



Department of Vermont Health Access

Therapeutic Class Review

Inhaled Antimuscarinics

Overview/Summary

The inhaled antimuscarinics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD). COPD is a condition characterized by progressive airflow restrictions that are not fully reversible.¹ Symptoms typically associated with COPD include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled antimuscarinics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled antimuscarinics in patients with COPD.¹

There are two inhaled antimuscarinics currently available, ipratropium (Atrovent[®] HFA) and tiotropium (Spiriva[®]). Both agents are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.^{2,3} Additionally, tiotropium is FDA-approved for reducing COPD exacerbations.⁴ The two agents are distinguishable based on differences in pharmacokinetic parameters. Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours requiring administration four times daily. The newer agent, tiotropium, has a duration of action of greater than 24 hours requiring once-daily administration and is classified as a long-acting bronchodilator. Comparative trials have reported that tiotropium may improve spirometry measurements to a greater degree than ipratropium.^{5,6} Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization.^{2,3} Tiotropium is available as a dry powder inhaler for oral inhalation.⁴ The ipratropium solution for nebulization is the only inhaled antimuscarinic product that is currently available generically.

In March of 2008, the manufacturers of Spiriva[®], Boehringer Ingeheim Pharmaceuticals Inc., notified the FDA of results from a pooled analysis of 29 clinical trials that suggested a small excess risk of stroke (two cases/1,000) with tiotropium over placebo. Later, in October of 2008, the FDA released an updated statement informing healthcare professionals that preliminary results from a large, four-year, placebo controlled clinical trial with Spiriva[®] in approximately 6,000 patients with COPD, demonstrated no increased risk of stroke with tiotropium compared to placebo.⁷ During this same time, however, two studies were published reporting an increased risk for mortality and/or cardiovascular events in patients who received tiotropium or other inhaled antimuscarinics.^{8,9} Results from one study demonstrated inhaled antimuscarinics significantly increased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke, compared to patients receiving control therapy ($P < 0.001$).⁸ In January of 2010, the FDA issued a follow-up communication upon its completed review of the Understanding the Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial. The FDA confirmed that the trial did not demonstrate a significant increased risk of stroke or cardiovascular death with Spiriva[®] compared to placebo. The FDA Pulmonary Allergy Drugs Advisory Committee also reviewed the data from the UPLIFT trial and voted that the findings adequately resolved the previous safety concerns for stroke and cardiovascular death.⁷

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of COPD. The guidelines state that regular use of long-acting β_2 -agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.¹ However, according to the National Institute for Clinical Excellence (NICE), short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators

should be used in patients who remain symptomatic with use of short-acting agents. The NICE guidelines maintain that once-daily long-acting antimuscarinic agents are preferred compared to four-times-daily short-acting antimuscarinics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an antimuscarinic agent.¹⁰

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Ipratropium (Atrovent HFA [®])	Inhaled antimuscarinic	✓ *
Tiotropium (Spiriva [®])	Inhaled antimuscarinic	-

*Solution for nebulization.

Indications

Table 2. Food and Drug Administration Approved Indications²⁻⁴

Generic Name	Maintenance Treatment of Bronchospasm Associated with Chronic Obstructive Pulmonary Disease, Including Chronic Bronchitis and Emphysema	Reducing Chronic Obstructive Pulmonary Disease Exacerbations
Ipratropium	✓	
Tiotropium	✓	✓

According to the package insert, ipratropium nebulizer solution can be administered alone or with other bronchodilators, especially β_2 -adrenergic agonists.²

In addition to its Food and Drug Administration-approved indication, ipratropium may also be used off-label as adjunctive therapy in moderate-to-severe exacerbations of acute asthma in patients presenting to an emergency department.¹¹

Pharmacokinetics

Table 3. Pharmacokinetics^{2-4,12}

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Ipratropium	15	6 to 8	2.8	None	2.0 to 3.8
Tiotropium	60	24	74.0	None	120 to 144

Clinical Trials

The inhaled antimuscarinics have demonstrated good clinical efficacy and safety in improving lung function and exercise tolerance in patients with chronic obstructive pulmonary disease. A few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.^{5,6} There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators. However, when tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.^{13,14} In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages.¹⁵ But, as with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.^{16,17}

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Casaburi et al¹⁸</p> <p>Tiotropium 18 µg QD</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥40 years of age with COPD and a FEV₁ ≤60% of predicted normal and a FEV₁/FVC of ≤70% participating in 8 weeks of PR</p>	<p>N=108</p> <p>25 weeks</p>	<p>Primary: Treadmill walking endurance time</p> <p>Secondary: TDI, SGRQ, rescue albuterol use</p>	<p>Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time than patients receiving placebo. The difference between the treatments was 1.65 minutes (<i>P</i>=0.183). Patients receiving tiotropium showed significantly longer exercise endurance times compared to placebo both after 13 weeks of treatment (including eight weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 minutes (<i>P</i>=0.025) and 6.60 minutes (<i>P</i>=0.018), respectively.</p> <p>The mean increase in endurance time from day 29 before PR to day 92 after PR was 80% in the tiotropium group and 57% in the placebo group (<i>P</i> value not reported).</p> <p>Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for placebo. On day 176, the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatment groups was 1.67 units (<i>P</i>=0.03; differences exceeding 1 unit were considered clinically meaningful).</p> <p>The SGRQ total score in the tiotropium group was lower (i.e., improved) on each test day compared to the placebo group. After PR, the SGRQ scores improved by 7.27 units in the tiotropium group compared with 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (<i>P</i> value not reported).</p> <p>On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication/day when compared to patients receiving placebo over 25 weeks of treatment (<i>P</i><0.05).</p>
<p>Tashkin et al¹⁹ (UPLIFT)</p> <p>Tiotropium 18 µg QD</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥40 years of age with moderate-to-very-severe COPD,</p>	<p>N=5,993</p> <p>4 years</p>	<p>Primary: Yearly rate of decline in the mean FEV₁ pre-bronchodilator and</p>	<p>Primary: The rate of decline in the mean post bronchodilator FEV₁ was greater in patients who prematurely discontinued a study drug as compared with those who completed the study period. There were no significant differences between the tiotropium group and the placebo group in the rate of decline in</p>

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vs placebo	with a FEV ₁ of 70% or less after bronchodilation and a FEV ₁ /FVC of 70% or less		<p>post-bronchodilator from day 30 until end of treatment</p> <p>Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions</p>	<p>the mean value for FEV₁ either prebronchodilator ($P=0.95$) or post bronchodilator ($P=0.21$) from day 30 to the end of study-drug treatment.</p> <p>Secondary: There were no significant differences between the treatment groups in the rate of decline in the mean value for FVC either prebronchodilator ($P=0.30$) or post bronchodilator ($P=0.84$). The rate of decline in the mean value for SVC was not reported.</p> <p>Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score ($P<0.0001$), although these differences on average were below what is considered to have clinical significance. The overall mean between-group difference in SGRQ total score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium ($P<0.001$).</p> <p>Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (P value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (P value not reported).</p> <p>During the four year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the four year study period plus 30 days included in the intent-to-treat analysis, 941 patients died; 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02).</p>
Decramer et al (UPLIFT) ²⁰ Tiotropium 18 µg QD vs	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV ₁ of 70% or less after	N=2,739 4 years	Primary: Yearly rate of decline in the mean FEV ₁ pre-bronchodilator and post-bronchodilator from	<p>Primary: Rate of decline of mean post-bronchodilator FEV₁ was lower in the tiotropium group compared to placebo ($P=0.024$).</p> <p>Rate of decline of mean pre-bronchodilator FEV₁ did not differ between groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>This was a subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.</p>	<p>bronchodilation and a FEV₁/FVC of 70% or less</p>		<p>day 30 until end of treatment</p> <p>Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions</p>	<p>Secondary: Mean values for pre- and post-bronchodilator FEV₁ were higher in the tiotropium group at all time points ($P<0.0001$).</p> <p>Mean pre-bronchodilator FVC and SVC were higher in the tiotropium group at all time points ($P<0.001$).</p> <p>Mean post-bronchodilator FVC was significantly higher in the tiotropium group at all time points ($P<0.01$).</p> <p>No significant difference in mean post-bronchodilator SVC was observed between groups.</p> <p>Health status was better in the tiotropium group compared to placebo for all time points ($P\leq 0.006$).</p> <p>Time to first exacerbation and time to exacerbation resulting in hospital admission were longer in the tiotropium group (HR, 0.82; 95% CI, 0.75 to 0.90 and 0.74; 95% CI, 0.62 to 0.88 respectively).</p> <p>Risk of mortality from lower respiratory tract conditions and from all causes were lower for the tiotropium group though differences between groups were not significant.</p>
<p>Troosters et al²¹ (UPLIFT)</p> <p>Tiotropium 18 µg QD vs placebo</p> <p>This was a subgroup analysis of patients in the UPLIFT trial who were not on other maintenance</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV₁ of 70% or less after bronchodilation and a FEV₁/FVC of 70% or less</p>	<p>N=810</p> <p>4 years</p>	<p>Primary: Yearly rate of decline in the mean FEV₁ pre-bronchodilator and post-bronchodilator from day 30 until end of treatment</p> <p>Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores,</p>	<p>Primary: After 30 days of treatment, pre-bronchodilator FEV₁ was significantly larger in the tiotropium group compared to the placebo group ($P<0.0001$).</p> <p>Trough FEV₁ remained significantly larger in the tiotropium group compared to placebo at all time points throughout the trial ($P<0.05$).</p> <p>Secondary: No significant differences between groups were observed in pre- or post-FVC ($P\geq 0.81$).</p> <p>Pre- and post-SVC was significantly higher in the tiotropium group ($P\leq 0.046$).</p> <p>The improvement in the SGRQ scores was significantly higher in the</p>

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treatment at randomization.			COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	<p>tiotropium group compared to the placebo group in the first six months of treatment ($P=0.0065$).</p> <p>SGRQ total score declined more slowly in the tiotropium group compared to the placebo group ($P=0.002$).</p> <p>No statistically significant difference in exacerbation rate was observed between groups ($P=0.08$).</p> <p>No statistically significant difference in time to first exacerbation was observed between groups ($P=0.24$).</p> <p>No statistically significant difference in exacerbations leading to hospitalizations was observed between groups.</p>
<p>Celli et al²² (UPLIFT)</p> <p>Tiotropium 18 µg QD vs placebo</p> <p>This analysis is a more in depth look at the effect of tiotropium and its discontinuation on mortality and its causes.</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV₁ of 70% or less after bronchodilation and a FEV₁/FVC of 70% or less</p>	<p>N=5,993</p> <p>Duration not specified</p>	<p>Primary: Yearly rate of decline in the mean FEV₁ pre-bronchodilator and post-bronchodilator from day 30 until end of treatment</p> <p>Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions</p>	<p>Primary: See previous results by Tashkin et al.¹⁹</p> <p>Secondary: See previous results by Tashkin et al.¹⁹</p> <p>A lower risk of death was observed in the tiotropium group (HR, 0.84; 95% CI, 0.73 to 0.97).</p> <p>Adjustments by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications did not alter the results.</p> <p>The most common causes of death included lower respiratory causes, cancer, general disorders, and cardiac disorders.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Van Noord et al⁵</p> <p>Tiotropium 18 µg QD vs ipratropium 40 µg QID</p>	<p>DB, DD, MC, PG</p> <p>Patients with stable COPD with mean age of 65 years and average FEV₁ of 41% of predicted values</p>	<p>N=288</p> <p>15 weeks</p>	<p>Primary: Changes in FEV₁ and FVC</p> <p>Secondary: Daily records of PEF, use of albuterol</p>	<p>Primary: The FEV₁ response, at all time points on days eight, 50, and 92, was significantly greater after tiotropium than after ipratropium (differences of 0.09, 0.11, and 0.08 L; <i>P</i><0.05). The results for FVC closely reflect those obtained for FEV₁. Tiotropium performed consistently better than ipratropium. The differences in trough FEV₁ values were most pronounced (<i>P</i><0.001), whereas differences in peak FEV₁ increase did not reach statistical significance (<i>P</i>>0.05).</p> <p>Secondary: The improvement in both morning and evening PEF was greater in the tiotropium group than in the ipratropium group. The difference in morning PEF between the groups was statistically significant up through week 10 (<i>P</i><0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (<i>P</i><0.05).</p> <p>In both groups, there was a drop in the use of rescue albuterol, the reduction being greater in the tiotropium group than in the ipratropium group (<i>P</i><0.05).</p>
<p>Vincken et al⁶</p> <p>Tiotropium 18 µg QD vs ipratropium 40 µg QID</p>	<p>DB, DD, MC, PG, RCT</p> <p>Patients with COPD ≥40 years of age with an FEV₁ of ≤65% of predicted normal value and ≤70% of FVC</p>	<p>N=535</p> <p>12 months</p>	<p>Primary: Changes in spirometry</p> <p>Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life</p>	<p>Primary: By the end of day eight, the mean trough FEV₁ was 140 mL above baseline for patients in the tiotropium group (12% increase) compared with 20 mL for the ipratropium group.</p> <p>Tiotropium was more effective than ipratropium at all time points on all test days except for the first two hours following the first dose and up to one hour after the dose, one week later (<i>P</i><0.05).</p> <p>At the end of one year, trough FEV₁ was 120 mL above the day one baseline for patients receiving tiotropium, and had declined by 30 mL for those receiving ipratropium (difference of 150 mL between groups; <i>P</i><0.001 at all time points).</p> <p>The FVC results paralleled the FEV₁ results. At the end of one year, the trough FVC was 320 mL above the day one baseline for patients receiving tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups).</p>

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				<p>Secondary: Throughout the one-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).</p> <p>On average, patients receiving tiotropium self-administered approximately four fewer inhalations of albuterol/week compared to patients receiving ipratropium ($P<0.05$ for 40 of the 52 weeks).</p> <p>The BDI focal scores for the two groups were comparable.</p> <p>Tiotropium significantly improved all components of the TDI on all test days compared to ipratropium ($P<0.05$). The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥ 1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; $P=0.004$).</p> <p>During the one-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30 ± 1.13 on day 364; $P<0.05$).</p> <p>Quality of life, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last two test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.</p>
<p>McCrary et al¹⁵</p> <p>Ipratropium (various strengths and dosage forms)</p> <p>vs</p>	<p>MA</p> <p>9 RCT's of adult patients with a diagnosis of COPD, symptoms consistent with an acute</p>	<p>N=525</p> <p>Duration ranged from 1 hour to 14 days</p>	<p>Primary: Short-term changes in FEV₁, WMD of long-term effects on FEV₁</p> <p>Secondary:</p>	<p>Primary: There was no significant difference in short-term FEV₁ changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported).</p> <p>The change in FEV₁ was not significant when ipratropium was added to a β_2-adrenergic agonist (WMD, 0.02 L; 95% CI, 0.08 to 0.12). These results were</p>

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<p>β_2-adrenergic agonist (various strengths and dosage forms), a combination of β_2-adrenergic agonists and ipratropium (various strengths and dosage forms), or placebo</p>	<p>exacerbation</p>		<p>Not reported</p>	<p>similar 24 hours post-dose (long-term) between the ipratropium and β_2-adrenergic agonist groups (WMD, 0.05 L; 95% CI, -0.14 to 0.05).</p> <p>Secondary: Not reported</p>
<p>Matera et al¹⁶</p> <p>Ipratropium 40 μg plus placebo</p> <p>vs</p> <p>salmeterol 50 μg plus placebo</p> <p>vs</p> <p>salmeterol 50 μg plus ipratropium 40 μg</p> <p>vs</p> <p>placebo plus placebo</p>	<p>RCT, SB, XO</p> <p>Male patients with COPD aged 40 years or older with an FEV₁ between 16 and 62% of predicted value</p>	<p>N=12</p> <p>4 days</p>	<p>Primary: Changes in FEV₁</p> <p>Secondary: Changes in the area under the FEV₁ response-time curve</p>	<p>Primary: The peak response (28.8\pm5.0%) for salmeterol was greater than that for ipratropium (26.0\pm9.1%), but equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0\pm4.2).</p> <p>All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared with placebo ($P<0.05$), but only salmeterol and salmeterol plus ipratropium induced a significant ($P<0.05$) spirometric increase over the 12 hour monitoring period.</p> <p>Secondary: All of the area under the curve values for active treatments were significantly greater than for placebo ($P<0.05$), and that for salmeterol and salmeterol plus ipratropium were significantly ($P<0.05$) greater than that for ipratropium alone.</p> <p>There was no significant difference ($P>0.05$) between the salmeterol and salmeterol plus ipratropium area under the curve.</p>
<p>Van Noord et al¹⁷</p> <p>Salmeterol 50 μg plus ipratropium matched placebo</p> <p>vs</p>	<p>DB, MC, PG, RCT</p> <p>Patients with COPD aged 40 to 75 years with a FEV₁ \leq75% of predicted value</p>	<p>N=144</p> <p>14 weeks</p>	<p>Primary: Spirometric changes after first dose of medication</p> <p>Secondary: Symptom scores, rescue medication</p>	<p>Primary: After inhalation of salmeterol, there was a mean\pmSEM peak increase in FEV₁ of 7.0\pm0.7% predicted after two hours, followed by a plateau. After 12 hours, the improvement was still 2.0\pm1.0% of predicted.</p> <p>Salmeterol plus ipratropium produced a peak increase in FEV₁ of 11.0\pm0.8% predicted after two hours. After 12 hours, the improvement was 3.0\pm0.8% predicted.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>salmeterol 50 µg plus ipratropium 40 µg</p> <p>vs</p> <p>salmeterol-matched placebo plus ipratropium-matched placebo</p>			<p>use, PEF, clinic lung function, adverse events, exacerbations</p>	<p>The improvement in FVC in the two active treatment groups was similar to that reported with FEV₁.</p> <p>Secondary: Throughout the treatment period there was a mean±SEM decrease in the daytime symptom score from 1.9±0.1 to 1.7±0.1 in the placebo group (<i>P</i>=NS), from 2.0±0.1 to 1.4±0.1 (<i>P</i><0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (<i>P</i><0.001) in the salmeterol plus ipratropium group.</p> <p>Compared with placebo, treatment with salmeterol and salmeterol plus ipratropium was associated with a higher percentage of days and nights without the use of additional albuterol (<i>P</i><0.01). No difference was observed between the two active treatment groups (<i>P</i>=0.35).</p> <p>Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (<i>P</i><0.001), whereas no difference was observed between the salmeterol and the salmeterol plus ipratropium groups.</p> <p>The changes in evening PEF were in favor of both active treatment arms compared with placebo (<i>P</i><0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs the salmeterol group (<i>P</i><0.01).</p> <p>During the 12-week treatment period, the mean±SEM increase in FEV₁ was 1.0±0.9% predicted for placebo, 5.0±0.9% predicted for salmeterol, and 8.0±0.8% for the salmeterol plus ipratropium group. All differences were statistically significant (<i>P</i><0.01). The change in FVC was 4.0±1.2% predicted after placebo, 7.0±1.2% predicted after salmeterol and 12.0±1.2% after salmeterol plus ipratropium. The differences between salmeterol plus ipratropium vs salmeterol alone and between salmeterol plus ipratropium vs placebo were both significant (<i>P</i><0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (<i>P</i>=0.055).</p> <p>The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>During the 12-week treatment period, 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group, and six (13%) in the salmeterol plus ipratropium group. The only significant difference was between the salmeterol plus ipratropium group and the placebo group ($P < 0.01$).</p>
<p>Barr et al²³</p> <p>Tiotropium vs placebo, or ipratropium, or a long-acting β_2-adrenergic agonists</p>	<p>MA</p> <p>9 RCT's with patients diagnosed with COPD, whose disease was stable</p>	<p>N=6,584</p> <p>1 month or greater</p>	<p>Primary: Exacerbations, hospitalizations, mortality</p> <p>Secondary: Change in FEV₁ and/or FVC, rescue medication use, adverse events</p>	<p>Primary: Reduced exacerbations were seen in the tiotropium group compared to placebo (OR, 0.75; 95% CI, 0.66 to 0.85) and compared to ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92).</p> <p>Hospitalizations for COPD exacerbations were reduced in the tiotropium group compared to placebo (OR, 0.65; 95% CI, 0.50 to 0.85) and compared to ipratropium or salmeterol but these differences were not statistically significant (OR, 0.59; 95% CI, 0.32 to 1.09; OR, 0.59; 95% CI, 0.29 to 1.23).</p> <p>Cumulative all-cause mortality was 1.5% in the control groups and there were no statistically significant differences between any of the treatment groups over the duration of the trials (P value not reported).</p> <p>Secondary:</p> <p>In the tiotropium group, there was a greater mean change in trough FEV₁ from baseline that was statistically significant compared to placebo (140 mL; 95% CI, 118 to 162), ipratropium (150 mL; 95% CI, 106 to 193) and salmeterol (40 mL; 95% CI, 12 to 68).</p> <p>In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to placebo (278 mL; 95% CI, 208 to 348) ipratropium (210 mL; 95% CI, 112 to 308) and salmeterol (90 mL; 95% CI, 35 to 145).</p> <p>In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to placebo (21 mL; 95% CI, 15 to 28) and ipratropium (16 mL; 95% CI, 7 to 25). There was no difference between the tiotropium and salmeterol groups (0 mL; 95% CI, -8 to 9).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Brusasco et al²⁴</p> <p>Tiotropium 18 µg QD</p> <p>vs</p> <p>salmeterol 50 µg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, PC, RCT</p> <p>Patients with COPD over the age of 40, with an FEV₁ ≤65% of predicted and an FVC ≤70%</p>	<p>N=1,207</p> <p>6 months</p>	<p>Primary: Exacerbations, health resource use, restricted activity</p> <p>Secondary: SGRQ, TDI, spirometry, adverse events</p>	<p>In the tiotropium group, dry mouth was significantly increased compared to placebo (OR, 5.4; 95% CI, 3.3 to 8.8), ipratropium (OR, 2.1; 95% CI, 1.05 to 4.2), and salmeterol (OR, 5.1; 95% CI, 2.2 to 12.0).</p> <p>Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (<i>P</i><0.01). The proportion of patients with at least one exacerbation was 32, 35, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (<i>P</i>>0.05). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups.</p> <p>The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant (<i>P</i> value not reported).</p> <p>The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared with 11.1 days in the salmeterol group and 10.9 days in the placebo group (<i>P</i><0.05).</p> <p>Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the six month trial for the tiotropium, salmeterol, and placebo groups, respectively. A significant difference was observed for tiotropium vs placebo (<i>P</i><0.01).</p> <p>TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (<i>P</i><0.001 and <i>P</i><0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (<i>P</i>=0.17).</p> <p>Tiotropium was statistically better than salmeterol in peak FEV₁ and AUC from 0 to three hours. For trough FEV₁ values, tiotropium exhibited a similar trend.</p> <p>Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%; <i>P</i> value not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Donohue et al²⁵</p> <p>Tiotropium 18 µg QD</p> <p>vs</p> <p>salmeterol 50 µg BID</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients with stable COPD (age ≥40) with an FEV₁ ≤60% of predicted normal and FEV₁/FVC of ≤70%</p>	<p>N=623</p> <p>6 months</p>	<p>Primary: Changes in spirometry</p> <p>Secondary: PEFR, TDI, SGRQ</p>	<p>Primary: At 24 weeks, trough FEV₁ had improved significantly over 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; <i>P</i><0.01).</p> <p>As with FEV₁, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (<i>P</i><0.01).</p> <p>Secondary: PEFR improved by 27.3, 21.4, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (<i>P</i><0.001) and tiotropium was better than salmeterol in improving evening PEFR (<i>P</i><0.05).</p> <p>At six months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (<i>P</i>=0.01), and 0.24 units for salmeterol (<i>P</i>=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference, 0.78 units; <i>P</i><0.05).</p> <p>At six months, the mean improvement in SGRQ was -5.14 units for tiotropium (<i>P</i><0.05 vs placebo), -3.54 units for salmeterol (<i>P</i>=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance (<i>P</i> value not reported).</p>
<p>Kurashima et al²⁶</p> <p>Tiotropium 18 µg QD</p> <p>vs</p> <p>fluticasone 200 µg and salmeterol 50 µg BID</p>	<p>OL, RCT, XO</p> <p>Patients >40 years of age with COPD and stable airway obstruction with post-bronchodilator FEV₁/FVC <70%, predicted FEV₁ 30 to 80%, and smoking history of >10 pack-years</p>	<p>N=78</p> <p>4 months (2 months/treatment arm)</p>	<p>Primary: Post-bronchodilator FVC and FEV₁</p> <p>Secondary: HRQL using the SGRQ</p>	<p>Primary: Both treatments significantly improved FVC and FEV₁ compared to baseline values (<i>P</i><0.0001).</p> <p>The increase in post-bronchodilator FVC was greater with tiotropium as compared with fluticasone and salmeterol (<i>P</i>=0.0021).</p> <p>Secondary: Significant improvements in SGRQ scores were observed in both groups compared to baseline, though no significant differences were observed between groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Aaron et al¹³</p> <p>Tiotropium 18 µg QD plus placebo</p> <p>vs</p> <p>tiotropium 18 µg QD plus salmeterol 50 µg BID</p> <p>vs</p> <p>tiotropium 18 µg QD plus fluticasone/salmeterol 500/50 µg BID</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients ≥35 years old with at least 1 COPD exacerbation in the last 12 months requiring systemic steroids or antibiotics, history of ≥10 pack-years of cigarette smoking, documented chronic airflow obstruction with an FEV₁/FVC <0.70 and a post-bronchodilator FEV₁ <65% of the predicted value</p>	<p>N=449</p> <p>1 year</p>	<p>Primary: Proportion of patients who experience a COPD exacerbation requiring systemic steroids or antibiotics</p> <p>Secondary: Mean number of COPD exacerbations/patient-year, total number of exacerbations resulting in urgent visits to a health care practitioner or emergency room, number of hospitalizations for COPD, total number of hospitalizations for all causes, changes in HRQL, dyspnea, and lung function</p>	<p>Primary: The proportion of patients who experienced at least one COPD exacerbation in the tiotropium plus placebo group (62.8%) did not significantly differ between the tiotropium plus salmeterol group (64.8%) and the tiotropium plus fluticasone/salmeterol group (60.0%).</p> <p>The absolute risk reduction was -2.0 percentage points (95% CI, -12.8 to 8.8) for the tiotropium plus salmeterol group vs tiotropium plus placebo (<i>P</i>=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8) for tiotropium plus fluticasone/salmeterol vs tiotropium plus placebo (<i>P</i>=0.62).</p> <p>The unadjusted OR risk for exacerbations was 1.03 (95% CI, 0.63 to 1.67) with tiotropium plus salmeterol vs tiotropium plus placebo and 0.85 (95% CI, 0.52 to 1.38) for tiotropium plus fluticasone/salmeterol vs tiotropium plus placebo.</p> <p>Secondary: The mean number of COPD exacerbations/patient-year did not significantly differ between the tiotropium plus placebo group (1.61) and the tiotropium plus salmeterol group (1.75) and the tiotropium plus fluticasone/salmeterol group (1.37). The incidence rate ratio was 1.09 (95% CI, 0.84 to 1.40) for tiotropium plus salmeterol compared with tiotropium plus placebo (<i>P</i>=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol vs tiotropium vs tiotropium plus placebo (<i>P</i>=0.24).</p> <p>Patients treated with tiotropium plus fluticasone/salmeterol had lower rates of severe COPD exacerbations requiring hospitalization than did patients treated with tiotropium plus placebo with an incidence rate ratio of 0.53 (95% CI, 0.33 to 0.86; <i>P</i>=0.01).</p> <p>All-cause hospitalizations were reduced in patients treated with tiotropium plus placebo (<i>P</i>=0.04). Similar benefits were not seen with tiotropium plus salmeterol compared with tiotropium plus placebo.</p> <p>The one-year change in total score on the SGRQ was -4.5 points in the tiotropium plus placebo group, -6.3 points in the tiotropium plus salmeterol group (<i>P</i>=0.02), and -8.6 points in the tiotropium plus fluticasone/salmeterol</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>group ($P=0.01$).</p> <p>Dyspnea scores improved over one year of observation but did not significantly differ among the treatment groups ($P=0.38$).</p> <p>Over 52 weeks, the absolute prebronchodilator FEV₁ increased by 0.027 L in the tiotropium plus placebo group compared with 0.086 L in the tiotropium plus fluticasone/salmeterol group ($P=0.049$). Additionally, the percent predicted FEV₁ increased by 1.3% in the tiotropium plus placebo group compared with 4.6% in the tiotropium plus fluticasone/salmeterol group ($P=0.005$). Lung function was not significantly better in the tiotropium plus salmeterol group than in the tiotropium plus placebo group.</p>
<p>Rabe et al¹⁴</p> <p>Tiotropium 18 µg QD plus formoterol 12 µg BID</p> <p>vs</p> <p>fluticasone 500 µg BID plus salmeterol 50 µg BID</p>	<p>DB, MC, PG, RCT</p> <p>Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV₁ <80% predicted and FEV₁/FVC <0% at visit 1, and predose FEV₁ ≤65% predicted at visit 2</p>	<p>N=605</p> <p>6 weeks</p>	<p>Primary: FEV₁ area under the curve₀₋₁₂, peak FEV₁</p> <p>Secondary: Morning predose FEV₁</p>	<p>Primary: After six weeks, the FEV₁ area under the curve₀₋₁₂ mean difference was 78 mL higher (95% CI, 34 to 122) with treatment with tiotropium plus formoterol compared to treatment with fluticasone plus salmeterol ($P=0.0006$).</p> <p>The difference in peak FEV₁ was 103 mL (95% CI, 55 to 150) in favor of tiotropium plus formoterol ($P<0.0001$).</p> <p>Secondary: The difference in predose FVC after six weeks favored tiotropium plus formoterol (95% CI, 11 to 147; $P<0.05$).</p>
<p>Singh et al⁸</p> <p>Any inhaled antimuscarinics for treatment of COPD</p>	<p>MA</p> <p>17 RCT's for any inhaled antimuscarinics with more than 30 days of follow up, study participants with a diagnosis of COPD of any severity, an inhaled anticholinergic as the intervention</p>	<p>N=14,783</p> <p>Duration ranged from 6 to 26 weeks</p>	<p>Primary: Composite of cardiovascular death, myocardial infarction, or stroke</p> <p>Secondary: All-cause mortality</p>	<p>Primary: In a MA of 17 trials of 14,783 participants, cardiovascular death, myocardial infarction, or stroke occurred in 1.8% (n=135) of patients receiving inhaled antimuscarinics and 1.2% (n=86) of patients receiving control therapy (RR, 1.58; 95% CI, 1.21 to 2.06; $P<0.001$).</p> <p>Among the individual components of the composite primary endpoint, inhaled antimuscarinics significantly increased the risk of myocardial infarction (1.2 vs 0.8% for control; RR, 1.53; 95% CI, 1.05 to 2.23; $P=0.03$) and cardiovascular death (0.9 vs 0.5% for control; RR, 1.80; 95% CI, 1.17 to 2.77; $P=0.008$) but did not significantly increase the risk of stroke (0.5 vs 0.4% for control; RR, 1.46; 95% CI, 0.81 to 2.62; $P=0.20$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including myocardial infarction, stroke, or cardiovascular death			<p>Secondary: Inhaled antimuscarinics did not significantly increased the risk of all-cause mortality (2.0 vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; $P=0.06$).</p>
<p>Lee et al⁹</p> <p>Exposure to inhaled corticosteroids, ipratropium, long-acting β_2-agonist, theophylline, and short-acting β_2-agonist</p>	<p>Nested case-control</p> <p>Patients treated in the United States Veterans Health Administration health care system</p>	<p>N=145,020</p> <p>Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004</p>	<p>Primary: All-cause mortality, respiratory mortality, cardiovascular mortality</p> <p>Secondary: Subgroup analyses of primary outcomes</p>	<p>Primary: After adjusted for differences in covariates, inhaled corticosteroids and long-acting β_2-agonist were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for inhaled corticosteroids and 0.92 (95% CI, 0.88 to 0.96) for long-acting β_2-agonist was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15).</p> <p>Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with long-acting β_2-agonist (OR, 1.12; 95% CI, 0.97 to 1.30), however the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with inhaled corticosteroids (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance.</p> <p>Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas inhaled corticosteroids exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). Long-acting β_2-agonist (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths.</p> <p>Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication.</p> <p>With current smoking associated with a relative risk for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for inhaled</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>corticosteroids, 1.08 for ipratropium, and 0.90 for long-acting β_2-agonist.</p> <p>Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of inhaled corticosteroids with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; $P<0.001$).</p> <p>In the all-cause mortality group, inhaled corticosteroids were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.</p>

Study abbreviations: DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover

Miscellaneous abbreviations: BDI=Baseline Dyspnea Index, BID=two times per day, CI=confidence interval, COPD=chronic obstructive pulmonary disease, FEV₁=forced expiratory volume in one second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease, HR=hazard ratio, HRQL=health related quality of life, NS=not significant, OR=odds ratio, PEF=peak expiratory flow, PEFr=peak expiratory flow rate, PR=pulmonary rehabilitation, QD=every day, QID=four times per day, RR=relative risk, SEM=standard error of the mean, SF-36=short form 36, SGRQ=St. George's respiratory questionnaire, SVC=slow vital capacity, TDI=transitional dyspnea index, WMD=weighted mean difference

Special Populations**Table 5. Special Populations**²⁻⁴

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ipratropium	No dosage adjustment required in the elderly. Safety and efficacy in children under the age of 12 have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Tiotropium	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown

Adverse Drug Events

Due to poor systemic absorption, systemic side effects associated with the use of inhaled antimuscarinics are limited. The most common side effect of these agents is dry mouth.

Table 6. Adverse Drug Events²⁻⁴

Adverse Event(s)	Ipratropium	Tiotropium
Cardiovascular		
Angina	-	1 to 3
Arrhythmia	-	<1
Chest pain	-	5 to 7
Hypotension	✓	-
Palpitations	✓	✓
Tachycardia	✓	-
Central Nervous System		
Depression	-	1.0 to 4.4
Dizziness	3	✓
Headache	6 to 7	5.7
Insomnia	-	4.4
Paresthesia	-	1 to 3
Dermatological		
Allergic skin reactions	✓	2 to 4
Angioedema	✓	<1
Dry skin	-	✓
Pruritis	✓	✓
Skin infection	-	✓
Skin rash	✓	2 to 4
Skin ulcer	-	✓
Urticaria	✓	✓
Endocrine and Metabolic		
Edema	-	3 to 5
Hypercholesterolemia	-	1 to 3
Hyperglycemia	-	1 to 3

Adverse Event(s)	Ipratropium	Tiotropium
Gastrointestinal		
Abdominal pain	5 to 6	-
Constipation	✓	1.0 to 5.1
Diarrhea	✓	-
Dyspepsia	1 to 5	1 to 6
Gastroesophageal reflux	-	1 to 3
Gastrointestinal pain	-	3 to 6
Intestinal obstruction	-	✓
Nausea	4	-
Vomiting	-	1 to 4
Genitourinary		
Urinary retention	✓	<1
Urinary tract infection	2 to 10	4 to 7
Musculoskeletal		
Arthralgia	-	4.2
Arthritis	-	≥3
Joint swelling	-	✓
Leg pain	-	1 to 3
Myalgia	-	4
Skeletal pain	-	1 to 3
Respiratory		
Bronchitis	10 to 23	-
Bronchospasm	✓	-
Chronic obstructive pulmonary disease exacerbation	8 to 23	-
Coughing	✓	≥3
Dyspnea	7 to 8	-
Pharyngitis	-	7.0 to 12.5
Rhinitis	≥3	3 to 6
Sinusitis	1 to 11	3 to 11
Upper respiratory tract infection	≥3	43 to 41
Other		
Accidents	-	5 to 13
Anaphylaxis	✓	-
Angioedema	-	<1
Back pain	2 to 7	-
Blurred vision	✓	-
Cataract	-	1 to 3
Conjunctival hyperaemia	✓	-
Corneal edema	✓	-
Dehydration	-	✓
Dry mouth	2 to 4	5.1 to 16.0
Dry throat	✓	-
Dysphagia	-	✓
Dysphonia	-	1 to 3
Epistaxis	-	1 to 4
Eye pain	✓	-
Gingivitis	-	✓
Glaucoma	✓	-
Glaucoma, worsening of narrow-angle	✓	-
Halo vision	✓	-
Herpes zoster	-	1 to 3
Hoarseness	-	✓

Adverse Event(s)	Ipratropium	Tiotropium
Hypersensitivity reaction	✓	1 to 3
Infection	-	1 to 4
Influenza-like symptoms	4 to 8	≥3
Intraocular pressure increased	-	✓
Laryngitis	-	1 to 3
Laryngospasm	✓	-
Moniliasis	-	3 to 4
Mouth edema	✓	-
Mydriasis	✓	-
Oropharyngeal candidiasis	-	✓
Stomatitis	✓	1 to 3
Taste perversion	<1	-
Throat irritation	✓	✓

✓ Percent not specified.

- Event not reported.

Contraindications/Precautions

Both ipratropium and tiotropium are contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any component of these agents.²⁻⁴

Inhaled antimuscarinics are indicated for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease and therefore should not be used as initial treatment of acute episodes of bronchospasm where rescue therapy is required for a rapid response.²⁻⁴

Immediate hypersensitivity reactions may occur after the administration of inhaled antimuscarinics including anaphylaxis, angioedema, bronchospasm, oropharyngeal edema, rash, and urticaria. In addition, inhaled medicines may cause paradoxical bronchospasm.²⁻⁴ Tiotropium should be used with caution in patients with a severe hypersensitivity to milk proteins.⁴

Antimuscarinics should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction due to the potential to worsen signs and symptoms of these conditions.²⁻⁴ In addition, as a predominately renally excreted drug, patients with moderate to severe renal impairment should be monitored closely if treated with tiotropium.⁴

In February 2008, the Food and Drug Administration issued a public health advisory to highlight the correct use of Spiriva[®] (tiotropium) capsules. Spiriva[®] capsules are to be used in the specific Spiriva[®] HandiHaler[®] devices to deliver the medicine to the lungs. The capsules are specifically designed to be inhaled through inhalation devices and will not treat a patient's breathing condition if the contents of the capsule are swallowed rather than inhaled.²⁷

Drug Interactions

Although the inhaled antimuscarinics are minimally absorbed, there is some potential for an additive interaction with concomitantly used antimuscarinic (anticholinergic) medications.^{2-4,12,28}

Dosage and Administration

Table 7. Dosing and Administration^{2-4,11,29}

Generic Name	Adult Dose	Pediatric Dose	Availability
Ipratropium	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema: Aerosol for oral inhalation: initial, 34 µg (2 inhalations) QID; maximum, do not exceed 204	Safety and efficacy in children under the age of 12 have not been established.	Aerosol for oral inhalation: 17 µg (200 actuations/unit) Solution for

Generic Name	Adult Dose	Pediatric Dose	Availability
	<p>µg (12 inhalations) in 24 hours</p> <p>Solution for nebulization: maintenance, 500 µg QID, dose six to eight hours apart</p>		nebulization: 500 µg (0.02%)
Tiotropium	<p><u>Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema and reducing chronic obstructive pulmonary disease exacerbations:</u></p> <p>Powder for oral inhalation: initial, 18 µg QD</p>	Safety and efficacy in children have not been established.	Powder for oral inhalation: 18 µg

QD=once daily, QID=four times daily

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
<p>Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)¹</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. • A diagnosis of COPD should be confirmed by spirometry. • The presence of a post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) <0.70 confirms the presence of airflow limitation that is not fully reversible. • Assessment of COPD severity is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia. • Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure. • Arterial blood gas tension measurements should be considered for all patients with FEV₁ <50% predicted or clinical signs suggestive of respiratory failure or right heart failure. • COPD is typically a progressive disease; therefore, lung function can be expected to worsen over time, even with the best available care. • Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy. In addition, symptom monitoring is used to determine when to modify therapy and to identify any complications that may develop. • Comorbidities are common in COPD and should be actively identified. Comorbidities often complicate the management of COPD, and vice versa. • Screening for α₁-antitrypsin deficiency may be valuable in patients of Caucasian decent who develop COPD at a young age (<45 years of age) or who have a strong family history of the disease. • In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing

Clinical Guideline	Recommendations
	<p>techniques and it is assumed that asthma and COPD coexist in these patients. In these instances, current management is similar to that of asthma. Other potential diagnoses (e.g., congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis) are usually easier to distinguish from COPD.</p> <p><u>Treatment</u></p> <ul style="list-style-type: none"> • The management of COPD should be individualized to address symptoms and improve the patient’s quality of life. • None of the medications for COPD have been shown to modify the long term decline in lung function that is hallmark of this disease. Treatment should be focused on reducing symptoms and complications. • Choice of agent within each medication class depends on the availability of medication and the patient’s response. • Bronchodilator medications are central to the symptomatic management of COPD. They are given on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. • Inhaled therapy is preferred. • When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential. COPD patients may have more problems in effective coordination with a metered dose inhaler compared to healthy patients; alternative breath-activated or spacer devices are available for most formulations. Dry powder inhalers may be more convenient and possibly provide improved drug deposition, although this has not been established in COPD. • Principle bronchodilators include β_2-agonists, anticholinergics and methylxanthines used as monotherapy or in combination. • Regular treatment with long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • The choice between β_2-agonists, anticholinergics, theophylline or combination therapy depends on availability and individual response in terms of symptom relief and side effects. • The order in which the bronchodilator medications are normally introduced into patient care (based on the level of disease severity and clinical symptoms) is: β-agonists, anticholinergics and methylxanthines. • Regular use of LABAs or short- or long-acting anticholinergics improves health status. • Long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. • Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All theophylline studies were performed with slow-release preparations. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • The addition of regular treatment with ICSSs to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV₁ <50% predicted and repeated exacerbations.

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	<ul style="list-style-type: none"> • Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV₁<50% of the predicted value and repeated exacerbations. • Treatment with ICSs increases the likelihood of pneumonia and does not reduce overall mortality. • An ICS combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status. • Combination ICS/LABA therapy increases the likelihood of pneumonia. • Addition of an ICS/LABA to an anticholinergic appears to provide additional benefits. • There is insufficient evidence to recommend a therapeutic trial with systemic corticosteroids in patients with Stage II, Stage III or Stage IV COPD and poor response to an inhaled bronchodilator. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • In COPD patients influenza vaccines can reduce serious illness. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV₁<40% of the predicted value. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. • Inhaled β₂-agonists (particularly inhaled β₂-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
<p>National Institute for Health and Clinical Excellence: Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)¹⁰</p>	<p><u>Diagnosis</u></p> <ul style="list-style-type: none"> • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV₁<80% predicted and FEV₁/FVC<70%. <p><u>Treatment</u></p> <ul style="list-style-type: none"> • Smoking cessation¹⁰ should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators (beta₂ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily long-acting muscarinic antagonists are preferred compared to four-times-daily short-acting muscarinic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in

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	<p>whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist.</p> <ul style="list-style-type: none"> ○ FEV₁ ≥50% predicted: long-acting β₂-agonist or long-acting muscarinic antagonist. ○ FEV₁ < 50% predicted: either long-acting β₂-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist. <ul style="list-style-type: none"> • In patients with stable COPD and FEV₁ ≥50% who remain breathless or have exacerbations despite maintenance therapy with a long-acting β₂-agonist, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist when inhaled corticosteroids are not tolerated or declined. • Consider a long-acting muscarinic antagonist in patients remaining breathless or having exacerbations despite therapy with long-acting β₂-agonist and inhaled corticosteroids and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β₂-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. <p><u>Management of exacerbations</u></p> <ul style="list-style-type: none"> • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The inhaled antimuscarinics, ipratropium and tiotropium, are Food and Drug Administration approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).²⁻⁴ Additionally, tiotropium is indicated for reducing COPD exacerbations.⁴ Ipratropium and tiotropium are both classified as bronchodilators but due to differences in pharmacokinetic parameters,

tiotropium is classified as a long-acting bronchodilator and ipratropium is classified as a short-acting bronchodilator. Tiotropium has a significantly longer duration of action compared to ipratropium and as a result is approved for once-daily dosing. Ipratropium has a duration of action of six to eight hours and is administered four times daily. Both agents have been shown to improve lung function and exercise tolerance in patients with COPD, however, comparative trials have noted improved outcomes with tiotropium over ipratropium.^{5,6} When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.^{13,14} In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages.¹⁵ But, as with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.^{16,17}

According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, inhaled bronchodilators are preferred for the management of COPD.¹ Principle bronchodilators include β_2 -agonists, anticholinergics and theophylline used as monotherapy or in combination. The guidelines state that regular use of long-acting β_2 -agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The National Institute for Health and Clinical Excellence guidelines maintain that once-daily long-acting antimuscarinic agents are preferred compared to four-times-daily short-acting antimuscarinics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an antimuscarinic agent.¹⁰

Appendix I: Utilization Within This Drug Class for DVHA: July 1, 2010 to December 31, 2010

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Spiriva Handihaler [®]	522	943	87.15	395,911.10	419.84
Atrovent HFA [®]	82	114	10.54	31,710.34	278.16
Ipratropium bromide neb	22	25	2.31	794.63	31.79
Class Total:	626	1,082	100%	\$428,416.07	\$395.95

Recommendations

In recognition of the well-established role of inhaled antimuscarinics in the treatment of chronic obstructive pulmonary disease and the limited availability of generic dosage forms, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (see below).

All agents in the class are preferred on the DVHA preferred drug list (PDL) and are available without a prior authorization, within the following quantity limits: 2 inhalers/25 days (Atrovent HFA[®]) and 1 capsule/day (Spiriva[®]).

References

1. Rodriguez-Roisin R, Anzueto A, Bourbeau J, deGuia T, Hui DSC, Jenkins C, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease updated 2010 [guideline on the internet]. 2010 [cited 2011 Feb]. Available from: <http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989>.
2. Ipratropium bromide [package insert]. Woodstock (IL): Cardinal Health; 2007 Sept.
3. Atrovent[®] HFA [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2010 Dec.
4. Spiriva[®] HandiHaler[®] [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2010 Jun.
5. Van Noord JA, Bantje TA, Eland ME, et al. A randomized controlled comparison of tiotropium and ipratropium in the treatment of COPD. *Thorax*. 2000;55(4):289-94.
6. Vincken W, van Noord JA, Greefhorst APM, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J*. 2002;19(2):209-16.
7. Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva[®] HandiHaler) [press release on the internet]. Rockville (MD): Food and Drug Administration (US): 2010 Jan 14 [cited 2011 Feb 1]. Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm197429.htm>.
8. Singh S, Loke Y, Furberg C. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease a systematic review and meta-analysis. *JAMA*. 2008;300(12):1439-50.
9. Lee T, Pickard A, Au D, Bartle B, Weiss K. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med*. 2008;149:380-90.
10. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). [guideline on the internet]. 2010 [cited 2011 Feb2]. Available from: www.nice.org.uk/guidance/CG101.
11. Ipratropium bromide: drug information. In Basow DS (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Feb 1]. Available from <http://www.utdol/utd/index.do>.
12. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2011 Feb1]. Available from: <http://www.thomsonhc.com/>.
13. Aaron S, Vanderheen K, Fegusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. *Ann Intern Med*. 2007;146:545-55.
14. Rabe K, Timmer W, Sagkrotis A, Viel K. Comparison of combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest*. 2008;143:255-62.
15. McCrory DC, Brown CD. Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2002, Issue 4. Art. No.:CD003900.
16. Matera MG, Caputi M, Cazzola M, et al. A combination with clinical recommended dosages of salmeterol and ipratropium is not more effective than salmeterol alone in patients with chronic obstructive pulmonary disease. *Respir Med*. 1996;90(8):497-9.
17. Van Noord JA, de Munck DRAJ, Bantje ThA, et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J*. 2000;15(5):878-85.
18. Casaburi R, Kukafka D, Cooper CB, et al. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest*. 2005;127(3):809-17.
19. Tashkin D, Celli B, Senn S, Burkhart D, Ketsen S, Menjoge S, et al. A 4-Year Trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543-54.
20. Decramer M, Celli B, Kesten S, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet*. 2009;374:1171-8.
21. Troosters T, Celli B, Lystig T, et al. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur Respir J*. 2010;36:65-73.
22. Celli B, Decramer M, Kesten S, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;180:948-55.

23. Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.:CD002876.
24. Brusasco V, Hodder R, Miravittles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax*. 2003;58(5):399-404.
25. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest*. 2002;122(1):47-55.
26. Kurashima K, Hara K, Yoneda K, et al. Changes in lung function and health status in patients with COPD treated with tiotropium or salmeterol plus fluticasone. *Respirology*. 2009;14:239-44.
27. Important Information on the Correct Use of Spiriva and Foradil Capsules [press release on the internet]. Rockville (MD): Food and Drug Administration (US): 2008 Feb 29 [cited 2011 Feb 1]. Available from: http://www.fda.gov/cder/drug/advisory/tiopropium_formoterol.htm.
28. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2010 [cited 2011 Feb 1]. Available from: <http://online.factsandcomparisons.com>.
29. Tiotropium: drug information. In Basow DS (Ed). *UpToDate* [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Feb 1]. Available from <http://www.utdol/utd/index.do>.