 12 patients using each patient as their own historical control[36] and found improved sleep time and efficiency, but no change in HRQL.

HRQL has also been used to assess home respiratory nursing care. In a controlled trial Bergner and colleagues showed no benefit in HRQL from specialised respiratory home care and concluded that current limited coverage of home care services by third party payers was appropriate.[9] Similarly, Toshima and colleagues evaluated a comprehensive pulmonary rehabilitation programme in comparison with an education only control programme.[10] They

showed improvements in exercise tolerance for the rehabilitation programme, but no difference in HRQL.

OVERVIEW OF HRQL IN THERAPEUTIC TRIALS FOR PATIENTS WITH COPD

These trials show a range of possible outcomes from using HRQL instruments. The HRQL instrument may agree with other outcome measures and thereby provide additional evidence either for or against the use of a specific treatment. The instrument may show no benefit when other outcomes such as survival show clear benefit. In this case it is important that clinicians and patients be aware of this discrepancy and consider it in the decision to use the treatment. If the benefit of treatment is considered to outweigh the lack of improvement in HRQL, the patient's awareness of this lack of benefit in HRQL may minimise disappointment with the treatment and consequent noncompliance. Finally, HRQL instruments may show a benefit when traditional outcomes do not, and these instruments may allow patients to receive important and effective treatment that would otherwise be assessed as ineffective.

Applicability of HRQL measures to clinical practice

USE OF HRQL MEASURES IN CLINICAL PRACTICE

In general the practising clinician assesses the HRQL of a patient with COPD by taking a careful history, eliciting symptoms, and assessing how these symptoms affect functional capacity and ability to perform the recreational and social activities the patient enjoys. The practising clinician generally does not need an HRQL instrument to perform this assessment. There may, however, be circumstances in which these instruments may be directly useful to the practising clinician as a self-administered generic or disease-specific HRQL instrument for patients to complete in the waiting room. This practice may identify specific areas of concern or changes over time that might not become obvious during routine visits. For this purpose the HRQL instrument would need to be not only reproducible, valid, and responsive, but also easily administered and interpreted in the clinical setting. Candidate instruments would include the MOS[44 45] and the SGRQ.

In addition, an HRQL instrument could be useful in the N of 1 trial. Guyatt and colleagues have described the utility and practice of N of 1 randomised controlled trials in detail[46] and this technique can be very useful in assessing an individual's response to different therapeutic approaches. In the N of 1 trial HRQL is an ideal outcome measure since the point of these trials is usually to determine the treatment which provides patients with the best HRQL.[16 46]

LESSONS TO THE CLINICIAN REGARDING HRQL IN COPD

Previous research has pointed out several important, but not widely known, features of the

HRQL of patients with COPD. Firstly, maximal improvement in physiological measures of disease severity such as FEV$_1$ or oxygenation may not be sufficient to maximally improve HRQL. The NOTT experience, for example, showed that continuous oxygen therapy improves oxygenation and survival, but did not change HRQL.[5] If we are interested in improving HRQL we must assess it directly. As a corollary of this point, it is possible to improve HRQL without changing any physiological measures of disease severity. The use of antidepressants in individuals with COPD and depression improved HRQL without changing FEV$_1$ or exercise tolerance.[21]

A second important lesson to the clinician provided by the studies of HRQL is that COPD has a major impact on specific facets of HRQL that might not be obvious, including depression, anxiety, sleep, and rest. It is not clear whether depression and anxiety cause a decrease in HRQL or vice versa. It seems likely that there is a complex interdependence of these factors, but it is clear that treating depression and anxiety can improve HRQL.[21]

A final generic lesson of these studies is that individuals vary as to what they consider to be the most important aspects of HRQL and these are not well correlated with disease severity, exercise tolerance, or other terms familiar to clinicians. In the assessment of an individual patient's HRQL it is important to ask directly what each person values about his or her life, including religious beliefs, value system, and their priorities. This is especially important in COPD because the disease predisposes patients to acute respiratory failure, where it is often appropriate to consider withholding or withdrawing life support measures such as mechanical ventilation. This decision depends on the likelihood of a reversible component and on the patient's acceptance or rejection of the treatment based on risks and benefits offered. The patient's response may depend on their HRQL before the acute event. Often patients will be unable to make a decision about life support based on a hypothetical scenario before the acute event, but early discussion will give clinicians and family members a better understanding of the patient's views should he or she be unable to participate once in respiratory failure. Without these discussions many physicians and families do not have a good understanding of the patient's wishes. This was documented by Uhlmann and colleagues who asked patients, their spouses, and physicians whether they wished cardiopulmonary resuscitation and mechanical ventilation to be given to the patient if they became critically ill. In approximately 40% of cases the wishes of both the patient's spouse and the physician differed from those of the patient.[47]

Summary
Assessment of HRQL is an important feature of the care of patients with chronic disease. The instruments will be used increasingly to assess the quality of life of patients with specific diseases and to help assess the impact of treatment. In addition, as outcome assessment becomes an increasing part of health care technology, HRQL will become a common outcome measure. To assess the importance or applicability of an HRQL measure clinicians must have a basic understanding of the field of HRQL assessment. Clinicians should expect the instrument used to be reproducible, valid, and responsive in patients with the disease under study. Studies describing new HRQL instruments should be expected to show the need for, or advantage of, a new instrument as opposed to one already developed and tested.

HRQL instruments have provided important insights into the lives of patients with moderate to severe COPD. They have also been essential in indicating that some treatments improve the lives of patients with COPD while others do not. We can expect that the HRQL instruments will continue this role in future research.

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