Salmeterol Plus Theophylline Combination Therapy in the Treatment of COPD*

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Background: Patients with COPD often require multiple therapies to improve lung function and decrease symptoms and exacerbations. Salmeterol and theophylline are indicated for the treatment of COPD, but the use of these agents in combination has not been extensively studied.

Objectives: To compare the efficacy and safety of salmeterol plus theophylline vs either agent alone in COPD.

Methods: Randomized, double-blind, double-dummy, parallel-group trial in 943 patients with COPD. After an open-label theophylline titration period (serum levels, 10 to 20 μg/mL), patients were randomly assigned to receive salmeterol (42 μg bid) plus theophylline, salmeterol (42 μg bid), or theophylline for 12 weeks. Serial pulmonary function tests were completed on day 1 and treatment week 12. Patients kept diary cards and noted their peak flow rates, symptom scores, and albuterol use, and periodically completed quality-of-life and dyspnea questionnaires.

Results: All three groups significantly improved compared with baseline. Combination treatment with salmeterol plus theophylline provided significantly (p < 0.045) greater improvements in pulmonary function; significantly (p < 0.048) greater decreases in symptoms, dyspnea, and albuterol use; and significantly fewer COPD exacerbations (p = 0.023 vs theophylline). In general, treatment with salmeterol provided greater improvement in lung function and satisfaction with treatment compared with theophylline. Salmeterol treatment was also associated with significantly fewer drug-related adverse events (p < 0.042) than either treatment that included theophylline. In general, the safety profile (adverse events, vital signs, and ECG findings) of the two treatments that included theophylline were similar.

Conclusion: Patients with COPD may benefit from combination treatment with salmeterol plus theophylline, without a resulting increase in adverse events or other adverse sequelae.

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Key words: chronic bronchitis; combination therapy; COPD; dyspnea; emphysema; exacerbations; FEV1; quality of life; salmeterol; theophylline

Abbreviations: ANOVA = analysis of variance; AUC = area under the curve; BDI = baseline dyspnea index; CI = confidence interval; CRDQ = chronic respiratory disease questionnaire; HRQL = health-related quality of life; MDI = metered-dose inhaler; PEF = peak expiratory flow; PFT = pulmonary function testing; SALM = salmeterol twice daily; SALM + THEO = salmeterol twice daily plus theophylline twice daily; TDI = transitional dyspnea index; THEO = theophylline twice daily

COPD is a progressive disease that is characterized by the presence of airflow obstruction due to chronic bronchitis and/or emphysema.1,2 Current treatments for COPD are aimed at increasing airflow, decreasing respiratory symptoms (particularly dyspnea), decreasing exacerbations, and improving the quality of life. Multiple therapies, including short-acting and long-acting bronchodilators, anticholinergics, methylxanthines, and corticosteroids, are used as single agents or more commonly in combination to treat patients with COPD.1,2

Theophylline, a methylxanthine derivative, has been used in the treatment of COPD for many years. Studies3–8 have shown that theophylline can increase lung function, decrease symptoms, and improve
Materials and Methods

Patient Selection

Male and female patients ≥ 45 years old with COPD due to chronic bronchitis or emphysema were recruited to participate from 74 outpatient clinics in the United States. Screening entry criteria required a smoking history of at least 20 pack-years, FEV₁ ≥ 0.70 L and ≤ 65% of predicted normal based on standards of Crapo et al.,10 and an FEV₁/FVC ratio of ≥ 70%. Patients with an FEV₁ < 0.70 L were eligible if their percent predicted FEV₁ was at least 40% of predicted normal. Patients with a history of asthma, a daily continuous oxygen requirement, a recent viral or bacterial pulmonary infection, congestive heart failure, or other clinically active diseases were excluded. Patients were not permitted to receive inhaled ipratropium during the study or have any changes in their regular COPD medications within 4 weeks from the screening visit. Stable doses of inhaled corticosteroids and/or oral corticosteroid doses (≤ 10 mg/d of prednisone or equivalent) were allowed.

Study Design and Conduct

This randomized, double-blind, double-dummy, parallel-group trial compared the efficacy and safety of three treatments for 12 weeks: (1) salmeterol, 42 µg bid via metered-dose inhaler (MDI) plus oral sustained-release theophylline twice daily; (2) salmeterol, 42 µg bid; or (3) oral sustained-release theophylline twice daily. The study protocol was approved by various institutional review boards, and all patients granted their permission to participate by signing written informed consent. This article combines the results of two identical, randomized, double-blind, double-dummy, parallel-group trials.

The study consisted of a screening visit, a 7- to 10-day baseline period, and 12 weeks of double-blind treatment. During the baseline period, patients continued to receive their regular COPD medications (not otherwise excluded) and complete diary cards. After at least 5 days, patients began the open-label theophylline titration period by taking the theophylline dose prescribed by the investigator. Patients returned to the clinic for serum theophylline concentration checks and had the dose adjusted as necessary until the target peak serum theophylline concentration of 10 to 20 µg/mL was achieved. Patients unable to reach the target theophylline concentration in three visits were withdrawn.

At visit 1 (after the theophylline titration), patients discontinued the use of the open-label theophylline and were randomly assigned to the oral medication component of their double-blind treatment using the dose identified during the titration period. Reversible patients (ie, those with at least a 200-mL and 12% improvement in FEV₁ within 30 min of inhalation of two puffs of albuterol) and nonreversible patients were stratified in order to ensure balance between the treatment groups.

Patients returned to the clinic within 3 to 5 days for visit 2, at which time they were randomized to the inhaled medication component of their treatment regimen. The purpose of this staggered randomization period was to permit a washout of the effects of theophylline for those patients assigned to salmeterol treatment alone. Serial spirometric assessments were obtained immediately predose (time 0, prior to the first dose of inhaled study medication) and at 0.5, 1, 2, 4, 6, 8, 10, and 12 h postdose.

Patients attended the clinic after 4 weeks, 8 weeks, and 12 weeks of treatment for evaluations of pulmonary function, dyspnea, HRQOL, and satisfaction with treatment. Dyspnea was assessed using the baseline dyspnea index (BDI) and the transitional dyspnea index (TDI).20 HRQOL was assessed by the chronic respiratory disease questionnaire (CRDQ), a 20-item questionnaire with four components (dyspnea, fatigue, emotional function, and the feeling of mastery over disease).21,22 The satisfaction with treatment questionnaire evaluated the patient’s overall satisfaction with his/her medication as well as attributes of satisfaction, including how well the medication worked, how fast it worked, how long it worked, how good it made the patient feel, and side effects using a 7-point scale, from 0 = very dissatisfied to 6 = very satisfied.

Patients recorded on diary cards their morning and evening peak expiratory flow (PEF), daily COPD symptoms, and albuterol use. COPD symptoms were rated by the patients with a 5-point scale, from 0 = no symptoms at all during the day to 4 = symptoms so severe that the patient was not able to do most daily activities. An albuterol treatment was defined as inhalation of two puffs from an MDI or one nebul of solution for nebulization. Compliance was assessed via patient report of medication use and by pill counts.

A COPD exacerbation was defined as a worsening of symptoms requiring an increase in drug therapy (not including albuterol). Exacerbations could be treated with oral/parenteral corticosteroids for ≤ 14 days. Patients who required hospitalization or who experienced more than one exacerbation during the study were withdrawn.

Treatments

Blinded study treatments were an MDI (salmeterol, 42 µg bid; Serevent Inhalation Aerosol; Glaxo Wellcome Inc; Research Triangle Park, NC) or matching placebo, and an oral theophylline capsule, 100 mg (Slo-Bid Gyrocaps; Aventis Pharma; Parsippany, NJ) or matching placebo. Patients were randomly assigned in a 1:1:1 ratio to receive salmeterol twice daily plus theophylline twice daily (SALM + THEO), salmeterol twice daily (SALM), or theophylline twice daily (THEO). All patients received albuterol (Ventolin Inhalation Aerosol and/or Ventolin Inhalation Solution, 0.5%; Glaxo Wellcome Inc) to use as necessary.

Statistical Methods

Data from five patients at one site were excluded from analyses of efficacy due to concerns about study conduct, but all data from
all sites were included in the analyses of safety. Data from patients withdrawn early were included in the analyses up to the time of study discontinuation. No interpolation was used for missing data. Statistical analyses were based on two-sided tests conducted at the 0.05 significance level and compared differences between pairs of treatment groups.

The primary efficacy measure was the mean change from baseline in the area under the FEV₁ vs time curve during 12-h serial pulmonary function testing (PFT) on day 1 and week 12. Secondary efficacy measures included other pulmonary function parameters (predose FEV₁, FEV₁, and FVC over the 12 h of serial testing), TDI focal scores, morning and evening PEF, symptom scores, albuterol use, COPD exacerbations, HRQOL, and treatment satisfaction.

Baseline FEV₁ area under the curve (AUC) was the screening FEV₁ value times 12 h. Baseline values for PEF, symptoms, and supplemental albuterol use were obtained from the 5 days of the screening period prior to theophylline titration. Comparisons among treatment groups for serial pulmonary function, PEF, dyspnea ratings (BDI/TDI), and albuterol use were made by analysis of variance (ANOVA) including terms for treatment, investigator, and baseline. Comparisons among treatment groups for symptoms, albuterol use, and percentage of symptom-free and albuterol-free days were made using a van Elteren test controlling for investigator. Ninety-five percent confidence intervals (CIs) for treatment differences were also calculated using analysis of covariance with treatment, investigator, and baseline in the model.

The mean changes from baseline in the CRDQ data and satisfaction with treatment data were compared among treatments using an ANOVA controlling for baseline and investigator. In addition to analyzing the mean changes from baseline in the CRDQ data, the proportion of patients with a clinically significant improvement in the overall and component parts of the CRDQ were compared between treatments using a Cochran-Mantel-Haenszel test controlling for investigator. A total improvement score of ≥ 10 points was considered clinically significant.

Safety was assessed by clinical adverse events, vital signs, ECG, and theophylline concentrations. Adverse events, reported either spontaneously by the patient or elicited during clinic visits, were recorded regardless of the suspected relationship with study treatment. The proportion of patients with adverse events, COPD exacerbations, and clinically significant ECG changes from baseline were compared using the Fisher’s Exact Test. Mean changes from baseline in vital signs and mean theophylline concentrations were compared between treatment groups using an ANOVA controlling for investigator and baseline.

**RESULTS**

**Disposition and Demographics**

A significant percentage of screened patients (242 of 1,185; 20%) were withdrawn during the open-label theophylline titration period (Fig 1). Of these, 107 of 242 patients (44%) were withdrawn due to adverse events related to theophylline, and an additional 30 of 242 patient (12%) failed to achieve the target theophylline concentration within the allotted time period. Once randomization to study treatment was complete, 86% (803 of 938) of the patients completed the study. The most common reason for withdrawal was adverse events, affecting 70 patients overall (19 patients [6%] in the SLM + THEO group, 25 patients [8%] in the SLM group, and 26 patients [8%] in the THEO group). Two patients died during the study from conditions unrelated to study drug: one patient died during the theophylline titration period (COPD exacerbation), and the other patient died during treatment with theophylline (pulmonary embolism).

The treatment groups were balanced at baseline with respect to demographics and COPD history (Table 1). Mean screening pulmonary function was generally comparable between treatments, reflecting moderate-to-severe COPD, and the distribution of reversible and nonreversible patients was similar (Table 2). Medication compliance rates, as recorded by the patients and by pill counts, were high (> 90%).

**Pulmonary Function**

Mean predose FEV₁ and FVC values significantly improved compared to baseline in both the SLM + THEO group and the SLM group at week 4, week 8, and week 12 (p < 0.001). The same was true for the THEO group (p ≤ 0.021), with the
exception of the predose FVC assessment at week 12. The SALM + THEO group experienced significantly greater improvement in FEV\textsubscript{1} and FVC than either the SALM group or the THEO group (p ≤ 0.020; Table 3). Although the improvements in the SALM group were slightly greater than those in the THEO group for both FEV\textsubscript{1} and FVC, the differences were not significant.

Serial PFT for FEV\textsubscript{1} (Fig 2) and FVC (Fig 3) showed that the SALM + THEO group experienced significantly greater improvement at most time points than the SALM group or the THEO group (p ≤ 0.045). At week 12, the 95% CIs for predose FEV\textsubscript{1} mean change from baseline treatment differences were 0.04 to 0.13 and 0.07 to 0.16 for the SALM + THEO – SALM groups and the SALM + THEO – THEO groups, respectively. With predose FVC at week 12, the 95% CIs for treatment differences were 0.04 to 0.21 and 0.09 to 0.26, respectively. The SALM group experienced significantly greater improvement than the THEO group in FEV\textsubscript{1} and FVC during the first several hours postdose, most notably on day 1 (p ≤ 0.046). The rank order of improvement (SALM + THEO > SALM > THEO) was similar in the reversible and nonreversible patients. Evaluations of the FEV\textsubscript{1} AUC showed that the SALM + THEO group experienced significantly greater improvement than the SALM group or the THEO group overall (all patients) and also for the subgroups of reversible and nonreversible patients on day 1 and week 12 (p ≤ 0.002; Fig 4). On day 1, the SALM group experienced significantly greater improvement than the THEO group overall and in the reversible patients (p ≤ 0.011). There was no difference between the SALM group and the THEO group at week 12. A similar pattern was observed for serial FVC results in the reversible and nonreversible patients (data not shown).

### Other Efficacy Measures and COPD Exacerbations

All secondary outcome measures were similar among the treatment groups at baseline and all experienced significant within-treatment group improvements from baseline during the study (Table 4). The SALM + THEO group experienced significantly greater improvements in dyspnea (TDI scores), albuterol-free days, and PEF, and required significantly fewer supplemental albuterol treatments than either the SALM group or the THEO group (p ≤ 0.048). Furthermore, the SALM + THEO group experienced significantly more symptom-free days (p = 0.023) compared with the THEO group. COPD exacerbations were experienced by significantly fewer patients in the SALM + THEO group (40 patients, 45 exacerbations) compared with the THEO group (62 patients, 96 exacerbations; p = 0.023), but not the SALM group (56 patients, 71 exacerbations; p = 0.076).

### HRQOL and Satisfaction With Treatment

Mean overall CRDQ scores at baseline (83 to 84 points, maximum 140) were similar among treatment groups and indicated moderate impact of disease on quality of life. During the study, each treatment group experienced significant improvements compared to baseline in overall CRDQ scores. The mean overall change from baseline in the SALM + THEO group (+11.2 points) was clinically meaningful (ie, ≥ 10 points) and was significantly greater (p ≤ 0.019) at week 4 compared to the SALM group and the THEO group (+6.3 points for the SALM group; +5.1 points for the THEO group). At week 12, mean improvements in overall CRDQ scores were +12.7 points in the SALM + THEO group, +7.6 points in the SALM group, and +8.6 points in the THEO group (p ≥ 0.052). A significantly higher percentage of patients in the SALM + THEO group (52 to 54%) experienced a clinically important improvement overall compared with the SALM group (36 to 45%) or the THEO group (31 to 42%) at week 4 and week 12 (p ≤ 0.014). Improvements in pulmonary function were contrasted with improvements in HRQOL and TDI scores and found to be positively, but weakly, correlated (r = 0.2 and r = 0.11 for

### Table 1—Demographics and COPD History*

<table>
<thead>
<tr>
<th>Variables</th>
<th>SALM + THEO</th>
<th>SALM</th>
<th>THEO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Group</td>
<td>Group</td>
</tr>
<tr>
<td>Age, yr (SEM)</td>
<td>65.2 (0.5)</td>
<td>64.4 (0.5)</td>
<td>64.7 (0.5)</td>
</tr>
<tr>
<td>Range</td>
<td>45–47</td>
<td>45–47</td>
<td>46–46</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>67/33</td>
<td>64/36</td>
<td>71/29</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>290 (93)</td>
<td>281 (91)</td>
<td>296 (95)</td>
</tr>
<tr>
<td>African-American</td>
<td>14 (4)</td>
<td>18 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (2)</td>
<td>11 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of COPD, yr (SEM)</td>
<td>6.8 (0.4)</td>
<td>6.7 (0.4)</td>
<td>6.6 (0.4)</td>
</tr>
<tr>
<td>COPD type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>72 (23)</td>
<td>57 (18)</td>
<td>67 (21)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>156 (50)</td>
<td>157 (51)</td>
<td>174 (55)</td>
</tr>
<tr>
<td>Mixed</td>
<td>85 (27)</td>
<td>96 (31)</td>
<td>74 (23)</td>
</tr>
<tr>
<td>Emergency care within 12 mo</td>
<td>40 (13)</td>
<td>43 (14)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Hospitalizations within 12 mo</td>
<td>24 (8)</td>
<td>28 (9)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>130 (42)</td>
<td>126 (41)</td>
<td>122 (39)</td>
</tr>
<tr>
<td>Pack-yrs, No. (SEM)</td>
<td>65.6 (1.8)</td>
<td>62.5 (1.5)</td>
<td>62.6 (1.6)</td>
</tr>
<tr>
<td>Inhaled corticosteroid use</td>
<td>112 (36)</td>
<td>112 (36)</td>
<td>123 (39)</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td>32 (10)</td>
<td>43 (14)</td>
<td>43 (14)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
FEV1 AUC and FVC vs HRQOL, respectively, and $r = 0.19$ and $r = 0.14$ for FEV1 AUC and FVC vs TDI, respectively).

SALM + THEO treatment was rated as providing significantly greater overall satisfaction with treatment compared with the THEO group at all time points ($p \leq 0.012$) and compared with the SALM group at week 8 and week 12 ($p \leq 0.041$). SALM treatment provided significantly greater satisfaction with respect to side effects than either treatment involving theophylline ($p \leq 0.028$).

### Adverse Events

The proportion of patients reporting adverse events (regardless of causality) was not significantly different among treatment groups. However, the proportion of patients reporting adverse events that were judged to be related to study drug was significantly higher in both of the groups that received theophylline compared with the SALM group, most notably for GI events ($p \leq 0.042$; Table 5). Drug-related cardiovascular events were reported relatively rarely (1 to 4% overall) and were similar among treatment groups.

### Table 3—Predose FEV1 and Predose FVC Changes From Screening Measures*

<table>
<thead>
<tr>
<th>Variables</th>
<th>SALM + THEO Group (n = 300)</th>
<th>SALM Group (n = 302)</th>
<th>THEO Group (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose FEV1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>+ 0.18 (0.01)†</td>
<td>+ 0.09 (0.02)</td>
<td>+ 0.07 (0.01)</td>
</tr>
<tr>
<td>Week 8</td>
<td>+ 0.17 (0.02)†</td>
<td>+ 0.08 (0.02)</td>
<td>+ 0.07 (0.02)</td>
</tr>
<tr>
<td>Week 12</td>
<td>+ 0.16 (0.02)†</td>
<td>+ 0.07 (0.02)</td>
<td>+ 0.05 (0.02)</td>
</tr>
<tr>
<td>Predose FVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>+ 0.30 (0.03)†</td>
<td>+ 0.15 (0.03)</td>
<td>+ 0.11 (0.03)</td>
</tr>
<tr>
<td>Week 8</td>
<td>+ 0.26 (0.03)†</td>
<td>+ 0.14 (0.03)</td>
<td>+ 0.07 (0.03)</td>
</tr>
<tr>
<td>Week 12</td>
<td>+ 0.24 (0.03)†</td>
<td>+ 0.10 (0.03)</td>
<td>+ 0.04 (0.03)</td>
</tr>
</tbody>
</table>

*Data are presented as L (SEM).
†Differs from salmeterol alone and theophylline alone ($p \leq 0.02$).

Serious adverse events were reported by 12 patients (4%) in the SALM + THEO group, 18 patients (6%) in the SALM group, and 16 patients (5%) in the THEO group. As expected, the most commonly reported serious events were either respiratory (including COPD exacerbations) or cardiovas-

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**Figure 2.** Mean change from baseline in FEV1 on treatment day 1 (top panel) and after 12 weeks of treatment (bottom panel). Baseline FEV1 for serial testing was the screening visit FEV1. The morning dose of study medication was taken immediately after the hour 0 PFT was obtained on each day.
cular (including rhythm disturbances, congestive failure, or myocardial infarction). A comparable percentage of patients (6 to 8%) from each group was withdrawn from the study due to adverse events.

**Cardiovascular Effects**

Mean heart rate significantly ($p \leq 0.004$) increased relative to baseline for all patients during the theophylline titration period (range, 5 to 7 beats/min). Once randomized to study treatment, however, mean heart rates returned to baseline levels in the SALM group, but remained significantly elevated relative to baseline (range, 2 to 5 beats/min; $p \leq 0.002$) in both groups receiving theophylline. There were no clinically significant changes in BP. Clinically significant changes from baseline on ECG were rare, comparable between the treatment groups, and generally limited to increases in premature ventricular contractions (three patients in the

**Theophylline Concentrations**

Mean peak serum theophylline concentrations remained within the target range of 10 to 20 $\mu$g/mL during the study. Thirty-four to 37% of patients had a theophylline concentration below the lower limit of 10 $\mu$g/mL; however, of these, the majority had theophylline concentrations in the 8- to 10-$\mu$g/mL range. One patient in the SALM + THEO group had a serum theophylline concentration $> 20$ $\mu$g/mL.

**DISCUSSION**

To our knowledge, this is the first study that has compared the efficacy and safety of combination

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**Figure 3.** Mean change from baseline in FVC on treatment day 1 (top panel) and after 12 weeks of treatment (bottom panel). Baseline FVC for serial testing was the screening visit FVC. The morning dose of study medication was taken immediately after the hour 0 PFT was obtained on each day.

**Figure 4.** Mean change from baseline in FEV$_1$ AUC values on day 1 (top panel) and week 12 (bottom panel) for all subjects and those classified at baseline as having reversible lung function and nonreversible lung function. AUC$_{12}$ = area under the FEV$_1$ vs time curve during 12-h serial pulmonary function testing.

SALM + THEO group, three patients in the THEO group) and nonspecific ST-T segment wave changes (four patients in SALM + THEO group, two patients in SALM group, and one patient in THEO group).

**Clinical Investigations**
treatment with salmeterol plus theophylline vs either agent alone in patients with COPD. All treatment groups significantly improved compared to baseline in a variety of efficacy measures, showing that both salmeterol and theophylline as single agents provide benefit to patients with COPD. However, combination treatment with salmeterol plus theophylline consistently provided significantly greater improvements compared to either treatment alone in pulmonary function and significantly greater reduction in dyspnea and albuterol use. Furthermore, combination treatment resulted in significantly fewer COPD exacerbations compared with theophylline and significantly greater improvements in HRQOL and patient’s satisfaction with treatment. Although the number of patients experiencing adverse events was similar among the three groups, patients in the groups receiving theophylline (alone or with salmeterol) experienced a higher frequency of GI side effects than those receiving salmeterol alone.

### Table 5—Most Frequently Reported Drug-Related Adverse Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>SALM + THEO Group (n = 315)</th>
<th>SALM Group (n = 311)</th>
<th>THEO Group (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event</td>
<td>201 (64)</td>
<td>199 (64)</td>
<td>189 (60)</td>
</tr>
<tr>
<td>Patients with any drug-related adverse event</td>
<td>67 (21)</td>
<td>36 (12)*</td>
<td>55 (17)</td>
</tr>
<tr>
<td>GI, any event</td>
<td>34 (11)</td>
<td>12 (4)*</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (2)</td>
<td>2 (&lt; 1)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Gastric upset</td>
<td>6 (2)</td>
<td>2 (&lt; 1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (2)</td>
<td>2 (&lt; 1)</td>
<td>3 (&lt; 1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (2)</td>
<td>1 (&lt; 1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Neurology, any event</td>
<td>17 (5)</td>
<td>12 (4)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (&lt; 1)</td>
<td>3 (&lt; 1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Lightheaded</td>
<td>5 (2)</td>
<td>1 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM) unless otherwise indicated. All treatment groups were comparable at baseline. All treatment groups experienced significant within-treatment group improvements from baseline (p ≤ 0.05).
†Differs from salmeterol alone and theophylline alone (p ≤ 0.048).
‡Differs from theophylline alone (p = 0.023).
§Change during weeks 1 to 12.
||95% CIs based on an analysis of covariance with treatment, investigator, and baseline in the model.

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†Differs from salmeterol alone and theophylline alone (p ≤ 0.048).
‡Differs from theophylline alone (p = 0.023).
§Change during weeks 1 to 12.
||95% CIs based on an analysis of covariance with treatment, investigator, and baseline in the model.
National and international guidelines have proposed a stepwise approach to medications for the treatment of COPD. Salmeterol, a relatively new agent indicated for COPD, is considered by some to be a first-line treatment. Although theophylline is considered to be a third-line agent after the use of β2-agonists and anticholinergics, it is more widely used than might be expected, perhaps because of its long, established history of use. Combination therapy with these agents has been observed to provide significantly greater improvement than monotherapy in numerous studies, including theophylline added to other β2-agonists and theophylline added to anticholinergic therapy. Anticholinergic therapy added to albuterol provided significantly greater improvement in FEV1 compared with either agent alone as did salmeterol plus ipratropium. This study extends these findings to include combination treatment with salmeterol plus theophylline.

The specific actions of salmeterol and theophylline in the treatment of COPD have not been as well characterized as they have in asthma, but the greater improvements in physiologic and clinical outcomes observed with combination treatment are likely due to the contribution of two different pharmacologic classes. COPD is characterized by predominantly neutrophilic inflammation, as opposed to the eosinophilic inflammation of asthma, with parenchymal destruction leading to airflow obstruction through dynamic compression. Although both salmeterol and theophylline are considered bronchodilators, theophylline may also increase respiratory muscle strength and delay the occurrence of diaphragmatic fatigue, and may possess some anti-inflammatory strength and delay the occurrence of diaphragmatic and theophylline are considered bronchodilators, it is more widely used than might be expected, perhaps because of its long, established history of use. Combination therapy with these agents has been observed to provide significantly greater improvement than monotherapy in numerous studies, including theophylline added to other β2-agonists and theophylline added to anticholinergic therapy. Anticholinergic therapy added to albuterol provided significantly greater improvement in FEV1 compared with either agent alone as did salmeterol plus ipratropium. This study extends these findings to include combination treatment with salmeterol plus theophylline.

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Physiologic improvements traditionally used to evaluate the benefits of therapies in COPD do not generally correlate well with clinical outcomes. Although both the lung function and clinical measures of COPD improved with combination therapy (SALM + THEO), the correlation coefficients for FEV1 and FVC vs measures of dyspnea (TDI) and HRQOL were low (≤ 0.2). The development of dynamic hyperinflation has been recently reported to correlate better with the severity of dyspnea than with spirometric measures.

Clinical outcomes such as improvement in dyspnea, HRQOL, and treatment satisfaction are at least as important as physiologic measures when evaluating therapies for COPD. Dyspnea is perhaps the most important symptom from the patient’s perspective and one of the most common reasons that patients seek medical attention. In a small 4-week study, salmeterol had a small, statistically significant increase in FEV1, and while there was no significant increase in FVC or in the distance walked in 6 min, patients reported a significant decrease in dyspnea when compared to placebo. In the current study, combination treatment with salmeterol plus theophylline added to albuterol added to spirometric measures.

10 points), was more marked with combination treatment of salmeterol plus theophylline (52%) than has been previously reported with either salmeterol (46% with ≥ 10 point improvement) or ipratropium bromide (39% with ≥ 10 point improvement). Additionally, combination treatment with salmeterol plus theophylline provided significantly higher overall satisfaction scores compared with either treatment alone, despite the fact that patients treated with salmeterol alone had significantly higher treatment satisfaction scores for side effects (and significantly fewer adverse events) than either of the two groups that received theophylline.

The magnitude of the response among the “non-reversible” subjects treated with the combination of salmeterol plus theophylline is perhaps the most intriguing aspect of these results. The underlying mechanistic actions to explain why these subjects should have such a marked improvement in FEV1 with combination therapy is not currently understood, but has been observed before when theophylline has been taken in combination with other therapies. These results highlight that the lack of an acute response to albuterol in patients with COPD is not always a reliable predictor of subsequent responses to long-acting β-agonists (alone or in combination) and underscores the importance of not undertreating patients who are believed to have little chance of benefitting from bronchodilators.

Issues with tolerability have always been a consistent limitation to the use of theophylline, particularly
in elderly patients. The results of the current study underscore this concern. Nearly 16% of patients withdrew during the theophylline titration period and prior to randomization due to adverse events commonly associated with theophylline or an inability to tolerate the dose during titration. The patients who were then randomized were, by definition, relatively theophylline tolerant. Nevertheless, adverse events attributable to theophylline therapy were considerable. Theophylline concentrations were titrated to a dose of 10 to 20 μg/mL in this study, which is the level suggested in the package insert. However, by the end of the study, more than one third of the patients had concentrations < 10 μg/mL. Most of these “low” theophylline concentrations were still within what is considered to be a therapeutic range of 8 to 10 μg/mL.2 Whether the tolerability of combination therapy could be improved (without an accompanying loss of efficacy) by titrating the theophylline dose downward requires further research.

In conclusion, patients with COPD treated with salmeterol alone, theophylline alone, or a combination of salmeterol plus theophylline experienced significant improvements in multiple outcomes. Patients receiving combination treatment experienced both statistically significant and clinically relevant improvements in objective measures of pulmonary function and subjective measures (dyspnea, HRQOL, and patient satisfaction) compared to either treatment alone. Our results suggest that combination therapy with salmeterol and theophylline may provide substantial benefits in both physiologic and clinical outcomes in symptomatic patients with COPD.

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