Therapeutic Class Overview
Inhaled Antimuscarinics

Therapeutic Class

- **Overview/Summary:** The inhaled antimuscarinics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD). Specifically, inhaled antimuscarinics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation.[1-6] Two single-agent inhaled antimuscarinics are currently available, ipratropium (Atrovent®, Atrovent® HFA) and tiotropium (Spiriva®). 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 and requires administration four times daily. Tiotropium has a duration of action of greater than 24 hours, requiring once-daily administration and is classified as a long-acting bronchodilator.[2-3] A combination product containing albuterol and ipratropium is available as an inhaler (Combivent®, Combivent Respimat®) and solution for nebulization (DuoNeb®*).[3-6] The Combivent Respimat® inhaler was developed in response to the Montreal Protocol, an international treaty requiring the elimination of inhalers that use chlorofluorocarbons as propellants (currently used in Combivent® aerosol metered dose inhaler [MDI]). Combivent Respimat® uses a spring mechanism to release the medication rather than a propellant.[5] The two formulations differ in their dosing and administration schedules. Combivent® aerosol MDI will be available until late 2013. By January 1, 2014, Combivent Respimat® will be the only one of these two products available.[7] Meaningful increases in lung function can be achieved with the use of inhaled antimuscarinics in patients with COPD.[8,9] The Global Initiative for Chronic Obstructive Lung Disease and National Institute for Health and Clinical Excellence guidelines have not made any recent changes in regard to the role of the inhaled antimuscarinics in the treatment of COPD.[1,10] Both ipratropium and the ipratropium/albuterol combination products are available generically as a solution for nebulization.[11]

Table 1. Current Medications Available in the Class[2-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Products			
Ipratropium (Atrovent®*, Atrovent HFA®)	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema	Aerosol for oral inhalation: 17 µg (200 actuations/unit) Solution for nebulization: 500 µg (0.02%)	a *
Tiotropium (Spiriva®)	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema, reducing chronic obstructive pulmonary disease exacerbations	Powder for oral inhalation: 18 µg	-
Combination Products			
Ipratropium/albuterol (Combivent®, Combivent Respimat®, DuoNeb®*)	Treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator	Aerosol for oral inhalation: 120/21 µg† (200 metered inhalations) Inhalation spray (inhaler): 100/20 µg† (120	a *

		actuations) Solution for nebulization: 3.0/0.5 mg (3 mL vials)	

*Solution for nebulization
†Delivering 103 µg of albuterol (90 µg albuterol base) and 18 µg of ipratropium.

Evidence-based Medicine

- The inhaled antimuscarinics have demonstrated safety and efficacy in improving lung function and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[8,9,12-39]
- Despite a limited number of head-to-head trials, significant differences in improvements in lung function have been reported with tiotropium compared to ipratropium.[8,9]
- There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators. In one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; *P*<0.001).[27] However, when tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[31,32]
- In a meta-analysis, the combination of tiotropium and formoterol significantly improved the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) compared to tiotropium alone (*P*<0.001 for both), but there was no difference in COPD exacerbation rates between the treatments.[23] In a second meta-analysis, tiotropium significantly reduced the odds of a COPD exacerbation compared to placebo (*P*=0.004) and ipratropium (*P*=0.020) but not compared to salmeterol (*P*=0.25).[24]
- In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[17,21,22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The Global Initiative for Chronic Obstructive Lung Disease guidelines state that inhaled bronchodilators are preferred for the management of chronic obstructive pulmonary disease (COPD). 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 use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.[1]
  - The National Institute for Clinical Excellence state that 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. 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]
- Other Key Facts:
  - The role of the inhaled antimuscarinics in the treatment of COPD has been well established.
  - The inhaled antimuscarinic 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.[8,9]
  - By January 1, 2014, the Combivent® aerosol MDI will be discontinued, and the recently-approved Combivent Respimat® will be the only one of these two products available.[7]

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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), a condition characterized by progressive airflow restrictions that are not fully reversible.[1] Symptoms associated with COPD typically 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]

The available single-entity inhaled antimuscarinics include ipratropium (Atrovent® HFA) and tiotropium (Spiriva®). A combination product containing albuterol and ipratropium is available as an inhaler Combivent®, Combivent Respimat®) and solution for nebulization formulation (DuoNeb®*).[2-6] Both ipratropium and tiotropium are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[2,3] In addition, tiotropium is FDA-approved for reducing exacerbations associated with COPD.[3] The albuterol/ipratropium combination is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator.[4-6] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Tiotropium has a duration of action of greater than 24 hours requiring once-daily administration and is classified as a long-acting bronchodilator.[2,3] Results from comparative trials have shown that tiotropium may improve spirometry measurements to a greater degree compared to ipratropium.[7,8] Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Tiotropium is available as a dry powder inhaler for oral inhalation. The ipratropium (Atrovent®) and ipratropium/albuterol solutions for nebulization are the only inhaled antimuscarinic products that are currently available generically.[9]

The combination of ipratropium and albuterol as a fixed-dose inhaler was approved for the treatment of COPD in 1996 as Combivent®, an aerosol metered dose inhaler (MDI).[4] Combivent Respimat®, approved in late 2011 differs in that it is a propellant-free inhaler that uses a slow moving mist to deliver the same amount of the two agents.[5] The new inhaler was developed in response to the Montreal Protocol, an international treaty requiring the elimination of inhalers that use chlorofluorocarbons as propellants, which are currently used in Combivent® aerosol MDI. Instead of a propellant, Combivent Respimat® (ipratropium bromide/albuterol) uses a spring mechanism to release the medication.[5] The two formulations differ in their dosing and administration schedules. Combivent® aerosol MDI will be available until late 2013. By January 1, 2014, Combivent Respimat® will be the only one of these two products available.[10] A solution for nebulization formulation of ipratropium bromide/albuterol is currently available generically and is not impacted by the Montreal Protocol.

In March of 2008, the manufacturer of tiotropium, 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 tiotropium in approximately 6,000 patients with COPD, demonstrated no increased risk of stroke with tiotropium compared to placebo.[11] 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. [12,13] 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).[12] 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,

confirming that tiotropium did not demonstrate a significant increased risk of stroke or cardiovascular death 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.[11]

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.[14]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Products		
Ipratropium (Atrovent®, Atrovent HFA®)	Inhaled antimuscarinic	a *
Tiotropium (Spiriva®)	Inhaled antimuscarinic	-
Combination Products		
Ipratropium/albuterol (Combivent®, Combivent Respimat®, DuoNeb®*)	Inhaled β_2-adrenegic agonists/anticholinergic	a *

*Solution for nebulization.

Indications

Table 2. Food and Drug Administration Approved Indications[2-6,15]

Generic Name	Maintenance Treatment of Bronchospasm Associated with Chronic Obstructive Pulmonary Disease, Including Chronic Bronchitis and Emphysema	Treatment of Bronchospasm Associated with Chronic Obstructive Pulmonary Disease in Patients Requiring More Than One Bronchodilator	Reducing Chronic Obstructive Pulmonary Disease Exacerbations
Single-Entity Products			
Ipratropium	a		
Tiotropium	a		a
Combination Products			
Ipratropium/albuterol		a	

The prescribing information for ipratropium nebulizer solution states that it can be administered alone or in combination 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] Tiotropium has been used off-label in the treatment of patients with asthma.[12]

Pharmacokinetics

Table 3. Pharmacokinetics[2-6,15]

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Products					
Ipratropium	15	6 to 8	2.8	None	2.0 to 3.8
Tiotropium	60	24	74.0	None	120 to 144
Combination Products					
Ipratropium/albuterol	0.16 to 2.00 (albuterol); 0.25 (ipratropium)	3 to 4 (albuterol); 2 to 5 (ipratropium)	30.0 (albuterol); 2.8 (ipratropium)	albuterol 4'-o-sulfate (albuterol); none (ipratropium)	3.8 (albuterol); 2.0 (ipratropium)

Clinical Trials

Clinical studies demonstrating the safety and efficacy of the inhaled antimuscarinics in respective Food and Drug Administration-approved indications are described in Table 4.[16-42]

In general, the inhaled antimuscarinics have been demonstrated to improve lung function and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). A few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[7,8]

There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators, although in one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; P<0.001).[31] When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[35, 36] In a meta-analysis by Wang et al, the combination of tiotropium and formoterol significantly improved the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) compared to tiotropium alone (P<0.001 for both); however, there was no difference in COPD exacerbation rates between the treatments.[28] In another meta-analysis, tiotropium significantly reduced the odds of a COPD exacerbation compared to placebo (P=0.004) and ipratropium (P=0.020) but not compared to salmeterol (P=0.25).[27] In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. In a systematic review, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported).[21] But, as with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[25, 26] Furthermore, the fixed-dose ipratropium/albuterol products have consistently demonstrated statistically significant improvements in FEV1 and FVC in clinical studies compared to either agent alone.[37-41]

The recently approved ipratropium/albuterol Combivent Respimat® inhaler has demonstrated improvements in FEV_1 that are equivalent to the aerosol metered dose inhaler (MDI). In a 12 week, active-controlled, double-blind, double-dummy, randomized controlled trial (N=1,480), patients with moderate to severe COPD were randomized to ipratropium bromide/albuterol 20/100 µg via Respimat® inhaler, ipratropium bromide/albuterol 36/206 µg via aerosol metered dose inhaler (MDI) or ipratropium bromide 20 µg via Respimat® inhaler; all administered four times daily. The results demonstrate that equivalent bronchodilation (change in FEV_1) was achieved with ipratropium bromide/albuterol Respimat® inhaler and ipratropium bromide/albuterol aerosol MDI, while significantly greater bronchodilation was achieved with the combination Respimat® inhaler compared to ipratropium bromide Respimat® inhaler (P<0.001). Overall, the safety profiles among the three treatments were similar; however, a lower

proportion of patients receiving ipratropium/albuterol Respimat® inhaler discontinued treatment due to an adverse event compared to ipratropium bromide/albuterol aerosol MDI (3.7 vs 6.9%).[42]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Casaburi et al[16] Tiotropium 18 µg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD and a FEV_1 ≤60% of predicted normal and a FEV_1/FVC of ≤70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ, rescue albuterol use	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 (*P*=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 (*P*=0.025) and 6.60 minutes (*P*=0.018), respectively. 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 (*P* value not reported). 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 (*P*=0.03; differences exceeding 1 unit were considered clinically meaningful). 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 (*P* value not reported). 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 (*P*<0.05).
Tashkin et al[17] (UPLIFT) Tiotropium 18 µg QD	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD,	N=5,993 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and	Primary: The rate of decline in the mean post bronchodilator FEV_1 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	with a FEV_1 of 70% or less after bronchodilation and a FEV_1/FVC of 70% or less		post-bronchodilator from day 30 until end of treatment 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	the mean value for FEV_1 either prebronchodilator (*P*=0.95) or post bronchodilator (*P*=0.21) from day 30 to the end of study-drug treatment. 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. 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). 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). 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).
Decramer et al (UPLIFT)[18] 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	Primary: Rate of decline of mean post-bronchodilator FEV_1 was lower in the tiotropium group compared to placebo (*P*=0.024). Rate of decline of mean pre-bronchodilator FEV_1 did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo This was a subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.	bronchodilation and a FEV_1/FVC of 70% or less		day 30 until end of treatment 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	Secondary: Mean values for pre- and post-bronchodilator FEV_1 were higher in the tiotropium group at all time points (P<0.0001). Mean pre-bronchodilator FVC and SVC were higher in the tiotropium group at all time points (P<0.001). Mean post-bronchodilator FVC was significantly higher in the tiotropium group at all time points (P<0.01). No significant difference in mean post-bronchodilator SVC was observed between groups. Health status was better in the tiotropium group compared to placebo for all time points ($P \leq 0.006$). 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). 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.
Troosters et al[19] (UPLIFT) Tiotropium 18 µg QD vs placebo This was a subgroup analysis of patients in the UPLIFT trial who were not on other maintenance	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 of 70% or less after bronchodilation and a FEV_1/FVC of 70% or less	N=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores,	Primary: After 30 days of treatment, pre-bronchodilator FEV_1 was significantly larger in the tiotropium group compared to the placebo group (P<0.0001). Trough FEV_1 remained significantly larger in the tiotropium group compared to placebo at all time points throughout the trial (P<0.05). Secondary: No significant differences between groups were observed in pre- or post-FVC ($P \geq 0.81$). Pre- and post-SVC was significantly higher in the tiotropium group ($P \leq 0.046$). The improvement in the SGRQ scores was significantly higher in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment at randomization.			COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	tiotropium group compared to the placebo group in the first six months of treatment (*P*=0.0065). SGRQ total score declined more slowly in the tiotropium group compared to the placebo group (*P*=0.002). No statistically significant difference in exacerbation rate was observed between groups (*P*=0.08). No statistically significant difference in time to first exacerbation was observed between groups (*P*=0.24). No statistically significant difference in exacerbations leading to hospitalizations was observed between groups.
Celli et al[20] (UPLIFT) Tiotropium 18 µg QD vs placebo This analysis is a more in depth look at the effect of tiotropium and its discontinuation on mortality and its causes.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 of 70% or less after bronchodilation and a FEV_1/FVC of 70% or less	N=5,993 Duration not specified	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment 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	Primary: See previous results by Tashkin et al.[17] Secondary: See previous results by Tashkin et al.[17] A lower risk of death was observed in the tiotropium group (HR, 0.84; 95% CI, 0.73 to 0.97). Adjustments by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications did not alter the results. The most common causes of death included lower respiratory causes, cancer, general disorders, and cardiac disorders.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van Noord et al[7] Tiotropium 18 µg QD vs ipratropium 40 µg QID	DB, DD, MC, PG Patients with stable COPD with mean age of 65 years and average FEV_1 of 41% of predicted values	N=288 15 weeks	Primary: Changes in FEV_1 and FVC Secondary: Daily records of PEF, use of albuterol	Primary: The FEV_1 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; *P*<0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than ipratropium. The differences in trough FEV_1 values were most pronounced (*P*<0.001), whereas differences in peak FEV_1 increase did not reach statistical significance (*P*>0.05). 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 (*P*<0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (*P*<0.05). 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 (*P*<0.05).
Vincken et al[8] Tiotropium 18 µg QD vs ipratropium 40 µg QID	DB, DD, MC, PG, RCT Patients with COPD ≥40 years of age with an FEV_1 of ≤65% of predicted normal value and ≤70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	Primary: By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared with 20 mL for the ipratropium group. 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 (*P*<0.05). At the end of one year, trough FEV_1 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; *P*<0.001 at all time points). The FVC results paralleled the FEV_1 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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). The BDI focal scores for the two groups were comparable. 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). 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). 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.
McCrory et al [21] Ipratropium (various strengths and dosage forms) vs	MA 9 RCT's of adult patients with a diagnosis of COPD, symptoms consistent with an acute	N=525 Duration ranged from 1 hour to 14 days	Primary: Short-term changes in FEV_1, WMD of long-term effects on FEV_1 Secondary:	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (*P* value not reported). The change in FEV_1 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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	exacerbation		Not reported	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). Secondary: Not reported
Donohue et al[22] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history ≥20 pack years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks vs placebo Secondary: Trough FEV_1 at 12 weeks vs tiotropium, FEV_1 at five minutes on day 1, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation, safety	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified minimum clinically important difference of 120 mL (*P* value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority ($P \leq 0.01$) and noninferiority ($P < 0.001$). FEV_1 at five minutes on day 1 was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium ($P < 0.001$ for all vs placebo and for indacaterol vs tiotropium). TDI total scores significantly increased relative to placebo ($P < 0.001$ for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks ($P < 0.05$ for all). Over the 26 weeks, the change from baseline in mean daily number of puffs of as needed albuterol was significantly reduced with both doses of indacaterol compared to placebo ($P < 0.001$ for both). Both doses of indacaterol were significantly "superior" to tiotropium ($P \leq 0.001$ for both). The proportion of days with no use of as needed albuterol was significantly lower with both doses of indacaterol compared to placebo ($P < 0.001$ for both) and tiotropium ($P \leq 0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The change from baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (*P*<0.001 for all) and tiotropium (morning; *P*≤0.001 for both, evening; *P*<0.05 and *P*<0.01). The proportion of nights with no awakenings (*P*<0.01 for both), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved relative to placebo with both doses of indacaterol at all assessments (*P*<0.01 for all) but not with tiotropium (*P* value not reported). Analysis of time to first COPD exacerbation showed a reduced risk compared to placebo with indacaterol 150 µg (HR, 0.69; 95% CI, 0.51 to 0.94; *P*=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; *P*=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; *P*=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments. Aside from this, cough within five minutes was observed in an average of 16.6 and 21.3% of patients per visit who were receiving indacaterol 150 and 300 µg, 0.8% of patients receiving tiotropium and 2.4% of patients receiving placebo (*P* values not reported). This cough typically had a median duration of six seconds and was not associated with bronchospasm or with increased discontinuation rates. Otherwise, adverse events were similar across treatment.
Vogelmeir et al[23] INTIME Indacaterol 150 µg QD vs indacaterol 300 µg QD vs	DB, DD, PC, RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and	N=169 12 weeks	Primary: Trough FEV_1 at 14 days vs placebo Secondary: Trough FEV_1 at 12 weeks vs tiotropium, trough FEV_1 after the first dose, FEV_1 at individual time	Primary: Trough FEV_1 was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200; *P*<0.001). Secondary: Both doses of indacaterol not only met the criterion for noninferiority compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. The *P* value for the statistical comparison of superiority between indacaterol 150 µg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tiotropium 18 µg QD vs placebo The trial consisted of three 14 day treatment periods, each of which was separated by a 14 day washout period. In each treatment sequence, patients received 3 of the 4 treatments listed above. Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed.	FEV_1/FVC <70%		points after the first dose and on day 14, safety	and tiotropium was 0.043, with a least-squares mean difference of 50 mL; this did not meet the requirement for superiority. FEV_1 after the first dose was significantly higher with both doses of indacaterol compared to placebo (*P*< 0.001 for all). No differences were noted between indacaterol and tiotropium (*P* value not reported). At all time points on both the first day and after 14 days of treatment, all active treatments achieved significantly higher FEV_1 measurements compared to placebo (*P*<0.05 for all). Indacaterol 300 µg achieved higher measurements compared to tiotropium at all time points, while indacaterol 150 µg only achieved higher measurements at the majority of time points. Both doses of indacaterol had a fast onset of action on day 1, achieving a significantly higher FEV_1 after five minutes compared to placebo (treatment difference, 120 and 130 mL, respectively; *P*<0.001 for both) and tiotropium (50 mL; *P*<0.004). The overall incidences of adverse events were similar across all treatments, and were predominantly mild or moderate in severity including cough, COPD worsening and nasopharyngitis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
The following medications were not permitted after the screening visit: long and short acting anticholinergics, LABAs, SABAs, xanthine derivatives and parenteral or oral corticosteroids.				
Buhl et al[24] INTENSITY Indacaterol 150 µg QD vs tiotropium 18 µg QD Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed. No other bronchodilator use was permitted.	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=1,593 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: FEV_1 and FVC at individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables, safety	Primary: Trough FEV_1 was 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be noninferior to tiotropium (*P*<0.001). Subsequent criteria for superiority were not met. Secondary: After five minutes on day 1, FEV_1 was higher with indacaterol (treatment difference, 70 mL; 95% CI, 60 to 80; *P*<0.00), and the difference remained significant after 30 minutes (*P*<0.001) and one hour (*P*<0.01). FVC measurements followed a similar pattern and were significantly higher with indacaterol (*P*<0.001, *P*<0.001 and *P*<0.05). TDI total scores after 12 weeks revealed a significantly greater reduction in dyspnea with indacaterol (treatment difference, 0.58; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores (OR, 1.49; *P*<0.001). SGRQ total scores after 12 weeks revealed significantly better health status with indacaterol (treatment difference, -2.1; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores (OR, 1.43; *P*<0.001). Patients receiving indacaterol significantly reduced the use of daily, daytime and nighttime use of rescue medications (*P*<0.001), and had a significantly greater proportion of days without rescue medication use (*P*=0.004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Diary data revealed that indacaterol and tiotropium resulted in similar increases from baseline of 2.0 and 1.9, respectively, in the proportion of days with no daytime COPD symptoms, 7.5 and 4.6 in the proportion of nights with no awakenings and 6.2 and 3.1 in the proportion of days able to undertake usual activities (*P* values not reported). Overall incidences of adverse events were similar between the two treatments, with the most common events generally reflecting the type of disease characteristics of COPD. The incidence of COPD worsening was 10.7 vs 8.3%; most cases were mild to moderate in severity. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium. (*P* values not reported).
Matera et al[25] Ipratropium 40 µg plus placebo vs salmeterol 50 µg plus placebo vs salmeterol 50 µg plus ipratropium 40 µg vs placebo plus placebo	RCT, SB, XO Male patients with COPD aged 40 years or older with an FEV_1 between 16 and 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in the area under the FEV_1 response-time curve	Primary: The peak response (28.8±5.0%) for salmeterol was greater than that for ipratropium (26.0±9.1%), but equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0±4.2). 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. 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. There was no significant difference ($P>0.05$) between the salmeterol and salmeterol plus ipratropium area under the curve.
Van Noord et al[26] Salmeterol 50 µg plus ipratropium matched placebo	DB, MC, PG, RCT Patients with COPD aged 40 to 75 years with a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary:	Primary: After inhalation of salmeterol, there was a mean±SEM peak increase in FEV_1 of 7.0±0.7% predicted after two hours, followed by a plateau. After 12 hours, the improvement was still 2.0±1.0% of predicted. Salmeterol plus ipratropium produced a peak increase in FEV_1 of 11.0±0.8%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 50 µg plus ipratropium 40 µg vs salmeterol-matched placebo plus ipratropium-matched placebo			Symptom scores, rescue medication use, PEF, clinic lung function, adverse events, exacerbations	predicted after two hours. After 12 hours, the improvement was 3.0±0.8% predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. 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 (*P*=NS), from 2.0±0.1 to 1.4±0.1 (*P*<0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (*P*<0.001) in the salmeterol plus ipratropium group. 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 (*P*<0.01). No difference was observed between the two active treatment groups (*P*=0.35). Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (*P*<0.001), whereas no difference was observed between the salmeterol and the salmeterol plus ipratropium groups. The changes in evening PEF were in favor of both active treatment arms compared with placebo (*P*<0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs the salmeterol group (*P*<0.01). During the 12-week treatment period, the mean±SEM increase in FEV_1 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 (*P*<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 (*P*<0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (*P*=0.055).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups. 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).
Yohannes et al[27] Tiotropium vs ipratropium vs LABA (salmeterol or formoterol)	MA (16 RCT) Trials lasting ≥12 weeks that compared tiotropium to placebo, ipratropium, or LABAs in patients ≥40 years of age with a diagnosis of COPD	N=16,301 Up to 52 months	Primary: Quality of life (SGRQ) scores, TDI scores, exacerbations, exacerbation-related hospitalizations and adverse events Secondary: Not reported	Primary: The proportion of patients achieving a clinically important improvement in SGRQ scores was greater with tiotropium compared to placebo (OR, 1.61; 95% CI, 1.38 to 1.88; *P*<0.001). Patients receiving treatment with tiotropium were also more likely to experience improvements in SGRQ scores compared to ipratropium (OR, 2.03; 95% CI, 1.34 to 3.07; *P*<0.001). There was no significant difference when tiotropium was compared to salmeterol (OR, 1.26; 95% CI, 0.93 to 1.69; *P*=0.13). There were statistically greater odds of achieving a clinically significant change in TDI score with tiotropium compared to placebo (OR, 1.96; 95% CI, 1.58 to 2.44; *P*<0.001). In addition, there were significantly greater odds of improving TDI scores associated with tiotropium compared to ipratropium (OR, 2.10; 95% CI, 1.28 to 3.44; *P*=0.003), but there was no significant difference when tiotropium was compared to salmeterol (OR, 1.08; 95% CI, 0.80 to 1.45; *P*=0.61). Tiotropium significantly reduced the risk of exacerbations compared to placebo (OR, 0.83; 95% CI, 0.72 to 0.94; *P*=0.004) and ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92; *P*=0.02). A reduction in exacerbations was observed in the two studies that compared tiotropium to salmeterol; however, the difference was not statistically significant (OR, 0.86; 95% CI, 0.67 to 1.11; *P*=0.25). Patients receiving treatment with tiotropium were less likely to have an exacerbation-related hospitalization compared to placebo (OR, 0.89; 95% CI, 0.80 to 0.98; *P*=0.02). There was a nonsignificant reduction in the odds of an exacerbation-related hospitalization with tiotropium compared to ipratropium (OR, 0.59; 95% CI, 0.32 to 1.09; *P*=0.09), salmeterol (OR, 0.54; 95% CI, 0.29

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to 1.00; *P*=0.051) and formoterol (OR, 4.98; 95% CI, 0.58 to 42.96; P=0.15) The number of patients who experienced a serious adverse event was not statistically significant when tiotropium was compared to placebo (OR, 1.06; 95% CI, 0.97 to 1.17; *P*=0.19) Only one study compared tiotropium to salmeterol, reporting a significantly lower risk of a serious adverse event with tiotropium (OR, 0.39; 95% CI, 0.16 to 0.95; *P*=0.04). Secondary: Not reported
Wang et al[28] Tiotropium and formoterol vs tiotropium	MA (8 RCT's) Patients diagnosed with COPD who had stable disease who were being treated with tiotropium and/or formoterol	N=1,868 Up to 24 months	Primary: Change in average (0 to 24 hour) and trough FEV_1 and FVC from baseline, COPD exacerbations, adverse events and TDI scores Secondary: Not reported	Primary: The mean improvement in average FEV_1 from baseline was greater in patients treated with tiotropium plus formoterol compared to those treated with tiotropium alone (WMD, 105 mL; 95% CI, 69 to 142; *P*<0.0001). The mean improvement in average FVC from baseline was greater with tiotropium plus formoterol compared to tiotropium alone (WMD, 135 mL; 95% CI, 96 to 174; *P*<0.0001). Treatment with tiotropium plus formoterol reduced COPD exacerbations compared to tiotropium alone, but the difference was small and not statistically significant (OR, 0.93; 95% CI, 0.45 to 1.93; *P*=0.85). The mean change in TDI score was greater with tiotropium plus formoterol than with tiotropium alone (WMD, 1.50; 95% CI, 1.01 to 1.99; *P*<0.00010). A similar result was observed for the proportion of patients with a clinically significant change in TDI (OR, 2.34; 95% CI, 1.58 to 3.46; *P*<0.0001). The overall cumulative incidence of adverse events was 33.2% in patients treated with tiotropium plus formoterol and 36.0% in patients treated with tiotropium alone. Tiotropium plus formoterol reduced adverse events compared with tiotropium alone, but the difference was not statistically significant (OR, 0.88; 95% CI, 0.70 to 1.11; *P*=0.28).
Barr et al[29] Tiotropium	MA 9 RCT's with patients	N=6,584 1 month or	Primary: Exacerbations, hospitalizations,	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo, or ipratropium, or a long-acting β_2-adrenergic agonists	diagnosed with COPD, whose disease was stable	greater	mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use, adverse events	0.64; 95% CI, 0.44 to 0.92). 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). 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). Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 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). 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). 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). 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).
Singh et al[12] Tiotropium 5 to 10 µg QD vs	MA (5 RCT) Trials of tiotropium solution using a mist inhaler (Respimat® Soft Mist Inhaler)	N=6,522 Up to 52 weeks	Primary: Mortality from any cause Secondary: Deaths from	Primary: The tiotropium mist inhaler was associated with a significantly increased risk of mortality compared with placebo (RR, 1.52; 95% CI, 1.06 to 2.16; P=0.02). Secondary: Although the numbers for cardiovascular death were low, tiotropium was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	versus placebo for COPD that evaluated mortality as an outcome and had a trial duration of more than 30 days		cardiovascular causes (myocardial infarction, stroke, cardiac death, and sudden death)	associated with a significantly increased relative risk in the five trials evaluating this outcome (RR, 2.05; 95% CI, 1.06 to 3.99; P=0.03).
Karner et al[30] Tiotropium and ICS/LABA vs tiotropium vs ICS/LABA	MA (3 RCT) The mean age of participants varied from 62 to 68 years with severity of COPD varied from moderate to very severe according to GOLD guideline definitions of COPD	N=1,051 Up to 52 weeks	Primary: All cause mortality, hospital admissions, exacerbations, pneumonia, SGRQ scores Secondary: Symptoms, FEV_1, non-fatal serious adverse events, adverse events, withdrawals	Primary: There was no difference in mortality rates between patients receiving therapy with ICS/LABA plus tiotropium and tiotropium alone (OR, 1.88; 95% CI, 0.57 to 6.23; *P*=0.30). There were fewer patients admitted to the hospital who received LABA/ICS plus tiotropium (41/474) compared to the tiotropium plus placebo group (50/487); however, the difference between groups was not significant (OR, 0.84; 95% CI, 0.53 to 1.33). The number of patients admitted to hospital with exacerbations was higher in the tiotropium plus placebo group (38/487) compared to the LABA/ICS plus tiotropium group (25/ 474); however, this difference was not significant (OR, 0.66; 95% CI, 0.39 to 1.13). Two studies examined the effect of LABA/ICS plus tiotropium on exacerbation rates compared to tiotropium alone. One study found no difference in exacerbations between the treatment groups (OR, 0.89; 95% CI, 0.56 to 1.41), while the other study reported a significant reduction with the triple therapy compared to tiotropium monotherapy (OR, 0.36; 95% CI, 0.22 to 0.60; *P* value not reported). The risk of developing pneumonia was low, and there was no statistically significant difference between treatment with LABA/ICS plus tiotropium and tiotropium plus placebo (OR, 1.35; 95% CI, 0.31 to 5.99). Changes in SGRQ scores significantly favored LABA/ICS plus ipratropium treatment compared to ipratropium plus placebo after five months (*P*=0.002) and one year (*P*=0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The addition of tiotropium to LABA/ICS significantly increased FEV_1 (MD, 0.06 L; 95% CI, 0.04 to 0.08 L), although this was below the threshold of 100 to 140 mL which is considered to be a clinically important increase. There were fewer patients suffering non-fatal serious adverse events in the tiotropium plus LABA/ICS group (12/504) compared to patients taking tiotropium plus placebo (20/517), although the difference was not significant (OR, 0.60; 95% CI, 0.29 to 1.25). A higher number of patients suffered adverse events while treated with tiotropium plus LABA/ICS (140/504) compared to patients tiotropium plus placebo (132/517), although the difference was not significant (OR, 1.12; 95% CI, 0.85 to 1.49). The difference between the number of patients who withdrew from the studies due to adverse events was not significantly different between patients taking tiotropium plus LABA/ICS and tiotropium plus placebo (OR, 0.92; 95% CI, 0.46 to 1.83).
Vogelmeier et al[31] Salmeterol 50 µg BID vs tiotropium 18 µg QD Patients receiving a fixed-dose ICA/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study.	AC, DB, DD, MC, PG, RCT Patients ≥40 years of age with a smoking history of ≥10 pack-years, a diagnosis of COPD with a FEV_1 after bronchodilation of ≤70% of the predicted value, a FEV_1/FVC ratio of ≤70%, and a documented history of ≥1 exacerbation leading to treatment with systemic glucocorticoids or antibiotics or	N=7,384 1 year	Primary: Time to the first exacerbation of COPD Secondary: Time-to-event end points, number-of-event end points, serious adverse events, and death	Primary: Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; *P*<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore it was not possible to calculate the median time to first exacerbation in this population. Secondary: Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; *P*<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; *P*<0.001). Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; *P*<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; *P*<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the double-blind treatment phase.	hospitalization within the previous year			0.86; *P*<0.001). The annual rate of exacerbations was 0.64 in the tiotropium group and 0.72 in the salmeterol group, representing a 11% reduction in the exacerbation rate with tiotropium (RR, 0.89; 95% CI, 0.83 to 0.96; *P*=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs 0.59; RR, 0.93; 95% CI, 0.86 to 1.00; *P*=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs 0.13; RR, 0.73; 95% CI, 0.66 to 0.82; *P*<0.001). The incidence of a serious adverse event was 14.7% compared to 16.5% in the tiotropium and salmeterol groups, respectively. The most common serious adverse event was COPD exacerbation. There were 64 exacerbations in the tiotropium group and 78 in the salmeterol group during the treatment period (HR for tiotropium, 0.81; 95% CI, 0.58 to 1.13).
Brusasco et al[32] Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, DD, PC, RCT Patients with COPD over the age of 40, with an FEV_1 ≤65% of predicted and an FVC ≤70%	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: SGRQ, TDI, spirometry, adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (*P*<0.01). The proportion of patients with at least one exacerbation was 32, 35, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (*P*>0.05). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. 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 (*P* value not reported). 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 (*P*<0.05). 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 (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (P<0.001 and P<0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17). Tiotropium was statistically better than salmeterol in peak FEV_1 and AUC from 0 to three hours. For trough FEV_1 values, tiotropium exhibited a similar trend. 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%; P value not reported).
Donohue et al[33] Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, MC, PC, PG, RCT Patients with stable COPD (age ≥40) with an FEV_1 ≤60% of predicted normal and FEV_1/FVC of ≤70%	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 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; P<0.01). As with FEV_1, 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 (P<0.01). 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 (P<0.001) and tiotropium was better than salmeterol in improving evening PEFR (P<0.05). At six months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference, 0.78 units; P<0.05). At six months, the mean improvement in SGRQ was -5.14 units for tiotropium (P<0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kurashima et al[34] Tiotropium 18 µg QD vs fluticasone 200 µg and salmeterol 50 µg BID	OL, RCT, XO Patients >40 years of age with COPD and stable airway obstruction with post-bronchodilator FEV_1/FVC <70%, predicted FEV_1 30 to 80%, and smoking history of >10 pack-years	N=78 4 months (2 months/ treatment arm)	Primary: Post-bronchodilator FVC and FEV_1 Secondary: HRQL using the SGRQ	Primary: Both treatments significantly improved FVC and FEV_1 compared to baseline values (*P*<0.0001). The increase in post-bronchodilator FVC was greater with tiotropium as compared with fluticasone and salmeterol (*P*=0.0021). Secondary: Significant improvements in SGRQ scores were observed in both groups compared to baseline, though no significant differences were observed between groups.
Aaron et al[35] Tiotropium 18 µg QD plus placebo vs tiotropium 18 µg QD plus salmeterol 50 µg BID vs tiotropium 18 µg QD plus fluticasone/ salmeterol 500/50 µg BID	DB, MC, PC, PG, RCT 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 FEV_1/FVC <0.70 and a post-bronchodilator FEV_1 <65% of the predicted value	N=449 1 year	Primary: Proportion of patients who experience a COPD exacerbation requiring systemic steroids or antibiotics 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,	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%). 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 (*P*=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8) for tiotropium plus fluticasone/salmeterol vs tiotropium plus placebo (*P*=0.62). 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. 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 (*P*=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol vs tiotropium vs tiotropium plus placebo (*P*=0.24).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			changes in HRQL, dyspnea, and lung function	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; *P*=0.01). All-cause hospitalizations were reduced in patients treated with tiotropium plus placebo (*P*=0.04). Similar benefits were not seen with tiotropium plus salmeterol compared with tiotropium plus placebo. 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 (*P*=0.02), and -8.6 points in the tiotropium plus fluticasone/salmeterol group (*P*=0.01). Dyspnea scores improved over one year of observation but did not significantly differ among the treatment groups (*P*=0.38). Over 52 weeks, the absolute prebronchodilator FEV_1 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 FEV_1 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.
Rabe et al[36] Tiotropium 18 µg QD plus formoterol 12 µg BID vs fluticasone 500 µg BID plus salmeterol 50 µg BID	DB, MC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC <0% at visit 1, and predose FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 area under the $curve_{0-12}$, peak FEV_1 Secondary: Morning predose FEV_1	Primary: After six weeks, the FEV_1 area under the $curve_{0-12}$ 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). The difference in peak FEV_1 was 103 mL (95% CI, 55 to 150) in favor of tiotropium plus formoterol (*P*<0.0001). Secondary: The difference in predose FVC after six weeks favored tiotropium plus formoterol (95% CI, 11 to 147; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ikeda et al[37] Ipratropium 40 µg via MDI vs ipratropium 80 µg via MDI vs albuterol 200 µg via MDI and ipratropium 40 µg via MDI vs albuterol 400 µg via MDI and ipratropium 80 µg via MDI vs placebo	DB, PC, RCT, XO Adult male patients with stable COPD with a history of >20 pack-years of cigarette smoking, and FEV_1 <60% and a FEV_1 /FVC<0.7, and chest radiographic findings compatible with pulmonary emphysema	N=26 5 separate visits over a period of 1 month	Primary: Change from baseline in FEV_1, FVC and the difference in adverse reactions reported Secondary: Not reported	Primary: All treatment groups showed a significant improvement in FEV_1 and FVC when compared with placebo at all time points evaluated *(P*<0.01). Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV_1 (*P*<0.05, *P*<0.01). The lower dose combination was significantly different in FVC response from the low-dose monotherapy (*P*<0.01), but not high-dose monotherapy. No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects (no *P* value reported). Secondary: Not reported
Bone et al[38] Albuterol 100 µg QID via MDI vs ipratropium 21 µg QID via MDI vs	DB, MC, PG, PRO, RCT Patient's 40 years of age and older diagnosed with COPD with stable disease, relative stable, moderately severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score, and safety Secondary: Not reported	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (*P*<0.001 to *P*=0.015). There was no difference in symptom score between the groups (*P* value not reported). Compared with either agent alone, the overall FVC response was significantly greater in the combination group (*P*<0.01 to *P*=0.04). There were no significant differences between any of the treatment groups in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
albuterol/ipratropium 100/21 µg QID via MDI	≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents for COPD control			terms of adverse effects or safety (*P* value not reported). Secondary: Not reported
Dorinsky et al[39] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of albuterol/ipratropium via MDI	DB, MC, PG, RETRO, RCT Patients 40 years of age and older diagnosed with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤0.70	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as an increase in FEV_1 of 12 and 15% from baseline) Secondary: Not reported	Primary: The percentage of patients demonstrating a 15% increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the albuterol/ipratropium group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day 1 and 2 (of 4) (*P*<0.05). The overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from 2 to 8% (*P* value not reported). A significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in the albuterol/ipratropium group compared to the individual treatment groups (*P*<0.05). Secondary: Not reported
Friedman et al[40] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of	DB, MC, PG, RETRO, RCT Patients 40 years of age and older diagnosed with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC from time 0-4 hours, total health care expenditures, and cost effectiveness ratios Secondary: Not reported	Primary: A statistically significant improvement in FEV_1 in the albuterol/ipratropium group was observed compared to other treatment groups on all test days (*P*<0.01). A significantly higher FEV_1 AUC_{0-4} in the albuterol/ipratropium group compared to the other treatment groups was observed on all test days (*P*≤0.008). The total cost of treating patients in the ipratropium group and the albuterol/ipratropium group was significantly less than the albuterol group (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
albuterol/ipratropium via MDI	≤65% predicted, FEV_1/FVC ratio ≤0.70			No statistical difference was observed between total costs in the ipratropium group and the albuterol/ipratropium group (*P* value not reported). A significantly greater cost effectiveness was observed in the ipratropium and albuterol/ipratropium groups compared to albuterol group (*P*<0.05). Secondary: Not reported
Tashkin et al[41] Albuterol/ipratropium solution for nebulization QID vs albuterol/ipratropium 2 inhalations QID via MDI vs albuterol/ipratropium solution for nebulization administered in the morning and albuterol/ ipratropium MDI administered in the afternoon and evening	MC, PG, RCT Men and women 50 years of age and older who met the American Thoracic Society/European Respiratory Society definition of COPD, had a history of >10 pack-years of cigarette smoking, an FEV_1 30 to 65% of the predicted value, and a post bronchodilator FEV_1/FVC ratio ≤0.70	N=140 12-weeks	Primary: Quality of life (St. George's Respiratory Questionnaire, completed at baseline, six weeks, and 12 weeks) Secondary: Patient symptom score, home morning and nighttime daily peak flow before dosing with the study medication and pre- and post-dose FEV_1 in the clinic, safety measures (vital signs, changes in physical findings, and investigator reported disease exacerbations)	Primary: After six weeks of treatment, the change from baseline in the total quality of life score was clinically (exceeding the 4-unit threshold) and statistically significant for the concomitant treat group (*P*<0.0196). Patients in the nebulizer-only treatment group approached clinically significant improvements (*P* value not reported). Differences between the treatment groups at week six were not statistically significant. A statistically significant improvement was seen in symptom sub-score at week six for patients using a nebulizer-only or concomitant treatment (*P*=0.019 and *P*<0.004, respectively). Only the concomitant therapy group achieved a clinically significant improvement from baseline at week six in the Impacts sub-score (-5.1±3.0), however results were not statistically significant (*P* value not reported). At week 12 only the concomitant therapy group approached a clinically significant improvement in total score (-3.5±2.64). Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the symptom sub-score (*P*=0.0186, *P* value not reported, respectively). None of the treatment groups reached a clinically significant improvement in the impact sub-score. Changes between the treatment groups in the endpoints measured were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Changes in pre- and post-bronchodilator FEV_1 with the treatment groups were not statistically significant at week six or at week 12; only the MDI inhaler treatment group demonstrated a statistically significant change from baseline at week six (*P*=0.0060). Mean patients symptom scores were similar among the treatment groups at baseline. All three-treatment groups demonstrated an improvement in patient symptom scores from baseline to week six and week 12. · Concomitant group o Baseline: 5.60±0.52 o Week six: 3.90±0.51; *P*=0.0312 o Week 12: 4.30±0.57; *P*=0.0490 · Nebulizer-only group o Baseline: 5.80±0.60 o Week six: 4.60±0.57; *P*=0.0539 o Week 12: 4.80±0.64; *P*=0.0461 · MDI-only group o Baseline: 5.80±0.53 o Week six: 4.50±0.50; *P* value not reported o Week 12: 4.30±0.56; *P* value not reported The differences in adverse events were not discussed.
Zuwallack et al[42] Ipratropium/albuterol 20/100 µg QID, administered via Respimat® inhaler vs ipratropium/albuterol 36/206 µg QID, administered via	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium/ albuterol via Respimat® inhaler vs aerosol MDI and ipratropium/ albuterol via Respimat® inhaler vs ipratropium via	Primary: On day 85, ipratropium/albuterol Respimat® inhaler was noninferior to ipratropium/albuterol aerosol MDI at zero to six hours, and was "superior" to ipratropium Respimat® inhaler with a difference of 0.047 L (*P*<0.001) at zero to four hours. At four to six hours, ipratropium/albuterol Respimat® inhaler was noninferior to ipratropium Respimat® inhaler. Ipratropium/albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all tests days. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aerosol MDI (Combivent®) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a 2 week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.			Respimat® inhaler Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC $AUC_{zero\ to\ six}$, $_{zero\ to\ four}$ and $_{four\ to\ six}$; peak FVC response on day one, 29, 57 and 85; safety	Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium/albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium/albuterol aerosol MDI (172 to 219 minutes) overall. Median duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (N=358), 74 (N=357) and 63% (N=295) of patients receiving ipratropium/albuterol Respimat® inhaler, ipratropium/albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event was lower with ipratropium/albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium/albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium/albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
Singh et al[43] Any inhaled antimuscarinics for treatment of COPD	MA 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 drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including myocardial infarction, stroke, or cardiovascular death	N=14,783 Duration ranged from 6 to 26 weeks	Primary: Composite of cardiovascular death, myocardial infarction, or stroke Secondary: All-cause mortality	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). 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). 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).
Lee et al[13] Exposure to inhaled corticosteroids, ipratropium, long-acting β_2-agonist, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses	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). Theophylline exposure was associated with a statistically significant increase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		30, 2003 and followed through September 30, 2004	of primary outcomes	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. 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. 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. 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 corticosteroids, 1.08 for ipratropium, and 0.90 for long-acting β_2-agonist. 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; $P<0.001$). 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.

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, FEV_1=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, MD=mean difference, 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[2-6,15]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Products					
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
Combination Products					
Ipratropium/ albuterol	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	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 Events[2-6,15]

Adverse Event(s)	Ipratropium	Ipratropium/albuterol	Tiotropium
Cardiovascular			
Angina	-	<2	1 to 3
Arrhythmia	-	<2	<1
Chest pain	-	0.3 to 2.6	5 to 7
Diastolic blood pressure increased	-	a	-
Elevated heart rate	-	a	-
Hypertension	-	<2	-
Hypotension	a	a	-
Myocardial ischemia	-	a	-
Palpitations	a	<2	a

Adverse Event(s)	Ipratropium	Ipratropium/albuterol	Tiotropium
Tachycardia	a	<2	-
Central Nervous System			
Asthenia	-	a	-
Central nervous system stimulation	-	a	-
Coordination difficulty	-	a	-
Depression	-	-	1.0 to 4.4
Dizziness	3	a	a
Drowsiness	-	a	-
Fatigue	-	a	-
Flushing	-	a	-
Headache	6 to 7	a	5.7
Insomnia	-	a	4.4
Mental disorder	-	a	-
Nervousness	-	a	-
Paresthesia	-	a	1 to 3
Tremor	-	a	-
Weakness	-	a	-
Dermatological			
Allergic skin reactions	a	-	2 to 4
Angioedema	a	0.3	<1
Dry skin	-	-	a
Pruritus	a	0.3	a
Skin infection	-	-	a
Skin rash	a	0.3	2 to 4
Skin ulcer	-	-	a
Urticaria	a	0.3	a
Endocrine and Metabolic			
Edema	-	-	3 to 5
Hypercholesterolemia	-	-	1 to 3
Hyperglycemia	-	-	1 to 3
Gastrointestinal			
Abdominal pain	5 to 6	-	-
Constipation	a	>1	1.0 to 5.1
Diarrhea	a	<2	-
Dry mouth	-	<2	-
Dry throat	-	a	-
Dyspepsia	1 to 5	<2	1 to 6
Gastrointestinal disease	-	a	-
Gastroesophageal reflux	-	-	1 to 3
Gastrointestinal pain	-	-	3 to 6
Heartburn	-	a	-
Intestinal obstruction	-	-	a
Motility disorder	-	a	-
Nausea	4	<2	-
Sore throat	-	a	-
Taste perversion	-	<2	-
Vomiting	-	<2	1 to 4
Genitourinary			
Urinary difficulty	-	a	-
Urinary retention	a	-	<1
Urinary tract infection	2 to 10	<2	4 to 7
Musculoskeletal			

Adverse Event(s)	Ipratropium	Ipratropium/albuterol	Tiotropium
Arthralgia	-	<2	4.2
Arthritis	-	-	≥3
Back pain	-	<2	-
Joint swelling	-	-	a
Leg cramps	-	1.4	-
Leg pain	-		1 to 3
Muscle spasms	-	a	-
Myalgia	-	a	4
Pain	-	1.2 to 2.5	-
Skeletal pain	-	-	1 to 3
Respiratory			
Bronchitis	10 to 23	1.7 to 12.3	-
Bronchospasm	a	0.3	-
Chronic obstructive pulmonary disease exacerbation	8 to 23	a	-
Coughing	a	4.2	≥3
Drying of secretions	-	a	-
Dyspnea	7 to 8	4.5	-
Hoarseness	-	a	-
Increased sputum	-	<2	-
Influenza	-	1.4	-
Irritation of aerosol	-	a	-
Lung disease	-	6.4	-
Nasal congestion	-	a	-
Pharyngitis	-	2.2 to 4.4	7.0 to 12.5
Pneumonia	-	1.3 to 1.4	-
Respiratory disorder	-	2.5	-
Rhinitis	≥3	1.1	3 to 6
Sinusitis	1 to 11	<2.3	3 to 11
Upper respiratory tract infection	≥3	10.9	43 to 41
Voice alterations	-	>1	-
Wheezing	-	a	-
Other			
Accidents	-	-	5 to 13
Alopecia	-	-	-
Anaphylaxis	a	a	-
Back pain	2 to 7	-	-
Blurred vision	a	a	-
Cataract	-	-	1 to 3
Conjunctival hyperaemia	a	a	-
Corneal edema	a	a	-
Dehydration	-	-	a
Dry mouth	2 to 4	-	5.1 to 16.0
Dry throat	a	-	-
Dysphagia	-	-	a
Dysphonia	-	-	1 to 3
Edema	-	a	-
Epistaxis	-	-	1 to 4
Eye pain	a	a	-
Gingivitis	-	-	a
Glaucoma	a	-	-
Glaucoma, worsening of narrow-angle	a	-	-

Adverse Event(s)	Ipratropium	Ipratropium/albuterol	Tiotropium
Halo vision	a	a	-
Herpes zoster	-	-	1 to 3
Hoarseness	-	-	a
Hypersensitivity reaction	a	-	1 to 3
Hyperhidrosis	-	a	-
Hypokalemia	-	a	-
Infection	-	-	1 to 4
Influenza-like symptoms	4 to 8	-	≥3
Intraocular pressure increased	-	-	a
Laryngitis	-	-	1 to 3
Laryngospasm	a	a	-
Moniliasis	-	-	3 to 4
Mouth edema	a	a	-
Mucosal ulcers	-	a	-
Mydriasis	a	a	-
Ocular irritation	-	a	-
Oropharyngeal candidiasis	-	-	a
Stomatitis	a	a	1 to 3
Taste perversion	<1	-	-
Throat irritation	a	-	a
Worsening glaucoma	-	a	-

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[2-6,15]

Contraindication	Ipratropium	Ipratropium/ albuterol	Tiotropium
Hypersensitivity to any component of the product, atropine or its derivatives	a	a	a
Hypersensitivity to soya lecithin or related food products such as soybeans and peanuts	-	a	-

Warnings/Precautions

Table 8. Warnings and Precautions[2-6,15]

Warning/Precaution	Ipratropium	Ipratropium/ albuterol	Tiotropium
Bladder neck obstruction; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	a	a	a
Clinically significant increases in pulse rate, blood pressure, and/or symptoms may occur; use with caution in patients with cardiovascular disorders	-	a	-
Convulsive disorders; use with caution in this patient population	-	a	-
Diabetes; large doses of intravenous albuterol have been	-	a	-

Warning/Precaution	Ipratropium	Ipratropium/ albuterol	Tiotropium
reported to aggravate diabetes mellitus and ketoacidosis			
Do not puncture contents of aerosol and do not use or store near heat or an open flame	a	-	-
Fatalities have been reported in associated with excessive use of inhaled sympathomimetic agents in patients with asthma	-	a	-
Hypersensitivity reactions may occur following administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and anaphylaxis	a	a	a
Hyperthyroidism; use with caution in this patient population	-	a	-
Hypokalemia; significant hypokalemia may occur in some patients predisposing them to cardiovascular effects	-	a	-
Indicated for maintenance therapy and should not be used for initial treatment of acute episodes of bronchospasm	a	-	a
Narrow-angle glaucoma; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	a	a	a
Paradoxical bronchospasm has been reported; discontinue treatment immediately if paradoxical bronchospasm is suspected	-	a	-
Prostatic hyperplasia; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	a	a	a
Use with caution in patients who are unusually responsive to sympathomimetic amines	-	a	-

Drug Interactions

Although the inhaled antimuscarinics are minimally absorbed, there is some potential for an additive interaction with concomitantly used antimuscarinic (anticholinergic) medications.[2-4,12,36]

Dosage and Administration

Table 9. Dosing and Administration[2-6,15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Products			
Ipratropium	Maintenance treatment of bronchospasm	Safety and	Aerosol for oral

Generic Name	Adult Dose	Pediatric Dose	Availability
	associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema: Aerosol for oral inhalation: initial, 34 µg (two inhalations) QID; maximum, do not exceed 204 µg (12 inhalations) in 24 hours Solution for nebulization: maintenance, 500 µg QID, dose six to eight hours apart	efficacy in children under the age of 12 have not been established.	inhalation: 17 µg (200 actuations/unit) Solution for nebulization: 500 µg (0.02%)
Tiotropium	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema and reducing chronic obstructive pulmonary disease exacerbations: Powder for oral inhalation: initial, 18 µg QD	Safety and efficacy in children have not been established.	Powder for oral inhalation: 18 µg
Combination Products			
Ipratropium/albuterol	Treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator: Aerosol for oral inhalation: two inhalations (albuterol/ ipratropium 120/21 µg) QID; maximum, 12 inhalations daily Inhalation spray (inhaler): one inhalation (albuterol/ipratropium 100/200 µg) QID; maximum, six inhalations a day Solution for nebulization: one vial (albuterol/ ipratropium 2.5/0.5 mg) QID; maximum, six vials daily	Safety and efficacy in children have not been established.	Aerosol for oral inhalation: 120/21 µg* (200 metered inhalations) Inhalation spray (inhaler): 100/20 µg* (120 actuations) Solution for nebulization: 3.0/0.5 mg (3 mL vials)

QD=once daily, QID=four times daily
* Delivering 103 µg of albuterol (90 µg albuterol base) and 18 µg of ipratropium.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2010)**[1]	Diagnosis · 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 (FEV_1)/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.

Clinical Guideline	Recommendations
	· 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 FEV_1 <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 α_1-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 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. <u>Treatment</u> · 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.

Clinical Guideline	Recommendations
	· 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 ICSs to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted and repeated exacerbations. · Regular treatment with ICSs has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV_1<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 FEV_1<40% of the predicted value. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. <u>Management of exacerbations</u> · The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. · Inhaled β_2-agonists (particularly inhaled β_2-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments

Clinical Guideline	Recommendations
	for exacerbations of COPD. · Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
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)**[14]	Diagnosis · 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 FEV_1<80% predicted and FEV_1/FVC<70%. Treatment · Smoking cessation 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 (beta$_2$ 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 whom a decision has been made to begin regular maintenance bronchodilator therapy with a muscarinic antagonist. o FEV_1 ≥50% predicted: long-acting β_2-agonist or long-acting muscarinic antagonist. o FEV_1 < 50% predicted: either long-acting β_2-agonist with an inhaled corticosteroid in a combination inhaler or a long-acting muscarinic antagonist. · In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a long-acting β_2-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 β_2-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 β_2-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.

Clinical Guideline	Recommendations
	Management of exacerbations · 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.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)**[44]	Diagnosis · Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. · Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment · For stable COPD patients with respiratory symptoms and an FEV_1 between 60% and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. · For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. · Patients who benefit the most from inhaled bronchodilators (anticholinergics or long-acting β-agonists) are those who have respiratory symptoms and airflow obstruction with an FEV_1 less than 60% predicted. The mean FEV_1 was less than 60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. · Monotherapy with long-acting inhaled anticholinergics or long-acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve heal-related quality of life. · The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. · There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and long-acting β-agonists) on mortality, hospitalizations, and dyspnea. · Inhaled corticosteroids are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. · Combination therapy with inhaled agents (long-acting inhaled

Clinical Guideline	Recommendations
	anticholinergics, long-acting inhaled β-agonists, or inhaled corticosteroids) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is long-acting inhaled β-agonists plus inhaled corticosteroids. · Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. · Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. · Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (PaO2 ≤55 mm Hg or SpO2 ≤88%).

Conclusions

The available single-entity inhaled antimuscarinics include ipratropium (Atrovent® HFA) and tiotropium (Spiriva®). Ipratropium is also available in combination with albuterol (Combivent®, Combivent Respimat®, DuoNeb®*), a short-acting β_2 receptor agonist.[2-6] Both ipratropium and tiotropium are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[2,3] In addition, tiotropium is FDA-approved for reducing exacerbations associated with COPD.[3] The ipratropium/albuterol combination is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator.[4-6] 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 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.[6,7,27] Meta-analyses have demonstrated significant clinical advantages when tiotropium is used in combination with a bronchodilator from a different pharmacologic class.[28,30,35,36] Ipratropium, while effective, does not appear to offer any significant advantages in comparison to other short-acting bronchodilators. As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[25,26]

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.[14]

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