Salmeterol vs Theophylline*
Sleep and Efficacy Outcomes in Patients With Nocturnal Asthma
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Study objectives: To compare the efficacy, safety, and effects on sleep quality of salmeterol and extended-release theophylline in patients with nocturnal asthma.

Design: Randomized, double-blind, double-dummy, three-period crossover.

Setting: Outpatients at a single center. Patients spent 1 night during screening and 2 nights during each study period in a sleep laboratory for completion of sleep studies.

Patients: Male and female patients who were at least 18 years old with nocturnal asthma (baseline FEV1, 50 to 90% of predicted) and who required regular bronchodilator therapy. Patients on inhaled corticosteroids, cromolyn, and nedocromil were allowed into the study if their dosing remained constant throughout the study.

Interventions: Inhaled salmeterol (42 μg per actuation), extended-release oral theophylline (titrated to serum levels of 10 to 20 μg/mL), and placebo taken twice daily.

Measurements and results: Efficacy measurements included nocturnal spirometry, nocturnal polysomnography, sleep questionnaires, and daily measurements of lung function and symptoms. Salmeterol was superior to theophylline (p ≤ 0.05) in maintaining nocturnal FEV1 levels and was superior to placebo (p ≤ 0.05) in improving morning and evening peak expiratory flow (PEF) and in decreasing nighttime albuterol use. The use of salmeterol significantly increased the percentage of days and nights with no albuterol use and decreased daytime albuterol use compared with theophylline and placebo (p ≤ 0.05). Sleep quality global scores significantly improved with salmeterol and placebo (p < 0.001) but not with theophylline. The effects on sleep architecture were similar across treatment groups.

Conclusions: Salmeterol (but not theophylline) was associated with sustained improvements in morning PEF, protection from nighttime lung function deterioration, reductions in albuterol use, and improvements in patient perceptions of sleep. No differences were seen in polysomnographic measures of sleep quality.

Key words: asthma; nocturnal asthma; salmeterol; sleep quality; theophylline

Abbreviations: EMG = electromyogram; PEF = peak expiratory flow; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement

Nocturnal symptoms of asthma may occur in > 70% of the asthma patient population¹ and are associated with impaired sleep quality.²,³ Investigations have shown that > 65% of deaths due to asthma occur during the night or early in the morning,¹⁵ highlighting the importance of managing the nighttime manifestations of this disease. With asthma prevalence increasing in the United States and other countries,⁶–¹² more research is focusing on therapeutic interventions to control nocturnal symptoms and to improve nocturnal lung function.

The goal of nocturnal asthma therapy is to maintain pulmonary function as close to normal as possible with no adverse effects on normal sleep patterns. Sleep deprivation and disturbances contribute to poor daytime function and judgment, and can promote social and mental problems.¹³ Fitzpatrick and colleagues¹⁴ studied patients with nocturnal asthma...
and found impairment of their daytime cognitive performance. Therapies used to control pulmonary function and the symptoms of nocturnal asthma need to be carefully considered for their impact on sleep quality and quantity.

Clinical studies have shown that both salmeterol and xinafoate, a highly selective, long-acting, inhaled bronchodilator, and theophylline, an oral derivative of xanthine, decrease the incidence of nocturnal asthma symptoms and reduce early morning bronchoconstriction. The effects of inhaled β-agonists and xanthine derivatives on sleep architecture and subjective sleep quality have been examined with inconclusive results. Previous reports indicate that two oral xanthine derivatives, theophylline and aminophylline, may delay and change normal sleep stage distribution. Conversely, theophylline has been shown to have no significant impact on sleep quality while proving superior to bitolterol in patient ratings of sleep quality.

Results from a European trial demonstrated that salmeterol, 50 μg per actuation taken twice daily, effectively treated nocturnal asthma while improving objective sleep outcome measurements. The authors concluded that a direct comparison of salmeterol and theophylline was necessary to determine the optimal treatment for nocturnal asthma. In a recently published study, Selby and colleagues compared salmeterol, 50 μg taken twice daily, with individually titrated doses of extended-release theophylline, taken twice daily, in patients with nocturnal asthma. In that study, few significant differences between salmeterol and theophylline were seen in pulmonary function, symptoms, adverse effects, polysomnography measurements, or patient perception of sleep quality.

This study further examined the effects of salmeterol, 42 μg taken twice daily, and individually titrated doses of extended-release theophylline, taken twice daily, on nocturnal asthma control and sleep quality through objective and subjective measures of efficacy.

Materials and Methods

Patient Population

Nonsmoking men and nonpregnant women who were ≥ 18 years of age and who had nocturnal asthma were selected for study participation. Nocturnal asthma was defined as asthma with symptoms of cough, wheezing, chest tightness, or shortness of breath causing awakenings at least two times a week on average in the 2 months prior to the initial screening visit, with the presence of a diurnal peak expiratory flow (PEF) variation of ≥ 15% on at least 3 of 10 days during the screening period. Entry criteria included a medical history of asthma that required regular bronchodilator therapy over the 6 months preceding the initial screening visit. Patients were required to demonstrate a baseline FEV₁ level of 50 to 90% of the predicted value with reversible airways disease documented by an increase in FEV₁ of ≥ 15% after inhalation of a short-acting β-agonist. The use of inhaled corticosteroids, cromolyn, and nedocromil was allowed if the dosage had remained constant over the 45 days prior to enrollment and was maintained throughout the study. The use of oral and/or parenteral corticosteroids was not allowed within 30 days prior to the initial screening visit. Those patients on stable doses of theophylline at the initial screening visit continued on the same dose until open-label theophylline titration began. Albuterol administered via metered-dose inhaler was provided for use as needed. No other asthma medications were allowed during the study.

Study Design

All patients were enrolled at a single outpatient center, and written informed consent prior to screening was obtained. An institutional review board approved both the protocol and the informed consent. Following the initial screening visit in which pulmonary function tests were performed, patients were sent home with a diary card on which morning and evening PEF levels, nocturnal awakenings, nocturnal symptom ratings, and daytime and nighttime albuterol use were recorded. After 7 to 10 days, eligible patients began an open-label, extended-release oral theophylline titration period, with initial dosing of at least 100 mg once every 12 h. Titration continued for up to 30 days (3 to 5 days allowed between each dosing change) until a steady-state serum theophylline concentration of 10 to 20 μg/mL was achieved and maintained. Serum concentrations were measured 5 to 9 h after the morning dose of medication.

Following an 8- to 10-day theophylline washout period, patients were assigned in a random, double-blind, crossover manner to 15-day treatment regimens of inhaled salmeterol, 42 μg taken twice daily, extended-release oral theophylline taken at the individually titrated dose twice daily, and placebo. Each of the three treatment periods was separated by a 5- to 10-day washout period in which no double-blind medication was taken. On days 1, 7, and 14 of each period, serum theophylline concentration was assessed 5 to 9 h after morning dosing, and the results were reviewed by an investigator who had no patient contact. The serum values were not discussed with anyone involved with the study unless safety concerns prompted withdrawal of the patient. No adjustments in theophylline dosing were allowed after randomization to double-blind treatment.

The safety of the medications was monitored during the study through adverse-event reports, exacerbations, vital sign measurements, physical examinations, and clinical laboratory tests. Adverse events reported as possibly, probably, or almost certainly related to study medication, as determined by the investigator, were summarized as being drug related. For the purposes of this protocol, an asthma exacerbation was defined as asthma symptoms requiring additional asthma therapy, the use of albuterol in excess of seven puffs per day above the baseline average on ≥ 2 days in a 7-day period, or a change in any concurrent asthma medication.

Sleep Studies

During the screening period, patients spent 1 night in the sleep laboratory for acclimatization purposes. After randomization, patients spent 2 nights in the sleep laboratory on days 14 and 15 of each treatment period. Nocturnal polysomnography was performed on day 14 to evaluate sleep quality and nocturnal heart rate. Hourly nocturnal spirometry was recorded on day 15.
On day 14 of each treatment period, nocturnal data collection was performed and measurements were recorded on a 12-channel polygraph (Grass Instruments Co; Quincy, MA). Sleep was monitored with standard silver cup electrodes, recording continuous EEG, electrooculogram, and submental electromyogram (EMG) signals. The two EEG signals most commonly employed were C3A2 and O2A1 or C4A1 and O1A2. A single-lead ECG was used to monitor heart rate and rhythm. Arterial oxyhemoglobin saturation was measured by an oximeter (Nonin Medical Corp; Plymouth, MN). In addition, to confirm that our study population did not include subjects with concomitant sleep disorders, such as sleep apnea or periodic leg movements, the following parameters were measured. Calf EMG was recorded to monitor periodic leg movements. The periodic leg movement data were not quantified since no subject demonstrated significant periodic leg movements. To detect apneas and hypopneas, piezoelectric crystal belts were used to record chest effort and abdominal movement, and airflow was monitored with a nasal/oral thermistor. For scoring purposes, apneas were defined as a complete cessation of airflow for $\geq 10$ s. Hypopneas were defined as a qualitative decline in airflow and/or respiratory effort associated with a $\geq 4\%$ oxyhemoglobin desaturation. Scoring of the polysomnography data was performed using standard criteria by a single, blinded investigator. In non-rapid eye movement (REM) sleep, arousals from sleep were identified by characteristic changes in electroencephalography and electromyography frequency for 3 to 15 s. In REM sleep, arousals were scored only when the EEG changes were accompanied by increases in submental EMG amplitude. Awakenings were identified by similar changes for $> 15$ s.

During the sleep study on day 15, hourly spirometry was performed using a water bath volume displacement spirometer (S & M Instrument Co; Doylestown, PA). Following the evening dose of medication, the baseline FEV$_1$ measurement was made just prior to lights out.

### Diary Card Assessments

Patients recorded morning and evening PEF measurements, nighttime awakenings, supplemental albuterol use, nocturnal symptom scores, and blinded study medication use in a daily diary record throughout their study participation. PEF measurements were made prior to taking the study drug on awakening and before bedtime using a hand-held peak flowmeter (Keller Medical Specialties; Antioch, IL). Nighttime symptoms of chest tightness, shortness of breath, wheezing, and cough were rated daily using a 5-point scale from 0 (no symptoms) to 4 (severe symptoms, no sleep). Baseline values for each treatment were obtained by averaging individual measurements over the 5 days prior to the respective treatment period.

### Sleep Quality

Patient-perceived impairment of sleep quality was measured at baseline (prior to theophylline titration) and on day 14 of each treatment period using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-administered questionnaire that utilizes a 4-point scale from 0 (no impairment of sleep) to 3 (severe impairment of sleep) to assess seven components of subjective sleep quality.$^{27}$ Scores are calculated for each of the individual components and are combined to obtain a global score, which is used to classify patients as “good” sleepers (global score $\leq 5$) or “poor” sleepers (global score $> 5$).

For the purposes of this study, the PSQI was modified such that questions to be completed by the patient’s bed partner were eliminated, and questions were adjusted to reflect problems over the previous week rather than the previous month. These changes have been shown to have no reported effect on the scoring of the instrument.$^{27}$

### Statistical Analysis

All analyses were performed on the intent-to-treat population (all patients randomized to treatment) with the goal of having 18 patients complete the study with equal numbers in each randomization sequence. Baseline data for PEF levels, symptom scores, nocturnal awakenings, and albuterol use were determined from the 5 days just prior to treatment day 1 of each treatment period. Descriptive and inferential analyses were used in evaluating safety and efficacy parameters. Efficacy measurement analyses for treatment effects, including polysomnography measurements and subjective sleep-quality questionnaires, were conducted using analysis of variance for a three-period, three-treatment crossover design in which effects for treatment period and sequence (carry-over effect) were tested.$^{28}$ Paired t tests were used for within-treatment tests. Treatment comparison tests were used to test two-sided hypotheses, and all treatment group differences were considered significant at $p \leq 0.05$. Adverse events and asthma exacerbations were analyzed by treatment group using Fisher’s Exact Test.$^{20}$

### Results

#### Patient Characteristics

Demographic data and characteristics of all randomized patients are summarized in Table 1. Of the 38 patients screened, 19 were randomized to study treatment after open-label theophylline titration. The 19 patients withdrawing prior to randomization did so due to failure to meet the enrollment criteria (8), theophylline titration failure (4), adverse events

### Table 1—Patient Demographics and Characteristics*$^*$

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>19</td>
</tr>
<tr>
<td>Age, yr</td>
<td>35.6 ± 2.7</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 11, Female 8</td>
</tr>
<tr>
<td>Screening FEV$_1$, L</td>
<td>3.81 ± 0.17</td>
</tr>
<tr>
<td>Screening FEV$_1$, % predicted</td>
<td>67.6 ± 2.77</td>
</tr>
<tr>
<td>Patients on concurrent asthma medications*</td>
<td>Tiostrinol acetate 6 (32), Flunisolide 4 (21), Sodium chromoglycate 2 (11), Albuterol 19 (100)</td>
</tr>
<tr>
<td>Patients with $\geq 2$ awakenings/wk†</td>
<td>2 awakenings 1 (5), 3 awakenings 5 (26), 4 awakenings 3 (16), $\geq 5$ awakenings 10 (53)</td>
</tr>
<tr>
<td>Patients receiving xanthine derivatives at screening</td>
<td>3 (16)</td>
</tr>
</tbody>
</table>

$^*$Values given as mean ± SEM or No. (%).

†Stable doses maintained throughout the study.

†Reported average number of awakenings due to asthma per week in the 2 months prior to screening.
(2), patient decision (2), protocol violation (1), asthma exacerbation (1), and failure to return (1). One of these patients withdrew during theophylline titration after experiencing headache, dry mouth, shakiness, and irritability that was considered to be related to theophylline use. One of the 19 randomized patients withdrew after experiencing an asthma exacerbation during washout following the second treatment period in which salmeterol was administered. Eighteen of the 19 randomized patients completed all three treatment periods of the protocol.

Serum theophylline levels of 10 to 20 μg/mL were achieved during titration in all randomized patients (Table 2). Following randomization, the mean serum theophylline concentration during theophylline treatment was 12.2 μg/mL on day 15, with values ranging from 6.2 to 18.6 μg/mL. Four of the 18 values measured during theophylline treatment were below 10 μg/mL. All theophylline levels measured during salmeterol and placebo treatment were reported to be < 2 μg/mL.

Sleep Studies

At least 7 h of polysomnography data on day 14 and nocturnal pulmonary function data on day 15 were recorded for all patients completing each treatment period. The time of lights out ranged from 9:00 PM to 10:45 PM, and the time of awakening ranged from 5:00 AM to 6:45 AM. The evening doses of study medication were taken prior to the initiation of the sleep studies.

During the sleep study on day 15, baseline FEV₁ values were measured during wakefulness just prior to lights out and were 2.96, 3.10, and 2.80 L for salmeterol, theophylline, and placebo, respectively. The overall mean nocturnal FEV₁ level fell significantly from baseline overnight after treatment with placebo (−0.16 L; p = 0.031) and theophylline (−0.22 L; p = 0.002), but it was preserved after treatment with salmeterol (−0.04; p > 0.05) (Fig 1).

The difference in the overall mean change in nocturnal FEV₁ level from baseline between salmeterol and theophylline was significant (p = 0.013), while the difference between salmeterol and placebo approached significance (p = 0.055). The difference between placebo and theophylline was not significant. The FEV₁ level was preserved at all hourly time points after treatment with salmeterol, whereas FEV₁ levels were significantly reduced (p < 0.05) from baseline at multiple timepoints after treatment with both theophylline and placebo (Fig 1).

During the sleep study on day 14, one patient (5%), five patients (28%), and eight patients (42%), respectively, experienced nocturnal awakenings and required supplemental albuterol after taking salmeterol, theophylline, and placebo. Salmeterol was statistically superior to placebo (p = 0.019) in preventing nocturnal awakenings and the use of albuterol. Overnight on day 15, fewer patients required albuterol while on salmeterol (16%) than while on placebo (53%) or theophylline (28%), with salmeterol showing superiority over placebo (p = 0.038).

The results of the polysomnography measurements taken on day 14 are found in Table 3. The only significant difference in sleep architecture indexes found on polysomnography was that less stage 2 sleep was seen after treatment with theophylline than after treatment with placebo (p = 0.034). Otherwise, sleep structure, as described by sleep efficiency, sleep latency, sleep-stage representation, and the number of arousals and awakenings from sleep, was not different among the treatment groups. There were also no differences in mean nocturnal heart rate, oxyhemoglobin saturation, or apneahypopnea index values among the treatments.

Diary Card Data

Analyses of diary card information revealed no significant differences in any baseline values. Salmeterol was significantly better (p ≤ 0.05) than both placebo and theophylline in improving morning PEF during the second week of treatment and was superior to placebo during the entire 15-day treatment period (Fig 2). Both salmeterol and theophylline were superior to placebo (p ≤ 0.05) in increasing evening PEF during the first week of treatment (31.9 and 22.4 L/min vs 6.8 L/min, respectively); however, only salmeterol maintained improvement (p = 0.007) over the entire 15-day period (30.0 L/min).

As illustrated in Figure 3, salmeterol significantly increased (p ≤ 0.05) the percentage of nights with no albuterol use compared with either theophylline or placebo over the 15 days of treatment. A similar increase was observed in the percentage of days with

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**Table 2—Serum Theophylline Concentration***

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Mean Serum Theophylline Concentration, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label theophylline titration period</td>
<td>12.4 (0.3)</td>
</tr>
<tr>
<td>Mean titrated serum theophylline concentration, μg/mL</td>
<td>12.4 (0.3)</td>
</tr>
<tr>
<td>Range of titrated concentration, μg/mL</td>
<td>11–15</td>
</tr>
<tr>
<td>Day 7 (blinded treatment period; n = 18)</td>
<td>13.0 (0.4)</td>
</tr>
<tr>
<td>Mean serum theophylline concentration, μg/mL</td>
<td>13.0 (0.4)</td>
</tr>
<tr>
<td>Range of concentration, μg/mL</td>
<td>10.9–16.9</td>
</tr>
<tr>
<td>Day 14 (blinded treatment period; n = 18)</td>
<td>12.2 (0.7)</td>
</tr>
<tr>
<td>Mean serum theophylline concentration, μg/mL</td>
<td>12.2 (0.7)</td>
</tr>
<tr>
<td>Range of concentration, μg/mL</td>
<td>6.2–18.4</td>
</tr>
</tbody>
</table>

*Values given as mean (SEM).
†Determined at the end of the open-label theophylline titration period.
no albuterol use. During the 15-day treatment period, mean daytime supplemental use of albuterol decreased by 1.81 puffs per day (38%) after treatment with salmeterol compared with a decrease of 0.06 puffs (1%) per day with placebo and an increase of 0.05 puffs per day (1%) with theophylline. The decrease in the nighttime supplemental use of albuterol was also significantly greater (p ≤ 0.05) after treatment with salmeterol (−0.87 puffs per night [60%]) compared with theophylline (−0.14 puffs per night [11%]) and placebo (−0.05 puffs per night [4%]) during the second week of therapy. Salme-

Table 3—Sleep Study Measurements on Day 14*

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Salmeterol n = 19</th>
<th>Theophylline n = 18</th>
<th>Placebo n = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>371.8 (12.2)</td>
<td>344.1 (14.0)</td>
<td>355.6 (10.6)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>90.4 (1.8)</td>
<td>86.2 (3.0)</td>
<td>88.6 (2.0)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>12.8 (5.2)</td>
<td>15.9 (6.2)</td>
<td>9.8 (3.2)</td>
</tr>
<tr>
<td>Time spent in sleep stage, % total sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>3.6 (0.6)</td>
<td>4.5 (0.5)</td>
<td>4.1 (0.6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>50.3 (1.9)</td>
<td>46.9 (1.8)†</td>
<td>48.9 (1.7)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>5.5 (0.5)</td>
<td>5.6 (0.6)</td>
<td>5.3 (0.4)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>15.6 (1.9)</td>
<td>16.1 (1.6)</td>
<td>17.5 (1.4)</td>
</tr>
<tr>
<td>REM</td>
<td>18.7 (1.2)</td>
<td>16.8 (1.4)</td>
<td>15.2 (1.3)</td>
</tr>
<tr>
<td>Wakefulness</td>
<td>6.6 (1.3)</td>
<td>10.6 (2.7)</td>
<td>9.4 (1.9)</td>
</tr>
<tr>
<td>Arousals, No./h of sleep</td>
<td>5.7 (0.6)</td>
<td>6.8 (1.3)</td>
<td>6.5 (0.9)</td>
</tr>
<tr>
<td>Nocturnal heart rate, bpm</td>
<td>68.6 (2.5)</td>
<td>66.7 (2.4)</td>
<td>67.0 (1.8)</td>
</tr>
<tr>
<td>Oxyhemoglobin saturation, %</td>
<td>96.1 (0.3)</td>
<td>95.9 (0.4)</td>
<td>95.7 (0.3)</td>
</tr>
<tr>
<td>Apnea-hypopnea index, avg/h of sleep</td>
<td>0.2 (0.1)</td>
<td>0.7 (0.3)</td>
<td>0.9 (0.5)</td>
</tr>
</tbody>
</table>

*Value given as mean (SEM); bpm = beats per minute.
†Data significantly different (p = 0.034) for theophylline vs placebo only. No other significant between-group differences were noted.
terol, but not theophylline, was superior to placebo (\(p < 0.023\)) over the entire treatment period in reducing the nighttime use of albuterol. Patient-rated nighttime asthma symptoms, the percentage of symptom-free nights, and the number of self-reported awakenings were similar for all the treatment regimens.

**Sleep Quality**

Both salmeterol and placebo treatments resulted in statistically significant improvements (\(p < 0.001\)) in the global scores of the PSQI, with decreases from the baseline score of 7.42 (a score of >5 indicating poor sleep quality) to 3.53 (a score of \(\leq 5\) indicating good sleep quality) after treatment with salmeterol and to 4.79 (indicating good sleep quality) after treatment with placebo (Table 4). No significant change in sleep quality classification from the baseline score occurred after theophylline treatment, with the mean global score remaining above 5. Significant improvements (\(p \leq 0.05\)) in individual component scores occurred with all three treatments but with more frequency following salmeterol treatment (5 of 7 components) than following theophylline (2 of 7 components) or placebo (3 of 7 components) treatments.

**Safety**

During the titration period, eight of the randomized patients (42%) experienced theophylline-related adverse events, and six patients (33%) experienced drug-related adverse events on theophylline after randomization. The adverse events reported during blinded theophylline treatment included headache, tremor, dizziness, anxiety, agitation, and nausea and vomiting. No drug-related adverse events were reported after treatment with either salmeterol or placebo. The difference in the reports of drug-related adverse events during blinded treatment was significantly greater (\(p < 0.008\)) after treatment with theophylline than after treatment with either salmeterol or placebo.

Two patients experienced asthma exacerbations after treatment with salmeterol and theophylline. One of the exacerbations attributed to salmeterol occurred during washout following salmeterol treatment and led to patient withdrawal from the study.

**Discussion**

Clinical studies have shown salmeterol\(^\text{15}\) and theophylline\(^\text{18,19}\) to be safe and effective in treating nocturnal asthma. In a comparison of the two medications, salmeterol was superior to sustained-release
theophylline in some objective measures of efficacy and was reported to be better tolerated by study patients. Similar results were seen in the current study, with salmeterol providing significantly greater improvements in lung function than theophylline or placebo while reducing the requirement for a rescue bronchodilator.

A direct comparison of the effects of salmeterol and theophylline on overnight FEV₁ measurements has not been reported previously. Both salmeterol and extended-release theophylline are twice-daily therapies; however, the difference reported here in the protective effects on overnight lung function between the two therapies was significant. Lung function after treatment with salmeterol remained essentially unchanged throughout the night, while deterioration in lung function occurred after treatment with theophylline.

The results of several previous studies with oral theophylline have shown no significant effects on sleep quality, while other studies have provided evidence that the medication causes sleep disturbance. In one such study, normal nonasthmatic patients were examined in order to eliminate asthma effects on sleep. The results showed that the administration of theophylline caused sleep disruption when compared with placebo, with a significant increase in the number of arousals and a decrease in total sleep time. Treatment with sustained-release theophylline has resulted in less total sleep time and time spent in slow-wave sleep than has treatment with placebo. In the current study, all sleep architecture indexes were similar among treatment groups, with the only significant difference being that theophylline was associated with a smaller percentage of stage 2 sleep.

In a comparison of salmeterol, 50 μg and 100 μg taken twice daily, with placebo, the 50-μg dose, but not the 100-μg dose, resulted in significant increases in time spent in deep sleep and decreases in time spent awake or in light sleep. As recently reported by Selby et al and as reported here, no such differences in treatments with salmeterol, theophylline, and placebo were found, indicating that neither active medication affected normal sleep patterns as measured by polysomnography. Using the American Sleep Disorder Association guidelines, we did not observe fewer arousals after treatment with salmeterol than after treatment with theophylline. This differs from the findings of Selby et al. However, their definition of microarousals required more transient (1.5-s) EEG and EMG changes. There has been considerable debate within the sleep research community regarding how to optimally measure sleep and arousals from sleep, and numerous experimental strategies have been considered. However, alternative techniques have not been widely adopted, standardized, or studied clinically. Therefore, we used the conventional arousal and sleep-stage scoring approaches.

Polysomnography indexes may not fully capture important differences in sleep quality. The PSQI was designed to provide a user-friendly and reliable subjective measure of sleep quality to help differentiate good and poor sleepers. A retrospective analysis of eight similar clinical trials in which this instrument was utilized showed that salmeterol therapy resulted in significantly (p ≤ 0.009) more good sleepers (PSQI global score, ≤ 5) and fewer poor sleepers (PSQI global score, > 5) than the other therapies studied. In the current study, both salmeterol and, to a lesser degree, placebo therapy resulted in a change in classification from poor sleepers to good sleepers after 14 days of treatment; theophylline did not provide this benefit. The subjective quality of sleep improvements observed after treatment with salmeterol may be related to the improvements seen in objective measures of nocturnal lung function and albuterol use even though no associated improvement in objective polysomnographic measurements of sleep quality were observed.

Unlike salmeterol, theophylline dosing is variable, requiring closely monitored titration during the initiation of therapy. Concerns over toxicity and side effects have limited the use of this medication. The recommended serum theophylline concentration is 10 to 20 μg/mL. A recent report suggests that a concentration of 5 to 15 μg/mL may be an appropriate range, especially in those patients experiencing adverse symptoms. In this study, all randomized patients achieved serum theophylline concentrations of 10 to 20 μg/mL during theophylline titration. Levels in four patients dropped below this range during blinded theophylline treatment, but the values remained at > 5 μg/mL.

Drug-related adverse effects reported during double-blind treatment were those commonly associated with the use of theophylline. Although no patients withdrew during the blinded treatment period due to adverse events, one patient did discontinue participation during theophylline titration after experiencing symptoms considered related to the medication. Similar types of adverse events occurred in another study comparing salmeterol with theophylline, with more theophylline-treated patients reporting drug-related adverse events than salmeterol-treated patients.

This study has shown that a 2-week regimen of salmeterol, 42 μg given twice daily, is associated with sustained improvements in morning and evening measures of lung function, in maintenance of lung function overnight, and in decreased use of supple-
The preservation of nocturnal pulmonary function observed in patients on salmeterol, but not on theophylline or placebo, was not associated with any demonstrated difference in sleep architecture as monitored by polysomnography. Subjective improvement in the PSQI mean global sleep score was observed in patients on salmeterol, with patients categorically changing from poor to good sleepers. These results suggest that for the 70% of asthma patients who experience nocturnal asthma symptoms and impaired sleep quality, salmeterol is superior to theophylline in managing nocturnal asthma and improving sleep quality.

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