The addition of salmeterol 50 μg bid to anticholinergic treatment in patients with COPD: A randomized, placebo controlled trial

Kenneth R Chapman MD[1], Peter Arvidsson MD[2], AG Chuchalin MD[3], DP Dhillon MD[4], Peter Faurschou MD[5], Roger S Goldstein MD[6], AF Kuipers MD[7]
on behalf of an international study group*

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BACKGROUND: In the past, the role of long-acting beta$_2$-agonists in chronic obstructive pulmonary disease (COPD) relative to other agents has been unclear.
OBJECTIVES: To compare the effect of adding salmeterol (50 μg bid) or placebo to concurrent anticholinergic therapy on symptom scores, quality of life, prebronchodilator lung function and exacerbations in patients with moderately severe COPD.
METHODS: This was a double-blind, randomized, parallel-group study in patients aged 40 years or older receiving anticholinergic medication. Patients were randomly assigned to treatment with placebo (n=207) or salmeterol (n=201) via a Diskus/Accuhaler inhaler for 24 weeks.
RESULTS: The morning trough (prestudy drug) forced expiratory volume in 1 s (FEV_1) increased significantly above baseline levels among the salmeterol-treated patients. Improvement in FEV_1 was greater in the salmeterol group than in the placebo group at four weeks (difference 0.06 L, P<0.005), eight weeks (0.06 L, P<0.005) and 16 weeks (0.05 L, P<0.05) after the start of treatment. There was a nonsignificant trend in favour of salmeterol after 24 weeks of treatment (P=0.198). Improvements in morning peak flow were significantly greater in the salmeterol group over 24 weeks (P<0.01). Although symptom scores were numerically higher in the salmeterol group than in the placebo group and there was less requirement for rescue bronchodilator use, these differences were not statistically significant. In the salmeterol group, fewer patients had exacerbations of COPD, and there was a trend toward an improved quality of life. The safety profile of the two groups was similar.
CONCLUSIONS: Salmeterol has a beneficial effect when added to existing anticholinergic therapy in patients with COPD. The regular use of salmeterol for six months was not associated

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Members of the international study group were from six countries: Canada (J Acres, E Amer, M Balter, G Bishop, S Blackie, J Bouchard, C Chan, K Chapman, G Cournoyer, A Denys, A Dhar, S Field, G Ford, R Goldstein, R Hodder, M Lertzman, P LeBlanc, GF MacDonald, R Maleki-Yazdi, DD Marciniuk, DG McCormack, D Morrison, D O'Donnell, L Passerini, P Renzi, D Stubbing); Denmark (JP Kampmann, P Faurschou, H Harving, M Christensen, H Rickers, J Heinig); the Netherlands (AF Kuipers, PW Oosterling, P Oostinge, HEJ Damste); Russia (VE Nonikov, BM Blokhin, AG Chuchalin, GI Drinov); Sweden (P Arvidsson, BA Hermansson, U Hero, E Piitulainen); and the United Kingdom (GS Basran, DP Dhillon, HSR Hosker, R O'Driscoll, JF O'Reilly, R Stevenson, A Stewart)
[1]*Toronto Western Hospital, Toronto, Ontario;* [2]*Sahlgrenska University Hospital, Gothenburg, Sweden;* [3]*Pulmonology Research Institute, Moscow, Russia;* [4]*Walsgrave Hospital, Coventry, United Kingdom;* [5]*Kas Gentofte Lungemedicinsk Afeling Y, Hellerup, Denmark;* [6]*West Park Hospital, Toronto, Ontario;* [7]*Isala Klinieken, Zwolle, the Netherlands*
Correspondence and reprints: Dr KR Chapman, Suite 011, Edith Cavell Wing, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8. Telephone 416-603-5499, fax 416-603-3456, kchapman@ca.inter.net

with worsening of the underlying airflow obstruction; rather, there was a tendency for the trough FEV_1 to improve above the baseline levels over the treatment period.

Key Words: *Anticholinergic agents; Beta$_2$-adrenergic agonist; Chronic obstructive pulmonary disease; Ipratropium; Lung function; Salmeterol*

L'ajout de 50 µg de salmétérol bid au traitement aux anticholinergiques des patients atteints de BPCO : Un essai aléatoire et contrôlé contre placebo

HISTORIQUE : Par le passé, le rôle des béta$_2$-agonistes à action prolongée dans la bronchopneumopathie chronique obstructive (BPCO) était nébuleux.

OBJECTIFS : Comparer l'effet de l'ajout de salmétérol (50µg bid) ou d'un placebo à un traitement concomitant aux anticholinergiques sur l'ensemble des symptômes, la qualité de vie, la fonction pulmonaire prébronchodilatatrice et les exacerbations chez les patients atteints d'une BPCO modérée.

MÉTHODOLOGIE : Cette étude aléatoire à double insu était menée auprès de groupes parallèles de patients de 40 ans ou plus prenant des anticholinergiques. Les patients étaient divisés de manière aléatoire entre un traitement placebo (n=207) ou au salmétérol (n=201) administré au moyen d'un inhalateur Diskus/Accuhaler pendant 24 semaines.

RÉSULTATS : Le creux matinal (médication avant le début de l'étude) du volume maximal expiratoire à la seconde (VMES) dépassait de beaucoup le taux de référence chez les patients traités au salmétérol. Les améliorations du VMES étaient supérieures dans ce groupe que dans celui traité au placebo quatre semaines (différence de 0,06 L, P<0,005), huit semaines (0,06 L, P<0,005) et 16 semaines (0,05 L, P<0005) après le début du traitement. Une tendance non significative en faveur du salmétérol s'observait après 24 semaines de traitement (P=0,198). Les améliorations du débit de pointe matinal étaient significativement plus élevées au sein du groupe traité au salmétérol au bout de 24 semaines (P<0,01). Bien que les symptômes étaient plus nombreux dans le groupe traité au salmétérol que dans celui traité au placebo et que le recours au bronchodilatateur de rattrapage n'était pas aussi fréquent, ces différences n'étaient pas significatives d'un point de vue statistique. Au sein du groupe traité au salmétérol, moins de patients ont présenté des exacerbations de leur BPCO, et une tendance vers une amélioration de la qualité de vie était relevée. Le profil d'innocuité des deux groupes était semblable.

CONCLUSIONS : Le salmétérol a un effet bénéfique lorsqu'il est ajouté à un traitement aux anticholinergiques existant chez des patients atteints de BPCO. Le recours régulier au salmétérol pendant six mois ne s'est pas associé à une aggravation de l'obstruction sous?jacente du débit d'air. Le creux de VEMS avait plutôt tendance à s'améliorer au point de dépasser le taux de référence pendant la période du traitement.

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, with significant social and economic consequences (1). Its management has been addressed in a number of treatment guidelines (2-4), including those under the aegis of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (1). Although smoking control is recognized as being key to the effective management of COPD, pharmacological therapy also has a significant role. Central to these recommendations is the use of bronchodilators such as short-acting beta$_2$-adrenergic agonists and anticholinergic agents (used individually or in combination), which have been shown to improve lung function, and to reduce the frequency and severity of symptoms (5-8). The combination of these agents is superior to either agent used alone, which is an advantage that may reflect the differing modes of action of the two classes or a dose effect when the agents are administered in conventional doses (9,10). The role of long-acting beta$_2$-agonists such as salmeterol (Serevent, GlaxoSmithKline, Canada) relative to other agents in COPD management remains to be clarified. However, early trials have confirmed that there are improvements in lung function and improved health status in patients with COPD given long-acting beta$_2$-agonists (1).

There is a wealth of data demonstrating the efficacy and safety of salmeterol in patients with asthma (11), and there is in vitro and in vivo evidence indicating its beneficial effects on ciliary function (12,13). Furthermore, placebo controlled studies in patients with COPD have shown that salmeterol 50 µg bid improves symptoms, reduces rescue bronchodilator use, increases morning peak expiratory flow rate (PEFR) (14,15) and improves quality of life (16,17). Salmeterol has also been found to improve lung function (17,18), reduce dyspnea (17) and increase the time to first COPD exacerbation (17) to a greater extent than the anticholinergic agent ipratropium bromide. There are, however, few data on the benefits of adding salmeterol to a regimen already containing an anticholinergic agent. Therefore, the present study investigated the efficacy and safety of salmeterol (50 µg bid) given via the Diskus/Accuhaler (GlaxoSmithKline, Canada) inhaler to patients with moderately severe COPD who were already receiving short-acting inhaled anticholinergic therapy.

PATIENTS AND METHODS

Study design

The study design was a double-blind, randomized, parallel-group study, carried out in 52 centres in Canada (28 centres), Denmark (six centres), the Netherlands (three centres), Russia (four centres), Sweden (four centres) and the United Kingdom (seven centres). A four-week run-in period was followed by 24 weeks of treatment and two weeks of follow-up. Patients visited the clinic at the start of the run-in period (visit 1), and after two weeks (visit 2) and four weeks (random assignment, visit 3) of run-in. During the treatment period, patients visited the clinic at four weeks (visit 4), eight weeks (visit 5), 16 weeks (visit 6) and 24 weeks (visit 7) after the start of treatment.

Patients

Men and women with COPD aged 40 years or older who were willing to give written, informed consent were considered for inclusion in the run-in period. Patients had to have been taking anticholinergic agents (alone or as a combina-

tion product) for at least four weeks, and had to demonstrate a history of smoking equivalent to at least 10 pack-years (ie, at least 20 cigarettes/day for 10 years or equivalent); sputum production on most days during at least three consecutive months for two consecutive years; baseline (visits 1, 2 or 3) forced expiratory volume in 1 s (FEV_1) 85% or less of predicted; baseline FEV_1/forced vital capacity ratio 70% or less of predicted; FEV_1 reversibility 5% to 15% of predicted, either by measurement 15 min after inhalation of salbutamol (400 μg via metered dose inhaler [MDI] or 800 μg via Diskhaler [GlaxoSmithKline, Canada]) at baseline or documented evidence of such reversibility after inhalation of a $beta_2$-agonist within the previous 12 months; and symptoms on at least seven out of the previous 14 day and night periods of the run-in phase.

Patients were excluded if they had suffered from a respiratory infection requiring prescribed medication or if they had been hospitalized for COPD within four weeks before the start of the run-in period. Patients with concurrent respiratory disorders were also excluded, as were pregnant or lactating women, or those likely to become pregnant during the study. Inability to use a Diskus/Accuhaler precluded entry into the trial.

Medication

At the start of the run-in period, all existing $beta_2$-agonists (including salmeterol and formoterol) were replaced by salbutamol sulfate (Ventolin, GlaxoSmithKline, Canada) (100 μg/actuation via an MDI or 400 μg Rotadisk [GlaxoSmithKline, Canada] via a Diskhaler) for use as a rescue medication throughout the study period. Patients were allowed to continue with all other prescribed medications for COPD, including methylxanthines, anticholinergic agents and inhaled or oral steroids. Patients taking combinations of anticholinergic agents and $beta_2$-agonists continued with these medications throughout the study period. Volumatic (GlaxoSmithKline, Canada) spacers were provided as necessary for patients using MDIs. After the run-in period, eligible patients were randomly assigned to treatment with either salmeterol xinafoate 50 μg bid or placebo, both via the Diskus/Accuhaler inhaler. Allocation of the study treatment was predetermined according to a sequence of continuous patient random assignment numbers, which were generated by computer in block sizes of four, with complete blocks allocated to each investigation site.

Measurements

Diary card recording: Daily record cards were used by patients to record the morning and evening PEFRs (the highest of three measurements was recorded), and the number of times rescue salbutamol was used during each day- and night-time period. Daytime symptom scores were recorded using a six-point scale ranging from 0 (no symptoms at rest or on exertion) to 5 (severe symptoms at rest, exertion impossible). Night-time symptom scores were recorded using a five-point scale ranging from 0 (no symptoms during the night) to 4 (symptoms so severe as to prevent sleep). These symptom scores have been used previously in the study of COPD and are responsive to treatment interventions (9,15). For the purposes of power calculation and assessment of efficacy, daytime and night-time symptom scores were the primary outcome variables.

Clinic visit data: Patients were asked to withhold study medications for 12 h and short-acting bronchodilators for 4 h before clinic visits. At each clinic visit, the highest of three FEV_1 measurements was recorded. The patient was also given the opportunity to mention any problems spontaneously. In addition, the investigator inquired about adverse events by asking the following standard questions: "Have you had any (other) medical problems since your last visit/assessment?" and "Have you taken any new medicines, other than those given to you within this study, since your last visit/assessment?" An exacerbation was defined as a worsening of respiratory disease requiring a change in medication and/or hospital care, emergency room care or an unscheduled outpatient visit.

Patients participating in the study in Canada, the Netherlands, Sweden and the United Kingdom also completed the St George's Respiratory Questionnaire (19) (a disease-specific quality of life questionnaire with components for symptoms, activity and impact on daily life) during the clinic visit, both at the start of the run-in period and at the end of the treatment period. Baseline quality of life data were collected at the first screening visit rather than the random assignment visit to allow for sufficient time to collect the questionnaire information in an unhurried fashion during a relatively brief clinical assessment. The countries participating in this element of the study were those for which a questionnaire validated in the local language was available.

Analysis

All analyses were carried out in an intent-to-treat manner using two-sided testing at the 5% level. All statistical tests reported represent a priori planned analyses.

It was planned to recruit 454 patients (227 for each treatment group) to provide 90% power at the 5% significance level to detect a clinically significant between-treatment difference (greater than 15%) in the proportion of patients with no or few daytime symptoms. With the actual number of patients who were randomly assigned, the trial had more than 85% power to detect a difference of 15% between the two treatments. The symptom score data and rescue salbutamol use over the 24-week treatment period were analyzed using the Wilcoxon rank sum test (adjusted for the effect of country using the van Elteren extension). The median treatment difference and associated 95% CIs were estimated using the Hodges-Lehmann method. Mean morning and evening PEFR and FEV_1 measurements were analyzed using an ANCOVA with an adjustment for age, sex, country and the pretreatment measurement; the baseline value was taken as the average value during the run-in period for the PEFR and the value recorded at the time of random assignment for the FEV_1. The change in each of the component scores and the total score of the St George's

TABLE 1
Patient demographics and baseline characteristics (intent-to-treat population) in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy

	Patients treated with salmeterol 50 µg bid (n=201)	Patients treated with placebo (n=207)
Sex		
Male (%)	129 (64)	132 (64)
Female (%)	72 (36)	75 (36)
Duration of chronic obstructive pulmonary disease		
Less than 10 years (%)	113 (56)	122 (59)
10 years or greater (%)	88 (44)	85 (41)
Smoking history		
Current smoker (%)	88 (44)	89 (43)
Ex-smoker (less than 6 months since last cigarette) (%)	113 (56)	118 (57)
Mean smoking duration (years)	39	37
Lung function tests		
Mean baseline forced expiratory volume in 1 s (L)	1.19	1.28
Mean predicted forced expiratory volume in 1 s (%)	44	46
Number of exacerbations in previous 12 months		
1 or more (%)	110 (55%)	107 (52%)
More than 2 (%)	26 (13%)	31 (15%)
1 or more hospitalization in previous 12 months (%)	27 (13%)	32 (15%)
Long-acting beta$_2$-agonists stopped at start of run-in period		
Salmeterol (%)	2 (<1%)	3 (1%)
Formoterol (%)	2 (<1%)	1 (<1%)
Concomitant medications continued during the trial		
Inhaled corticosteroids (%)	136 (68%)	113 (55%)
Theophylline (%)	48 (24%)	36 (17%)

Respiratory Questionnaire (19) were also analyzed using ANOVA, adjusting for age, sex and country. Additionally, within-group changes were analyzed using paired *t* tests on pretreatment versus the last recorded on-treatment value for each of the component scores and the total score. The number of patients experiencing at least one exacerbation was analyzed using logistical regression, adjusting for the effect of age and sex. The number of patients having more than two exacerbations was analyzed in a similar manner.

RESULTS

Of 506 patients screened, 408 were randomly assigned (201 to receive salmeterol; 207 to receive placebo). The most common reason for patients to be withdrawn before random assignment was failure to meet entry criteria (44 patients). After random assignment, 28 patients were withdrawn from the placebo group and 20 were withdrawn from the salmeterol group. The most common reasons for withdrawal were adverse events (12 placebo-treated patients and 13 salmeterol-treated patients) and treatment failure or noncompliance (three placebo-treated patients and one salmeterol-treated patient). The single most common adverse event causing withdrawal from the study was exacerbation of COPD, accounting for four withdrawals in each of the treatment groups. All randomly assigned patients were included in the intent-to-treat population for analysis, and demographic details for these patients are presented in

TABLE 2
Symptom scores and rescue bronchodilator use during the 24-week treatment period in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy

	Patients treated with salmeterol 50 µg bid (n=201)	Patients treated with placebo (n=207)
Median percentage of days with symptom score <2	85	76
Median percentage of nights with symptom score <2	99	97
Median number of salbutamol puffs/24 h period	2	3

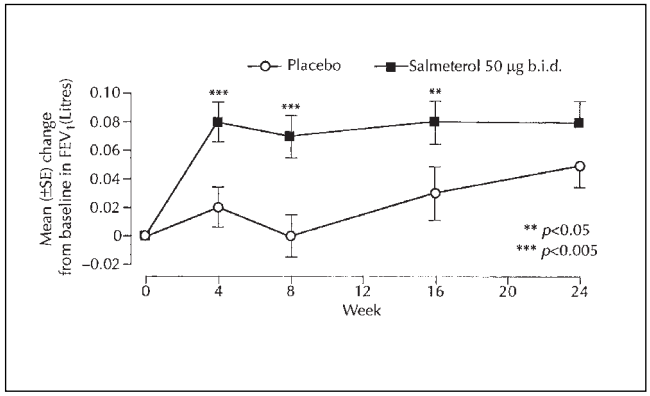

Figure 1) *Adjusted mean change from baseline in forced expiratory volume in 1 s (FEV_1) in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy*

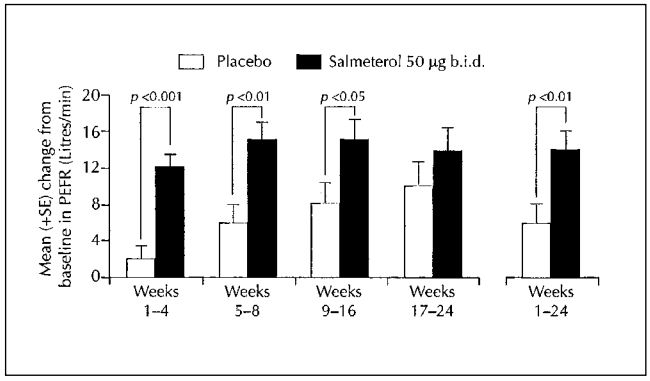

Figure 2) *Morning peak expiratory flow rate (PEFR): adjusted mean change from baseline in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy*

Table 1. The groups were well matched for age, baseline lung function, symptom scores, duration of disease, the number of previous exacerbations of COPD and smoking history. Few patients in either group were taking long-acting $beta_2$-agonists that were stopped at the start of the run-in period.

Day- and night-time symptom scores

Baseline symptom scores were low in both groups (daytime score: median 1, range 0 to 4; night-time score: median 0, range 0 to 3). During the treatment period, the median proportions of days or nights with a symptom score of less than 2 were higher in the salmeterol than the placebo group (Table 2), although these differences did not reach statistical significance. These results were reflected in the use of rescue salbutamol, which was low at baseline in both groups (median of three puffs/24 h for both groups, range 0 to 12) and somewhat decreased in the salmeterol group during the treatment period (median of two puffs/24 h compared with three puffs/24 h for placebo) (Table 2). Again, this difference did not reach statistical significance.

TABLE 3
Unscheduled use of health care resources as recorded at each clinic visit in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy

	Patients treated with salmeterol 50 µg bid (n=201)	Patients treated with placebo (n=207)
Patients with unscheduled health care contact (%)	68 (34)	76 (37)
Hospital contacts		
Accident and emergency department (days)	24	22
Intensive care unit (days)	2.5	3.0
General ward (days)	66	64
Outpatient visits (n)	14	21
General practitioner contacts		
Daytime home visits (n)	8	12
Telephone contacts (n)	1	2
Clinic visits (n)	83	89

Lung function

Among salmeterol-treated patients, morning pretreatment or trough FEV_1 levels improved significantly above baseline levels, which was an improvement that persisted during the six-month treatment period (Figure 1). These improvements in lung function with treatment were significantly greater in the salmeterol group than in the placebo group for all but the last clinic visit. The adjusted treatment difference was significant at week 4 (0.06 L, P<0.005), week 8 (0.06 L, P<0.005) and week 16 (0.05 L, P<0.05) of treatment, but not at week 24 (0.03 L, P=0.198) (Figure 1).

Figure 2 shows the adjusted mean change from baseline in the mean morning PEFR as recorded in the diary cards. Analysis of adjusted treatment differences showed that the mean improvement over the 24-week treatment period was significantly higher in the salmeterol group than in the placebo group (P<0.01). There was also a trend toward greater improvements in the mean evening PEFR with salmeterol, although this failed to reach statistical significance (P=0.097).

Exacerbations and health care use

During the treatment period, 26% of salmeterol-treated patients and 33% of placebo-treated patients experienced at least one exacerbation of COPD (P=0.117). Fewer salmeterol-treated patients experienced more than two exacerbations (salmeterol group less than 1%, placebo group 4%), but this difference was not statistically significant (P=0.063). In the 12 months before the study, 13% of salmeterol-treated patients and 15% of patients in the placebo group had been hospitalized at least once. During the treat-

TABLE 4
Quality of life scores (St George's Respiratory Questionnaire) in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy

	Patients treated with salmeterol 50 µg bid (n=148)			Patients treated with placebo (n=151)			Placebo versus salmeterol
Component	Baseline*	Change from baseline†	P	Baseline*	Change from baseline†	P	P (95% CI)‡
Symptoms	66	–4.0±16.5	0.003	65	–0.9±17.1	0.5	0.1 (–0.7 to 6.2)
Activity	70	–1.4±16.2	0.3	69	–0.6±14.4	0.6	0.8 (–2.9 to 3.6)
Impact on daily life	39	–2.5±15.9	0.05	38	–0.9±14.9	0.4	0.4 (–1.9 to 4.7)
Total	53	–2.4±12.7	0.02	52	–0.9±12.2	0.4	0.3 (–1.3 to 4.0)

**Baseline equals mean score determined at visit 1; †Change from baseline equals visit 7 (end of treatment) score minus baseline score (± SD); ‡95% CI of adjusted treatment difference. Significance levels are shown for differences between end of treatment and baseline for each measure, and for the comparison between treatment group*

ment period, health care use was similar between the treatment groups (Table 3). During the study, oral corticosteroids were initiated in 38 patients (18%) in the placebo group and 27 patients (13%) in the salmeterol group.

Quality of life

As shown in Table 4, scores for the St George's Respiratory Questionnaire (19) were reduced from baseline for all components of the questionnaire (symptoms, activity, impact on daily life) among patients in the salmeterol group, with a significant improvement in the symptom component ($P<0.005$), the impact on daily life component ($P=0.05$) and the total score ($P<0.05$). Although these improvements were greater than the improvements in the placebo group, the between-treatment differences were not statistically significant.

Safety

The incidence of adverse events recorded during the study were similar for both treatment groups (Table 5), with at least one adverse event being reported by 72% of patients in the salmeterol group and 71% of patients in the placebo group. The most commonly reported events were related to the respiratory system in both treatment groups, with exacerbations of COPD being the most common event reported by 45 patients (22%) receiving placebo and 41 patients (20%) receiving salmeterol. Events that were considered to be related to drug treatment were recorded in 11% of patients in the salmeterol group and 10% of patients in the placebo group. The most common treatment-related events were headache, tremor and tachycardia. In 6% of salmeterol-treated patients and 5% of placebo-treated patients, adverse events (most commonly exacerbations of COPD) resulted in study withdrawal.

TABLE 5
Summary of adverse events reported during treatment in a study investigating the role of salmeterol in patients with moderately severe chronic obstructive pulmonary disease already receiving anticholinergic therapy

	Patients treated with salmeterol 50 µg bid (n=201)	Patients treated with placebo (n=207)
≥1 adverse event (%)	145 (72)	146 (71)
≥1 treatment-related event (%)	23 (11)	20 (10)
Treatment-related events		
Headache (%)	1 (<1)	4 (2)
Tremor (%)	1 (<1)	4 (2)
Tachycardia (%)	2 (<1)	4 (2)

DISCUSSION

In the present study, we found that the addition of salmeterol to anticholinergic therapy significantly improved lung function compared with placebo in patients with COPD, with improvements in prebronchodilator morning FEV_1 being significantly greater at all time points up to 16 weeks of therapy. Although this improvement over placebo was not statistically significant at 24 weeks of treatment, this was due to an apparent improvement in the placebo group and not to tachyphylaxis in the salmeterol group; improvement in the salmeterol group did not decrease from week 16. Trends toward improved symptom scores, improved quality of life, a reduced exacerbation rate and decreased oral corticosteroid administration were not statistically significant.

It is important to note that the pulmonary function test used to compare treatment groups was the trough FEV_1, reflecting lung function approximately 12 h after the last dose of study medication was taken. Similar findings have been reported previously after chronic anticholinergic but not adrenergic bronchodilator therapy for COPD (20). Absolute changes in the FEV_1 from baseline (5% to 6% change, approximately 80 mL) were relatively small, but changes of similar magnitude with salmeterol therapy have been reported to be of symptomatic benefit (15). This improvement in the trough FEV_1 could simply represent a lingering bronchodilator effect of salmeterol measurable 12 h postdose. It is also possible that the regular use of salmeterol produces sustained improvements in lung function via non-bronchodilator mechanisms (21).

The observed changes in FEV_1 that we observed were mirrored by improvements in the morning PEFR, which was significantly higher in the salmeterol group during the first 16 weeks of the study, but not thereafter. As for the FEV_1, this relative reduction in treatment differences for both lung function parameters reflects a steady increase in lung function in the placebo group over the latter part of the study. In contrast, the salmeterol group showed a prompt increase in lung function, which was maintained thereafter. The increase in the placebo group may be an effect of participating in a controlled trial; the protocol permitted patients to continue with concurrent COPD therapy, and compliance with medication might have been expected to improve with close monitoring. More important, patients in the placebo-treated group tended to use more as-needed bronchodilators during the study, and this might have perturbed morning spirometry and PEFR measurements. Although patients were asked to abstain from as-needed bronchodilators for 4 h before spirometry, it is plausible that more dyspneic patients used bronchodilating medication in this interval.

In line with the lung function improvements, patients in the salmeterol group reported more days and nights with low symptom scores, as well as a lower use of rescue salbutamol, than patients in the placebo group. These differences did not, however, reach statistical significance. This is again in contrast to the observations from a previous study (15), in which there were significant differences in the distribution of median day- and night-time symptom scores between both doses of salmeterol and placebo, as well as significantly less rescue bronchodilator use in the salmeterol groups. In that study, baseline symptom scores were higher (median score 2), with perhaps a greater room for improvement than in our study (median score 1). The fact that the lung function improvements were relatively small may account for the minimal symptom improvement; it has been shown previously that there is only a weak relationship between the breathlessness score and spirometry (22).

Over 50% of the patients in our study had reported at least one exacerbation in the 12 months before entering the study, with approximately one-quarter of those experiencing more than two exacerbations in that period. This is consistent with previous work (23). During treatment, similar proportions of patients in each group experienced at least one exacerbation. Fewer patients in the salmeterol group experienced more than two exacerbations, as has been shown previously in a comparison of salmeterol, ipratropium bromide and placebo (17), but statistical significance between salmeterol and placebo was not achieved in the present study.

Reduced lung function, poor symptom control and disease exacerbations often result in marked impairment in the quality of life of COPD patients. This has been quantified using disease-specific tools such as the St George's Respiratory Questionnaire (19). Using this scale, a clear improvement from baseline in both the impact on daily life and the total scores has been noted when adding salmeterol to concurrent therapy, as well as a significant difference between salmeterol and placebo for these components (16). In the present study, adding salmeterol to concurrent anticholinergic therapy improved the impact on daily life, symptom and total scores compared with baseline. Although there was a suggestion of a greater effect with salmeterol than with placebo, which also improved from baseline, the difference between the groups was not significant. Disease severity was similar to that in the study of Jones and Bosh (16), although fewer patients in that trial were on concurrent anticholinergic therapy, suggesting under-treatment at baseline compared with the present study; thus, there was a greater potential for clear treatment effect. As noted earlier, two bronchodilators used in combination are more effective than either agent used alone, either as the consequence of their different mechanisms of action or because of a simple additive effect of their bronchodilator effects. Nevertheless, these two studies appear to support the observation that even modest changes in lung function and symptom scores with bronchodilator therapy may be associated with a clinically significant gain in health and well-being in patients with COPD. This may be because bronchodilators, including salmeterol, decrease dynamic hyperinflation during exercise in such patients (24,25). Dynamic hyperinflation is a key determinant of dyspnea and, therefore, presumably, quality of life in patients with COPD (24,26), probably because of its adverse mechanical effects on the lung (27,28).

The promising efficacy of salmeterol compared with anticholinergic agents in improving lung function and the symptoms of COPD (17,18), as well as in providing additional benefits in patients already receiving anticholinergic therapy (as shown in our study and previously [9]), may be explained in part by salmeterol's long duration of bronchodilation (29) and in part by additional nonbronchodilator effects of the agent. These include a cytoprotective effect on the epithelium (30), increasing ciliary function (12,13) and protection from infection (30,31). Further research should reveal the precise mechanisms and clinical relevance of these effects for the treatment of COPD.

CONCLUSIONS

The addition of salmeterol 50 μg bid to a regimen including anticholinergic agents significantly improved pre-bronchodilator lung function, with a trend toward improvements in symptom control compared with placebo. Salmeterol is safe and well tolerated. Previously published results have shown that salmeterol is a more effective monotherapy in COPD than short-acting bronchodilators alone. The present study shows potentially useful additive effects of salmeterol when given with short-acting anticholinergic agents.

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