

Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids

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Background: Traditional clinical outcomes have demonstrated that salmeterol improves pulmonary function and reduces asthma symptoms. However, they do not evaluate how patients perceive the effect of therapeutic intervention on day-to-day functioning and well-being.

Objective: We sought to evaluate the impact of salmeterol on disease-specific quality of life with the Asthma Quality-of-Life Questionnaire, as well as the efficacy and safety of salmeterol in patients with stable asthma who were symptomatic despite daily use of inhaled corticosteroids.

Methods: This was a randomized, double-blind, placebo-controlled, parallel-group study of 506 patients. Patients were treated with 42 µg salmeterol or placebo twice daily for 12 weeks delivered through a metered dose inhaler.

Results: Mean change from baseline in asthma quality-of-life scores was significantly greater ($p \leq 0.006$) after 12 weeks of treatment with salmeterol compared with placebo ("as-needed" albuterol) in global scores (1.08 vs 0.61) and individual domains (activity limitations, 0.91 vs 0.54; asthma symptoms, 1.28 vs 0.71; emotional function, 1.17 vs 0.65; and environmental exposure, 0.84 vs 0.47). Patients treated with salmeterol experienced significantly greater improvements from baseline to week 12 compared with placebo in FEV₁ (0.42 L vs 0.15 L, $p < 0.001$), morning peak expiratory flow (47 L/min vs 14 L/min, $p < 0.001$), evening peak expiratory flow (29 L/min vs 11 L/min, $p < 0.001$), and asthma symptom scores (daytime scores reduced by 0.55 vs 0.30, $p < 0.001$). Patients treated with salmeterol used significantly less supplemental albuterol (reduced by 3 puffs/day vs 1 puff/day, $p < 0.001$).

Conclusion: Salmeterol provided significantly greater improvement in quality-of-life outcomes in patients whose asthma symptoms are not well controlled with inhaled corticosteroids. These results demonstrate that the benefits of salmeterol are not limited to conventional clinical measures of efficacy. (J Allergy Clin Immunol 1998;101:188-95.)

Key words: Salmeterol, asthma, quality of life, pharmacoeconomics

An improved understanding of the pathophysiology of asthma has led to the creation of guidelines for the long-term management of this disease.¹ Controller medications, particularly inhaled corticosteroids, should be administered daily to reduce and control airway inflammation.¹ If symptoms persist despite inhaled corticosteroid therapy, then long-acting inhaled β_2 -adrenoceptor agonists may provide additional benefit by improving control of asthma symptoms.^{1, 2} Salmeterol is a selective, long-acting, β_2 -adrenoceptor agonist that has a 12-hour duration of action,^{3, 4} which provides sustained improvements in pulmonary function and control of asthma symptoms.³⁻⁸

Although the effect of salmeterol on pulmonary function and asthma symptoms is well-defined, its effect on asthma-specific quality of life, particularly in distinct patient populations (i.e., inhaled steroid-naïve versus inhaled steroid-dependent patients), has not been extensively evaluated. With the recent development of disease-specific quality-of-life instruments, it is now possible to quantify the effect of therapeutic intervention on the day-to-day functioning and well-being of patients. The Asthma Quality of Life Questionnaire (AQLQ) is a validated asthma-specific instrument that is sensitive enough to detect changes in patients who respond to treatment and to differentiate the amount of change between treatment groups.⁹ This instrument is more sensitive than other disease-specific questionnaires or general health status instruments¹⁰; it is also reproducible in patients who have stable asthma.⁹ A major advantage of this type of questionnaire is its ability to detect beneficial changes that the patient can perceive.¹¹

Previous studies have demonstrated that salmeterol improves asthma-specific quality of life in patients with mild to moderate asthma.^{10, 12-16} However, these studies were limited by small numbers of patients, as well as by mixed populations of asthmatic subjects (i.e., various degrees of asthma severity) who may or may not have been concurrently treated with inhaled corticosteroids. The present double-blind, randomized, placebo-controlled study conducted in a large number of patients was designed to determine the effects of salmeterol on asthma-specific quality of life in patients whose symp-

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Abbreviations used

AQLQ: Asthma Quality-of-Life Questionnaire
PEF: Peak expiratory flow

toms were not well controlled while undergoing inhaled corticosteroid therapy.

METHODS

Patients

Male or female patients (≥ 12 years of age) were eligible for enrollment if they met the criteria for asthma as defined by the American Thoracic Society,¹⁷ had an average daytime or nighttime symptom score of 1 on a 0 to 3 point scale over a 2-week screening period, used a short-acting bronchodilator on a daily basis, and used a fixed dose of inhaled corticosteroid that was within package insert guidelines (i.e., beclomethasone dipropionate, 252 to 840 $\mu\text{g}/\text{day}$; flunisolide, 1000 to 2000 $\mu\text{g}/\text{day}$; or triamcinolone acetonide, 600 to 1600 $\mu\text{g}/\text{day}$). Patients were excluded if any of the following were present: tobacco use, oral corticosteroid therapy, immunotherapy requiring dosage change, inability to withdraw asthma/allergy medications before pulmonary function testing at screening (e.g., oral β_2 -agonists for 12 to 24 hours or xanthines for 12 to 48 hours) or at 4, 8, and 12 week visits (e.g., inhaled β_2 -agonists for 8 hours, anticholinergic eye drops for 24 hours, and antihistamines [except hydroxyzine and astemizole] for 48 hours), cystic fibrosis, chronic obstructive pulmonary disease, any significant uncontrolled disease state other than asthma, any other significant illness, pregnancy or lactation, contraindication to study medications, or inability to complete baseline quality-of-life assessment. Patients also had to have stable asthma that did not require excess albuterol use, which was defined as either more than 12 puffs daily or 12 puffs for 3 or more days per week. In addition, patients could not have required hospitalization for asthma within 3 months, mechanical ventilation during an asthma exacerbation within 2 years, or more than 2 albuterol (or equivalent) inhalers per month within 3 months of screening. All patients gave written informed consent; the protocol was approved at each clinical center by an institutional review board.

Study design

Forty-four centers participated in a placebo-controlled, parallel-group study conducted over a 14-week period consisting of a 2-week screening period followed by a 12-week randomized, double-blind, treatment period. During screening, patients used albuterol on an as-needed basis to relieve breakthrough symptoms in addition to inhaled corticosteroids.

The purpose of the screening period was to assess eligibility, to evaluate the stability of each patient's asthma, to educate patients on the use of study medications and tests, and to collect baseline data. At the screening visit, patients had to have a FEV₁ of 40% to 80% of their predicted value^{18, 19} and reversible airways disease as demonstrated by a 15% or greater increase in FEV₁ from baseline within 30 minutes after two inhalations of albuterol. Pulmonary function tests were measured in triplicate with spirometry equipment that met American Thoracic Society performance standards.²⁰ During the screening period, patients used albuterol as needed for breakthrough symptoms and inhaled corticosteroids to treat their asthma, measured morning and evening peak expiratory flow (PEF), and assessed daytime

TABLE I. Patient demographics, disposition, and baseline pulmonary function and AQLQ scores

Variable	Placebo	Salmeterol
No. of patients	254	252
Sex (M/F [%])	48/52	45/55
Age (yr)		
Mean $\pm$ SEM	41.6 $\pm$ 1.0	42.0 $\pm$ 1.0
Range	12-78	12-85
Pulmonary function (mean FEV ₁ $\pm$ SEM)		
L	2.17 $\pm$ 0.04	2.16 $\pm$ 0.04*
% Predicted	63 $\pm$ 1	63 $\pm$ 1*
Mean PEF (L/min)†		
Morning	369 $\pm$ 6	372 $\pm$ 7
Evening	394 $\pm$ 6	401 $\pm$ 7
AQLQ scores $\pm$ SEM		
Global	4.27 $\pm$ 0.06	4.30 $\pm$ 0.06
Activity limitation	4.57 $\pm$ 0.07	4.64 $\pm$ 0.07
Asthma symptoms	4.05 $\pm$ 0.06	4.07 $\pm$ 0.07
Emotional function	4.02 $\pm$ 0.09	3.96 $\pm$ 0.09
Environmental exposure	4.45 $\pm$ 0.09	4.50 $\pm$ 0.09
No. of patients completed	207 (81%)	227 (90%)
No. of patients withdrawn	47 (19%)	25 (10%)
Withdrawn because of		
Lack of efficacy	9 (4%)	2 (<1%)
Adverse event	5 (2%)	7 (3%)
Failure to return	7 (3%)	2 (<1%)
Other	26 (10%)	14 (6%)

*FEV₁ data were not available for two patients in the salmeterol group.

†Pretreatment mean for baseline (at the end of the screening period).

and nighttime asthma symptoms. Albuterol (Ventolin [albuterol, USP]; Glaxo Wellcome Inc., Research Triangle Park, N.C.) was supplied as an inhalation aerosol that delivered 90 μg per actuation. Patients were instructed on the use of the PEF meter.

To be eligible for randomization, patients had to maintain their diary cards throughout the screening period and have symptomatic, but stable, asthma. Patients had to have an average symptom score for the screening period of at least 1 in at least one of the following four symptom categories: daytime symptoms of chest tightness, wheezing, and shortness of breath and sleep symptoms. Each symptom category was rated by the patients on a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Patients meeting all entry criteria were randomly assigned to receive either salmeterol or placebo. Salmeterol (Serevent; Glaxo Wellcome Inc.) was supplied as salmeterol xinafoate in a metered dose inhaler that delivered 21 μg (each actuation delivers 21 μg of salmeterol from the actuator) of salmeterol per inhalation (total dose, 42 μg). Patients were instructed to take two inhalations twice daily in the morning and evening (approximately 12 hours apart) and to continue to use albuterol on an as-needed basis to relieve breakthrough symptoms. Patient-obtained morning and evening PEF measurements, daytime and nighttime symptom scores, the number of nocturnal awakenings, and the number of inhalations of supplemental albuterol were recorded daily on diary cards.

During the double-blind study period, patients were evaluated in the clinic on treatment day 1 and after 4, 8, and 12 weeks of treatment. At each visit diary cards were evaluated, vital signs

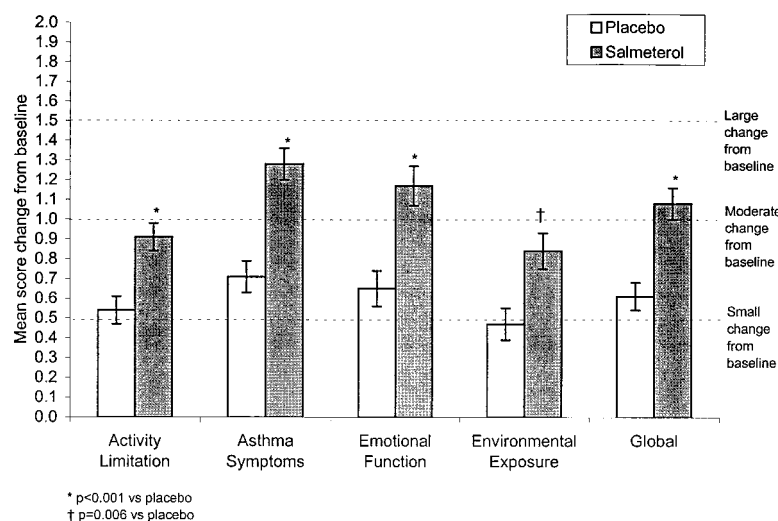


FIG. 1. Change in asthma quality-of-life scores from baseline to week 12. * $p < 0.001$; † $p = 0.006$.

were recorded, pulmonary function tests were performed, and adverse events and asthma stability were reviewed. Patients were required to withhold as-needed albuterol for 8 hours before performing pulmonary function tests but were not required to withhold blinded study medications.

Patients completed the AQLQ⁹ at the screening visit; on treatment day 1; and at the 4-, 8-, and 12-week visits. This disease-specific, self-administered instrument assesses quality of life over the previous 2-week time interval. Each item is scored on a scale from 1 to 7, with lower scores indicating greater impairment in quality of life and higher scores indicating less impairment in quality of life. Items are grouped into four domains: activity limitation (assesses the amount of limitation of individualized activities that are important to the patient and are impacted by asthma); asthma symptoms (assesses the frequency and degree of discomfort of shortness of breath, chest tightness, wheeze, chest heaviness, cough, difficulty breathing out, fighting for air, heavy breathing, and difficulty getting a good night's sleep); emotional function (assesses the frequency of being afraid of not having medications, concerned about medications, concerned about having asthma, and being frustrated); and environmental exposure (assesses the frequency of exposure to and avoidance of irritants such as cigarette smoke, dust, and air pollution). Individual domain scores are calculated, as well as a global score. A change of 0.5 (both for global and individual domain scores) represents the smallest difference perceived by patients as beneficial.

Statistical analyses

The target enrollment size of 300 patients per treatment group was chosen to provide 80% power of detecting differences in efficacy variables at a significance level of 0.05. A target enrollment size of approximately 80 patients per treatment arm was necessary to detect a clinically significant difference of 0.5 in AQLQ scores at a significance level of 0.05. The AQLQ global score was the primary endpoint. Statistical inferences for AQLQ data were made on the basis of the global score; therefore adjustments for multiple comparisons were not made when discussing the individual domains. Efficacy measures included FEV₁, morning and evening PEF,

diurnal variation in PEF (measured as the difference between mean evening and next morning PEF), patient-rated symptom scores, and supplemental albuterol use. Safety was assessed by monitoring adverse events, asthma exacerbations, and vital signs. Adverse events were potentially considered treatment related if investigators determined that the adverse events were possibly, probably, or almost certainly related to the study drug. Safety analyses were done on the basis of data from the intent-to-treat population (i.e., all patients exposed to the study drug), and efficacy analyses (including AQLQ analyses) were done on the basis of data from the intent-to-treat population minus patients excluded because of significant protocol violations. By-visit analyses were performed only on data from patients remaining in the study at that specific visit.

Demographic and baseline disease characteristics were summarized and tested for group differences with the Cochran-Mantel-Haenszel test and analysis of variance for nonparametric and parametric variables, respectively, each controlling for investigator. Terms for investigators were included in the statistical models to adjust for site-to-site differences. For parametric variables such as pulmonary function test and quality-of-life data, within-group differences were analyzed by *t* tests and paired by patient. Between-group differences were analyzed by analysis-of-variance *F* tests on change from baseline, controlling for investigator. For nonparametric variables such as symptoms, between-group comparisons of differences from baseline were analyzed by the van Elteren test,²¹ controlling for investigator. Analyses of patient-rated PEF rates and symptoms were done on the basis of 7-day averages within subjects that were then averaged over treatment groups. The incidence of adverse events was tabulated by treatment group and analyzed for treatment differences with Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Five hundred eighty-one patients were eligible for entry into the study and entered the screening period. Five hundred six patients were randomized and evenly distributed between the two treatment groups with re-

spect to patient demographics and pulmonary function at the screening visit (Table I). Seventy-two (14%) patients did not complete the 12-week treatment period; however, the majority of these patients were withdrawn because of failure to return or protocol violations. Withdrawal because of lack of efficacy occurred in 4% of patients in the placebo group compared with less than 1% in the salmeterol group.

Quality of life

At baseline, the AQLQ domain and global scores were not significantly different between treatment groups (Table I). At weeks 4, 8, and 12, both treatment groups showed significant ($p < 0.001$) improvements from their baseline domain and global scores. However, the improvement in all domains was significantly ($p \leq 0.016$) greater in salmeterol-treated patients compared with placebo-treated (i.e., as-needed albuterol) patients. Fig. 1 shows the mean change from baseline to week 12 for the two treatment groups.

The salmeterol group met the reported criteria for clinically significant improvements (i.e., small change = 0.5; moderate change = 1.0; large change = 1.5) in all domains (and global) first evident at week 4 (Table II) and continuing through week 12 (mean score change, ≤ 1.28 ; Fig. 1). By week 4, the placebo group scores did not meet the criteria for a small change in any of the domains. However, by week 12, the placebo group scores met the criteria for a small change from baseline for all domains (mean score change, ≤ 0.71 ; Fig. 1, Table II) except the environmental exposure domain. The difference between treatment groups for mean AQLQ score changes from baseline was at least 0.5 points greater (range, 0.51 to 0.66) for salmeterol at weeks 4, 8, and 12 for the asthma symptoms and emotional function domains and at week 8 for the global score (Table II).

Moderate, statistically significant ($p < 0.001$) correlations between the changes in quality-of-life and clinical asthma indices efficacy variables were observed and are presented in Table III.

Clinical asthma indices

Patients treated with salmeterol experienced significantly greater increases in morning PEF ($p < 0.001$) and evening PEF ($p < 0.037$), whereas diurnal variation in PEF decreased ($p < 0.002$) compared with patients treated with placebo throughout 12 weeks of treatment. Mean change from baseline in morning PEF at week 12 was 47 L/min and 14 L/min after treatment with salmeterol and placebo, respectively ($p < 0.001$). Mean change from baseline in evening PEF at week 12 was 29 L/min and 11 L/min after treatment with salmeterol and placebo, respectively ($p < 0.001$). Mean change from baseline in diurnal variation of PEF at week 12 was -19 L/min and -2 L/min after treatment with salmeterol and placebo, respectively ($p < 0.001$). There was no deterioration or decrease in PEF with either treatment during the 12-week treatment period.

TABLE II. Mean AQLQ score changes from baseline $\pm$ SEM and differences between treatment groups

Domains	Placebo	Salmeterol	Difference between treatment groups
Global			
Week 4	0.39 $\pm$ 0.06	0.85 $\pm$ 0.07	0.46
Week 8	0.51 $\pm$ 0.07	1.02 $\pm$ 0.07	0.51
Week 12	0.61 $\pm$ 0.07	1.08 $\pm$ 0.08	0.47
Activity limitation			
Week 4	0.36 $\pm$ 0.06	0.71 $\pm$ 0.06	0.35
Week 8	0.46 $\pm$ 0.07	0.80 $\pm$ 0.06	0.34
Week 12	0.54 $\pm$ 0.07	0.91 $\pm$ 0.07	0.37
Asthma symptoms			
Week 4	0.47 $\pm$ 0.07	1.03 $\pm$ 0.08	0.56
Week 8	0.59 $\pm$ 0.08	1.25 $\pm$ 0.08	0.66
Week 12	0.71 $\pm$ 0.08	1.28 $\pm$ 0.08	0.57
Emotional function			
Week 4	0.37 $\pm$ 0.08	0.93 $\pm$ 0.09	0.56
Week 8	0.53 $\pm$ 0.09	1.13 $\pm$ 0.09	0.60
Week 12	0.65 $\pm$ 0.09	1.17 $\pm$ 0.10	0.52
Environmental exposure			
Week 4	0.23 $\pm$ 0.07	0.63 $\pm$ 0.08	0.40
Week 8	0.41 $\pm$ 0.08	0.77 $\pm$ 0.08	0.36
Week 12	0.47 $\pm$ 0.08	0.84 $\pm$ 0.09	0.37

$p \leq 0.016$, salmeterol versus placebo at all time points for mean change from baseline.

Patients treated with salmeterol experienced significantly greater improvement in FEV₁ than patients treated with placebo throughout the 12-week treatment period ($p < 0.001$). Mean change from baseline in FEV₁ was 0.42 L and 0.15 L at week 12 for salmeterol and placebo, respectively.

Patients treated with salmeterol experienced greater improvement in symptom scores and reductions in supplemental albuterol use than patients treated with placebo; all between-group differences were significant for weeks 1 through 12 ($p < 0.001$; Table IV). In the salmeterol group, the combined daytime symptom score for symptoms of chest tightness, wheezing, and shortness of breath progressively decreased from baseline over the treatment period, from a 32% decrease at week 1 to a 51% decrease at week 12. Corresponding scores in the placebo group decreased by 10% at week 1 and 33% at week 12. Fig. 2 illustrates that the percentage of symptom-free days increased progressively more in the salmeterol group than it did in the placebo group ($p < 0.001$). Mean daytime supplemental albuterol use decreased from 4.94 puffs to 2.20 puffs in patients treated with salmeterol and from 4.65 puffs to 3.61 puffs in patients treated with placebo ($p < 0.001$). Mean nighttime supplemental albuterol use decreased from 1.26 puffs to 0.53 puffs in patients treated with salmeterol and from 1.25 puffs to 1.06 puffs in patients treated with placebo ($p < 0.001$). Mean change from baseline in

TABLE III. Relationship between changes in quality of life and changes in efficacy variables

Efficacy variable	Spearman correlation coefficient for relationship with quality-of-life variable				
	Activity	Symptoms	Emotions	Environment	Global
FEV ₁	0.31	0.35	0.30	0.24	0.35
PEF					
Morning	0.39	0.48	0.41	0.30	0.47
Evening	0.34	0.41	0.33	0.25	0.39
Supplemental albuterol					
Daytime	-0.36	-0.47	-0.44	-0.32	-0.46
Nighttime	-0.36	-0.45	-0.36	-0.25	-0.42
Nighttime awakenings	-0.38	-0.51	-0.35	-0.27	-0.46
Symptom score	-0.46	-0.59	-0.45	-0.34	-0.54

All correlations are significant at $p < 0.001$.

TABLE IV. Mean change from baseline in patient-rated symptoms

Variable	Mean change from baseline $\pm$ SEM (% change)	
	Placebo	Salmeterol
Symptoms (mean)*		
Daytime†	-0.30 $\pm$ 0.03 (-25%)	-0.55 $\pm$ 0.03 (-45%)
Nighttime†	-0.26 $\pm$ 0.04 (-21%)	-0.65 $\pm$ 0.04 (-52%)
Supplemental albuterol (puffs/day)		
Daytime†	-1.06 $\pm$ 0.12 (-23%)	-2.73 $\pm$ 0.16 (-55%)
Nighttime†	-0.18 $\pm$ 0.07 (-14%)	-0.75 $\pm$ 0.07 (-60%)
% Without supplemental albuterol		
Days†	13.6 $\pm$ 1.8 (223%)	38.1 $\pm$ 2.3 (693%)
Night†	9.5 $\pm$ 1.8 (20%)	29.2 $\pm$ 2.4 (62%)

*Symptom scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

† $p < 0.001$, between-group difference in change from baseline.

supplemental albuterol use is shown in Table IV. The percentage of days without supplemental albuterol use increased five- to eightfold in the salmeterol group and one- to threefold in the placebo group. Analogous findings were observed for nighttime symptoms and nighttime supplemental albuterol use. The percentage of nights without awakenings at week 12 increased by 61% from baseline in the salmeterol group compared with an increase of 30% in the placebo group ($p < 0.001$).

Safety

Adverse events were reported in 53% and 51% of patients treated with salmeterol and placebo, respectively. Most adverse events were not considered to be related to treatment as treatment-related adverse events occurred in only 13 patients (5%) in the placebo group and in 11 patients (4%) in the salmeterol group. No single treatment-related adverse event (which included insomnia, migraine, paresthesias, chest tightness/pain, heat sensation, pharyngeal complaints, shortness of breath, dyspnea, respiratory failure, flushing, increased blood pressure, anxiety, agitation, muscle cramp, and macular rash) affected more than 1% of patients in either treatment group. Twelve patients (2%) did not

complete the study because of adverse events; five were treated with placebo and seven were treated with salmeterol (see Table I). Of those patients who were discontinued from the study, only three patients experienced adverse events that were considered by the investigator to be potentially related to treatment (salmeterol, chest tightness; placebo, shortness of breath; placebo, chest pain). One salmeterol-treated patient experienced a serious adverse event (respiratory failure) that the investigator judged to be possibly related to the study drug. There were no clinically significant changes in blood pressure or pulse rate.

Asthma exacerbations were reported in 59 patients (22%) treated with placebo and in 53 patients (20%) treated with salmeterol. The most common reason cited for the cause of asthma exacerbation was respiratory infection.

DISCUSSION

The results of this study demonstrate that the addition of salmeterol to the treatment regimen of patients with symptoms while taking inhaled corticosteroids results in significant improvements in asthma-specific quality of life. These results support previous studies in which

traditional clinical outcome measures were used to show the efficacy of salmeterol in patients also treated with inhaled corticosteroids.²⁻⁵ Symptomatic patients treated with salmeterol experienced significantly greater improvements in asthma-specific quality of life than did patients treated with placebo (as-needed albuterol). The benefits of salmeterol were evident in all domains measured by the AQLQ, specifically asthma symptoms, activity limitation, emotional function, and environmental exposure. Salmeterol-induced improvements were significantly greater at the first treatment observation period at 4 weeks and persisted throughout the 12-week study period. Although patients in both groups experienced improvement, the changes were higher in the salmeterol group than in the placebo group. Importantly, the changes in the salmeterol group consistently met the criteria¹¹ for changes that were of at least minimal (≥ 0.5 points) or moderate (≥ 1.0 points) importance to the patient. In contrast, only some changes in the placebo group met the criteria for minimally important improvement. These small improvements noted with placebo may reflect the traditional "placebo effect" or the increased level of care from health care providers in the clinical study environment, which encourages patient compliance and which may give patients the perception that management of their disease is better. Furthermore, patients treated with placebo in this study were also being treated with significantly more as-needed albuterol, which may have had some impact on reported improvements in that group.

These results corroborate the outcomes of previous studies showing that salmeterol produces greater improvements in asthma-specific quality of life than placebo,^{12, 15, 16} previous therapies,¹³ albuterol,^{10, 15} or cromolyn sodium.¹⁴ Two of these studies^{10, 15} are of particular interest because they used the same questionnaire as that used in this study. The study designs were generally similar to the current design except for the enrollment of only 120¹⁰ or 140¹⁵ patients, inclusion of patients with mild to moderate persistent asthma in one study,¹⁵ and use of albuterol as an active control instead of¹⁰ or in addition to¹⁵ placebo. Rutten-van Mölken et al.¹⁰ reported that a 6-week course of salmeterol produced significantly greater improvements than albuterol in two of four domains and in global scores. Juniper et al.¹⁵ reported that a 12-week course of salmeterol produced significantly greater improvement than albuterol or placebo in all four domains and in global scores. In that study the between-group differences for mean AQLQ score change from baseline were considered to be clinically important (mean difference in score ≥ 0.5) to the patient in the asthma symptoms and emotional function domains as well as in global scores. Similarly, in this study clinically significant differences between treatment groups were noted in the asthma symptoms and emotional function domains throughout the study and in global scores at week 8.

Moderate correlations between the changes in quality-of-life and clinical asthma indices were observed in this

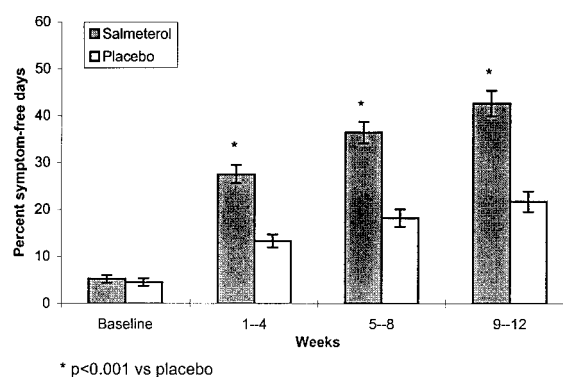


FIG. 2. Percent of days without symptoms. * $p < 0.001$.

study. These results are consistent with moderate correlations observed in other studies^{10, 15} with salmeterol suggesting that the AQLQ evaluates a separate component of asthma that is not effectively evaluated by conventional physiologic measures. Wisniewski et al.²² confirm this observation with a principle component analysis conducted on data from 770 patients who participated in six randomized, double-blind studies comparing salmeterol (42 μ g twice daily) to placebo over 12 weeks of treatment. The analysis revealed four independent categories of asthma measures (quality-of-life measures, clinical measures, daytime patient-rated symptoms, and nighttime patient-rated symptoms). The authors concluded that, "Although quality of life as determined by the AQLQ has a symptom measure component, it is not linked completely to symptom and clinical measures. Therefore, quality of life should be considered as a separate collection of measures for asthma."²²

Salmeterol significantly improved pulmonary function measurements compared with placebo at each assessment in this study. Patients receiving salmeterol also had significantly fewer asthma symptoms and required less supplemental albuterol use, both during the day and night. The extent of improvement in clinical outcomes in this study was generally consistent with that described in other double-blind comparisons of salmeterol with placebo,^{3, 4} inhaled corticosteroid^{2, 23} or albuterol,³⁻⁵ oral terbutaline,⁷ or theophylline.^{6, 8, 24} The studies by Greening et al.² and Woolcock et al.²³ are of interest because their enrollment criteria were similar to those of this study. For example, in the study by Greening et al.,² patients had persistent symptoms despite treatment with beclomethasone dipropionate 200 μ g (168 μ g) twice daily; patients continued corticosteroid therapy and were randomized to either add salmeterol 50 μ g (42 μ g) twice daily or increase the dosage of beclomethasone to 500 μ g (420 μ g) twice daily, each for 6 months (the above doses reflect the amount of drug that is released from the valve of the metered dose inhaler, with ex-actuator doses indicated in parentheses). In patients

receiving salmeterol, the improvements at 3 months in morning (13% versus 9%²) and evening PEF values (7% versus 5%²) were slightly higher in this study compared with improvements reported by Greening et al.² Corresponding changes in disturbance-free nights (61% versus 55%²) and supplemental albuterol use during the day (-61% versus -40%²) and night (-60% and -43%²) also indicated greater improvement in the current study. Results from the Greening and Woolcock studies suggest that in patients who remain symptomatic despite treatment with low doses of inhaled corticosteroids, the addition of an inhaled, long-acting bronchodilator is a more effective treatment option than increasing the dose of inhaled corticosteroids. Consistent with the results of other studies, there was no deterioration in asthma control as measured by symptom scores, rescue medication use, pulmonary function tests, or quality-of-life scores with regular use of salmeterol for 12 weeks.

Salmeterol was well tolerated in this study. Importantly, in this study asthma exacerbations and the type and incidence of adverse events were evenly distributed between treatment groups, which is consistent with the results from other studies,^{3-5, 25} except in the study⁶ in which salmeterol was associated with a quantitatively lower incidence of selected adverse events than was theophylline.

In summary, we believe this study provides important new information regarding the benefits of adding salmeterol to the treatment regimen of patients whose asthma is not well controlled by the use of inhaled corticosteroids. In these patients salmeterol provides significant improvements in asthma-specific quality of life and clinical efficacy measures without any additional safety risks.

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