Quality-of-life in a long-term multicentre trial in chronic nonspecific lung disease: assessment at baseline


ABSTRACT: Quality-of-life (QOL) in patients with respiratory illness is a topic of increasing interest to clinicians and researchers. In a multicentre trial, which studies the long-term effects of three medication regimens (β-agonist plus either placebo, anticholinergic agent or corticosteroid, all by inhalation) in patients with chronic nonspecific lung disease (CNSLD: asthma and chronic obstructive pulmonary disease (COPD)), quality-of-life was included as an additional outcome measure. We wanted to provide a baseline assessment of quality-of-life in 274 adult patients with a mild to moderate degree of CNSLD.

Quality-of-life was measured using a set of six standardized tests: Anxiety, Depression and Sleep Disorders, Optimism and Stigma, and Activities of Daily Living were assessed via scales with adequate validity and reliability, as established in previous work in Dutch patients with CNSLD.

We found that quality-of-life was mildly impaired in these patients. Although differences with a reference group were present throughout, these were not significant, probably due to selection of relatively young, clinically stable, and highly motivated patients for our study. Quality-of-life scores showed higher correlation coefficients (0.20-3-0.38) to symptom scores than did results of pulmonary function tests (r=0.15).

In logistic regression models, absence from work and hospitalizations due to CNSLD were partly determined by quality-of-life scores.

These results are in line with other behavioural research in patients with CNSLD: the response of the patient to the illness, in combination with more objective characteristics of the illness, determines the impact of CNSLD on the quality-of-life of the patient. In the clinical management of and research on patients with CNSLD, quality-of-life should be taken into account. There is also a need for co-operation between behavioural and medical experts in the development of a disease-specific quality-of-life instrument for patients with CNSLD.

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Chronic nonspecific lung disease (CNSLD) encompasses both asthma and chronic obstructive pulmonary disease (COPD) [1, 2]. The prevalence of CNSLD in The Netherlands is considerable since some 10% of the Dutch population has corresponding symptoms [3, 4]. The sociomedical sequelae for the patient are substantial: absence from school and work, disruption of social activities, and psychological morbidity (e.g. anxiety, anger and social isolation) [5, 6]. The consequences of a disease for the individual's daily life have been conceptualized in the term "quality-of-life", which encompasses the physical, psychological and social functioning of a patient [7].

Quality-of-life in patients with respiratory illness has been studied rather sparsely in comparison with that of patients with, e.g. cardiovascular disease, cancer or diabetes. Recently, however, several workers have begun to explore the issue of quality-of-life in patients with CNSLD.

In North America, GUYATT and co-workers [8, 9] have developed instruments that delineate the consequences of asthma and COPD for the daily functioning of patients. In Europe, HYLAND et al. [10], JONES et al. [11], and KAPTEIN and co-workers [12-14] have applied to patients with CNSLD instruments, of which some originate from the psychology domain. Results of these studies suggest that quality-of-life is impaired in patients with CNSLD [15]. Moreover, pulmonary function is only weakly related to quality-of-life.

Behavioural scientists involved in respiratory illness have discarded psychosomatic theories as outdated [5]. Their main focus of interest, at present, concerns the reaction of a patient towards his illness (illness behaviour), and the way this illness behaviour influences medical outcome. Pulmonary physicians appear to recognize the relevance of these issues. In the design of a multicentre trial on long-term...
medical intervention in patients with CNSLD it was, therefore, decided to measure quality-of-life, in addition to generally assessed outcome variables in intervention studies, such as pulmonary function. In this paper, we will describe the methodology and the results of quality-of-life assessment, performed when the patients entered the trial, and the relationship of quality-of-life measurements to pulmonary symptoms and lung function measurements.

**Material and methods**

For this report, we used baseline data from a multicentre trial, sponsored by the Dutch government. The main goal of this trial is to compare the effect of three different treatment regimens (β-agonist plus either placebo, anticholinergic agent or corticosteroid, all by inhalation) on the long-term course and outcome of CNSLD. Details on methodology and baseline assessment have recently been published in the Journal [16].

At six university pulmonary out-patient clinics, adult (18-60 yrs) patients with CNSLD were selected, according to the following functional criteria: baseline forced expiratory volume in one second (FEV1), level ranging 4.5-1.64 standard deviations (so) below the predicted value, and larger than 1.2 L, or FEV1/inspiratory vital capacity ratio lower than 1.64 so below the predicted value, provided that total lung capacity was higher than 1.64 so below the predicted level [16]. Another selection criterion was hypersensitivity to inhaled histamine (provocative concentration producing a 20% fall in FEV1, PC20 <8 mg·ml⁻¹, see below).

Pregnant women, patients with a history of occupational asthma or concomitant serious diseases (e.g. tuberculosis, myocardial infarction or malignancies), patients who used oral corticosteroids, beta-blockers, nitrates, or anticoagulants, and patients who continuously used antibiotics were excluded. Atopy, smoking habits, and previous diagnosis of asthma or COPD were deliberately not used as selection criteria.

The study protocol was approved by the Medical Ethics Committees of all participating centres. All patients gave written informed consent.

**Baseline data**

Before entering the baseline period of the study, patients discontinued their usual maintenance treatment for at least 1 month (ketotifen, antihistamines), 2 weeks (inhaled corticosteroids, cromolyn sodium), and 2 days (theophyllines). All measurements were performed during clinically stable periods (i.e. not within 3 weeks of an exacerbation or discontinuation of an oral corticosteroid course).

Spirometry was performed using calibrated water-sealed spirometers, according to standardized guidelines [17]. FEV1 and inspiratory (slow) vital capacity (IVC) were measured until three reproducible (less than 5% difference) recordings were obtained. Highest values were used for analyses. Reference values are those of the European Community for Coal and Steel [17]. Details of the assessment in this study of reversibility of air flow obstruction, histamine provocation tests, and determination of PC20 have been reported previously [16].

**Quality-of-life questionnaire**

Quality-of-life measures should meet certain conditions [7]: they must be valid, reliable and sensitive to change. In addition, the measures must have been validated in other samples of patients with the illness under study. At the outset of this trial, no Dutch instrument was available which met these conditions. Therefore, it was decided to assess quality of life via an index which consisted of instruments that had been used before in samples of Dutch patients with CNSLD [12, 15, 18], and had been cross-validated with scales with known validity and reliability.

A set of six tests comprised the quality-of-life (QOL) questionnaire. Tests with established validity and reliability were used:

1. from the Symptom Check List, 90 items (SCL-90) [18, 19]: the subscales Anxiety, Depression and Sleep Disorders;
2. from the Respiratory Illness Opinion Survey (RIOS) [20, 21]: the subscales Optimism and Stigma;
3. from the Activities of Daily Living (ADL) [13, 22, 23]: the 11 items of this scale assess the degree to which patients are able to perform daily activities despite their illness.

Anxiety, Depression and Sleep Disorders were chosen because these three dimensions assess aspects of quality-of-life in patients with asthma and COPD which have been shown to be affected by the illness, [10, 12, 13]. Optimism and Stigma represent the perceived social consequences of respiratory illness [15, 20]; these two scales have also been extensively validated for Dutch patients [12, 14, 15]. The Activities of Daily Living scale was applied as an indicator of the degree to which the functional status of the patient is being affected by respiratory symptoms. The 11 items of this scale have been published recently [13].

The six tests tap the three aspects of quality-of-life (psychological, social, functional) which should be assessed according to the literature [7, 9] and have adequate psychometric qualities.

The QOL questionnaire was presented in a booklet to the patients by assistants who were specifically trained for this purpose (AAK and FWD). Patients filled out the questionnaires at the hospital, following assessment of the medical parameters.

The scores on the Anxiety, Depression, and Sleep Disorders subscales of the SCL-90 obtained in our study population were compared to those of a healthy reference population [19]. This reference group was composed of 907 persons who had co-operated in a study on "Environment and Perceived Health" and who were representative of the Dutch population regarding gender, age and marital status.

**Symptoms**

Respiratory symptoms were assessed with a standardized questionnaire, which was filled out by the patients...
Table 1. – Patient characteristics (n=274)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height cm</td>
<td>174 (10)</td>
<td>Age yrs 40 (18-60)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>2.33 (0.74)</td>
<td>Smoking pack yrs 4.5 (0-123)</td>
</tr>
<tr>
<td>% pred</td>
<td>64 (15)</td>
<td></td>
</tr>
<tr>
<td>FEV₁/VC %</td>
<td>55 (11)</td>
<td></td>
</tr>
<tr>
<td>% pred</td>
<td>68 (13)</td>
<td></td>
</tr>
<tr>
<td>Bronchodilator response</td>
<td></td>
<td>Current smoker 98 (36)</td>
</tr>
<tr>
<td>ΔFEV₁ % pred</td>
<td>11.9 (8.9)</td>
<td>Exsmoker 88 (32)</td>
</tr>
<tr>
<td>Δlog PC₉₀ mg/ml⁻¹</td>
<td>-1.95 (2.30)</td>
<td>Lifelong nonsmoker 88 (32)</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in one second; IVC: inspiratory vital capacity; ΔFEV₁, % pred: change in FEV₁ after bronchodilator expressed as a percentage of predicted FEV₁; Δlog PC₉₀ result of histamine provocation test (for details see [16]); PC₉₀: provocative concentration of histamine producing a 20% fall in FEV₁.

[16]. Among other symptoms, dyspnoea on exertion and chronic cough were graded as absent, mild, moderate, or severe. Absence from work during the past three months and hospitalization during the past three years due to CNSLD were also recorded.

Patients

Two hundred and seventy four patients completed the baseline period of the study and were randomized to blinded treatment [16]. Clinical characteristics of these patients are depicted in Table 1.

In general, patients with moderate to severe airways obstruction and rather severe airways hyperresponsiveness were included in the study.

Statistical analysis

Results of the QOL questionnaire were tested for internal consistency, using Cronbach’s α. QOL-scores obtained were compared to those of healthy individuals and of other patient populations using Student's t-tests. Spearman rank correlations were computed between QOL-scores, symptom scores, and lung function variables, controlling for age (partial correlation). To establish the influence of several physiological and psychological variables on pulmonary symptoms and complications, backward stepwise multiple logistic regression models were built [24]. For this purpose, symptom scores were dichotomised (no or mild symptoms=value 0; moderate to severe symptoms=value 1). Dependent variables for which models were built were: dyspnoea on exertion, daily cough, absence from work due to CNSLD during the past three months, and hospitalization due to CNSLD during the past 3 yrs. Independent variables were: age, sex, smoking status, FEV₁ % pred, FEV₁/VC % pred, Δlog PC₉₀, the change in FEV₁ after inhalation of a bronchodilator expressed as a percentage of the predicted FEV₁, and the scores on the psychological scales (Anxiety, Depression, Sleep Disorders, Optimism, and Stigma). Odds ratios and confidence intervals were calculated in order to express the relationships between independent and dependent variables. A similar model was built with the ADL score as dependent variable, using multiple linear regression analysis to allow for analysis of the full range of daily activity scores. All analyses were performed using the Statistical Package for the Social Sciences (SPSS).

Results

QOL scores

We found that the reliability of the QOL scales was good to very good (α=0.70, except for the Optimism scale (α=0.59)). Although all scores in the CNSLD patients in our study indicated more disturbances than those of a healthy reference population [19], none of these differences were statistically significant (all p values >0.1), except for Sleep Disorders in men (p=0.022): Anxiety (range 10-50; patients 14.6±5.4, norm 13.8±5.0), Depression (range 16-80; patients 21.9±7.3, norm 21.2±7.1), Sleep Disorders (range 3-15; patients 5.3±2.6, norm 4.9±1.1).

Correlations of QOL scores with symptom scores and lung function parameters

A Spearman rank correlation matrix was computed in order to study the relations between QOL scores, respiratory symptom scores and lung function parameters. Significant correlations were observed between age and all quality-of-life scores, with older patients scoring lower on Optimism (r=-0.22) and higher on the other five scales (r ranging from 0.08 to 0.19), indicating a poorer quality-of-life with older age. We therefore used partial correlation to control for age (table 2).

Absence from work was significantly related to all QOL scores, and dyspnoea to all scores but one. FEV₁ % pred was unrelated to QOL scores and FEV₁/VC % pred was associated to Anxiety and Sleep disorders scores.

Influence of physiological and QOL variables on respiratory symptoms, absence from work, and hospitalizations

Results of the logistic regression analyses on respiratory symptoms, absence from work, and hospitalizations due to CNSLD are presented in Table 3. Only those variables are presented which showed a significant (p<0.05), independent influence on the dependent variable under study. Table 3 presents the relative contribution of quality-of-life-measures to important medical outcome parameters. Variables from different domains have been included on purpose, in order to single out the independent contribution
Results are presented as adjusted Odds Ratios (OR), which may be interpreted as independent relative risks.[24]. For example, women have a 2.36 times higher chance than men of having dyspnoea on exertion, adjusted for the other QOL measures and physiological variables in the model. Similarly, an increase of the Stigma score of 1 point raises the risk of absence from work due to CNSLD by 10% (table 3).

Finally, a stepwise multiple regression analysis was performed with the ADL as the dependent variable and various psychological and physiological scores as independent variables. The ADL score was significantly related to the

of various aspects of quality-of-life to the variables under study.

Table 2. Partial correlation coefficients between QOL scores, symptom scores, lung function parameters and smoking, controlling for age (n=274)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Optimism</th>
<th>Stigma</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Sleep</th>
<th>ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>-0.057</td>
<td>0.125*</td>
<td>0.192**</td>
<td>0.186**</td>
<td>0.188**</td>
<td>0.383**</td>
</tr>
<tr>
<td>Cough</td>
<td>0.045</td>
<td>0.106*</td>
<td>0.045</td>
<td>0.032</td>
<td>0.081</td>
<td>0.012</td>
</tr>
<tr>
<td>Absence from work</td>
<td>-0.190**</td>
<td>0.237**</td>
<td>0.189**</td>
<td>0.214**</td>
<td>0.210**</td>
<td>0.290**</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.039</td>
<td>-0.009</td>
<td>0.083</td>
<td>0.077</td>
<td>0.082</td>
<td>-0.083</td>
</tr>
<tr>
<td>FEV, % pred</td>
<td>0.076</td>
<td>-0.006</td>
<td>0.035</td>
<td>-0.013</td>
<td>0.066</td>
<td>-0.083</td>
</tr>
<tr>
<td>FEV,FVC % pred</td>
<td>0.037</td>
<td>-0.020</td>
<td>0.013*</td>
<td>0.085</td>
<td>0.142*</td>
<td>0.040</td>
</tr>
<tr>
<td>FEV, pf % pred</td>
<td>0.126*</td>
<td>-0.012</td>
<td>0.037</td>
<td>-0.016</td>
<td>0.069</td>
<td>-0.086</td>
</tr>
<tr>
<td>Log PC_{20}</td>
<td>-0.035</td>
<td>0.033</td>
<td>-0.059</td>
<td>-0.012</td>
<td>-0.046</td>
<td>0.091</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.036</td>
<td>0.005</td>
<td>0.154**</td>
<td>0.140**</td>
<td>0.034</td>
<td>0.166**</td>
</tr>
</tbody>
</table>

Table 3. Adjusted odds ratio (OR) and 95% confidence intervals (CI) of the influence of different variables on respiratory symptoms, absence from work and hospitalisations due to CNSLD

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea on exertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female: male sex</td>
<td>2.36</td>
<td>1.31-4.25</td>
</tr>
<tr>
<td>Age (10 yrs)</td>
<td>1.58</td>
<td>1.18-2.00</td>
</tr>
<tr>
<td>FEV_{20} (1 doubling dose)</td>
<td>1.14</td>
<td>1.02-1.30</td>
</tr>
<tr>
<td>Sleep score (1 point)</td>
<td>1.13</td>
<td>1.01-1.25</td>
</tr>
<tr>
<td>Daily cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>3.06</td>
<td>1.77-5.31</td>
</tr>
<tr>
<td>FEV_{20} (1 doubling dose)</td>
<td>1.20</td>
<td>1.06-1.36</td>
</tr>
<tr>
<td>Sleep score (1 point)</td>
<td>1.14</td>
<td>1.03-1.26</td>
</tr>
<tr>
<td>Absence from work due to CNSLD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (10 yrs)</td>
<td>0.65</td>
<td>0.51-0.81</td>
</tr>
<tr>
<td>Stigma score (1 point)</td>
<td>1.10</td>
<td>1.05-1.16</td>
</tr>
<tr>
<td>Anxiety score (1 point)</td>
<td>1.09</td>
<td>1.03-1.15</td>
</tr>
<tr>
<td>Admission to hospital due to CNSLD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female: male sex</td>
<td>3.03</td>
<td>1.13-8.00</td>
</tr>
<tr>
<td>FEV_{20} (1 doubling dose)</td>
<td>1.19</td>
<td>1.00-1.44</td>
</tr>
<tr>
<td>Anxiety score (1 point)</td>
<td>1.05</td>
<td>1.00-1.13</td>
</tr>
</tbody>
</table>

Anxiety score (β=0.265, p<0.001), the Optimism score (β=0.270, p<0.001), and smoking (β=0.125, p=0.026). None of the lung function variables entered the model at a significant level (p<0.05).

Discussion

In this study, we found that the quality-of-life of the patients with CNSLD, studied in a multicentre trial, was mildly impaired. Quality-of-life was assessed via questionnaires with established validity and reliability, supporting the soundness of this finding. Our second finding pertains to the observed relationships between quality-of-life scores and respiratory symptoms on the one hand, and the lack of association between QOL scores and measures of pulmonary function on the other (table 2); this is in accordance with earlier studies[12,13,25]. A third finding concerns the results of the logistic regression models, which indicate that absence from work and hospitalisation due to CNSLD are partly determined by QOL scores (table 3).

The results of our study are in accordance with previous work on QOL in patients with asthma and chronic obstructive pulmonary disease[8,11,13], and with quality-of-life research as applied to other illnesses e.g. lung cancer[26]. The individual response of the patient to his or her illness and the medical treatment does have a bearing on the outcome of medical interventions.

Some limitations of our study should be mentioned. In contrast to some other studies on QOL in patients with CNSLD, QOL was only mildly impaired in our study population: although differences with a reference population were present they did not reach statistical significance. This may be due to selection of patients for three reasons. Firstly, the patients in our study had relatively mild and stable CNSLD. All of them completed the 4 week baseline period of our study with only bronchodilators as rescue therapy[16]. Secondly, these patients agreed to participate in a study with long-term (3 yrs) follow-up requiring intensive co-operation. Thus, as a group, the patients in our study were highly motivated. A recent review suggested that patients who volunteer to undergo various diagnostic and therapeutic procedures in medication trials have better...
coping skills and a higher psychological stability than patients who decline to participate [27]. This selection bias may be more pronounced in a long-term study, such as ours. Thirdly, the average age of patients in our study was considerably lower than that in other studies [12, 13, 28-30].

One of our original hypotheses was that QOL could be used as a measure of treatment effects in our long-term study. The small baseline impairment in QOL, however, makes it unlikely that significant treatment effects can be demonstrated after completion of follow-up. Although measures of QOL have been proven to be disease specific, valid and reliable [9, 10], and although the methods we used cover all areas that comprise useful assessment of QOL [7], this observation questions the usefulness of currently available QOL measures for studies of patients with CNSLD. New instruments, such as the Sickness Impact Profile [31], have recently been used in patients with CNSLD [13]. It appears, however, that more sensitive instruments, specifically designed for studies of patients with asthma and COPD, are needed. Increased co-operation of health psychologists and pulmonary physicians is required, to design and validate new instruments of measuring QOL in patients with CNSLD. These new instruments should be disease-specific, in order to be sensitive to change via medical treatment and should pay attention to the different consequences of asthma or COPD for the quality-of-life of these patients.

Two points should be taken into consideration as far as generalization of our results is concerned: 1) the patients in this study have been selected from university outpatient clinics; and 2) they have a relatively mild degree of CNSLD. In a previous study, we have emphasized differences between patients seen in an asthma centre [14], hospital setting [15], out-patient clinic [12], or general practice setting [13], regarding quality-of-life. Nevertheless, it appears justified to conclude that reporting of respiratory symptoms, absence from work and hospitalization in patients with CNSLD is a matter both of physiology and psychology. This implies that optimal treatment of patients with CNSLD should be aimed not only at improvement of lung function but also at improvement of illness behaviour. This latter goal may be achieved by education programmes addressing issues such as adequate use of medication, avoidance of stimuli that trigger exacerbations, and not being afraid and ashamed about the social consequences of the disease [32, 33]. The beneficial effects of such educational programmes have been demonstrated in children [34] and adults with asthma [35, 36], and in patients with chronic obstructive pulmonary disease [37].

Somewhat provocatively, we feel that the results of our study may be summarized in one sentence: quality-of-life in patients with CNSLD is a relevant and important concept, that should be taken into account when one wants to provide medical care of high quality.

In conclusion, this study indicates that respiratory symptoms, absence from work and hospitalization due to CNSLD are related to a combination of physiological and psychological factors. This implies that both these areas are important in the clinical management and in studies of patients with CNSLD.

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