Quality of life measurement for patients with diseases of the airways

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Treatment for diseases of the airways is largely palliative, being directed in the main towards the reduction of acute exacerbations and limitation of the impact of disease on daily life. For the purposes of measurement, the latter may be regarded as a series of different activities, some of which are listed in the right hand box of figure 1. Disturbance of these activities may result from a range of pathophysiological disorders, which mediate their effects through a limited number of symptoms. Despite the palliative nature of treatment for airways disease, relatively little regard has been paid to the activities listed in the right hand box of figure 1 as possible measures of therapeutic outcome. It is generally assumed that a measured improvement in the disease processes shown on the left of figure 1 will be accompanied by improved health and wellbeing. This assumption is based on the belief that the arrows in this figure imply a direction of causality that holds both during the development of a disease and with the response to treatment. In fact, there is surprisingly little scientific evidence that treatment improves the overall state of patients with a chronic disease. Before we consider treatment, the processes by which disease activity in the lungs leads to the disruption of daily living are worth examining. The disturbances in physiological function listed in the left hand box of figure 1 are well documented. There is also a growing body of literature describing measured disturbances of the activities listed in the right hand box. But how are these disturbances linked and what are the quantitative relationships between them?

To illustrate this problem, it is worth looking more closely at the effects of breathlessness. Figure 1 suggest a simple linear sequence, but the scheme in figure 2 is more realistic. This model is not complete, and I make no claim that it provides profound insights; but there is experimental evidence for most of the links between the boxes, and other links are reasonable hypotheses based on current knowledge. The pathway is not tidy; some arrows linking two boxes are bidirectional and some paths form loops. The loops are important because they allow positive feedback, which then enables the system to become autonomous. Even if the precipitating event were entirely corrected, the resulting disturbances would persist and only decay at a rate fixed by the time constants of the system’s individual components. An obvious example is the muscle wasting that results from reduced physical activity. In a study of 152 patients with airways obstruction who performed a 10 minute paced step test, 45 stopped because of breathlessness, whereas 73 stopped because of factors such as fatigue and weak legs (C M Baveystock, P W Jones, unpublished observations). Some pathways illustrated in figure 2 may even be irreversible—loss of employment, for example. The scheme in figure 2 is presented hierarchically. At each level additional factors are fed in and interact with signals coming up from below. These factors may be unrelated to the basic disease, yet may modulate the signal produced by the underlying pathological process quite profoundly. Without knowledge of the operating characteristics of the individual processes and information on the size of the outside influences, we could not predict the magnitude of the disturbances at the top of this system from a knowledge of a disturbance at the bottom, no matter how accurately it was measured.

Breathlessness: the link between lung disease and disability

Quality of life measurement is concerned with the events at the top of figure 2, but some intermediate steps must be considered. Breathlessness is the critical link between lung disease and ensuing disability, yet the factors that determine it are poorly understood. Studies during standardised ergometer exercise tests in normal subjects have shown wide variations between individuals in the intensity of perceived dyspnoea in relation to ventilation.¹ ³ The reasons for this diversity are still unknown. There is also evidence that the level of distress that normal subjects associate with their breathlessness during exercise is unrelated to their perception of its intensity.⁴ Comparable studies in patients have not been performed and we do not know which aspects of breathlessness limit daily activity. The generation of breathlessness is a critical process in the production of impaired exercise tolerance, but currently we can neither predict an individual patient’s level of breathlessness nor quantify the effect of changes in lung function on it.

Spirometry, exercise tolerance, and disability

In patients with obstructive airways disease the correlation between the results of spirometry and walking distance are poor.¹⁶ Even with
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Figure 1 List of disease processes, symptoms, and activities that may be disturbed by chronic diseases of the airways. Note that spiritual activity is bracketed, because unlike the other listed types of activity, it does not have reliable methods of measurement.

PATHOPHYSIOLOGY
- Mucus hypersecretion
- Airway obstruction
- Lung overinflation
- Compliance changes
- V/Q mismatch
- Pulmonary hypertension
- Right ventricular failure
- Polycythaemia

SYMPTOMS
- Cough
- Sputum
- Wheeze
- Breathlessness

ACTIVITIES
- Physical
- Social
- Emotional
- Intellectual
- Economic (Spiritual)

- External Environment
- Attitudes and expectations
- Disability
- Anxiety and depression
- Exercise limitation
- Breathlessness
- Disturbed lung physiology
- Damage and inflammation

General health questionnaires
Disturbance to health may be viewed as a series of impacts on daily life and wellbeing. Measurement of health related quality of life can therefore be defined as “quantification of the impact of disease on a patient’s life and perceived wellbeing in a formal and standardised manner” (the italics emphasise my own prejudice). The most comprehensive measurements of quality of life currently available are provided by general health questionnaires such as the Quality of Wellbeing Scale (QWBS) and the Sickness Impact Profile (SIP). Detailed reviews are available elsewhere. These questionnaires were developed to express, in numerical terms, disturbances to health as seen from the patient’s viewpoint. They were the result of painstaking research directed towards the development of methods by which a large proportion of the spectrum of human disease could be quantified in the most economical way (that is, by compressing the maximum amount of information into the smallest number of terms). There was, of course, no “gold standard” against which the questionnaires could be judged, so during their development extensive tests of validity were carried out. These concentrated on content, structure, internal reliability, and repeatability. The methods have been described in detail.
General health questionnaires in airways disease

The Quality of Wellbeing Scale and the Sickness Impact Profile have been used in patients with airways disease. Their scores have been shown to correlate with several relevant indices of disease activity, disability, and distress and their ability to distinguish between different levels of disease activity has been clearly shown. For example, in patients whose breathing never returned to normal between attacks of breathlessness and wheeze quality of life measured in terms of the Sickness Impact Profile score was considerably worse than in patients who had symptom free periods. Spirometric measures in general have been correlated relatively poorly with general health indices such as the Quality of Wellbeing Scale and the Sickness Impact Profile. In contrast, the minute walking distance has been shown to account for 40% of the variance in the Sickness Impact Profile score. This score has also been shown to correlate quite well with disability as assessed by the MRC dyspnoea scale and the oxygen cost diagram. Nevertheless, although these correlations were statistically significant, they were too low for general health to be accurately predicted from simple measurements of disability. This overall picture is rather similar to the pattern of correlations observed between spirometric measurements, walking distance, and disability.

The Sickness Impact Profile was designed for application to a very wide range of diseases, and inevitably its content provides restricted coverage of any particular clinical condition. This may limit its precision and result in low sensitivity. For example, in patients with chronic obstructive airways disease, Sickness Impact Profile scores did not differ in patients with the two mildest grades of disability on the MRC dyspnoea scale, but did show progressive differences between the three higher grades. There also appears to be a non-linear relation between disease severity, as measured by pre-bronchodilator FEV₁ and Sickness Impact Profile score (summarised in fig 3). In studies in which the mean FEV₁ was less than 50% predicted there was a progressive worsening in the score by comparison with studies in which the mean FEV₁ was above this level. This relative insensitivity for mild to moderate disease could mean that the questionnaire is more responsive to deterioration than to improvement. This may be critically important for attempts to measure the response to treatment.

Advantages of standardised health questionnaires

General health measures such as the Sickness Impact Profile and Quality of Wellbeing Scale are standardised. Each patient completes exactly the same questionnaire, which is always scored in the same way. Both of these questionnaires produce a single index or summary score, and with the Sickness Impact Profile a profile of category scores may also be calculated to provide a more detailed description of the disturbances of daily life. Such profiles for patients with different levels of airflow limitation have been published. The advantage of standardised health scores is that they allow comparisons not only between subjects within a given study but across study populations, as shown in figure 3. Furthermore, if a standardised questionnaire were sufficiently sensitive, its score would allow direct comparisons of efficacy between therapeutic trials. Some of the solutions to the problem of designing a sensitive questionnaire have overlooked this property. Examples include some otherwise good and successful measures. One of these is the Mahler transition score for breathlessness, which measures one symptom only, though an important and disabling one. Therapeutic benefit from theophylline and targeted muscle training has been demonstrated with this measure. As its name suggests, this measure grades changes in symptoms with respect to each patient's baseline state, so it allows only semiquantitative comparisons between patients from different departments or studies. The first quality of life measure developed specifically for chronic airflow limitation, the Chronic Respiratory Questionnaire, is also not completely standardised. It has the worthy property of allowing patients partially to tailor the questionnaire to suit their state, but unfortunately this "individualisation" does not allow a standardised score to be calculated. Use of this measure has shown quality of life benefits of bronchodilators, but direct comparisons of efficacy between this and other studies in which the same questionnaire may be used will not be possible. This problem has been exemplified recently in a study using the chronic respiratory questionnaire to compare patients with chronic obstructive airways disease and cystic fibrosis. In that study the authors had to adjust the scores from the patients with cystic fibrosis to allow comparisons with the patients with chronic obstructive airways disease because the former identified fewer areas of daily life causing dyspnoea.

Disease specific measures of quality of life

There is a need for a standardised and sensitive measure of the impact of chronic airways diseases on the daily life and perceived well-being of patients with these conditions. As discussed previously, comprehensive coverage of many different diseases may render the measure too insensitive for specific disease states. Sensitivity may be increased by limiting
the questionnaire’s content to items selected to reflect a broad range of effects of a specific disease or a limited group of related diseases. This restriction of the questionnaire’s content has occasionally led to the criticism that a disease specific measure is something less than a “true” quality of life measure as it addresses a limited area of disturbance to health. Such criticism may be based on a narrow understanding of the varied and complex nature of any single disease. General health measures are a best attempt to cover the whole spectrum of disease, but this inevitably reduces the number of items referable to a specific clinical condition. For example, the Sickness Impact Profile includes items concerned with intravenous feeding, but has a few items that are relevant to

patients with airways disease. In a study of 152 patients with moderately severe chronic obstructive airways disease 20% of the items in this questionnaire were left completely unanswered by every patient, and a quarter of the questionnaire items accounted for two thirds of the total number of positive responses (P W Jones, C M Baveystock, unpublished observations). The overall effect of this is to produce very low scores even in patients who have moderate levels of disability. A correctly designed and appropriately applied disease specific questionnaire might therefore provide a better and more precise measurement of quality of life than a general index.

The St George’s respiratory questionnaire
We have developed a measure of impaired health in patients with diseases causing airway obstruction, both asthma and chronic obstructive airways disease, known as the St George’s respiratory questionnaire. This questionnaire is divided into three components: symptoms, activity, and impacts. A total score is also calculated. The “impacts” section covers social and emotional disturbances due to the disease. Although some items in this section relate to the psychological impact of the disease, questions designed specifically to measure anxiety and depression were excluded as several suitable questionnaires are available for this purpose. Each item in the St George’s respiratory questionnaire is accorded a weight for the amount of distress associated with the symptom or state described. These weights were obtained during the questionnaire’s development from studies in 140 asthmatic patients in six countries. Factors such as age, sex, and the duration, severity, and variability of disease each contributed to less than 2% of the variance in weights between patients.35 There was no significant difference in the weights obtained in England, Finland, Italy, Thailand, or the United States; but the weights from the Netherlands were on average 19% higher than those obtained in the other countries. No obvious explanation was found for this exception. The weights in asthmatic patients were almost identical to weights collected in a group of older patients with chronic obstructive airways disease who had more severe disease.36 As a result of these studies, we have concluded that the weights are suitable for a wide range of patients with airways disease.

The final version of the questionnaire has good repeatability for this type of measure.37 To assess its reliability—that is, its ability to distinguish between different levels of health—the questionnaire was compared with other measures of disease severity, disability, and distress, including spirometric measurements, bronchodilator response, results of oximetry during exercise, six minute walking distance, the MRC respiratory questionnaire, the hospital anxiety and depression scale,38 and the Sickness Impact Profile, in a study on large numbers of patients with a wide spectrum of airflow obstruction.39 The component parts of
the questionnaire correlated with appropriate reference measures and the total score was shown to sum a range of different disturbances to health. The pattern of correlations between the St George’s respiratory questionnaire scores and the reference variables closely followed the pattern obtained with the Sickness Impact Profile, but the St George’s questionnaire was over twice as sensitive to differences in disease severity as the Sickness Impact Profile. 39

Measurements performed one year apart showed that changes in the St George’s respiratory questionnaire scores correlated with changes in the reference measures listed above and showed that the total score aggregated changes in several different areas of disease activity. 37

Quality of life questionnaires in clinical trials

“Quality of life” measures are now beginning to appear in clinical trials, but are they anything more than a marketing ploy? I believe that they are. Most people would agree, that with a lifelong disease, a major requirement of any therapy should be a clear demonstration of its beneficial effects on daily life and wellbeing. As discussed earlier, it is not possible to make reliable predictions of a patient’s disability or impaired wellbeing from measurements of airways function. There is as yet, limited data concerning the relationship between changes in spirometry following therapy and changes in health, but the available evidence suggests a generally poor correlation. In patients with asthma studied over an eighteen month interval, changes in FEV1 correlated with changes in quality of life measured with the quality of wellbeing scale (r² = 0.40). 41 In a study of patients with chronic obstructive airways disease there was a significant correlation (r² = 0.30) between FEV1 and quality of life as determined by the chronic respiratory questionnaire. 42 In both of these studies the correlations, though moderately good, were too low to allow accurate prediction of the quality of life score from the FEV1. In another study in patients with chronic obstructive airways disease over a one year interval changes in quality of life as assessed by the St George’s respiratory questionnaire score correlated poorly with change in FEV1, but rather better with the patient’s walking distance or the MRC dyspnoea score. 37 A study on the effect of salbutamol in chronic obstructive airways disease found a very low and non-significant correlation between changes in spirometric values and perceived breathlessness. 33 Finally, in a study using theophylline, breathlessness improved but with no significant change in spirometric results, arterial blood gas tensions, or walking distance. 30 Clearly we cannot assume that improvement in subjective health or disability will accompany a measured improvement in airways function.

Health questionnaires were developed as a scientific response to the problem of quantifying aspects of disease severity that could not be assessed by existing measures. Properly developed health related quality of life questionnaires are validated measures of the impact of a disease on the patient’s daily life and perceived wellbeing. In tests of drug efficacy it is clearly appropriate to measure the drug’s...
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