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An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD)

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An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). G. Boyd, A.H. Morice, J.C. Pounsford, M. Siebert, N. Peslis, C. Crawford, on behalf of an international study group. ©ERS Journals Ltd 1997.

ABSTRACT: The objectives of this study were to compare the efficacy and safety of salmeterol xinafoate (50 and 100 µg *b.i.d.*) with that of placebo, when added to existing therapy, in the treatment of patients with chronic obstructive pulmonary disease (COPD).

Six hundred and seventy four patients were randomized to receive either salmeterol 50 µg *b.i.d.*, salmeterol 100 µg *b.i.d.*, or placebo treatment for a period of 16 weeks.

The results showed a significant improvement in daily symptom scores noted for patients taking either 50 µg (p=0.043) or 100 µg *b.i.d.* salmeterol (p=0.01) compared with placebo, with a corresponding decrease in additional daytime salbutamol requirements for both salmeterol groups. The same pattern was reflected for night-time symptoms and additional salbutamol use. During treatment, forced expiratory volume in one second (FEV_1) measurements improved significantly in each salmeterol group, with up to a 7% improvement observed at the end of the study. Although no difference was observed between treatment groups for the distance walked in 6 min, patients treated with salmeterol 50 µg *b.i.d.* were significantly less breathless than those treated with placebo after their 6 min walk, after 8 weeks (p=0.024) and 16 weeks (p=0.004) of therapy. Adverse events were similar in all three groups except for tremor, which was significantly higher in the 100 µg *b.i.d.* salmeterol group (p=0.005) compared both with 50 µg *b.i.d.* salmeterol and placebo.

Salmeterol offered further positive improvement to the effect of therapy in patients with chronic obstructive pulmonary disease when added to their existing regimens. This clinical improvement was similar both with 50 and 100 µg *b.i.d.* dosage, although the group receiving 50 µg *b.i.d.* tolerated the drug better than those receiving 100 µg *b.i.d.* salmeterol.

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Chronic obstructive pulmonary disease (COPD) includes a spectrum of respiratory conditions, which are all associated with airflow obstruction. As a clinical syndrome, it is frequently associated with deterioration of lung function, and ultimately with the development of respiratory failure. COPD may be asymptomatic, but is more frequently characterized by exertional breathlessness and chronic cough, and increased secretion of mucus for several months of the year. It is one of the leading causes of death worldwide [1], and recent reports suggest an increase in mortality from COPD, which has been observed in many countries [1–4]. Cigarette smoking is the most important aetiological factor in COPD and significantly increases the rate of decline in lung function [5]. The majority of smokers (about 70–80%) have either a normal or increased decline of forced expiratory volume in one second (FEV_1) without disabling airflow obstruction. In the remaining 20–30%, however, the decline is more rapid (60–80 $mL \cdot yr^{-1}$) and results in disabling airflow obstruction around the sixth decade. Within any group of patients with COPD, therefore, there will be those who are more susceptible to cigarette smoke, in whom irreversible decline in pulmonary function advances more rapidly [6].

The use of salmeterol in asthma is well-documented [7, 8]. However, little research has been carried out into the use of salmeterol in patients with COPD, although there is evidence that treatment with bronchodilators may improve symptoms and lung function in patients with COPD [9–13].

This study was designed to compare the efficacy and safety of two doses of salmeterol xinafoate with placebo in patients with COPD, when added to an existing drug regimen. The two doses of salmeterol were 50 µg *b.i.d.*, which has been shown to be the effective dose in patients with mild-to-moderate asthma, and 100 µg *b.i.d.*, which has superior efficacy to 50 µg *b.i.d.* in more severe cases of asthma [14].

Materials and methods

Patients

Patients had to meet the following criteria for inclusion in the study: 1) current or previous smokers aged 40–75 yrs, who had coughed up sputum on most days during at least three consecutive months in two consecutive years; 2) at or between Visits 1, 2 and 3, a measurement of FEV_1 of ≤70% of predicted normal and a FEV_1/forced vital capacity (FVC) ratio of ≤60%; 3) at Visits 1, 2 or 3 (or documented in the previous 12 months), an increase in FEV_1 of 5–15%, 15 min after inhalation of 400 or 800 µg of salbutamol from a metered-dose inhaler (MDI) or Diskhaler™ inhaler (Glaxo-Wellcome, London, UK), or 5 mg salbutamol nebulized for 3 min at 8 $L \cdot min^{-1}$ from a nebulizer; and 4) a daytime symptom score of ≥2 on at least 4 of the 7 days prior to randomization (see "Day-time symptom score" below).

Patients were excluded if they had: clinical or laboratory evidence of serious uncontrolled systemic disease; respiratory disorders other than COPD (as indicated by clinical history, examination or chest radiography); or were pregnant and lactating. In addition, patients were excluded if in the 4 weeks prior to the start of the study they were hospitalized for COPD, were treated for an acute respiratory infection, changed their regular medication, or were given newly prescribed COPD medication. Patients with a known or suspected hypersensitivity to salmeterol or salbutamol, or who were receiving beta-blocker therapy or other research medication (in the 4 weeks prior to the start of the run-in period) were also excluded, as were those on oxygen therapy or who were unable to attempt a 6 min walk.

Study design

This was a multicentre, multinational, randomized, double-blind, parallel group study involving 75 centres from 18 countries. After a 2 week run-in period, the second week of which acted as the baseline period, patients were treated for 16 weeks, with a 2 week follow-up period. Patients visited the clinic at recruitment (Visit 1), after 1 week (Visit 2), 2 weeks (Visit 3, the randomization visit), 6 weeks (Visit 4), 10 weeks (Visit 5), 18 weeks (Visit 6), and 14 days later at 20 weeks (Visit 7) for follow-up.

Medication

Patients continued to take their usual non-β_2-agonist COPD therapy throughout the study. During the run-in period, patients received salbutamol on an as-needed basis for symptom relief. Eligible patients were then randomized to receive either salmeterol 50 µg *b.i.d.*, salmeterol 100 µg *b.i.d.* or placebo, from an MDI for 16 weeks. Patients were allowed to receive salbutamol (from an MDI or Diskhaler inhaler) for symptomatic relief. During the follow-up period, patients could be prescribed appropriate bronchodilator medication for their COPD if required. A Volumatic spacer (Glaxo-Wellcome) could be used in conjunction with the study inhaler by individual patients as appropriate.

Measurements

Diary cards. Diary cards were used to record respiratory symptom scores (daytime and night-time), and use of additional salbutamol for symptomatic relief during the day and night.

Night-time symptom score: 0 = no symptoms during the night; 1 = symptoms causing you to wake once or wake early; 2 = symptoms causing you to wake twice or more (including waking early); 3 = symptoms causing you to be awake most of the night; 4 = symptoms so severe that you did not sleep at all. The five point symptom score for night-time use has been used previously in asthma studies [14].

Daytime symptom score: 0 = no symptoms at rest or on exertion; 1 = no symptoms at rest but symptoms on moderate exertion, *e.g.* walking quickly, climbing stairs, rushing out to work; 2 = no symptoms at rest but symptoms on mild exertion, *e.g.* getting dressed or washed; 3 = minimal symptoms at rest, *e.g.* while sitting down reading or watching the television; 4 = moderate symptoms at rest, *e.g.* while sitting down reading or watching the television; and 5 = severe symptoms at rest, unable to carry out any activity requiring exertion. The daytime symptom score was specifically designed for this study by adapting the baseline dyspnoea index of MAHLER and WELLS [15] and the modified Medical Research Council (MRC) Dyspnoea Scale.

Clinic visit data. Lung function was assessed at each clinic visit (FEV_1 and FVC). The distance walked in 6 min (6MWD) was recorded along with breathlessness using the Borg scale [16] before and after the walk. Exacerbations of COPD, which required a change in medication and/or hospitalization, were recorded.

Safety. Safety was assessed by monitoring adverse events, biochemical and haematological laboratory tests, vital signs, and electrocardiography (ECG) at baseline and at the end of treatment. A chest radiograph was taken at Visit 1.

Analysis

Symptom scores, bronchodilator use (over Weeks 1–16 of treatment), and the Borg score at each clinic visit were analysed parametrically.

In all parametric analyses, the type I sum of squares was used. The treatment effects were adjusted for the effects of country, age, sex and baseline value. In all nonparametric analyses, the difference in distribution of response between each pair of treatments was calculated using a Wilcoxon rank sum test, in each case using the van Elteren extension to control for country [17]. An unstratified analysis was also performed to ensure consistency of the results. An analysis of covariance (ANCOVA) was performed on the 6MWD at each visit and the change in lung function from baseline.

The study was conducted in accordance with the Declaration of Helsinki, amended by the 41st World Medical Assembly in Hong Kong in September 1989. The study was approved by the Research Ethics Committee local to each participating centre, and written informed consent was obtained from each patient prior to entry into the study.

Four hundred and twenty evaluable patients were required to give 90% power to detect a difference of one in the five point daytime symptom score, between any two treatment groups. A p-value of less than 0.05 was considered significant.

Results

Six hundred and seventy four patients were randomized and received at least one dose of study medication. They were analysed on an intention to treat basis. Overall, 71 patients were withdrawn after randomization, 21 (3%) placebo patients, 23 (3%) salmeterol 50 µg *b.i.d.* patients, and 27 (4%) of salmeterol 100 µg *b.i.d.* patients. Demographic details are presented in table 1, from which it can be seen that the patients were well-matched for all parameters. Medication usage was comparable between the treatment groups.

Day and night-time symptom scores

The overall median daytime symptom score at baseline was 2.0 in all three treatment groups. For the placebo-treated group, there was no change in the median response on treatment, although there was a decrease to 1.0 at Weeks 5–8, which continued throughout Weeks 9–16 in both of the salmeterol groups. There was a statistically significant difference in the distribution of the median daytime symptom scores between the 50 µg *b.i.d.* salmeterol-treated and placebo-treated groups (p=0.043), and between the 100 µg *b.i.d.* salmeterol-treated and placebo-treated groups (p=0.01) (fig. 1). The 95% confidence intervals (95% CI) for the median difference were 0.00–0.00 in both cases. When both active treatment arms were compared, no difference was demonstrated between the median daytime symptom scores (p=0.602).

Table 1. – Demographic details and concurrent medication

	Placebo	Salmeterol 50 µg *b.i.d.*	Salmeterol 100 µg *b.i.d.*
Patients n	227	229	218
Sex M/F	171/56	189/40	172/46
%	75/25	83/17	79/21
Age yrs#	61 (39–75)	62 (40–75)	63 (39–75)
Smoking history			
Ex-smoker n (%)	137 (60)	127 (55)	120 (55)
Current smoker n (%)	90 (40)	102 (45)	98 (45)
Baseline FEV_1 L	1.31 (0.53)	1.31 (0.51)	1.23 (0.47)
Patients reporting use of one or more COPD medication n	198	187	179
Beta-receptor agonists n	11	5	12
Corticosteroids			
Inhaled	148	128	127
Oral and *i.m.*	8	10	13
Methylxanthines	92	97	89
Anticholinergics	45	42	43
Other medication for COPD	35	32	22

#: mean, and range in parenthesis; M: male; F: female; FEV_1: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease.

The median night-time symptom score was 1.0 at baseline in the placebo and salmeterol 50 µg *b.i.d.* treatment groups, and 0.0 in the salmeterol 100 µg *b.i.d.* group. The median night-time symptom score decreased to 0.0 during Weeks 1–4 in the salmeterol 50 µg *b.i.d.* group, and continued at this level throughout the remainder of the treatment period. However, no change was observed in the median scores during treatment for the other two groups. A statistically significant difference was observed in the distribution of median night-time symptom scores between the 50 µg *b.i.d.* salmeterol-treated and placebo-treated groups (p<0.001), and between 100 µg *b.i.d.* salmeterol-treated and placebo-treated groups (p=0.001) (fig. 1). The 95% CI around the median difference was 0.0–0.0 for both comparisons. When both

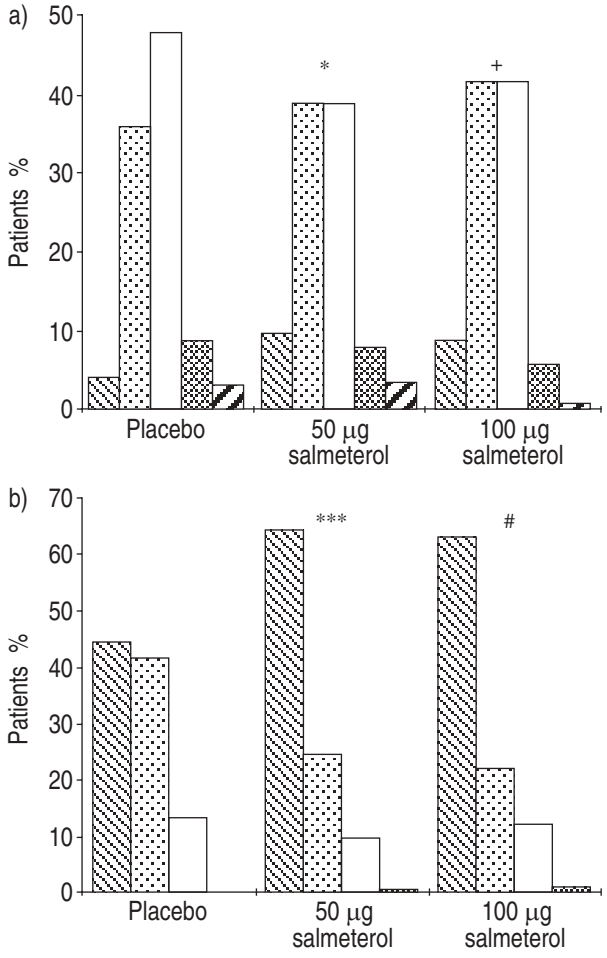

Fig. 1. – Distribution of median: a) daytime; and b) night-time symptom scores after 1–16 weeks of treatment. Symptom score key: ▨: 0; ⁘: 1; □: 2; ▩: 3; ◪: 4+5. *: p<0.05; +: p=0.01; ***: p<0.001; #: p=0.001, comparing the difference in distribution between symptom scores for placebo and active groups.

active treatment arms were compared, no difference was demonstrated between the median night-time symptom scores (p=0.662).

Additional bronchodilator usage

A consistent difference in favour of salmeterol compared with placebo for both salmeterol groups was shown in terms of the amount of additional bronchodilator used during the day, recorded as the number of times a patient took salbutamol. Figure 2 shows the mean percentage of days with no additional daytime bronchodilator usage for each treatment group.

There was evidence of a statistically significant difference in the median daytime use between each salmeterol group and placebo (p<0.001 in each case) in favour of salmeterol, but not between the different salmeterol treatment groups (p=0.845). The mean percentage difference between baseline and the end of treatment was 11% for the placebo group, 24% for the salmeterol 50 µg *b.i.d.* group and 25% for the salmeterol 100 µg *b.i.d.* group. Additional bronchodilator usage was also reduced at night, following a similar pattern. A statistically significant difference was noted between each salmeterol group and placebo (p=0.014 for 50 µg *b.i.d.* salmeterol, and p=0.005 for 100 µg *b.i.d.* salmeterol) in favour of salmeterol, but not between the two salmeterol groups (p=0.711). At baseline, the mean percentage of nights with no additional bronchodilator usage was 53, 58 and 58% for placebo, salmeterol 50 µg *b.i.d.* and salmeterol 100 µg *b.i.d.*, respectively. By Weeks 9–16 the mean percentage of nights with no additional bronchodilator use had increased to 60% (+7%), 75% (+17%) and 74% (+16%), respectively.

Lung function

A consistent difference in favour of both salmeterol groups compared with placebo was shown for lung function, as measured by FEV1. Patients receiving salmeterol therapy continued to improve at each visit, with up

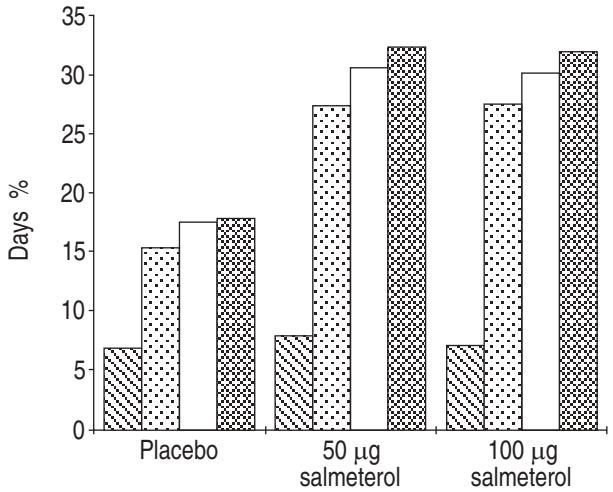

Fig. 2. – Mean percentage of days with no additional daytime bronchodilator medication. ▨: baseline; ⬚: Weeks 1–4; □: Weeks 5–8; ▩: Weeks 9–16.

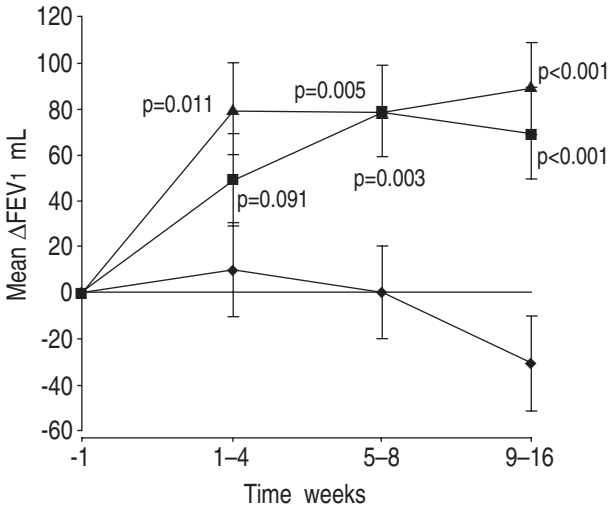

Fig. 3. – Mean change in forced expiratory volume in one second (ΔFEV1) from baseline (-1 week). Values are presented as mean±SEM. —◆—: placebo; —■—: 50 µg salmeterol; —▲—: 100 µg salmeterol. The p-values refer to comparison with the placebo group.

to a 7% improvement observed at the end of treatment. In contrast, the lung function of patients receiving placebo had declined by the end of the study, showing a 2% reduction from baseline. Figure 3 shows the mean FEV1 change from baseline for all three treatment groups. The mean baseline FEV1 prior to treatment was 1.31, 1.32 and 1.23 L for the placebo, salmeterol 50 µg *b.i.d.* and salmeterol 100 µg *b.i.d.* treatment groups, respectively. There was no significant difference between the FEV1 measurements in each of the salmeterol-treated groups at 1–4 weeks (p=0.379), 5–8 weeks (p=0.951), and at 9–16 weeks (p=0.404).

Patients in this study were selected to show minimal reversibility of FEV1 to salbutamol at the start of the study. The distribution of reversibility during the run-in period was similar between all groups. Eight percent of patients had a reversibility of ≤5%, whereas 42 and 50% showed reversibility of ≤10%, or >10% but ≤15%, respectively.

The effect of baseline reversibility in FEV1 response was consistent in each treatment group, and no significant effect of baseline reversibility in response was seen at Weeks 4, 8 and 16, so that the degree of reversibility which each person demonstrated initially did not affect the degree of response to salmeterol that was observed.

Six minute walk and breathlessness

At each visit, the median Borg score for breathlessness before a 6 min walk was 1.0 in all three treatment groups, and increased to 3.0 following the walk. However, between the salmeterol 50 µg *b.i.d.* and placebo groups there was evidence of a statistically significant difference in the distribution of the breathlessness score after the walk at 8 weeks (p=0.024) and 16 weeks (p=0.004) of treatment. At the end of placebo treatment, 74 patients reported scores of less than 3 after the walk compared with 100 patients in the salmeterol 50 µg *b.i.d.* group. Seventy six patients in the salmeterol 100 µg *b.i.d.* group also reported scores of less than 3 at the end of

Table 2. – Summary of the most common adverse events reported during treatment

	Placebo	Salmeterol 50 µg *b.i.d.*	Salmeterol 100 µg *b.i.d.*
Patients n	227	229	218
Patients with an adverse event	140 (62)	130 (57)	133 (61)
Exacerbation of symptoms of COPD	98 (43)	75 (33)	91 (42)
Headache	14 (6)	11 (5)	12 (6)
Tremors	2 (<1)	2 (<1)	13 (6)

Values are presented as the absolute number of patients experiencing an adverse event, and percentage of total patients in the group in parenthesis. COPD: chronic obstructive pulmonary disease.

treatment after walking for 6 min, which was significantly different to the salmeterol 50 µg *b.i.d.* group (p=0.010). There was no significant difference between the three treatment groups in the distance walked in 6 min at each visit (mean values were 401–422 m).

Exacerbations

The incidence of COPD exacerbations was similar between the groups. In the placebo group, there were 59 patients (26%) who had at least one exacerbation of COPD during treatment. The corresponding numbers of patients in the salmeterol groups were 47 (21%) for the 50 µg *b.i.d.* group and 54 (25%) for the 100 µg *b.i.d.* group.

Safety

The incidence of patients who reported an adverse event that was considered by individual investigators to be related to the study medication was similar for placebo and salmeterol 50 µg *b.i.d.*, 18 and 16%, respectively, but was slightly higher (24%) in patients receiving salmeterol 100 µg *b.i.d.*, mainly due to increased tremor, a pharmacologically predictable event. The most commonly reported adverse events were respiratory symptoms, headache and tremor (table 2).

Two patients died whilst receiving treatment. The cause of death was bronchopneumonia for one patient receiving placebo, and malignant neoplasm of the bronchus with metastases for one patient receiving 50 µg *b.i.d.* salmeterol.

There were no clear treatment effects on vital signs or on ECG tracings, and no clinically relevant changes were reported in any of the parameters measured during clinical chemistry or haematological screening.

Discussion

COPD represents a variety of obstructive lung conditions, including chronic bronchitis and emphysema, all of which are characterized by a reduction in FEV_1 [14]. In general, the approach to therapy is variable, although recently a consensus statement on the optimal assessment and management of COPD has been published on behalf of the European Respiratory Society [18]. Whilst all physicians acknowledge that the first step in patient management is the cessation of smoking, the role of specific treatment is not clear, and debate continues as to the benefit of inhaled bronchodilators and inhaled corticosteroids [12, 13, 18–22].

This study specifically investigated the effect of adding a long-acting β_2-agonist, salmeterol, to the existing treatment regimen in patients with COPD. Salmeterol was shown to have a positive effect on airflow obstruction, as measured by improvements in lung function. An improvement in FEV_1 of 70–90 mL on a baseline FEV_1 of 1.3 L (up to a 7% change) was demonstrated after 16 weeks of treatment, which represented a relatively large improvement when the more limited lung function and lower potential reversibility of COPD patients was considered. In contrast, the patients receiving placebo (*p.r.n.* salbutamol), demonstrated a slight decline in FEV_1 at the end of treatment. These improvements in lung function in patients given salmeterol were associated with significant improvements in daytime and night-time symptom scores, and a reduction in additional bronchodilator usage, when compared to those given placebo. Daytime symptom scores also improved considerably in patients given placebo in addition to those receiving salmeterol. This is likely to reflect on overall study effects associated with increased compliance with therapy and improved access to rescue salbutamol. Even when this was taken into account, greater improvements both in daytime and night-time symptom scores were recorded in both salmeterol-treated groups.

Patients in this study were selected to show minimal reversibility in FEV_1, although this was greater in some patients than in others. However, at least 50% of all patients demonstrated an improvement in FEV_1 of less than 10% following salbutamol, and any improvement that occurred during the study was unrelated to the degree of reversibility at baseline, regardless of the treatment the patient received. Improvements following the introduction of salmeterol cannot be ascribed to the introduction of *p.r.n.* salbutamol in patients who were receiving methylxanthines or anticholinergic agents. Furthermore, those patients who were receiving corticosteroids did not react any differently to those who were not.

Thus, the positive response following salmeterol treatment was not influenced by concurrent medication or the degree of airways reversibility at baseline, but was most likely to reflect the long-term course of action of salmeterol. It is probable that this altered the distribution of air within the lungs with a reduction in gas-trapping and a concomitant enhancement of respiratory muscle function. This would then reduce the overall work of breathing and improve the overall level of symptoms. O'DONNELL [23] has proposed this as a method by which bronchodilator therapy may benefit patients with chronic airflow limitation, and a number of authors have demonstrated that relief of breathlessness can be achieved with various bronchodilators in the presence of only small improvements in FEV_1 [24–26]. Furthermore, reduced exertional breathlessness following anticholinergic medication has been shown to be a function of reduced lung hyperinflation [27].

A subgroup of patients in this study also completed quality of life questionnaires, and the results were published separately [28]. The introduction of salmeterol 50 µg *b.i.d.* was associated with significant improvement, that, when compared with the placebo group, was in excess of the threshold for a clinically significant change. There was also a positive correlation with the quality of life (QOL) scores and both the patient and physician estimates of treatment efficacy. QOL scores also showed a weak but significant relationship with clinical spirometry [28]. However, although clinical results from patients given 100 µg *b.i.d.* salmeterol were no different from the results from patients receiving 50 µg *b.i.d.* salmeterol, a significant difference was noted between the two groups for QOL score, in favour of the 50 µg *b.i.d.* dose.

This study demonstrated that salmeterol offered some improvement for patients in the short-term; however, information relating to longer periods of treatment is not yet available. A 2 year prospective bronchodilator trial suggested that continuous treatment with a bronchodilator (ipratropium or salbutamol) was associated with a higher annual decline in FEV_1 than in symptomatically-treated patients [29]. However, further critical analysis at 4 yrs [30] did not confirm this finding, but demonstrated no change in lung function between the treatment groups. In these studies, treatment with salbutamol or ipratropium was not shown to influence symptoms, findings contrary to the results from the present study with salmeterol. There were significant differences in the patient populations between these and the present study, so that any direct comparison of results is in fact inappropriate. In asthma, significant improvements in FEV_1 have been observed in patients with salmeterol over a 3 month period, with no evidence of deterioration over the next 9 months [31–34].

This multinational study has demonstrated that the addition of regular salmeterol to existing treatment regimens in chronic obstructive pulmonary disease had a positive effect on airflow obstruction and on the level of symptoms, resulting in improvement in estimates of quality of life. These effects were not influenced by any pre-existing medication, and no clinical difference was noted between the effects of salmeterol 50 µg *b.i.d.* and 100 µg *b.i.d.*

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