How Should Health-Related Quality of Life Be Assessed in Patients With COPD?*

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The traditional approach of caring for patients with chronic respiratory disease has been to rely on pulmonary function tests to quantify the severity and to assess response to therapy. However, patients with respiratory conditions seek medical attention because of symptoms, particularly dyspnea, and impaired ability to function, which clearly impact on an individual’s health-related quality of life (HRQOL). Accordingly, instruments have been developed to provide a standardized method to measure health status and levels of impairment. One of the major reasons for measuring HRQOL is to detect how much HRQOL has changed in response to therapy (an evaluative instrument). A minimum clinically significant change has been established for some HRQOL instruments in order to indicate the relative value of any measured change and to guide the interpretation as to whether the change is “clinically meaningful.” Selected studies using disease-specific instruments have demonstrated that β₂-agonist, anticholinergic, and theophylline medications can improve HRQOL, as compared with placebo therapy.

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Key words: bronchodilator therapy; disease-specific instrument; dyspnea; generic health measure; minimum clinically significant change

Abbreviations: CRQ = Chronic Respiratory Questionnaire; HRQOL = health-related quality of life; MCSC = minimum clinically significant change; SF-36 = Short-Form 36-item questionnaire; SGRQ = St. George’s Respiratory Questionnaire; SOLQ = Seattle Obstructive Lung Disease Questionnaire

Health-related quality of life (HRQOL) refers to the physical, psychological, and social domains of health that are unique to each individual.¹ Each of these domains can be measured by the objective assessments of functioning or health status and the subjective perceptions of health. Other valued aspects of life exist that are not generally considered as “health,” including income, freedom, and the environment.²

Interest in HRQOL over the past decade has increased substantially because of recognition of the following factors: (1) individual patients are most concerned about their symptoms (e.g., dyspnea) and their function (e.g., ability to perform physical tasks), rather than objective measures such as expiratory airflow; (2) HRQOL is a unique construct that is different from physiologic measures or survival³; and (3) the goals of therapy have been expanded to include relief of symptoms and improvement in HRQOL in addition to the standard physiologic outcomes.⁴⁵

Types of Instruments to Measure HRQOL

These instruments were designed to provide a standardized method by which health status or levels of health impairment could be measured and compared in individual patients as well as in groups of patients. There are three distinct types of instruments to measure HRQOL.²

Utility Scale

This type of instrument attempts to quantify different states of health on a continuum from perfect health (one anchor) to death (another anchor). This approach is particularly valuable to health economists.

General or Generic Health Measures

These instruments quantify a wide range of diseases and disease states and are anchored at one end by perfect health and at the other end by the worst possible health. Examples include the Sickness Impact Profile,⁶ the Short-Form 36-item questionnaire (SF-36),⁷ and the Nottingham Health Profile.⁸ Although such measures can provide valid estimates of impaired health in chronic respiratory disease, this approach appears to be relatively insensitive to detect small changes in response to a therapeutic intervention.
Disease-Specific Measures

These questionnaires were developed to consider the major or key components that influence the specific disease. In patients with COPD, Guyatt et al\textsuperscript{4} reported that dyspnea, fatigue, emotional function, and mastery were the major concerns of patients and are measured as four components in the Chronic Respiratory Questionnaire (CRQ); Jones et al\textsuperscript{9} proposed that symptoms, activity, and impacts were the important constructs as included in the St. George’s Respiratory Questionnaire (SGRQ); and Tu et al\textsuperscript{10} incorporated the dimensions of physical function, emotional function, coping skills, and treatment satisfaction in the Seattle Obstructive Lung Disease Questionnaire (SOLQ).

The characteristics of selected general and disease-specific questionnaires for measuring HRQOL in patients with COPD are listed in Table 1. Harper et al\textsuperscript{11} compared results from both generic (SF-36 and the Eurocol Classification of Health) and disease-specific (CRQ and SGRQ) instruments with physiologic measurements in patients with COPD at baseline and at follow-up at 6 months and 12 months. Based on comparative analyses, they concluded that the SF-36 was superior to the Eurocol Classification of Health and that the CRQ performed slightly better than the SGRQ.

Why Measure HRQOL?

One important reason for measuring HRQOL in patients with chronic respiratory disease is to differentiate between patients who have a better health status and those who have a worse health status (a discriminative instrument). For example, Mahler et al\textsuperscript{12} showed that patients with symptomatic COPD had lower scores for HRQOL compared with all patients evaluated by one of 536 primary care physicians or specialists (Fig 1).\textsuperscript{13} Furthermore, Hajiro et al\textsuperscript{14} and Mahler and Mackowiak\textsuperscript{15} found that patients with COPD who reported more severe dyspnea and exhibited more impaired lung function had, in general, lower scores for HRQOL. Ferrer et al\textsuperscript{16} reported that different stages of COPD based on the FEV\textsubscript{1} percent of predicted separated groups of patients with varying degrees of impairment in HRQOL using the SGRQ. Even patients with stage I disease (FEV\textsubscript{1} \(\approx 50\%\) predicted) had lower values for HRQOL compared with a normal population.\textsuperscript{16,17}

The most widely used application (for both clinical and research purposes) for measuring HRQOL is to detect how much HRQOL has changed in response to therapy (an evaluative instrument). The responsiveness of an evaluative instrument is an essential criterion to evaluate the impact/benefit of a specific intervention on the outcome of health status. Related to the responsiveness criterion of a HRQOL questionnaire is the threshold for a clinically meaningful change. A minimum clinically significant change (MCSC) has been established for some HRQOL instruments in order to indicate the relative value of any measured change in health status and to guide the interpretation as to whether the change in scores is “clinically meaningful.”\textsuperscript{18} The proposed values for a MCSC are as follows: a change of at least 4 points in the overall score for the SGRQ\textsuperscript{9}; a change of approximately 5 points on the SOLQ\textsuperscript{10}; and a change of at least 10 points for the CRQ.\textsuperscript{4}

HRQOL as an Outcome Measure for Evaluating Pharmaceutical Therapy

\(\beta_2\)-Agonist Therapy

Guyatt et al\textsuperscript{19} reported that salbutamol, 200 \(\mu\)g qid, improved dyspnea, physical function, and emo-

<table>
<thead>
<tr>
<th>Instruments</th>
<th>No. of Components</th>
<th>No. of Items (Type of Response)</th>
<th>Method of Administration</th>
<th>Time to Complete, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickness Impact Profile\textsuperscript{6}</td>
<td>12 components</td>
<td>136 (Dichotomous, responses, weighted)</td>
<td>Self or interviewer</td>
<td>15–25</td>
</tr>
<tr>
<td>SF-36\textsuperscript{7}</td>
<td>8 components</td>
<td>36 (Likert Scales)</td>
<td>Self</td>
<td>5–10</td>
</tr>
<tr>
<td>Nottingham Health Profile\textsuperscript{8}</td>
<td>First section-6 components</td>
<td>38 (Yes or no; items weighted)</td>
<td>Self</td>
<td>5–10</td>
</tr>
<tr>
<td>CRQ\textsuperscript{4}</td>
<td>4 components</td>
<td>20 (Each with 7-point scale)</td>
<td>Interviewer</td>
<td>15–25 (first time)</td>
</tr>
<tr>
<td>SGRQ\textsuperscript{9}</td>
<td>3 components</td>
<td>50 (76 weighted responses)</td>
<td>Self</td>
<td>10–15 (subsequent)</td>
</tr>
<tr>
<td>SOLQ\textsuperscript{10}</td>
<td>4 components</td>
<td>29 (5- to 7-point scale)</td>
<td>Self</td>
<td>5–10</td>
</tr>
</tbody>
</table>
tional function (components of the CRQ), as well as lung function and walking distance compared with placebo therapy, 2 puffs qid, over 2 weeks in 19 patients with symptomatic COPD. Jones and Bosh\textsuperscript{20} evaluated changes in the SGRQ in patients with COPD treated with placebo (n = 95); salmeterol, 50 μg bid (n = 94); and salmeterol, 100 μg bid (n = 94), for 16 weeks. Compared with placebo, the 50 μg dose of salmeterol provided significant improvements in the “Total” and “Impacts” scores of the SGRQ that exceeded the threshold for a clinically significant change. The absence of any significant improvement in HRQOL with the 100 μg dose of salmeterol may have been related to side effects such as tremor and central nervous stimulation.

Comparison of β\textsubscript{2}-Agonist and Anticholinergic Medications

Van Schayck et al\textsuperscript{17} reported no significant differences in changes in the Nottingham Health Profile between salbutamol, 400 μg qd, and ipratropium, 160 μg qd, over a 2-year period in 93 patients with mild COPD (FEV\textsubscript{1} ≤ 50% predicted). However, the authors commented that a disease-specific HRQOL instrument might have been more sensitive to detect an improvement in health status. In a 12-week, multicenter trial of 411 patients with COPD (FEV\textsubscript{1} ≤ 65% predicted), Mahler et al\textsuperscript{21} found that groups who received salmeterol, 42 μg bid, or ipratropium bromide, 36 μg qid, had higher overall scores (improvement) on the CRQ compared with placebo therapy, 2 puffs qid (Fig 2). Furthermore, the proportion of patients who achieved an increase of ≥ 10 points (the MCSC) in the total score was significantly higher for salmeterol (46%; p = 0.007) and ipratropium (39%; p = 0.041) groups compared with the placebo group (27%). There were also greater improvements in the clinical ratings of dyspnea (the Transition Dyspnea Index) over the study period in patients treated with salmeterol or ipratropium compared with placebo.

Theophylline

Several studies have demonstrated that theophylline improves dyspnea in patients with moderate to severe COPD.

\textbf{Figure 1.} Group mean values for health components on the Medical Outcomes Study 20-item questionnaire in 11,186 patients who visited a primary care physician or a specialist\textsuperscript{13} compared with 110 patients with symptomatic COPD\textsuperscript{12}. Patients with COPD had substantially lower values for physical and role functioning as well as health perceptions compared with a general patient population.

\textbf{Figure 2.} Changes from baseline in the total score for the CRQ (Δ CRQ) after 12 weeks of treatment with salmeterol (n = 135), ipratropium bromide (n = 135), or placebo (n = 143) in patients with COPD (FEV\textsubscript{1} ≤ 65% predicted). Both salmeterol and ipratropium had significantly higher scores (improvement in HRQOL) compared with placebo (p = 0.007). Data from Mahler et al\textsuperscript{21}. 
severe COPD compared with placebo therapy. However, a more relevant clinical question is whether theophylline provides further benefit when added to inhaled bronchodilator therapy. McKay et al examined the addition of theophylline to inhaled β2-agonist and ipratropium therapy in 15 patients with severe COPD (FEV1 31 ± 15% predicted). Although there were no significant changes in FEV1 or FVC with theophylline compared with placebo, patients experienced significant improvements in dyspnea (mean change, 15 points) and reductions in fatigue (mean change, 9 points) on the CRQ with high-dose therapy (theophylline level of 16.8 ± 4.2 mg/L). However, there were no differences in emotional and mastery scores compared with placebo therapy.

Mahon et al studied 68 patients with “irreversible” COPD who were able to tolerate theophylline and were uncertain as to whether previous use of theophylline was beneficial. One half of the patients received standard therapy (patients stopped taking theophylline but resumed it if their dyspnea worsened), while the other 34 patients received an “n of 1” trial (randomized, double-blind, multiple crossover comparisons of theophylline and placebo treatments in a single patient). Although there were no differences in the CRQ scores between groups over 1 year, the investigators reported that 21% of patients in the n of 1 trial showed improvement in dyspnea with theophylline.

**SUMMARY**

HRQOL has become an established outcome measure for evaluating the efficacy of therapeutic interventions, particularly bronchodilator medications, in patients with COPD. Both patients and physicians find the items of a disease-specific instrument more relevant to the individual’s medical problems. Also, these questionnaires are more responsive and therefore have greater potential to demonstrate a significant and meaningful change. With a generic instrument, previously unrecognized adverse effects may be detected and comparisons can be made across patient populations.

**REFERENCES**