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Two-Year Bronchodilator Treatment in Patients with Mild Airflow Obstruction*

Contradictory Effects on Lung Function and Quality of Life

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In a two-year randomized controlled study, we studied the effects of bronchodilator treatment on the lung function and the quality of life in patients with mild airflow obstruction. The patients were randomly divided to receive either continuous or symptomatic bronchodilator treatment. Within these treatment groups, they received salbutamol in the first year and ipratropium bromide in the second or vice versa. In addition, the quality of life of the patients was compared to that of the general population. One hundred and forty-four patients completed the study. When compared to the general population, these patients showed a serious impairment in quality of life. No differences between the two drugs were found, but the results indicated that FEV_1 decline in the continuously treated group was significantly larger than in the symptomatically treated group. However, this was not reflected in a significant deterioration of the quality of life in the continuous group as measured by means of the Nottingham Health Profile and the Inventory of Subjective Health. Decline in FEV_1 showed no correlation with changes in quality of life scores. This may be due to a relatively rapid adjustment of the patients to a decline in FEV_1, as a result of which it has no direct effect on the *experienced* quality of life. Another reason may be that continuous bronchodilation masks the worsening of the disease. This lack of awareness might in turn be caused by the continuous symptom relief of bronchodilators. ***(Chest 1992; 102:1384-91)***

ANCOVA = analysis of covariance; ISH = inventory of subjective health; KR-20 = Kruder-Richardson formula 20; NHP = Nottingham health profile; PC20 = provocative concentration of histamine producing a 20% fall in FEV_1; RAST = radioallergosorbent test.

The progressive nature of asthma and COPD indicates the relevance of studying the effects of drug therapy in an early stage, that is in patients with mild to moderate airflow obstruction. These patients are commonly treated with inhaled bronchodilator drugs. However, controlled studies of the long-term effects of these drugs in patients with a mild to moderate degree of airflow obstruction are scarce.[1-3] There are some retrospective or uncontrolled studies indicating that the continuous use of β_2-adrenergic drugs may have adverse effects.[4,5] The aim of this study was to address the long-term effects of continuous vs symptomatic bronchodilator treatment, as well as the long-term effects of the β_2-adrenergic drug, salbutamol, vs the anticholinergic drug, ipratropium bromide, in patients suffering from mild asthma or mild COPD. Lung function decline (FEV_1) and quality of life, as well as the relationship between these two outcome measures are reported. A detailed description of lung function in relation to other clinical and physiologic outcome parameters is provided elsewhere.[1]

Lung function parameters are essential for monitoring the course of asthma and COPD, because of their known relationship to disease prognosis.[6] However, the subjectively experienced quality of life may be equally important to the patients in defining treatment benefit. Since only a low correlation between quality of life and lung function parameters was found in previous studies,[7-12] one cannot rely on the severity of airflow limitation as an indicator of the impact of chronic airflow limitation on patients' quality of life.[13] The measurements of the quality of life and of lung function may address different treatment aspects. So far, few data on the quality of life of patients suffering from a mild form of airflow limitation are available.[12] Therefore, an additional objective of this paper is to compare the quality of life of patients with that of the general population, in order to determine the extent to which quality of life is affected by a mild degree of airflow obstruction.

Patients and Methods

Patients

This study included both asthma and COPD patients aged 30 and over with a mild to moderate airflow obstruction ($FEV_1 \leq$ predicted value − 2 SD, but $FEV_1 \geq 50$ percent predicted value) and/or established bronchial hyperresponsiveness (PC20≤8 mg/ml

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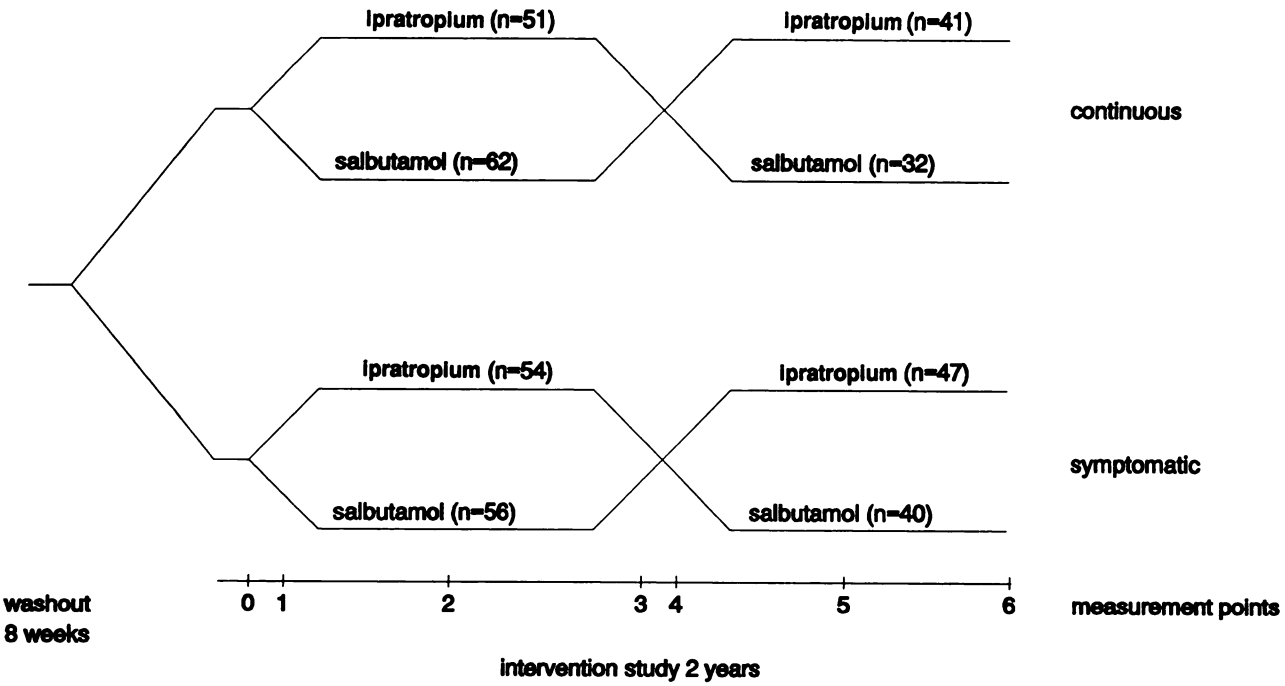

FIGURE 1. Study design. n = number of patients at the start and end of the study.

histamine). Patients were recruited from 29 family practices.[14] Those who were corticosteroid-dependent or suffering from other pulmonary or life-threatening diseases were excluded. After giving informed consent and proving their capability of recording symptoms and peak flows, 223 patients entered the study. There was no selection bias.[14] The study was approved by the Nijmegen University Medical Ethics Committee.

The criteria for the diagnosis of asthma and COPD were based on the standards for diagnosis of the American Thoracic Society.[15] Chronic obstructive pulmonary disease was defined as a continuous airflow obstruction (FEV_1<85 percent of the predicted value for three measurements in one year) combined with chronic cough or chronic sputum production for at least three months a year, and in at least two successive years. Asthma was defined as a reversible obstruction (increase in $FEV_1 \geq 15$ percent of the initial value, 60 min after the inhalation of both 400 μg salbutamol and 80 μg ipratropium, for three measurements in one year) in combination with bronchial hyperresponsiveness (PC20<8 mg/ml for three measurements in one year) and dyspnea, wheezing and/or allergy. The combination of these features was mutually exclusive in the study population.[1]

Study Design

After a wash-out period of eight weeks, patients were randomly chosen to receive either continuous or symptomatic bronchodilator treatment. Within each of these parallel groups we randomly selected one half the patients to receive salbutamol for one year followed by ipratropium for the second year. The other one half received the drugs in reverse order (Fig 1). This was a single blind study, with a blind observer.

In the continuously treated group, patients inhaled four dry powder inhalations of 400 μg salbutamol or four dry powder inhalations of 40 μg ipratropium bromide daily. Symptomatically treated patients only used medication during exacerbations or periods of dyspnea, with a maximum of four dry powder inhalations per day. Exacerbations were defined according to Boman et al[16] and were treated in a standard way by the general practitioner with an antibiotic (broad spectrum) and a ten-day course of orally administered prednisone. Otherwise, no corticosteroids or bronchodilators other than the research medication were permitted. Patient compliance was maintained by regular telephone contact and home visits and checked by counting the unused medication every three months.

Outcome Measures

At baseline, lung function (FEV_1, FEV_1/EVC), reversibility of airflow obstruction, bronchial hyperresponsiveness, allergy, and quality of life were measured. Reversibility was measured 60 min after inhalation of 400 μg salbutamol followed by 80 μg ipratropium. Bronchial hyperresponsiveness was defined according to Cockcroft et al.[17] Allergy was tested by means of seven RAST tests for common allergens. Patients were considered allergic if there was at least one positive RAST test result. Outcomes were assessed in terms of annual decline in FEV_1 and quality of life.

The FEV_1 was measured at each visit (measurements 0 to 6 in Fig 1), according to a standard procedure, using the integrating flowmeter (Microspiro HI-298).[18] Data were derived from the curve with the largest sum of FVC and FEV_1 out of three satisfactory measurements. Medication was discontinued for at least 8 h before the start of the FEV_1 measurement. The measurement was only performed when patients were exacerbation-free.

Quality of life was measured at baseline and after the first and second year of treatment (measurements 1, 3, and 6 in Fig 1) using a Dutch version of the Nottingham Health Profile (NHP) and the Inventory of Subjective Health (ISH).

The NHP is a generic, self-administered questionnaire designed to measure perceived physical, emotional, and social health problems.[19,20] The emphasis is on the respondent's subjective perception of his or her health status. The NHP asks directly about feelings and emotions, not about changes in behavior. It consists of two parts, only the first being used here. This contains 38 items relating to six dimensions as follow: physical mobility (eight items), pain (eight items), social isolation (five items), emotional reactions (nine items), energy (three items), and sleep (five items). The items were drawn from interviews with patients suffering from various acute or chronic diseases, and from other health questionnaires such as the Sickness Impact Profile. All items have a yes/no answer format. Their weights were derived by McKenna from a sample of both

patients and nonpatients using Thurstone's method of paired comparisons.[21] Dimension scores range from 0 to 100: the higher the score, the greater the perceived health problems. Separate NHP dimension scores are presented as a profile, not integrated into an overall score.

While the NHP was originally developed as a survey instrument to measure perceived health status in a population, it has been used extensively in evaluation studies and is claimed to be sensitive to change in disease severity.[22-24] The NHP has proved to be reliable (four weeks test-retest ranges from 0.77 to 0.88) and can easily be administered, with small demands on patient time and effort.[19]

The Inventory of Subjective Health, developed by Dirken,[25] is a generic, commonly used Dutch scale which contains 21 questions related to subjective physical complaints such as tiredness, chest and heart problems, gastric problems, indigestion, headache, etc. Most complaints can be grouped according to the organ system they refer to.[26] The remainder relate to overall physical condition. The ISH items were partly drawn from the Cornell Medical Index, complemented by items drawn from expert interviews about the influence of physical stress on health. Its internal consistency and reliability are good (KR-20 ranges from 0.84 to 0.91, and three to six months test-retest = 0.67), and answers to the ISH do not appear to be influenced by social desirability.[26,27] The overall ISH score is made up of the number of affirmative answers. The more physical complaints reported, the higher the score.

Statistical Analysis

A within-patient analysis comparing the two drugs could only be performed if it could be shown that there was no period effect or carry-over effect.[28] A period effect would occur if patients, on average, improve or deteriorate during the second year regardless of the drug used. A carry-over effect refers to the influence of the drug used in year 1 on the effect of the drug used in year 2. The continuously treated and symptomatically treated groups could only be compared, as groups, if no significant difference was found between salbutamol and ipratropium.

The FEV_1 slopes were all calculated by averaging individual slopes. The individual slopes were calculated with a regression analysis of the seven assessments of FEV_1. A number of covariables, such as the number of pack-years before the study, number of cigarettes smoked during the study, sex, age, height, allergy, initial FEV_1 (as a percentage of the predicted value), initial PC20, and drug use prior to the study were controlled for. Differences in slopes were tested by means of ANCOVA (analysis of covariance).

Spearman coefficients were calculated for the correlations between the FEV_1 and the quality of life at the start of the study and between the change in quality of life and the change in lung function (FEV_1 slope).

Since the quality of life data do not appear to be normally distributed, they were analyzed using nonparametric tests such as the Mann-Whitney U-test for the comparison of two independent groups (asthma vs bronchitis, continuous vs symptomatic treatment) and the Wilcoxon matched pairs signed rank test for within-patient comparisons of salbutamol vs ipratropium.

Results

Baseline Patient Characteristics

Of the 223 patients who started the study, 144 patients completed the two-year period with cross-over medication. Seventy-nine patients dropped out, 56 because of pulmonary problems and 23 for reasons unrelated to lung disease or the medication being studied, such as lack of motivation (17), emigration (1), death (2), and the presence of malignant disorders (3). Those who dropped out for these other reasons did not significantly differ from those who completed the study. The 56 patients who dropped out because of pulmonary problems had greater airflow obstruction, greater bronchial hyperresponsiveness, and were more likely to be asthmatic patients. Because of their pulmonary problems, these 56 patients were given additional medication (*eg*, inhaled corticosteroids).

As for the characteristics of the 144 patients (Table 1) who completed the study with cross-over medication, there were no significant differences between the four treatment groups, except for smoking history. Continuously treated patients receiving salbutamol followed by ipratropium had a significantly higher number of pack years than symptomatically treated patients receiving salbutamol followed by ipratropium (t value -2.113, $p=0.038$). This difference was not caused by selective drop out.

With respect to age, sex, FEV_1, and ISH score, asthma patients did not differ significantly from COPD patients. Of the 93 COPD patients, 87 percent were smokers or exsmokers, compared to 71 percent of the 51 asthmatic patients (χ^2 5.892, $p=0.015$). The COPD patients experienced more health problems with respect to the NHP dimensions of sleep (z value

Table 1—*Patient Characteristics at Baseline

Characteristic	Completed the Study	Dropped Out: Pulmonary Problems	Dropped Out: Other Reasons
Number	144	56	23
Sex, % male	56	50	74
Asthmatic patients, %	35	52†	43
Age, yr	52 (12)	54 (13)	55 (12)
Exsmokers, %	81	80	87
Allergic, %	24	37	26
FEV_1, L	2.41 (0.79)	2.12 (0.64)†	2.34 (0.59)
Reversibility obstruction, %	16 (18)	21 (20)	14 (10)
Geometric PC20, mg hist/ml	8	6†	8
NHP score energy	23.6 (31.3)	24.6 (33.1)	32.1 (33.5)
NHP score pain	11.3 (22.1)	12.8 (22.3)	23.9 (31.4)
NHP score sleep	21.0 (28.1)	19.2 (25.0)	26.7 (29.6)
NHP score emotional reaction	12.7 (19.4)	12.7 (17.8)	14.8 (17.0)
NHP score social isolation	8.1 (19.7)	6.3 (12.9)	12.0 (22.0)
NHP score physical mobility	9.2 (14.5)	9.0 (13.8)	13.5 (15.8)
ISH score	7.0 (4.5)	7.1 (4.8)	9.0 (5.7)

*Averages and standard deviations (in parentheses). Differences between the group that completed the study and the two groups of drop-outs were tested. The ISH and NHP scores for those who dropped out for other reasons seem to be somewhat higher, although not significantly so. When the 3 patients with malignant disorders and the 2 patients who died are excluded, the mean ISH and NHP scores in this group decrease, although their scores still remain somewhat higher.

†$p<0.05$.

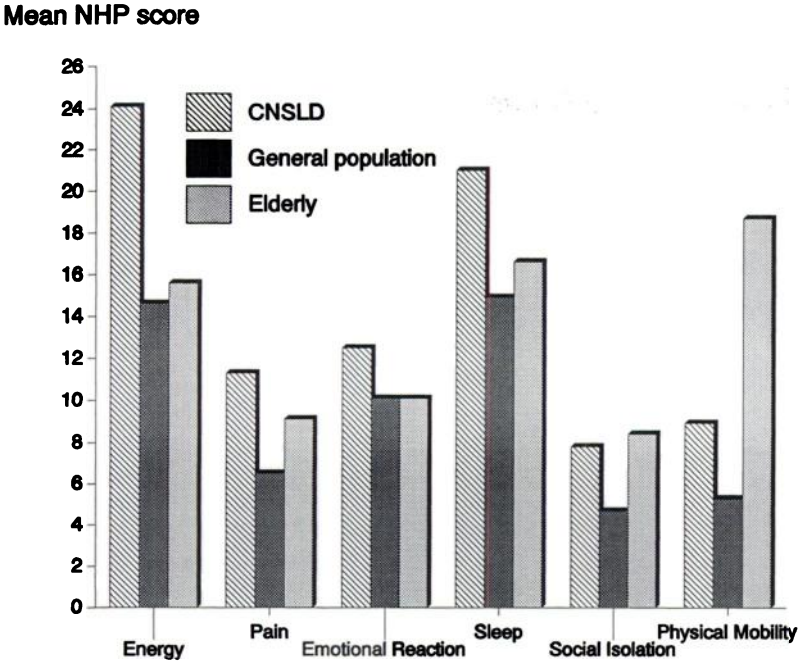

FIGURE 2. Mean scores on the dimensions of the Nottingham health profile for the study population (n = 144), the general population (n = 1,297) and the elderly (n = 1,366).

−2.3632, p = 0.0181) and pain (*z* value −2.0191, p = 0.0435) than patients with asthma. No significant differences between asthma and COPD patients were found for the remaining NHP dimensions.

Baseline Quality of Life Impairment Compared to the General Population

Baseline scores in the six NHP dimensions are summarized in Figure 2. No data on quality of life impairments in asthma and COPD measured by means of this instrument have been published before. Therefore, we present mean NHP dimension scores for patients alongside general population means, although formal statistical comparisons could not be made. With due reserve, we used NHP reference data from a random sample of 1,297 people from the Nottingham area,[19] since for the Netherlands, no general population NHP scores were available. As reference material, we also present NHP scores of 1,366 elderly persons (mean age 74; SD 7.8; 55 percent women) randomly selected from the registers of family physicians in a Dutch province.[20]

When compared to a general population, there is an obviously impaired quality of life in the study population. Energy and sleep scores in particular were worse (Fig 2). Patients with mild chronic airflow limitation also experience more health problems on all NHP dimensions than do elderly persons, except for the aspects of social isolation and physical mobility. Eighty percent of the study population reported one or more problems on the NHP, while in the general population, only 46 percent did so.[29] The NHP item most frequently affirmed is, "I soon run out of energy." It was affirmed by nearly 60 percent of our respondents reporting at least one problem, compared to 25 percent of the general population respondents reporting at least one problem. The next most frequently reported problems were as follow: "I'm waking up in the early hours of the morning" (51 vs 59 percent); "I'm feeling on edge" (40 vs 17 percent); "I find it hard to stand for long" (39 vs 17 percent); "It takes me a long time to get to sleep" (33 vs 27 percent); "I sleep badly at night" (31 vs 22 percent); "I lose my temper easily these days" (30 vs 28 percent); and "I'm tired all the time" (26 vs 16 percent). The general population reference percentages were obtained by Kind and Carr-Hill[29] from a sample of 1,598 residents (49 percent men) of York and Yorkshire, a sample which, like our study population, was weighted toward middle and old age. The least impairment was reported with regard to physical mobility, a finding which was undoubtedly related to the severity of the items in this dimension.

Much the same picture can be drawn from the ISH score. The mean ISH score of 7.6 (SD of 4.3) for the study population was almost twice the general population mean of 3.3.[30] Patients' baseline responses to the eight most frequently affirmed questions of the ISH are presented in Table 2. The questions most frequently affirmed relate to problems of the chest and tiredness. For all items, a higher score was obtained in our study population than in a random sample of 22,000 people in the noninstitutionalized general population over 16 years of age.[26]

Effect of Treatment on Lung Function and Quality of Life: Salbutamol vs Ipratropium

Salbutamol and ipratropium had a similar effect on

Table 2—*Inventory of Subjective Health: Percentage of Affirmative Responses to the Eight Most Frequently Affirmed Items*

Items	Study Population % Positive Responses	Rank	General Population % Positive Responses	Rank
Do you often feel tired?	63.2	1	25.6	2
Do you get short of breath easily?	55.9	2	17.2	6
Do your bones or muscles ever ache?	52.8	3	22.8	4
Do you get tired sooner than you would consider normal?	50.0	4	17.0	8
Are you often troubled by backache?	44.8	5	29.0	1
Do you often feel sleepy or sluggish?	43.7	6	18.3	5
Do you often feel tight in the chest?	43.1	7	9.4	17
Do you generally get up feeling tired and unrested in the morning?	38.9	8	17.2	6

the decline in FEV_1, both in asthma and COPD patients. No period or carry-over effect on the FEV_1 was found. The NHP dimension scores and the ISH score were not significantly influenced by a period effect either, except for scores for social isolation. As for social isolation, patients in the continuously treated group, on average, deteriorated during the second year, irrespective of the drug used ($z = -2.068$, $p = 0.0386$). Since a period effect only occurred in one NHP dimension and no carry-over effect was found, it was considered legitimate to compare salbutamol and ipratropium with regard to the NHP and the ISH. In both the continuous and the symptomatic treatment groups, no significant differences in quality of life were found between salbutamol and ipratropium. This finding holds for both asthma and COPD patients.

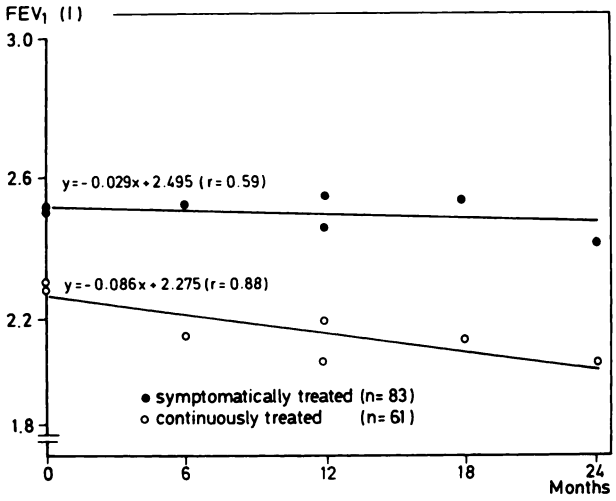

FIGURE 3. Decline of FEV_1: comparison between the symptomatic (n=83) and continuous treatment group (n=61); y=FEV_1; x=number of months.

Table 3—*Mean Change in NHP and ISH Scores: Comparison Between Continuous and Symptomatic Treatment Groups**

	Mean Change in NHP and ISH Scores (2-Year Follow-up Minus Baseline) Symptomatic	Continuous	p-Value
NHP: Energy	−0.8 (23.5-24.3)	1.7 (23.6-21.9)	0.5214
Pain	−2.1 (11.9-14.0)	5.9 (13.5-7.7)	0.0267
Emotional reaction	−1.1 (11.8-13.0)	−0.1 (12.1-12.3)	0.1582
Sleep	−2.1 (19.5-21.6)	2.0 (22.4-20.3)	0.3806
Social isolation	−0.2 (8.1-8.3)	0.0 (7.8-7.8)	0.6477
Physical mobility	−0.3 (6.9-6.4)	0.9 (10.5-9.6)	0.6132
ISH	−0.5 (6.4-6.9)	0.3 (7.4-7.1)	0.1949

*Differences between the change in the symptomatic group and the change in the continuous group were tested.

Effect of Treatment on Lung Function and Quality of Life: Continuous vs Symptomatic

Figure 3 shows that the decline in FEV_1 in continuously treated patients was 86.10^{-3} L/yr compared to 29.10^{-3} L/yr in symptomatically treated patients. After correction for confounding factors, the FEV_1 declined 72.10^{-3} L/yr in the continuous group compared to 20.10^{-3} in the symptomatic group ($p<0.05$), irrespective of the drug used. The difference in decline between continuously and symptomatically treated patients is comparable for asthma (92.10^{-3} vs 25.10^{-3} L/yr) and COPD (82.10^{-3} vs 31.10^{-3} L/yr).

In contrast to the observed difference in decline in lung function, there was no significant difference between the continuous and symptomatic treatment groups with respect to the changes in NHP dimension scores and the ISH score after one and two years of treatment (Table 3), for either asthma or COPD. Although there seems to be a tendency toward improved quality of life in the symptomatic treatment group (a negative change indicates improvement), and a tendency toward deteriorating quality of life in the continuous treatment group, this difference was not significant. Apparently, the clinically significant difference in lung function decline was not reflected in a detectable difference in quality of life impairment. There is one exception: for the change in NHP pain score between baseline and the two-year follow-up period, there is a significant difference between the continuous and the symptomatic treatment group ($z = -2.2162$, $p = 0.0267$). In the continuous treatment group, the patients deteriorated significantly on the pain dimension ($z = -2.9431$, $p = 0.0032$), while in the symptomatic treatment group, patients remained unchanged on the pain dimension ($z = -0.8548$,

Table 4—*Correlations Between (Change in) FEV_1 and (Change in) Quality of Life*

FEV_1 with	Correlation Between Baseline Values r	p	Correlation Between Two-Year Change Values r	p
Symptomatic treatment (n = 83)				
NHP: Energy	−0.09	0.44	0.01	0.95
Pain	−0.28	0.01	0.10	0.35
Emotional reaction	−0.27	0.02	0.03	0.78
Sleep	−0.10	0.37	0.05	0.66
Social isolation	−0.16	0.15	−0.12	0.27
Physical mobility	−0.12	0.28	0.01	0.94
ISH	−0.11	0.32	−0.09	0.43
Continuous treatment (n = 61)				
NHP: Energy	−0.10	0.45	0.09	0.51
Pain	−0.03	0.82	0.12	0.37
Emotional reaction	0.11	0.41	0.32	0.02
Sleep	−0.08	0.55	−0.16	0.24
Social isolation	−0.04	0.77	0.10	0.47
Physical mobility	−0.18	0.16	0.04	0.76
ISH	0.01	0.99	0.03	0.79

$p = 0.3926$). The same tendency was also found after one year, but it was not significant. The difference between the continuous and symptomatic treatment group on the pain dimension is comparable for asthma and COPD. Although all analyses were made using nonparametric statistics, Table 3 gives mean NHP scores to ease the interpretation.

Within-Patient Comparison of Lung Function and Quality of Life

Table 4 shows that the correlations between the FEV_1 and the quality of life at the start of the study were very low ($|r| \leq 0.28$). In the symptomatic treatment group, pain and emotional reaction were significantly correlated with lung function. In continuously treated patients, none of the items was correlated with lung function.

When the change in quality in quality of life was related to the lung function decline (FEV_1 slope), the correlation was again low ($|r| \leq 0.32$). Neither the change in the ISH score nor the changes in NHP dimension scores correlated significantly with the lung function decline, except for emotional reaction in the continuous treatment group (Table 4). There was no difference between asthma and COPD in this respect.

Discussion

When compared to general population reference groups, the NHP and ISH results show that patients suffering from light to moderate airflow obstruction experience substantially more health problems. Patients with this degree of disease severity are commonly treated with an inhaled bronchodilator drug, either symptomatically or continuously. The results of this study show that continuous bronchodilator treatment does not appear to protect against decline in lung function as has been suggested.[31,32] On the contrary, the annual decline in FEV_1 for continuously treated patients was found to be significantly higher than for those treated symptomatically, even after correction for confounding variables. The difference in the rate of decline was not caused by any difference in the characteristics of the treatment groups at the start of the study.[1] Increased decline during continuous treatment might be explained by bronchodilators failing to influence the inflammatory processes underlying the disease. A long-term continuous bronchodilator treatment without antiinflammatory treatment may thus lead to adverse effects.[2,3]

However, the decline in lung function is not reflected in perceived quality of life as it was measured in our study, except for the pain dimension of the NHP. On eight of the nine items which make up the pain dimension, the number of affirmative responses in the continuous group increased during the trial. The highest and only significant increase of 13.1 percent was found for "I have pain at night" ($p = 0.021$). We checked whether this increase (which was similar for asthma and COPD) was related to an increase in coughing, which in turn might have caused an increase of chest-related pain at night. However, no such increase in coughing was reported on the MRC-questionnaire. Thus, the increase in pain-related complaints in the continuous group may be due to chance, as a result of multiple testing. This is confirmed by the fact that the change in the NHP pain dimension is not related to the change in lung function in either continuously or symptomatically treated patients ($r = 0.03$ and 0.15, respectively).

If a decline in lung function leads directly to a lower quality of life, then the deterioration should also have been found for dimensions other than pain, because at baseline, about 24.5 percent of the patients in the continuous group reported no health problem on the NHP at all and only 14.5 percent affirmed 11 or more items. This indicates that a deterioration, if there was any, would have been easy to measure.

The decision to use generic outcome measures such as the NHP and the ISH may be responsible for our not measuring a deterioration in the quality of life. Williams[33] argues that generic instruments such as the NHP may be too much oriented toward musculoskeletal problems and disabilities which are often more extreme in nature. Disease-specific quality of life scales, which are often more sensitive to change, might have reflected the decline in lung function in this study. But, although important for measuring quality of life impairment directly related to the disease, their focus may be too narrow to capture

other, more general aspects of the overall health status. As a result, they do not allow comparisons between various health care interventions, which are possible using generic instruments. There is, as a consequence, a growing consensus in family medicine to use standardized generic quality of life measures.[34] The inclusion of severe problems in a generic quality of life instrument, however, may be necessary in order to avoid the detection of large numbers of false positives.[23] This does not imply that the more subtle impairments and disabilities from which asthma and COPD patients suffer cannot show up on the profile, for the NHP was also successful in drawing a profile of migraine sufferers, which gives an indication of its ability to detect impairment, even if motion and mobility are not affected.[24] Sensitivity to change was also found to be a concomitant of, for example, the recovery from fractures,[35] the physical and emotional changes throughout pregnancy,[19] and the effects of minor surgery.[36]

The ISH is particularly directed at long-term physical problems, since it contains few items related to temporary complaints. A strong relationship between the ISH score and the presence, number, and nature of chronic diseases has been found earlier.[26] Frequently affirmed questions relate to fatigue, reduced energy, reduced vitality, dyspnea, and other chest problems. These complaints are generally considered to be related to asthma and COPD. Affirmative answers are also frequently given to the pain-related questions of the ISH (Table 2). This may be explained by the less severe nature of the pain questions rather than by an inclination to complain. Reduced physical activity and vitality caused by fatigue and dyspnea itself, or by the ever-present fear of dyspnea, lead to poor physical condition which in turn causes minor pains and discomfort. Therefore, it seems likely that the ISH measures physical, mostly organ-specific problems directly or indirectly related to having a particular disease. But why then do we not find a significant decline in the quality of life?

It may be that because of the rapid bronchodilating response in the day-by-day control of symptoms, continuous bronchodilation masks the ongoing decline in lung function and the deterioration of the disease. Patients with continuous bronchodilator therapy may tolerate precipitating situations better, and may as a result become more exposed to sensitizing agents.[1,2,37] Continuous bronchodilation without antiinflammatory treatment may therefore mask the worsening of the disease so that patients are not aware of it. This was confirmed by the finding that, as compared to symptomatic treatment, we could not detect any increase in asthma and COPD-related symptoms as measured by means of the MRC-questionnaire.[1] A time lag between lung function decline and deterioration in the quality of life may cause a decline in lung function only experienced by the patients in the long run. Such an explanation is consistent with the study by McSweeny and Labuhn,[38] that indicates that physiologic factors are more predictive of quality of life for patients with advanced COPD than for patients with mild to moderate COPD.[38]

In addition, patients may learn to live with their disease, particularly those suffering from chronic diseases such as asthma and COPD. After an adjustment period, their limitations seem normal. In that case, a significant decline in lung function may have no direct effect on *experienced* quality of life. As we, and many authors before us have found, the correlation between various measures of pulmonary function and quality of life appears to be relatively weak.[7-12] Other factors such as psychological and sociological aspects may serve as intervening factors between lung function and quality of life. The patient's attitude, expectations, emotions, and other factors may not allow declining lung function to be fully expressed in terms of a reduced quality of life.

The effects of continuous vs symptomatic bronchodilator treatment in terms of FEV_1 and quality of life do not point in the same direction. Lung function and overall quality of life seem to be two different and weakly related expressions of asthma and COPD. Therefore, we feel that meaningful outcome assessments should include both lung function measures and various disease-specific quality of life questionnaire, as well as the overall evaluation of quality of life, for improvement in the latter is one of the important goals of health care. The rationale for disease-specific instruments, each covering one or more aspects of quality of life directly related to having a particular disease, lies in their potential for increased responsiveness. But particularly when the results of these measures do not point in the same direction, an overall evaluation by means of generic quality of life instruments is desirable. To increase confidence in the use of generic quality of life measures in therapeutic studies, their relationship with lung function and the prognosis of the disease in the long run, and their relationship with disease-specific quality of life measures will have to be further explored. It seems warranted, therefore, to apply both generic and disease-specific quality of life measures alongside physiologic measures in future studies.

Since an accelerated decline in lung function is known to be an objective physiologic measure of progression of the disease, the main conclusion of this study is that continuous bronchodilator treatment is not as beneficial as is often assumed. Overall quality of life measurements suggest that continuous treatment leads to a lack of awareness of a declining lung function. This may be misleading to both patients and

physicians and may have negative effects on future compliance with medication.

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