

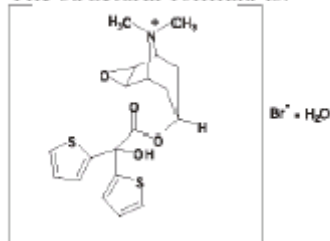
Bon Secours Richmond
Pharmacy and Therapeutics Committee
Tiotropium (Spiriva HandiHaler®)

Recommendation:

Tiotropium inhalation powder is recommended for addition to formulary. It is more effective than ipratropium inhalation aerosol and salmeterol inhalation powder when compared by FEV1, PEFR, functional residual capacity, duration of action, tachyphylaxis, health related quality of life, and concomitant use of bronchodilators. It has a low incidence of side effects with dry mouth being most common. It is 3.3 times more expensive than ipratropium. It is administered once daily.

Findings:

The structural formula is:



- Tiotropium is a long-acting anticholinergic bronchodilator with specificity for muscarinic receptors (M1-M5). Pharmacological effects are through blockade of the M1 and M3 receptors leading to bronchodilation and reduced mucus secretion. Tiotropium is structurally related to ipratropium, but has a unique kinetic selectivity for M1 and M3 versus M2 (which is thought to account for some cases of paradoxical bronchoconstriction) receptors and dissociates 100 times more slowly than ipratropium.
- Tiotropium is indicated for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
 - Tiotropium is not indicated for the initial treatment of acute episodes of bronchospasm and should not be used for immediate relief of breathing problems.
- Tiotropium 18 mg per capsule is supplied as a dry powder for inhalation using the HandiHaler inhalation device and requires an inspiration rate of ≥ 20 liters/minute
- Dosage: inhale contents of one capsule every day.
 - No dosage adjustment is required for geriatric, hepatically impaired, or renally impaired patients.
 - Patients with moderate to severe renal impairment should be monitored closely
- As with any inhaler, any drug that is not inhaled into the lungs is deposited into the gastrointestinal tract. Tiotropium is poorly absorbed from the GI tract, with an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.
- With chronic once-daily inhalation by COPD patients, pharmacokinetic steady state is reached after 2-3 weeks with no accumulation thereafter. Steady state peak effects occur in 8 days.
- The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the capsule outside the blister pack.
- The most commonly reported adverse drug reaction in studies was dry mouth, which was usually mild and often resolved during continued treatment. Other reactions reported included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.
- In addition to adverse events identified during clinical trials, the following have been reported in the worldwide post-marketing experience: epistaxis, palpitations, pruritus, and urticaria.
- Tiotropium is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of the product.
- As an anticholinergic agent, tiotropium may potentially worsen signs and symptoms associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.
- Spiriva has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions, including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids. However, co-administration with other anticholinergic-containing drugs (ipratropium) is not recommended.
- Pregnancy Category : C - Tiotropium should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.
- Tiotropium has been shown to be excreted into breast milk in rodent studies.
- Acute intoxication by inadvertent oral ingestion of tiotropium capsules is unlikely since it is not well-absorbed systemically.

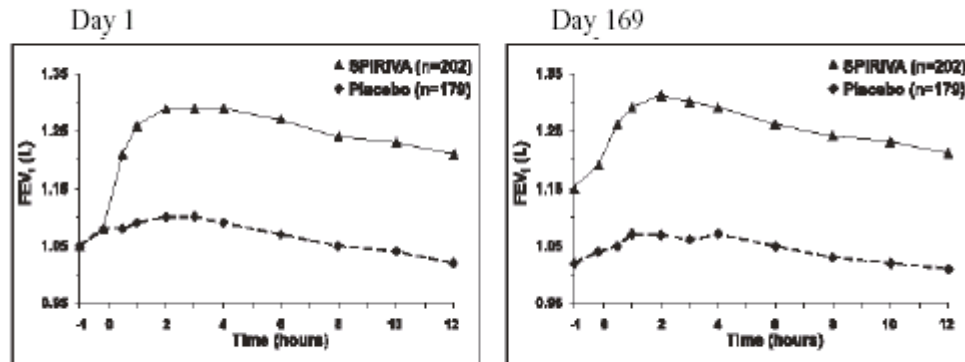
- Spiriva comes as a light green, hard gelatin capsule containing 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate)
- The Spiriva capsule is a dry powder formulation, intended for oral inhalation only with the HandiHaler inhalation device.

| | Tiotropium Powder HandiHaler | Ipratropium |
|--|------------------------------|------------------|
| Bioavailability Inhaled | 19.5% | 7% |
| Oral Absorption | 2-3% | |
| Metabolism | 26% | ND |
| Volume of Distribution (L/kg) | 32 | ND |
| Protein Binding | 72% | 9% |
| Half Life | 5-6 Days | 1.6 hours |
| Peak Plasma Levels | 18 pg/ml | ND |
| Steady State Trough Levels | 3-4 pg/ml | ND |
| Fraction Excreted Unchanged Renally | 74% | 50% |
| % of Inhaled Dose Excreted Unchanged Renally | 14% | |
| Peak Effect after Dose | 3 hours | 1-2 hours |
| Time to Steady State Peak Effect | Day 8 | |
| FEV1 Increase at 30 minutes | 13% | |
| Peak Increase FEV1 day 1 | 24% | |
| Peak Increase FEV1 at 8 days | 28-31% | |
| Dosage | Once daily | Four Times Daily |

| | Daily Dose | Cost Per Day |
|---------------------------|---------------------------------|--------------|
| Ipratropium Inhaler | 36 mcg (2 puffs) Four Times Day | \$1.30 |
| Tiotropium (Spiriva) | 18 mcg Once a Day | \$4.25 |
| Long Acting Beta2 Agonist | | |
| Salmeterol Diskus Inhaler | 42 mcg Twice a Day | \$2.50 |

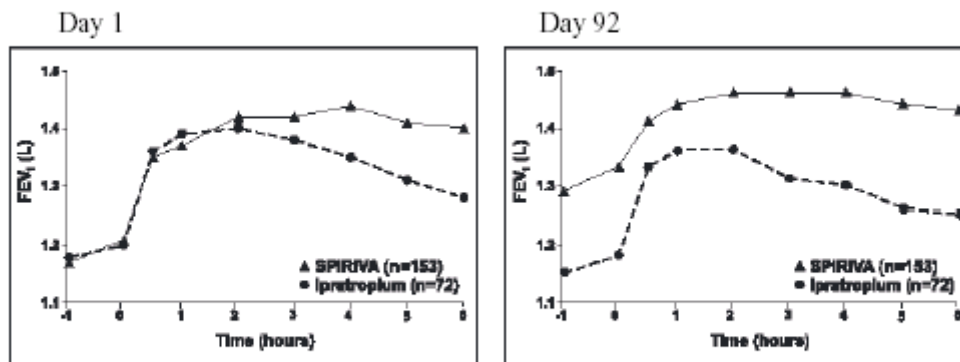
Package Insert Studies

Figure 1: Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Figure 2: Mean FEV₁ Over Time (0 to 6 hours postdose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*



* Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Table 1: Adverse Experience Incidence (% Patients) in One-Year -COPD Clinical Trials

| <u>Body System (Event)</u> | Placebo-Controlled Trials | | Ipratropium-Controlled Trials | |
|--|----------------------------------|----------------------------|--------------------------------------|--------------------------------|
| | SPIRIVA [n=550] | Placebo [n=371] | SPIRIVA [n=356] | Ipratropium [n=179] |
| Body as a Whole | | | | |
| Accidents | 13 | 11 | 5 | 8 |
| Chest Pain (non-specific) | 7 | 5 | 5 | 2 |
| Edema, Dependent | 5 | 4 | 3 | 5 |
| Gastrointestinal System Disorders | | | | |
| Abdominal Pain | 5 | 3 | 6 | 6 |
| Constipation | 4 | 2 | 1 | 1 |
| Dry Mouth | 16 | 3 | 12 | 6 |
| Dyspepsia | 6 | 5 | 1 | 1 |
| Vomiting | 4 | 2 | 1 | 2 |
| Musculoskeletal System | | | | |
| Myalgia | 4 | 3 | 4 | 3 |
| Resistance Mechanism Disorders | | | | |
| Infection | 4 | 3 | 1 | 3 |
| Moniliasis | 4 | 2 | 3 | 2 |
| Respiratory System (upper) | | | | |
| Epistaxis | 4 | 2 | 1 | 1 |
| Pharyngitis | 9 | 7 | 7 | 3 |
| Rhinitis | 6 | 5 | 3 | 2 |
| Sinusitis | 11 | 9 | 3 | 2 |
| Upper Respiratory Tract Infection | 41 | 37 | 43 | 35 |
| Skin and Appendage Disorders | | | | |
| Rash | 4 | 2 | 2 | 2 |
| Urinary System | | | | |
| Urinary Tract Infection | 7 | 5 | 4 | 2 |

A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease.

The Dutch Tiotropium Study Group.

van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ.

Department of Respiratory Diseases, Atrium Medisch Centrum, Heerlen, The Netherlands.

Thorax. 2000 Apr;55(4):289-94.

OBJECTIVE: To evaluate and compare the efficacy and safety of tiotropium and ipratropium during long term treatment in patients with stable chronic obstructive pulmonary disease (COPD).

METHODS: A randomized, double blind, double dummy, parallel group study conducted in 14 centers in the Netherlands. 288 patients at least 40 years old and a current or previous smoker (≥ 10 pack years) with a clinical diagnosis of COPD according to the ATS criteria with $FEV_1 < 65\%$ predicted and a ratio of FEV_1 to FVC $< 70\%$. Patients were randomized after a run in period of two weeks to receive either tiotropium 18 μg once daily from a dry powder inhaler (191 patients) or ipratropium 40 μg four times daily from a metered dose inhaler (97 patients) for a period of 13 weeks. Outcome measures included lung function, with FEV_1 and FVC measurements obtained one hour and immediately before inhalation and at 0.5, 1, 2, 3, 4, 5, and 6 hours after inhalation (on days 1, 8, 50, and 92) and a patient daily diary looking at morning and evening peak expiratory flow (PEF) and concomitant salbutamol use.

RESULTS: During treatment, tiotropium achieved a significantly greater improvement than ipratropium ($p < 0.05$) in trough, average, and peak FEV_1 levels and in trough and average FVC levels. The trough FEV_1 response on days 8, 50, and 92 ranged between 0.15 l (95% CI 0.11 to 0.19) and 0.16 l (95% CI 0.12 to 0.20) for tiotropium and between 0.01 l (95% CI -0.03 to 0.05) and 0.03 l (95% CI 0.01 to 0.07) for ipratropium. The trough FVC response on days 8, 50, and 92 ranged between 0.34 l (95% CI 0.28 to 0.40) and 0.39 l (95% CI 0.31 to 0.47) for tiotropium and between 0.08 l (95% CI 0.00 to 0.16) and 0.18 l (95% CI 0.08 to 0.28) for ipratropium. On all test days tiotropium produced a greater improvement in FEV_1 than ipratropium starting three hours after inhalation ($p < 0.05$).

During treatment, weekly mean morning and evening peak expiratory flow (PEF) was consistently better in the tiotropium group than in the ipratropium group, the difference in morning PEF being significant up through week 10 and in evening PEF up through week 7 of treatment ($p < 0.05$). The use of rescue salbutamol decreased in both groups, but there was a greater reduction seen in the tiotropium group than in the ipratropium group ($p < 0.05$). No significant differences were seen in the incidence of adverse events between the treatment groups. The only drug related adverse event was dry mouth (tiotropium 14.7%, ipratropium 10.3% of patients).

CONCLUSIONS: Tiotropium in a dose of 18 μg inhaled once daily using the HandiHaler was significantly more effective than 40 μg ipratropium four times daily in improving trough, average, and peak lung function over the 13 week period. The safety profile of tiotropium was similar to ipratropium. These data support the use of tiotropium as first line treatment for the long-term maintenance treatment of patients with airflow obstruction due to COPD.

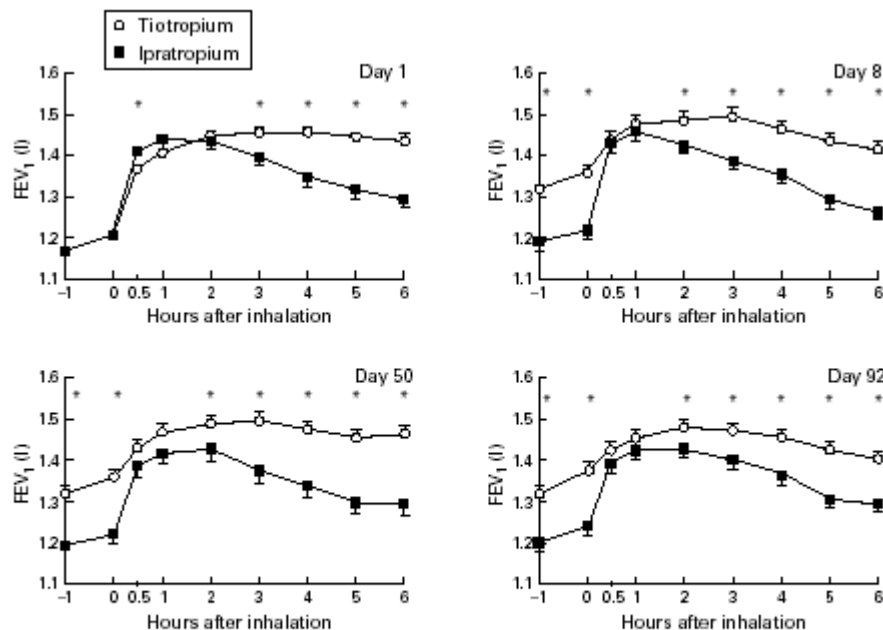


Figure 1 Mean (SE) values of forced expiratory volume in one second (FEV_1) before and during six hours after inhalation of tiotropium and ipratropium. The baseline means are adjusted for centre effects. All other means are adjusted for centre effects and baseline FEV_1 (tiotropium 1.21 l, ipratropium 1.15 l, $p > 0.05$). The common baseline mean FEV_1 is 1.19 l. The SE for the mean differences between treatments ranged from 0.01 to 0.02 l (day 1), 0.02 to 0.03 l (day 8), and was 0.03 l for days 50 and 92. * $p < 0.05$ tiotropium versus ipratropium.

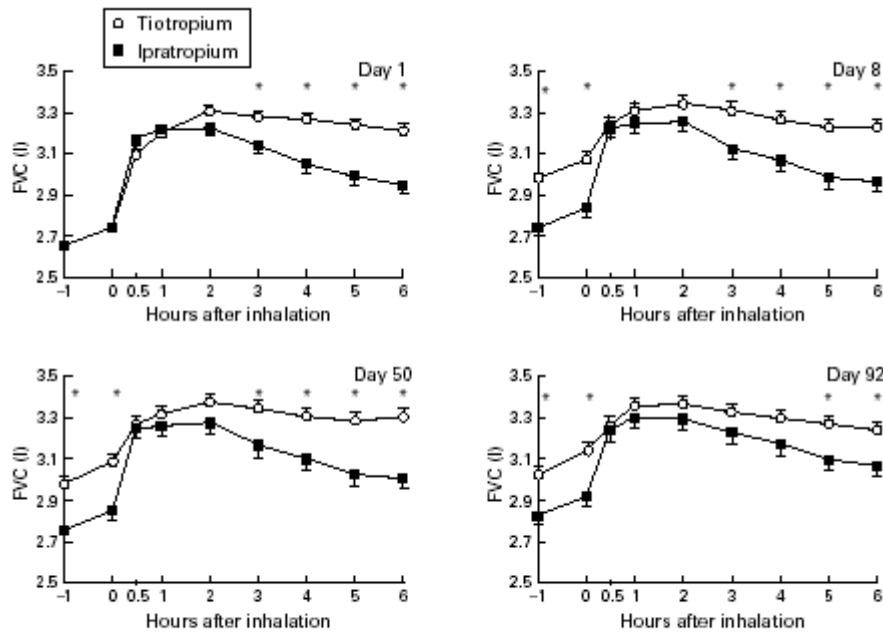


Figure 2 Mean (SE) values of forced vital capacity (FVC) before and during six hours after inhalation of tiotropium and ipratropium. The baseline means are adjusted for centre effects. All other means are adjusted for centre effects and baseline FVC (tiotropium 2.75 l, ipratropium 2.57 l, $p > 0.05$). The common baseline mean FVC is 2.69 l. The SE for the mean differences between treatments ranged from 0.02 to 0.05 l (day 1), 0.05 to 0.06 l (day 8), 0.05 to 0.07 l (day 50), and 0.06 to 0.07 l (day 92). * $p < 0.05$ tiotropium versus ipratropium.

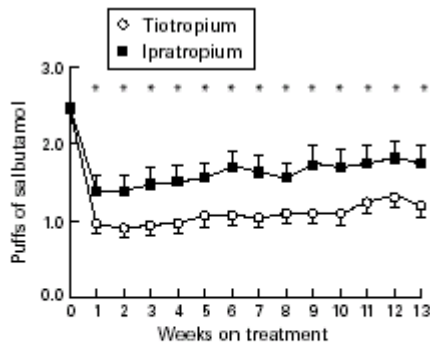


Figure 4 Mean (SE) doses of supplemental salbutamol per day over one week periods during treatment with tiotropium and ipratropium. The baseline means are adjusted for centre effects. All other means are adjusted for centre effects and baseline value (tiotropium 2.7 puffs, ipratropium 2.2 puffs, $p > 0.05$). The common baseline mean puffs per day is 2.5. * $p < 0.05$ tiotropium versus ipratropium.

Table 4 Adverse events

| | Tiotropium (n = 191) | Ipratropium (n = 97) |
|-----------------------------------|-------------------------|-------------------------|
| Total with any adverse event | 129 (67.5) | 62 (63.9) |
| General | | |
| Chest pain | 5 (2.6) | 0 |
| Fatigue | 4 (2.1) | 1 (1.0) |
| Headache | 10 (5.2) | 10 (10.3) |
| Influenza-like symptoms | 6 (3.1) | 8 (8.2) |
| Pain, non-site specific | 4 (2.1) | 1 (1.0) |
| Upper respiratory | | |
| Dry mouth | 28 (14.7) | 10 (10.3) |
| Pharyngitis | 6 (3.1) | 0 |
| Upper respiratory tract infection | 35 (18.3) | 11 (11.3) |
| Lower respiratory | | |
| COPD exacerbation | 21 (11.0) | 12 (12.4) |
| Cough | 5 (2.6) | 5 (5.2) |
| Pneumonia | 5 (2.6) | 2 (2.1) |

Values are number (%) of patients. No significant differences were seen between the two groups.

Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium.

Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, Cornelissen PJ; Dutch/Belgian Tiotropium Study Group.

Respiratory Division, AZ VUB (Academic Hospital University of Brussels), Belgium.

Eur Respir J. 2002 Feb;19(2):209-16.

OBJECTIVE: The van Noord et al. 3-month study comparing tiotropium with ipratropium was continued for one year. This report was designed to look at the combined results of this study and a second large multicenter 1-year trial comparing the effect of tiotropium 18 µg once daily with that of ipratropium 40 µg qid on lung function, dyspnoea, exacerbation rate and health-related quality of life (HRQOL) in patients with COPD.

METHODS: The two 1-year studies incorporated a randomized, double-blind, double dummy, parallel group design. Randomization to tiotropium 18 µg once daily in the morning (n = 356) or ipratropium 40 µg qid (n = 179) occurred on a 2:1 ratio, such that twice as many patients were exposed to tiotropium. Spirometric results, peak expiratory flow rate (PEFR), salbutamol use, effects on dyspnoea, health-related quality of life and COPD exacerbations were assessed.

RESULTS: Patients showed a significant bronchodilator response within 30 minutes after the first dose of tiotropium. By the end of the first week, the mean trough FEV₁ was 140 mL above baseline for patients in the tiotropium group (a 12% increase) compared with 20 mL for those in the ipratropium group. Tiotropium was superior to ipratropium (p < 0.05) at all time points on all test days except for the first 2 hours following the first dose and up to 1 hour after the dose 1 week later. Trough FEV₁ at 1 year improved by 0.12 ± 0.01 L with tiotropium and declined by 0.03 ± 0.02 L with ipratropium (p < 0.001). The FVC results paralleled the FEV₁ results. Throughout the 1-year treatment period, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group (p < 0.01 at all weekly intervals). Tiotropium significantly improved all three components of the TDI, as well as the focal score on all test days compared to ipratropium (p < 0.05). The differences in TDI focal score between the tiotropium and ipratropium groups at 9 and 12 months were 0.97 ± 0.25 and 0.90 ± 0.26, respectively. Significant improvement in the St George's Respiratory Questionnaire total and impact scores were seen with tiotropium (p < 0.01). Tiotropium reduced the number of exacerbations by 24% (p < 0.01), and increased time to first exacerbation (p < 0.01) and time to first hospitalization for a COPD exacerbation (p < 0.05) compared with ipratropium. Apart from an increased incidence of dry mouth in the tiotropium group (12.1%), adverse events were similar between treatments.

CONCLUSION: Tiotropium was effective in improving dyspnoea, exacerbations, health-related quality of life and lung function in patients with chronic obstructive pulmonary disease, and exceeds the benefits seen with ipratropium. The data support the use of tiotropium once daily as first-line maintenance treatment in patients with chronic obstructive pulmonary disease.

A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol.

Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, Kesten S, Towse L.

Division of Pulmonary Medicine, University of North Carolina, Chapel Hill, NC 27599-7020, USA.

Chest. 2002 Jul;122(1):47-55.

OBJECTIVE: To compare the efficacy and safety of tiotropium and salmeterol with multiple outcome measures, including lung function, dyspnea, and health-related quality of life (HRQoL) in patients with COPD.

METHODS: A 6-month, randomized, placebo-controlled, multicenter, double-blind, double-dummy, parallel-group study of tiotropium, 18 µg once daily via dry-powder inhaler (n = 209), compared with salmeterol, 50 µg bid via metered-dose inhaler (n = 219), was conducted in 623 patients with COPD (n = 201 for placebo group). Efficacy was assessed by 12-hour monitoring of spirometry, transition dyspnea index (TDI), and the St. George's Respiratory Questionnaire (SGRQ). Additionally, morning and evening peak flow rate and rescue medication use (salbutamol) were recorded by the patient daily.

RESULTS: The groups were similar in age (mean, 65 years), gender (75% men), and baseline FEV₁ (mean, 1.08 ± 0.37 L; percent predicted, 40 ± 12% [± SD]). The increase in FEV₁ during 12 hours after the first dose of tiotropium and salmeterol was similar. At 24 weeks, trough FEV₁ had improved significantly above placebo by 137 mL in the tiotropium group and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL, p < 0.01). Also, average FEV₁ from 0 to 3 hours and FEV₁ from 0 to 12 hours, and peak FEV₁ showed tiotropium was superior to salmeterol and both active treatments were better than placebo. At the end of the study, trough FVC had improved significantly above placebo by 247 mL in the tiotropium group (p < 0.0001) and by 134 mL in the salmeterol group (p < 0.001). The difference between tiotropium and salmeterol was 112 mL (p < 0.01). Tiotropium was significantly better than salmeterol in improving evening PEFR (p < 0.05) and in improving TDI focal score (difference, 0.75 U; p < 0.05). Tiotropium also appeared to improve dyspnea consistently over time, where there appeared to be a deterioration from the middle to the end of the trial for the other groups. Superiority of tiotropium was also seen in the proportion of patients achieving a clinically meaningful improvement in SGRQ (p < 0.05). The most common adverse event related to tiotropium was dry mouth (10%), however, this did not lead to any patients discontinuing use of the study medication. Both active drugs reduced the need for rescue albuterol (p < 0.0001).

CONCLUSIONS: Tiotropium once daily produces superior bronchodilation, improvements in dyspnea, and proportion of patients achieving meaningful changes in HRQoL compared to twice-daily salmeterol in patients with COPD.

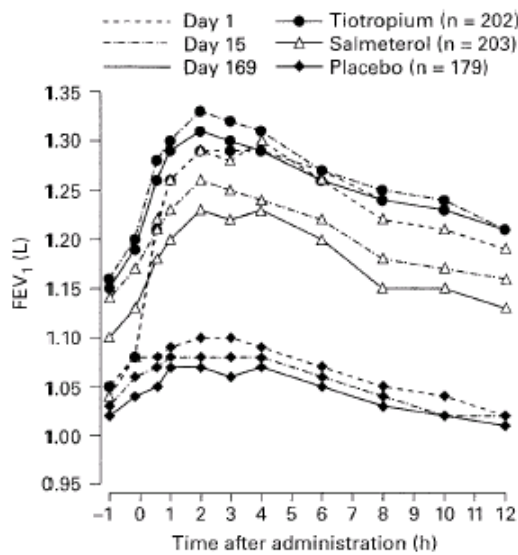


FIGURE 1. Mean FEV₁ before and after administration of tiotropium, salmeterol, and placebo on days 1, 15, and 169 of treatment. $p < 0.001$ for tiotropium vs placebo on all test days posttreatment; $p < 0.05$ for tiotropium vs salmeterol on all test days except day 1 and -1 h on day 15.

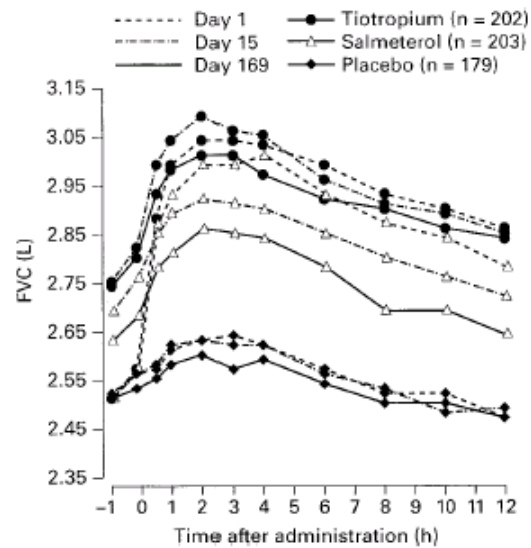


FIGURE 2. Mean FVC before and after administration of tiotropium, salmeterol, and placebo on days 1, 15, and 169 of treatment. $p < 0.001$ for tiotropium vs placebo on all test days posttreatment; $p < 0.05$ for tiotropium vs salmeterol on all test days except day 1 and -1 h and -10 min on day 15.

Table 2—Differences Between Treatment Groups for FEV₁ Values Following 24 Weeks of Treatment With Either Tiotropium, Salmeterol, or Placebo*

| Variables | TIO vs PBO | TIO vs SAL | SAL vs PBO |
|---------------------|-------------------|------------------|-------------------|
| Trough response, mL | 137 ± 20 (0.0001) | 52 ± 20 (0.0088) | 85 ± 20 (0.0001) |
| Average 0–3 h, mL | 222 ± 23 (0.0001) | 77 ± 22 (0.0005) | 145 ± 22 (0.0001) |
| Average 0–12 h, mL | 215 ± 22 (0.0001) | 77 ± 22 (0.0004) | 138 ± 22 (0.0001) |
| Peak 0–3 h, mL | 244 ± 24 (0.0001) | 83 ± 23 (0.0004) | 161 ± 24 (0.0001) |

*Data are presented as mean ± SEM (p value). TIO = tiotropium; PBO = placebo; SAL = salmeterol.

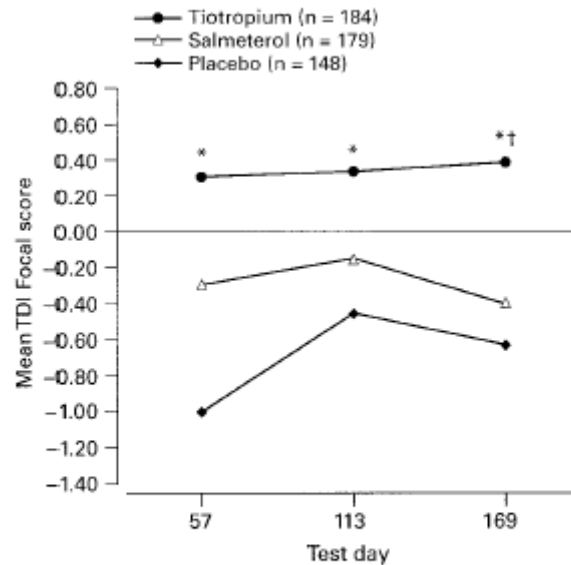


FIGURE 4. TDI focal scores at days 57, 113, and 169 for the tiotropium, salmeterol, and placebo groups. * $p < 0.05$ for tiotropium vs placebo. † $p < 0.05$ for tiotropium vs salmeterol.

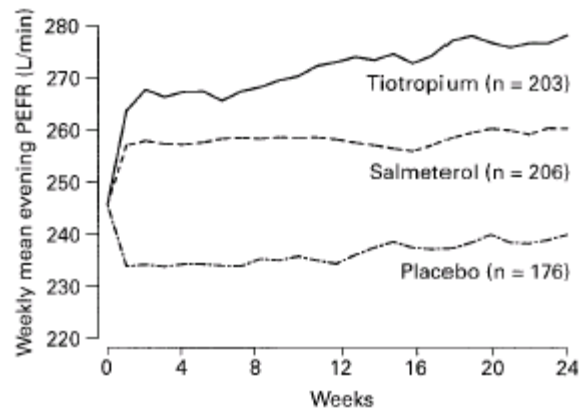
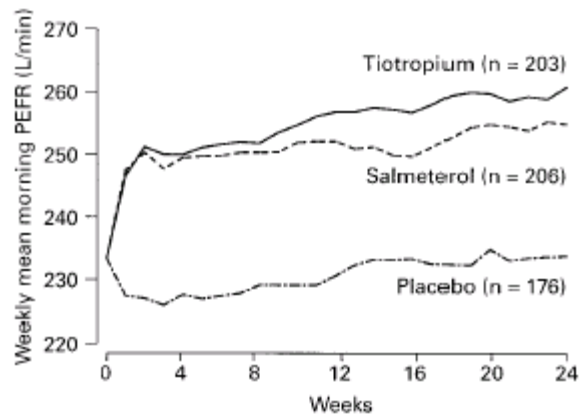


FIGURE 3. Mean of weekly means for morning (*top*) and evening (*bottom*) predose PEF over 6 months for the tiotropium, salmeterol, and placebo groups. Morning PEF = $p < 0.001$ for tiotropium vs placebo at all weeks. $p < 0.001$ for salmeterol vs placebo at all weeks except 15 and 16. Tiotropium vs salmeterol was not significant. Evening PEF = $p < 0.001$ for tiotropium vs placebo at all weeks. $p < 0.001$ for salmeterol vs placebo at all weeks; $p < 0.05$ for tiotropium vs salmeterol at all weeks except week 6.

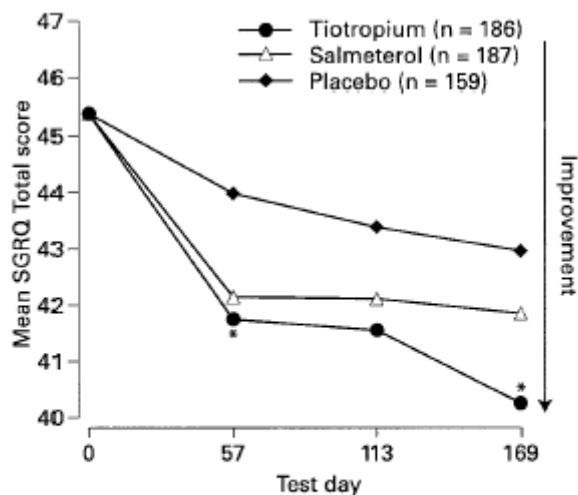


FIGURE 6. SGRQ total score at baseline and at days 57, 113, and 169 for the tiotropium, salmeterol, and placebo groups. * $p < 0.05$ for tiotropium vs placebo at day 57 and day 169. Salmeterol vs placebo is not significant. Tiotropium vs salmeterol is not significant.

Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD.

Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S.

Facolta di Medicina e Chirurgia, Universita di Genova, Genova, Italy.

Thorax. 2003 May;58(5):399-404.

OBJECTIVE: To evaluate the efficacy of tiotropium in comparison with salmeterol and placebo in COPD.

METHODS: Two 6-month randomized, placebo controlled, double blind, double dummy parallel studies which were combined for analysis of health outcomes consisting of exacerbations, health resource use, dyspnoea assessed by the transitional dyspnoea index (TDI), health related quality of life (assessed by St George's Respiratory Questionnaire, SGRQ), and spirometry. 1207 patients were randomized to receive either tiotropium 18 µg once daily via the HandiHaler plus MDI placebo (n = 402), salmeterol 50 µg twice daily via a metered dose inhaler plus HandiHaler placebo (n = 405) or a combination of placebos (n = 400).

RESULTS: Compared with placebo, tiotropium but not salmeterol was associated with a significant delay in the time to onset of the first exacerbation. Fewer COPD exacerbations/patient year occurred in the tiotropium group (1.07) than in the placebo group (1.49, $p < 0.05$); the salmeterol group (1.23 events/year) did not differ from placebo. The tiotropium group had 0.10 hospital admissions per patient year for COPD exacerbations compared with 0.17 for salmeterol and 0.15 for placebo (not statistically different). For all causes (respiratory and non-respiratory) tiotropium, but not salmeterol, was associated with fewer hospital admissions while both groups had fewer days in hospital than the placebo group. The number of days during which patients were unable to perform their usual daily activities was lowest in the tiotropium group (tiotropium 8.3 (0.8), salmeterol 11.1 (0.8), placebo 10.9 (0.8), $p < 0.05$). SGRQ total score improved by 4.2 (0.7), 2.8 (0.7) and 1.5 (0.7) units during the 6-month trial for the tiotropium, salmeterol and placebo groups, respectively ($p < 0.01$ tiotropium v placebo). Compared with placebo, TDI focal score improved in both the tiotropium group (1.1 (0.3) units, $p < 0.001$) and the salmeterol group (0.7 (0.3) units, $p < 0.05$). Evaluation of morning pre-dose FEV₁, peak FEV₁ and mean FEV₁ (0-3 hours) showed that tiotropium was superior to salmeterol while both active drugs were more effective than placebo.

CONCLUSIONS: Exacerbations of COPD and health resource usage were positively affected by daily treatment with tiotropium. With the exception of the number of hospital days associated with all causes, salmeterol twice daily resulted in no significant changes compared with placebo. Tiotropium also improved health related quality of life, dyspnoea, and lung function in patients with COPD.

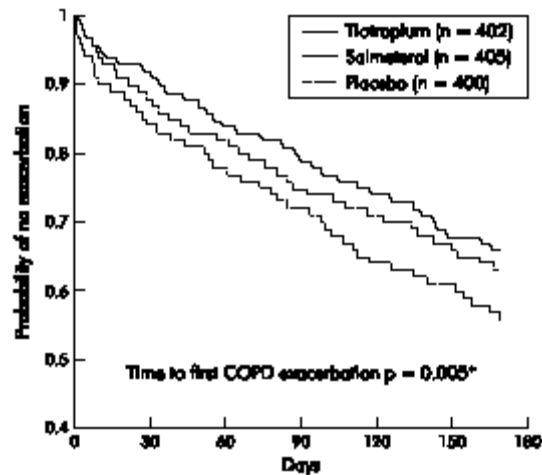


Figure 2 Kaplan-Meier estimates of the probability of no COPD exacerbations over 6 months of treatment. * $p=0.005$ tiotropium versus placebo (log rank test).

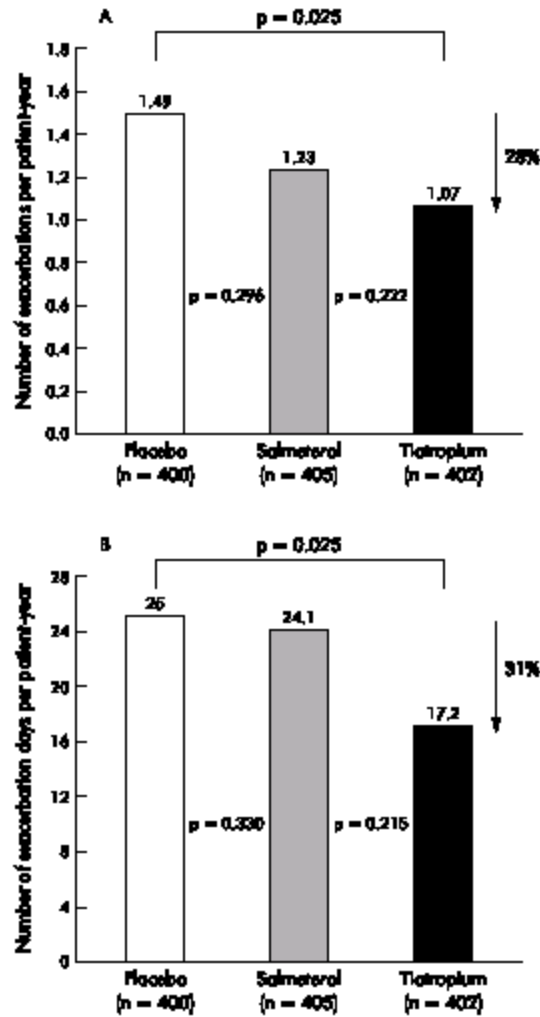


Figure 3 Number of (A) COPD exacerbations and (B) exacerbation days.

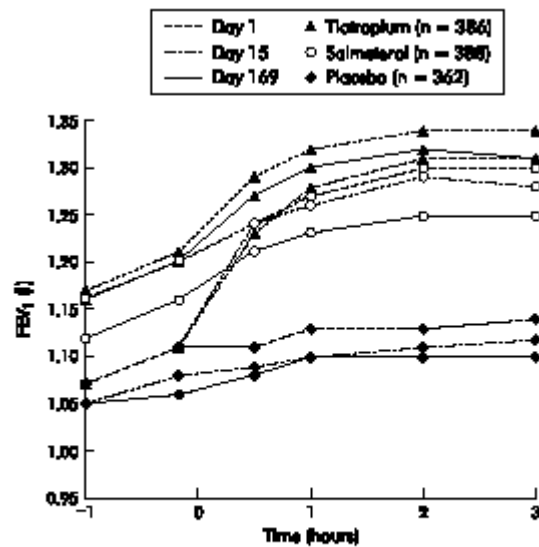


Figure 4 Mean FEV₁ before and after treatment on days 1, 15 and 169 of study; p<0.001 for tiotropium versus placebo on all test days after treatment; p<0.05 for tiotropium versus salmeterol on all test days except day 1 and -1 hour on day 15.

| | Tiotropium | Salmeterol | Placebo |
|--|--------------|---------------|-------------|
| Exacerbations† | | | |
| Hospital admissions | 0.10 | 0.17 | 0.15 |
| Days in hospital | 0.98 | 1.14 | 1.88 |
| Unscheduled physician visits | 1.51 [0.22] | 1.73 [0.22] | 1.51 [0.22] |
| All cause‡ | | | |
| Hospital admissions | 0.43* [0.22] | 0.65 [0.00] | 0.86 [0.22] |
| Days in hospital | 2.38* [0.65] | 3.46** [0.65] | 4.97 [0.65] |
| Unscheduled physician visits | 2.16 [0.22] | 2.59 [0.22] | 2.59 [0.22] |
| Days of restricted activity‡ [all cause] | 8.3* [0.8] | 11.1 [0.8] | 10.9 [0.8] |

*p<0.05 tiotropium v placebo; **p<0.05 salmeterol v placebo.
†Expressed as events per patient year.
‡Expressed as events per 24 patient weeks

Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes.

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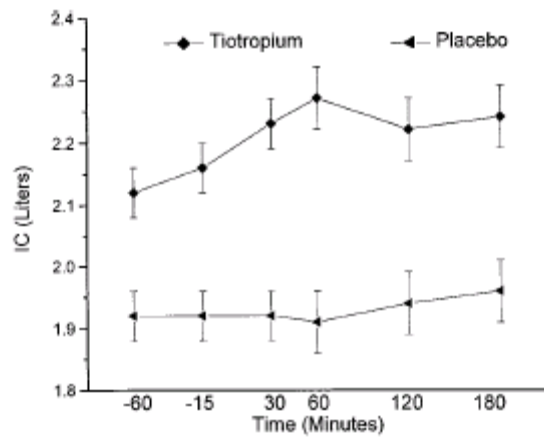
Chest. 2003 Nov;124(5):1743-8.

OBJECTIVE: In patients with COPD, changes in inspiratory capacity (IC) have shown a higher correlation to patient-focused outcomes, such as dyspnea with exercise, than other standard spirometric measurements. This study was designed to evaluate the acute and chronic bronchodilator response to tiotropium in patients with COPD by measuring inspiratory capacity (IC), slow vital capacity (SVC) and thoracic gas volume (TGV).

METHODS: A 4-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 81 patients with stable COPD (FEV₁ > 30% but < 65% of predicted values and lung hyperinflation demonstrated by TGV ≥ 120% of predicted value). The patients were randomized to either receive one capsule daily of tiotropium 18 µg or placebo through the HandiHaler inhalation device for 28 days. At each of the visits (weeks 0, 2, and 4), FEV₁, FVC, IC, SVC and TGV were measured prior to administration of study drug (- 60 and - 15 min) and after administration of study drug (30 min, 60 min, 120 min, and 180 min).

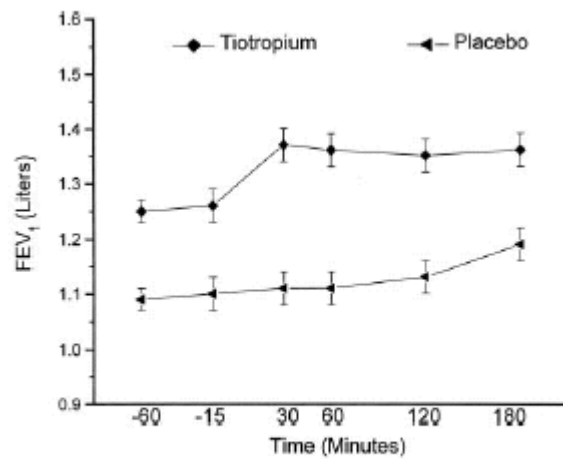
RESULTS: Mean age was 64 years; 72% were ex-smokers; there were more men in the tiotropium group than the placebo group (70% vs. 54%). Mean baseline FEV₁ values were greater (p < 0.05) in the tiotropium group (1.23 L; 46% predicted) compared with the placebo group (1.01 L; 41% predicted). Patients treated with tiotropium had significant increases in AUC₀₋₃ and trough IC in comparison to placebo patients. The differences between the tiotropium and placebo groups in AUC₀₋₃ and trough IC were 0.30 and 0.22 L, respectively, on day 28 (p < 0.001). Tiotropium significantly increased spirometric measures (FEV₁, FVC, and SVC) at all time points on all test days compared to placebo (p < 0.01). The mean differences (tiotropium - placebo) in FEV₁ trough (morning before drug), peak, and area under the curve over 3 hour values (adjusted for baseline and center differences) at week 4 were 0.16 L, 0.22 L, and 0.22 L, respectively (p < 0.01 for all); differences in IC for these variables were 0.22 L, 0.35 L, and 0.30 L (p < 0.01 for all). Differences in TGV were - 0.54 L, - 0.60 L, and - 0.70 L, respectively (p < 0.01 for all). The percentage improvement in area under the curve above baseline with tiotropium was similar among FEV₁ and lung volumes (FEV₁, 18%; FVC, 20%; SVC, 16%; IC, 16%; TGV, 14%).

CONCLUSIONS: Observed improvements in IC and reductions in TGV with once-daily tiotropium reflect improvements in hyperinflation that are maintained over 24 hours.



$p < 0.001$ vs placebo at all timepoints

FIGURE 1. Changes in IC over 3 h following 4 weeks of treatment with tiotropium or placebo.



$p < 0.001$ vs placebo at all timepoints

FIGURE 2. Changes in FEV₁ over 3 h following 4 weeks of treatment with tiotropium or placebo.

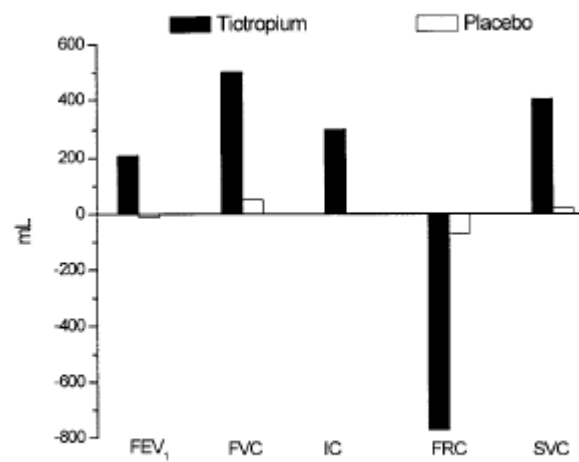


FIGURE 5. Changes in lung volumes and spirometry following 4 weeks of treatment with tiotropium or placebo.

Table 2—The Mean Differences (Tiotropium–Placebo) in Predrug (Trough), Peak, and AUC_{0–3} Values for FEV₁ and Lung Volumes Following 4 Weeks of Treatment*

| Variables | Predrug | Peak | AUC _{0–3} |
|------------------------------|---------|-------|--------------------|
| FEV ₁ , L | 0.16 | 0.22 | 0.22 |
| FVC, L | 0.33 | 0.48 | 0.45 |
| SVC, L | 0.29 | 0.39 | 0.37 |
| IC, L | 0.22 | 0.35 | 0.30 |
| TGV, L | –0.54 | –0.60 | –0.70 |
| Raw, cm H ₂ O/L/s | –1.00 | –1.10 | –1.33 |

*All differences were statistically significant (p < 0.01).

Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Littner MR, Ilowite JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, Witek TJ Jr.

Sepulveda Ambulatory Care and Nursing Home, Veterans Administration Greater Los Angeles Healthcare System, Sepulveda, CA, USA.

Am J Respir Crit Care Med. 2000 Apr;161(4 Pt 1):1136-42.

OBJECTIVE: To evaluate the dose-response characteristics of tiotropium inhalation powder given once daily to stable patients with chronic obstructive pulmonary disease (COPD), looking at doses of 4.5, 9, 18, and 36 µg.

METHODS: A randomized, double-blind, parallel group, placebo-controlled trial conducted in 9 centers. 169 patients were randomized to receive 0, 4.5, 9, 18, or 36 µg of tiotropium once daily at noon for 4 weeks, with spirometry measurements done before and hourly for 6 hours after dosing. Patients also measured and recorded their peak expiratory flow rates (PEFRs) three times each day. The primary end point was the trough FEV₁ and other efficacy measurements included peak and average FEV₁.

RESULTS: Significant dose-related improvement in FEV₁ and significant improvement in FVC occurred within 1 hour after the first dose of tiotropium as compared with placebo. Over the 29 days of the study, all doses of tiotropium produced significant increases over placebo in trough, peak, and 6-hour post-dose average FEV₁ and FVC, and in PEFR, without a significant difference among the different doses investigated. PEFR gradually returned to pretreatment baseline levels over a 3-wk evaluation period following the discontinuation of tiotropium. Beyond the 4.5 µg dose, little dose-dependent improvement was seen in spirometric results, however, a trend toward a higher PEFR was seen in the 36 µg group. The overall safety profile for tiotropium doses of 36 µg or less was similar to that of placebo.

CONCLUSION: Tiotropium was shown to be safe and effective in doses ranging from 4.5 to 36 µg delivered once daily. The improvements in spirometry with once-daily dosing confirm the long duration of action of tiotropium reported in single-dose studies, and its sustained improvement of spirometric measures over the 1 month of testing in the study points to utility of tiotropium as a maintenance bronchodilator for patients with COPD. On the basis of the comparable bronchodilator response at doses from 9 to 36 µg, and advantages suggested by the safety profile at doses below 36 µg, a dose of 18 µg once daily was selected for use in long-term studies of the safety and efficacy of tiotropium.

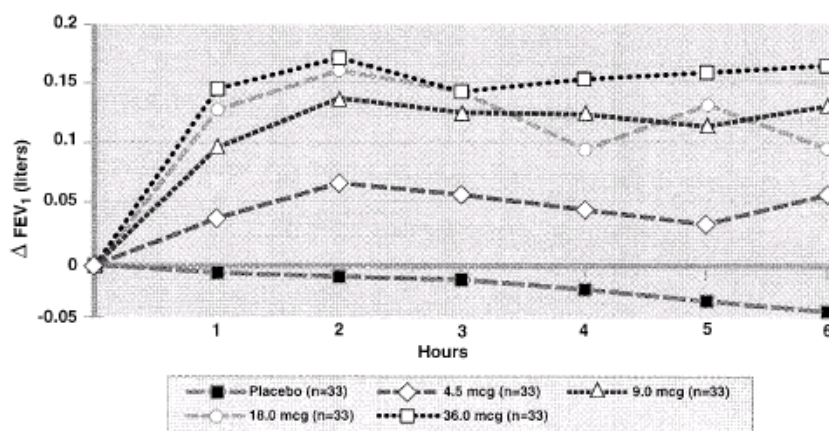


Figure 1. Mean change from predose FEV₁ (liters) following first dose of study medication. A significant dose-related increase was seen over time, with all doses of tiotropium significantly superior to placebo. p < 0.05.

TABLE 2
 MEAN PEAK* AND AVERAGE[†] FEV₁ AND FVC RESPONSE OVER 6 h IN
 LITERS (CHANGE FROM BASELINE) FOLLOWING FIRST DOSE

| | Tiotropium Bromide | | | | | | | | | |
|------------------------------------|--------------------|--------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Placebo | | 4.5 µg | | 9 µg | | 18 µg | | 36 µg | |
| | FEV ₁ | FVC | FEV ₁ | FVC | FEV ₁ | FVC | FEV ₁ | FVC | FEV ₁ | FVC |
| Sample size | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 | 33 |
| Baseline: mean | 1.00 | 2.24 | 1.01 | 2.36 | 1.06 | 2.31 | 1.21 | 2.46 | 0.94 | 2.11 |
| SE | (0.06) | (0.12) | (0.06) | (0.10) | (0.07) | (0.15) | (0.08) | (0.14) | (0.05) | (0.13) |
| Peak response* mean | 0.05 | 0.17 | 0.15 [†] | 0.34 [†] | 0.22 [†] | 0.43 [†] | 0.24 [†] | 0.47 [†] | 0.23 [†] | 0.45 [†] |
| SE | (0.01) | (0.04) | (0.02) | (0.04) | (0.03) | (0.06) | (0.03) | (0.07) | (0.04) | (0.06) |
| Average response [†] mean | -0.02 | -0.01 | 0.05 [†] | 0.13 [†] | 0.12 [†] | 0.25 [†] | 0.13 [†] | 0.29 [†] | 0.16 [†] | 0.28 [†] |
| SE | (0.01) | (0.03) | (0.02) | (0.04) | (0.02) | (0.06) | (0.02) | (0.06) | (0.03) | (0.05) |

* The largest value observed over the 6-h measurement period minus the baseline FEV₁ or FVC.

[†] The average change from baseline FEV₁ or FVC over the 6-h observation period.

[‡] p < 0.05 versus placebo.

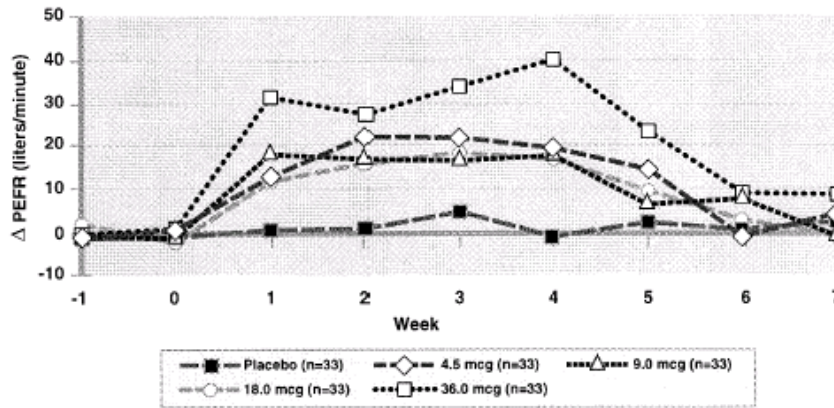


Figure 3. Mean change from baseline in mean weekly morning PEFs. Means were adjusted for treatment, center, treatment-by-center interaction, and baseline. All tiotropium doses produced significantly greater increases than did placebo (p < 0.05) during the treatment period. Note the gradual return to baseline over the 3 wk following discontinuation of treatment.

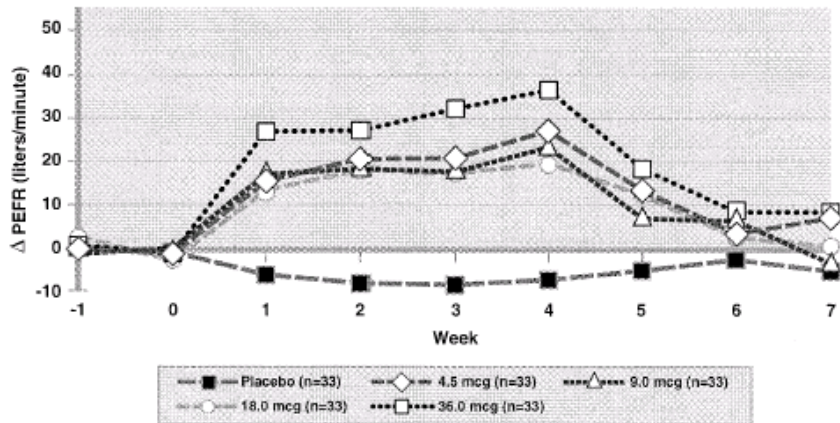


Figure 4. Mean change from baseline in mean weekly evening PEFs. Means were adjusted for treatment, center, treatment-by-center interaction, and baseline. All tiotropium doses produced significantly greater increases than did placebo (p < 0.05) during the treatment period. Note the gradual return to baseline over the 3 wk following discontinuation of treatment.

The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group.

Casaburi R, Briggs DD Jr, Donohue JF, Serby CW, Menjoge SS, Witek TJ Jr.

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Chest. 2000 Nov;118(5):1294-302.

OBJECTIVE: To evaluate the efficacy and safety of 18 µg tiotropium inhalation capsules administered once daily for 92 days in patients with COPD.

METHODS: A 3-month, randomized, multicentered, double-blind, placebo-controlled trial. Four hundred seventy patients 40 years or older with stable COPD ($FEV_1 \leq 65\%$ predicted) and a smoking history of > 10 pack years were randomized within each center to receive either tiotropium 18 µg ($n = 279$) or placebo ($n = 191$) once daily. Pulmonary function testing was conducted on treatment day 1 and after 1, 7, and 13 weeks of therapy, where FEV_1 and FVC were recorded 1 hour and immediately before dosing and at 30, 60, 120, and 180 minutes after study drug administration. The primary end point was trough FEV_1 response on the final treatment visit (92 days after initiation of therapy). Secondary end points included the peak and average FEV_1 and FVC responses during the first 3 hours after study drug administration.

RESULTS: Tiotropium produced significant improvement in trough FEV_1 and FVC, averaging 12% greater than baseline on day 8; these improvements were maintained on days 50 and 92. Onset of a clinically significant increase in both the FEV_1 and FVC occurred within 30 minutes after the first dose. All FEV_1 responses were significantly greater than placebo ($p < 0.001$). The improvement in morning PEFr, measured before dosing was significantly greater in the tiotropium group than in the placebo group for the entire 13 weeks. Also, the significantly higher morning PEFr values confirmed that the duration of action of tiotropium is ≥ 24 hours. The difference between the two treatment groups for any given week ranged from 16 to 24 L/min during the treatment period ($p < 0.01$ at all 13 weeks). Physician global evaluations on test days were significantly improved ($p < 0.001$) for patients receiving tiotropium relative to placebo from week 1 through week 13. Albuterol use was maintained in the placebo group whereas use decreased approximately 30% in the first week (from 3.7 to 2.6 doses) and remained at approximately this level for the entire 13-week treatment period in the tiotropium group ($p < 0.001$). The safety profile indicates a low incidence of adverse events in the tiotropium group, comparable to that seen in the patients taking placebo. The most common reported adverse event after tiotropium was dry mouth (9.3% vs 1.6% relative to placebo; $p < 0.05$). No significant changes in heart rate or BP were detected after study drug administration in either group.

CONCLUSIONS: These data demonstrate that tiotropium is a safe and effective once-daily anticholinergic bronchodilator and should prove useful as first-line maintenance therapy in COPD.

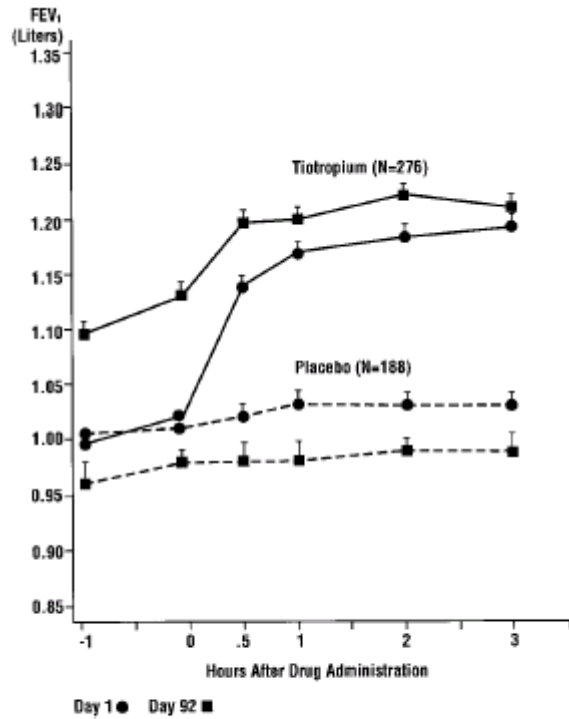


FIGURE 1. Time course of mean FEV₁ response after first dose ($p < 0.001$) and response after 3 months of therapy ($p < 0.001$) for tiotropium and placebo. The SEM for differences ranged from 0.01 to 0.02 L. Note the trough effect after 3 months of therapy is approximately 11% greater than the first-day baseline value.

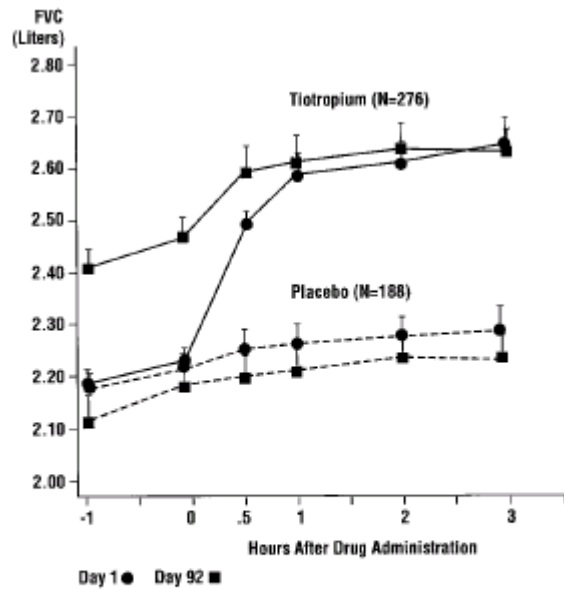


FIGURE 2. Time course of mean FVC response after first dose ($p < 0.001$) and response after 3 months of therapy ($p < 0.001$) for tiotropium and placebo. The SEM for differences ranged from 0.01 to 0.04 L. Note the trough effect after 3 months of therapy is approximately 10% greater than the first-day baseline value.

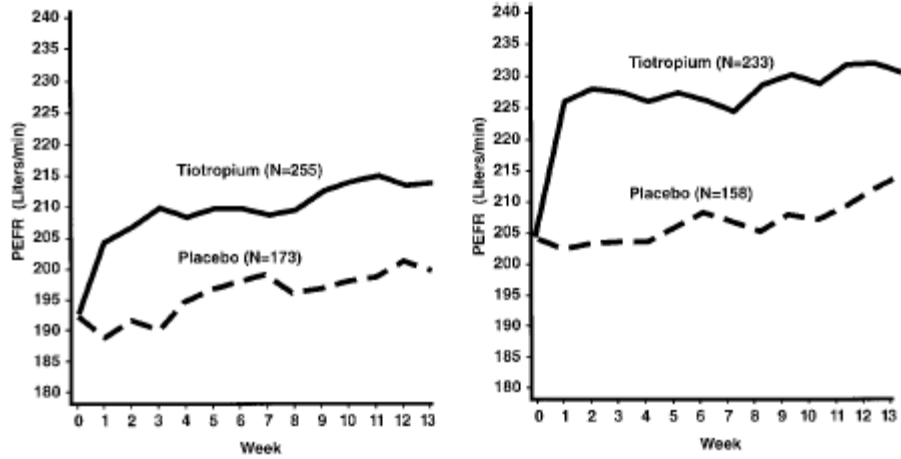


FIGURE 4. *Left*: mean of weekly means for morning PEFrs during 13 weeks for tiotropium and placebo ($p < 0.05$ at 10 of 13 weeks). The SEM for differences ranged from 4 to 7 L/min. *Right*: mean of weekly means for evening PEFrs during 13 weeks for tiotropium and placebo ($p < 0.01$ at all times). The SEM for differences ranged from 4 to 7 L/min.

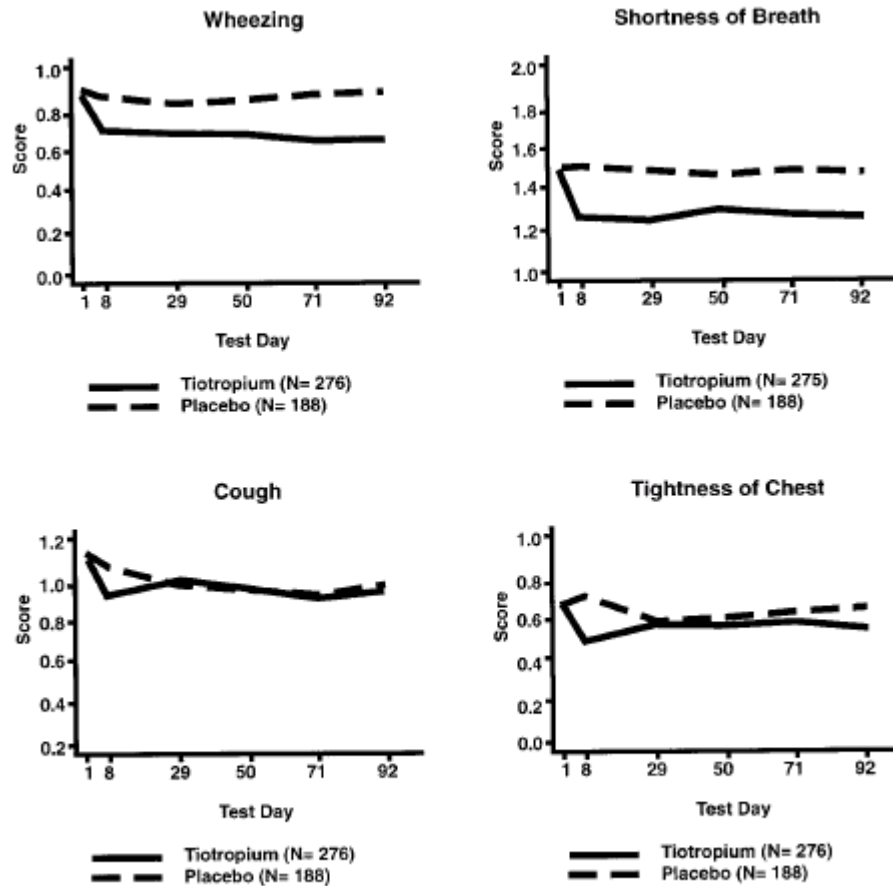


FIGURE 6. Mean COPD symptom severity scores (0 = none, 1 = mild, 2 = moderate, 3 = severe) during 13 weeks for tiotropium and placebo ($p < 0.05$ for wheezing and shortness of breath). The SEM for differences ranged from 0.05 to 0.07.