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.[1-7] Three single-agent inhaled antimuscarinics are currently available including aclidinium (Tudorza®), ipratropium (Atrovent®, Atrovent® HFA) and tiotropium (Spiriva®). These 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. Aclidinium and tiotropium are classified as long-acting bronchodilators and are administered twice- and once daily, respectively.[2,3,7] A combination product containing ipratropium and albuterol 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). 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 metered dose inhaler will be available until late 2013. By January 1, 2014, Combivent Respimat® will be the only one of these two products available.[8] Meaningful increases in lung function can be achieved with the use of inhaled antimuscarinics in patients with COPD.[9,10] 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.[1,11] Both ipratropium and the ipratropium/albuterol are available generically as a solution for nebulization.[12]

Table 1. Current Medications Available in Therapeutic Class[2-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Aclidinium (Tudorza®)	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease	Powder for oral inhalation: 400 µg	-
Ipratropium (Atrovent®*, Atrovent HFA®)	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema	Aerosol for oral inhalation (Atrovent HFA®): 17 µg (200 actuations/ unit) Solution for nebulization (Atrovent®*): 500 µg (0.02%)	✔
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®,	Treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator	Aerosol for oral inhalation (Combivent®): 21/120 µg† (200 metered inhalations)	✔

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
DuoNeb®*)		Inhalation spray (inhaler) (Combivent Respimat®): 20/100 µg† (120 actuations) Solution for nebulization (DuoNeb®*): 0.5/3.0 mg (3 mL vials)	

* Generic available in at least one dosage form or strength.
†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).[8,9,15-42]
- In a large study of current or former smokers with COPD, patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline trough forced expiratory volume in one second (FEV_1), was significantly higher in patients receiving aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; *P*<0.0001).[13]
- In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group (86 and 124 mL, respectively; *P*<0.0001 for both).[14]
- 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.[27,34,35]
- In a meta-analysis, the combination of tiotropium and formoterol significantly improved 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.[26] 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).[27]
- 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.[20,24,25]

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 states 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 antimuscarinic agents 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.[11]

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- Other Key Facts:
  - Aclidinium (Tudorza®), approved in July 2012, is the newest inhaled antimuscarinic agent to be approved by the Food and Drug Administration (FDA).[7]
  - Tiotropium (Spiriva®) is the only agent within the class that is FDA-approved to reduce the risk of COPD exacerbations.[3]
  - 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.[9,10] Head-to-head studies comparing aclidinium to other agents within the class are not available.
  - By January 1, 2014, the Combivent® aerosol meter dose inhaler will be discontinued, and the recently- approved Combivent Respimat® will be the only one of these two products available.[8]

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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 aclidinium (Tudorza®) ipratropium (Atrovent®, Atrovent® HFA) and tiotropium (Spiriva®). A combination product containing ipratropium and albuterol is available as an inhaler (Combivent®, Combivent Respimat®) and solution for nebulization (DuoNeb®).[2-7] Aclidinium, ipratropium and tiotropium are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[2,3,7] Tiotropium is the only inhaled antimuscarinic that is FDA-approved for reducing exacerbations associated with COPD.[3] Ipratropium/albuterol 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. Aclidinium and tiotropium are both considered long-acting bronchodilators. Aclidinium is dosed twice daily, while tiotropium has a duration of action of greater than 24 hours and therefore, is administered once daily.[3,7] The results from comparative studies have shown that tiotropium may improve spirometry measurements to a greater degree compared to ipratropium.[8,9] Head-to-head studies comparing aclidinium to other agents in the class have not been conducted. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Both aclidinium and tiotropium are available as dry powder inhalers for oral inhalation. The ipratropium (Atrovent®) and ipratropium/albuterol solutions for nebulization are the only inhaled antimuscarinic products that are currently available generically.[10]

Ipratropium/albuterol as a fixed-dose inhaler was approved for the treatment of COPD in 1996 as Combivent®, an aerosol metered dose inhaler.[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 metered dose inhaler. Instead of a propellant, Combivent Respimat® uses a spring mechanism to release the medication.[5] The two formulations differ in their dosing and administration schedules. Combivent® aerosol metered dose inhaler will be available until late 2013. By January 1, 2014, Combivent Respimat® will be the only one of these two products available.[11]

In March 2008, the manufacturer of tiotropium, Boehringer Ingelheim 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.[12] 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.[13,14] 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).[13] 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

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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.[12]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of 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 GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the sue of 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.[15]

Medications

Table 1. Medications Included Within Class Review

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

* Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[2-7,16]

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 Agents			
Aclidinium	✔		
Ipratropium	✔		
Tiotropium	✔		✔
Combination Products			
Ipratropium/albuterol		✔	

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. Tiotropium has been used off-label in the treatment of patients with asthma.[16]

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Pharmacokinetics

Table 3. Pharmacokinetics[2-6,16]

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents					
Aclidinium	10	12	54 to 65	None	5 to 8
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 their respective Food and Drug Administration-approved indications are described in Table 4.[7,8,12,13,17-47]

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]

In a large study of current or former smokers with COPD (N=828), patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline in trough forced expiratory volume in one second (FEV_1), the primary endpoint, was significantly higher in patients treated with aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; *P*<0.0001).[17] In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group (86 and 124 mL, respectively; *P*<0.0001 for both).[18] Singh and colleagues conducted a small, five-way crossover study evaluating 100, 200 and 400 µg of aclidinium, formoterol 12 µg or placebo. Following seven days of treatment, the change from baseline in FEV_1 area under the curve over 12 hours (FEV_1 AUC_{0-12}) was 154 mL in the aclidinium 100 µg group, 176 mL in the aclidinium 200 µg group, 208 mL in the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group compared to placebo (*P*<0.0001 for all compared to placebo). The difference in FEV_1 AUC_{0-12} between the aclidinium 400 µg and formoterol 12 µg treatment groups was not statistically significant (*P* value not reported).[19]

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).[35] When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[39, 40] In a meta-analysis by Wang et al, the combination of tiotropium and formoterol significantly improved the 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.[32] 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).[31] 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).[25] As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[29,30] Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV_1 and FVC in clinical studies compared to either agent alone.[41-45]

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The recently approved ipratropium/albuterol (Combivent Respimat®) inhaler has demonstrated improvements in FEV_1 that are equivalent to the aerosol metered dose inhaler. 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 receive ipratropium/albuterol 20/100 µg via Respimat® inhaler, ipratropium/albuterol 36/206 µg via aerosol metered dose inhaler or ipratropium 20 µg via Respimat® inhaler; all administered four times daily. The results demonstrate that equivalent bronchodilation (change in FEV_1) was achieved with the ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol metered dose inhaler, while significantly greater bronchodilation was achieved with the combination Respimat® inhaler compared to ipratropium 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/albuterol aerosol metered dose inhaler (3.7 vs 6.9%).[46]

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jones et al[17] ATTAIN Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD and an FEV_1/FVC <70% and FEV_1 <80% who were current or former smokers with a ≥10 pack-years history	N=828 24 weeks	Primary: Change from baseline in trough FEV_1 at 24 weeks Secondary: Change from baseline in peak FEV_1 at 24 weeks, proportion of patients experiencing clinically significant improvements in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) scores at 24 weeks	Primary: After 24 weeks of treatment, the mean trough FEV_1 was significantly higher in patients treated with aclidinium 200 µg (99±22 mL; *P*<0.0001) or 400 µg (128±22 mL; *P*<0.0001) when compared to patients treated with placebo. Secondary: At 24 weeks, the mean change from baseline in peak FEV_1 was significantly higher in patients treated with aclidinium 200 µg (185±23 mL) or 400 µg (209±24 mL) compared to patients receiving placebo (*P*<0.0001 for both). A significantly higher proportion of patients treated with aclidinium 200 or 400 µg experienced a clinically significant improvement in SGRQ score when compared to patients treated with placebo at 24 weeks (56.0 and 57.3 vs 41.0%; *P*<0.001 for both). A significantly greater proportion of patients treated with aclidinium 200 or 400 µg achieved a clinical improvement in TDI score when compared to patients treated with placebo at 24 weeks (53.3 and 56.9 vs 45.5%; *P*≤0.05 for both). After 24 weeks, the mean total daily use of relief medication was significantly lower with aclidinium 200 (0.61 inhalations/day; *P*=0.0002) or 400 µg (0.95 inhalations/day; *P*<0.0001) compared to placebo; however, this was not a pre-specified endpoint. The rates of COPD exacerbations of any severity were decreased with both aclidinium 200 and 400 µg compared to placebo; however, this was not statistically significant and was not a pre-specified endpoint.
Kerwin et al[18] Aclidinium 200 µg BID vs aclidinium 400 µg BID	DB, PC, PG, RCT Patients ≥40 years of age diagnosed with moderate to severe stable COPD and a post-bronchodilator	N=561 12 Weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Change from	Primary: Treatment with aclidinium 200 or 400 µg significantly increased trough FEV_1 from baseline compared to patients receiving placebo (86 and 124 mL, respectively; *P*<0.0001 for both). Secondary: Treatment with aclidinium 200 or 400 µg significantly increased the peak

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	FVC <70% and FEV_1 ≥30% and <80% predicted and who were current or former smokers with a ≥10 pack-years history		baseline in peak FEV_1 at week 12, FEV_1 on day one, trough and peak FEV_1 at weeks one, four and eight, $AUC_{0\text{-}3/3h}$ FEV_1, trough, peak and $AUC_{0\text{-}3/3h}$ FVC and trough IC at 12 weeks, changes in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) at weeks four, eight and 12, nighttime symptoms, COPD exacerbations and safety	FEV_1 from baseline compared to patients receiving placebo (146 and 192 mL, respectively; *P*<0.0001 for both). There was a statistically significant improvement from baseline in peak FEV_1 at week 12 for patients receiving aclidinium 200 or 400 µg compared to patients receiving placebo (*P*<0.0001 for both). The changes from baseline in trough and peak FEV_1 were significantly higher in all aclidinium treatment groups at all time points evaluated compared to the placebo group (*P*<0.0001 for all). Patients randomized to receive aclidinium 200 or 400 µg experienced statistically significant increases in $AUC_{0\text{-}3/3h}$ FEV_1 compared to the placebo group (144 and 192 mL, respectively; *P*<0.0001 for both). At 12 weeks, a statistically significant improvements in peak FVC within three hours after dosing occurred for the aclidinium 200 (312 mL; *P*<0.0001) and 400 µg (359 mL; *P*<0.0001) groups compared to those randomized to placebo. Compared to the placebo group, there was a significant improvement from baseline in trough IC in both the aclidinium 200 (48 mL; *P*<0.001) and 400 µg (67 mL; *P*<0.0001) groups. At week four, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ score compared to treatment with placebo (-3.2 and -3.6, respectively; *P*<0.001 for both). At study end, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ scores compared to treatment with placebo (- 2.7 and -2.5, respectively; *P*=0.013 and *P*=0.019, respectively). At 12 weeks, a higher proportion of patients receiving aclidinium 200 µg experienced a decrease ≥4 units in SGRQ compared to patients receiving placebo (P<0.05); however, there was no difference in responder rates between patients receiving aclidinium 400 µg or placebo. At 12 weeks, a higher proportion of patients receiving aclidinium 200 or 400

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				µg achieved a clinically meaningful improvement (≥1 unit) in TDI scores compared to the placebo group (*P*<0.05 for both). Compared to placebo, patients receiving either dose of aclidinium experienced significantly improved nighttime COPD symptoms (*P*<0.05 for both). At week 12, there was a statistically significant decrease in the number of nighttime awakenings in the aclidinium 400 µg group compared to the placebo group (*P*<0.05). A reduction in the rate of moderate to severe COPD exacerbations per-patient per-year was observed with aclidinium 200 and 400 µg compared to placebo (33 and 34%, respectively; *P*>0.05 for both); however, these results were not statistically significant. The incidence of adverse events was similar between the aclidinium and placebo groups. Treatment-emergent adverse events occurred in 44.7% of patients receiving aclidinium 400 µg, 50.5% of those receiving aclidinium 200 µg and 52.2% of the placebo group. A COPD exacerbation was the only adverse effect that was reported in >5% of patients in all groups, with a lower incidence in the aclidinium 400 µg group compared to the aclidinium 200 µg and placebo groups.
Singh et al[19] Aclidinium 100 µg BID vs aclidinium 200 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID	AC, DB, DD, MC, PC, XO Patients ≥40 years of age with a diagnosis of stable moderate to severe COPD and a FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history	N=79 7 days (each treatment arm had a 5 to 9 day washout period)	Primary: Mean change from baseline in FEV_1 $AUC_{0–12}$ on day seven Secondary: Change from baseline in FEV_1 $AUC_{12–24}$, FEV_1 $AUC_{0–24}$, trough FEV_1 on day seven, FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at day seven,	Primary: The change from baseline in FEV_1 $AUC_{0–12}$ on day seven compared to placebo was 154 mL for the aclidinium 100 µg group, 176 mL for the aclidinium 200 µg group, 208 mL for the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group (*P*<0.0001 for all compared to placebo). Aclidinium 400 µg was associated with statistically significant improvements in FEV_1 $AUC_{0–12}$ compared to the 100 µg dose (*P*<0.01) while the difference between patients receiving aclidinium 400 µg or formoterol 12 µg was not significantly different. Secondary: Improvements in FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–24}$ at day seven were significantly greater for all doses of aclidinium and formoterol compared to the placebo group (*P*<0.0001 for all). There was no difference between treatment with aclidinium 400 µg and formoterol with regard to changes in FEV_1

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			morning peak FEV_1 on day one and 7, morning trough FVC on day seven, use of relief medication after seven days and safety	AUC_{0-24}. Patients treated with aclidinium 400 µg experienced a statistically significant improvement in FEV_1 AUC_{12-24} compared to treatment with formoterol (56 mL; *P*<0.01). Compared to placebo the mean change from baseline in trough FEV_1 was 106, 114 and 154 and 148 mL with aclidinium 100, 200 and 400 µg, and formoterol, respectively (*P*<0.0001 for all compared to placebo). Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{0-12} compared to patients treated with placebo (243, 254, 274 and 301 mL, respectively; *P*<0.001 for all) on day seven. Following seven days of treatment, patients receiving aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{12-24} compared to patients receiving placebo (260, 255, 302 and 383 mL, respectively; *P*<0.001 for all). Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{0-24} compared to patients treated with placebo (251, 255, 283 and 338 mL, respectively; *P*<0.001 for all) on day seven. After seven days of treatment, patients receiving aclidinium 100 µg, 200 µg and 400 µg or formoterol demonstrated a statistically significant increase in morning peak FEV_1 on day one (140, 176, 223 and 221 mL, respectively, *P*<0.0001 for all) and day seven (189, 201, 242 and 246 mL, respectively, *P*<0.0001 for all) compared to placebo. Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in morning trough FVC (147, 191, 218 and 213 mL, respectively; *P*<0.001 for all) on day seven compared to patients treated with placebo. Patients treated with aclidinium 100, 200 and 400 µg or formoterol required significantly fewer daily inhalations of rescue medication compared to

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients treated with placebo (-0.27, -0.39, -0.48 and -0.67, respectively; *P*<0.05 for all). The majority of adverse events were mild or moderate in severity and more prevalent in the placebo group (*P* value not reported). Four serious adverse events were reported, but none was treatment-related. There were no clinically relevant changes in laboratory parameters, and the incidence of ECG abnormalities was similar between placebo and active treatments.
Casaburi et al[20] 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 ≤70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ and rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time compared to patients receiving placebo. The difference between the treatments was 1.65 minutes (*P*=0.183). Patients receiving tiotropium experienced significantly longer exercise endurance times compared to patients receiving placebo 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 (*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 one 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 to 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (*P* value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[21] (UPLIFT) Tiotropium 18 µg QD vs placebo	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=5,993 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, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: The rate of decline in the mean post bronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug as compared to 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 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

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[22] (UPLIFT) Tiotropium 18 µg QD vs placebo This was a subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=2,739 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, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: Rate of decline of mean post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group (*P*=0.024). Rate of decline of mean pre-bronchodilator FEV_1 did not differ between groups. 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 the placebo group for all time points (*P*≤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[23] (UPLIFT) Tiotropium 18 µg QD	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-	N=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-	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).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo This was a subgroup analysis of patients in the UPLIFT trial who were not on other maintenance treatment at randomization.	very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less		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	Trough FEV_1 remained significantly larger in the tiotropium group compared to the placebo group at all time points throughout the trial ($P<0.05$). Secondary: No significant differences between groups were observed in pre- or post-FVC ($P\geq0.81$). Pre- and post-SVC was significantly higher in the tiotropium group ($P\leq0.046$). The improvement in the SGRQ scores was significantly higher in the 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[24] (UPLIFT) Tiotropium 18 µg QD vs placebo This analysis is a more in depth look at the effect of tiotropium	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 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	Primary: See previous results by Tashkin et al.[21] Secondary: See previous results by Tashkin et al.[21] 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.

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and its discontinuation on mortality and its causes.			SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	The most common causes of death included lower respiratory causes, cancer, general disorders, and cardiac disorders.
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 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 following tiotropium compared to 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 $\geq$40 years of age with an FEV_1 $\leq$65% of predicted normal value and $\leq$70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	Primary: By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared to 20 mL for the ipratropium group. Tiotropium was more effective compared to ipratropium at all time points on all test days except for the first two hours following the first dose and up to one hour after the dose, one week later ($P<0.05$).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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 $\geq$1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; *P*=0.004). During the one-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30$\pm$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

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 [25] Ipratropium (various strengths and dosage forms) vs β_2-adrenergic agonist (various strengths and dosage forms), a combination of ipratropium and β_2-adrenergic agonists (various strengths and dosage forms), or placebo	MA 9 RCT's of adult patients with a diagnosis of COPD, symptoms consistent with an acute exacerbation	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: Not reported	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 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[26] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history of ≥20 pack-years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Trough FEV_1 at 12 weeks, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and 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 NI ($P < 0.001$). FEV_1 at five minutes post dose on day one 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

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.				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 26 weeks, the change from baseline in mean daily number of inhalations of as-needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (*P*<0.001 for both). Significantly fewer inhalations of as-needed albuterol were required with either indacaterol dose compared to tiotropium (*P*≤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*≤0.001). 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 with both doses of indacaterol at all assessments compared to the placebo treatment group (*P*<0.01 for all) but not compared to tiotropium (*P* value not reported). Analysis of time to first COPD exacerbation showed a reduced risk with indacaterol 150 µg compared to placebo (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.
Vogelmeir et al[27] INTIME Indacaterol 150 µg QD	DB, DD, PC, RCT, XO Patients ≥40 years of age with moderate to	N=169 12 weeks	Primary: Trough FEV_1 at 14 days	Primary: After 14 days of treatment, trough FEV_1 was significantly higher with indacaterol 150 and 300 µg compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200, respectively;

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs indacaterol 300 µg QD vs 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. Permitted concomitant medications included ICS, if the dose and regimen were stable for one month prior to screening. Patients previously on ICS/LABA combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as	severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 30 to <80% predicted and FEV_1/FVC <70%		Secondary: Trough FEV_1 at 12 weeks, trough FEV_1 after the first dose, FEV_1 at individual time points after the first dose and on day 14 and safety	*P*<0.001). Secondary: Patients receiving indacaterol 150 µg and 300 µg not only met the criterion for NI compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. 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 one, 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.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
needed.				
Buhl et al[28] INTENSITY Indacaterol 150 µg QD vs tiotropium 18 µg QD Patients previously on ICS/LABA combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed.	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack-years, post-bronchodilator FEV_1 30 to <80% 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 and safety	Primary: Trough FEV_1 was 1.44L and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be NI to tiotropium (*P*<0.001). Subsequent criteria for superiority were not met. Secondary: Five minutes following administration on day one, 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*≤0.05 for all). Statistically significant improvements in TDI total scores occurred after 12 weeks with indacaterol compared to tiotropium (treatment difference, -0.58; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores compared to patients receiving tiotropium (OR, 1.49; *P*<0.001). SGRQ total scores after 12 weeks were significantly improved with indacaterol compared to tiotropium (treatment difference, -2.1; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores compared to tiotropium (OR, 1.43; *P*<0.001). Patients receiving indacaterol were able to significantly reduce their use of daily, daytime and nighttime use of rescue medications (*P*<0.001), and experienced a significantly greater proportion of days without rescue medication use compared to the tiotropium treatment group (*P*=0.004). Diary data revealed that indacaterol and tiotropium resulted in similar improvements from baseline, in the proportion of days with no daytime COPD symptoms, proportion of nights with no awakenings and proportion of days able to undertake usual activities (*P* values not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium, respectively (*P* values not reported).
Matera et al[29] Ipratropium 40 µg plus placebo vs salmeterol 50 µg plus placebo vs ipratropium 40 µg plus salmeterol 50 µg vs placebo plus placebo	RCT, SB, XO Male patients ≥40 years of age with COPD and an FEV_1 between 16 and 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in FEV_1 AUC	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 ipratropium plus salmeterol (28.0±4.2). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared to placebo (*P*<0.05), but only salmeterol and ipratropium plus salmeterol induced a significant (*P*<0.05) spirometric increase over the 12 hour monitoring period. Secondary: The AUC for active treatments were significantly increased compared to placebo (*P*<0.05), and salmeterol and ipratropium plus salmeterol significantly increased FEV_1 compared to ipratropium alone (*P*<0.05). There was no significant difference (*P*>0.05) between the salmeterol and ipratropium plus salmeterol AUC.
Van Noord et al[30] Salmeterol 50 µg plus ipratropium matched placebo vs ipratropium 40 µg plus salmeterol 50 µg vs	DB, MC, PG, RCT Patients 40 to 75 years of age with COPD, a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication use, PEF, clinic lung function, adverse events and exacerbations	Primary: After inhalation of salmeterol, there was a mean±SEM peak increase in FEV_1 7.0±0.7% predicted after two hours. After 12 hours, the improvement was 2.0±1.0% of predicted value. Ipratropium plus salmeterol produced a peak increase in FEV_1 11.0±0.8% of predicted after two hours. After 12 hours, the improvement was 3.0±0.8% of predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary:

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
salmeterol-matched placebo plus ipratropium-matched placebo				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 ipratropium plus salmeterol group. Compared to placebo, salmeterol and ipratropium plus salmeterol 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 greater in both active treatment groups compared to the placebo group (*P*<0.001), while there was no difference between the salmeterol and the ipratropium plus salmeterol treatment groups with regard to morning PEF. The improvements in evening PEF were greater in both active treatment arms compared to the placebo arm (*P*<0.001), whereas the improvement was better in the ipratropium plus salmeterol group compared to the salmeterol group (*P*<0.01). During the 12-week treatment period, the mean±SEM increase in FEV_1 was 1.0±0.9% of predicted for placebo, 5.0±0.9% of predicted for salmeterol, and 8.0±0.8% for ipratropium plus salmeterol. All differences were statistically significant (*P*<0.01). The change in FVC was 4.0±1.2% of predicted with placebo, 7.0±1.2% of predicted with salmeterol and 12.0±1.2% with ipratropium plus salmeterol. The differences between ipratropium plus salmeterol and salmeterol alone and between ipratropium plus salmeterol and 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). The reported incidence and nature of possible and probably drug-related adverse events were similar among the three groups. During the 12-week treatment period, 35 patients experienced a COPD exacerbation, 18 (36%) patients in the placebo group, 11 (23%) patients in

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the salmeterol group, and six (13%) patients in the ipratropium plus salmeterol group. The only significant difference was between the ipratropium plus salmeterol group and the placebo group (*P*<0.01).
Yohannes et al[31] 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: SGRQ and 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 tiotropium were also more likely to experience improvements in SGRQ scores compared to patients receiving 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); however, 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 tiotropium were less likely to have an exacerbation-related hospitalization compared to patients receiving 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 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;

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[32] Tiotropium and formoterol vs tiotropium	MA 8 RCT's of 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, 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). 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 to tiotropium alone, but the difference was not statistically significant (OR, 0.88; 95% CI, 0.70 to 1.11; *P*=0.28). Secondary: Not reported
Barr et al[33] Tiotropium	MA 9 RCT's with patients diagnosed with	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations and mortality	Primary: Reduced exacerbations were seen with tiotropium compared to placebo (OR, 0.75; 95% CI, 0.66 to 0.85) and compared to ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo, or ipratropium, or a LABA	COPD, whose disease was stable		Secondary: Change in FEV_1 and/or FVC, rescue medication use and adverse events	Hospitalizations for COPD exacerbations were reduced with tiotropium 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 and 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 the placebo group (140 mL; 95% CI, 118 to 162), the ipratropium group (150 mL; 95% CI, 106 to 193) and the salmeterol group (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 the placebo group (278 mL; 95% CI, 208 to 348), the ipratropium group (210 mL; 95% CI, 112 to 308) and the salmeterol group (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 the placebo group (21 mL; 95% CI, 15 to 28) and the ipratropium group (16 mL; 95% CI, 7 to 25). There was no difference between the tiotropium and salmeterol treatment groups (0 mL; 95% CI, -8 to 9). In the tiotropium group, dry mouth was significantly increased compared to the placebo group (OR, 5.4; 95% CI, 3.3 to 8.8), the ipratropium group (OR, 2.1; 95% CI, 1.05 to 4.2) and the salmeterol group (OR, 5.1; 95% CI, 2.2 to 12.0).
Singh et al[12] Tiotropium 5 to 10 µg	MA 5 RCT's of tiotropium solution using a mist	N=6,522 Up to 52 weeks	Primary: Mortality from any cause	Primary: The tiotropium mist inhaler was associated with a significantly increased risk of mortality compared to placebo (RR, 1.52; 95% CI, 1.06 to 2.16; *P*=0.02).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	inhaler (Respimat® Soft Mist Inhaler) vs placebo for COPD that evaluated mortality as an outcome and had a trial duration of more than 30 days		Secondary: Deaths from cardiovascular causes (myocardial infarction, stroke, cardiac death, and sudden death)	Secondary: Although the numbers for cardiovascular death were low, tiotropium was associated with a significantly increased RR in the five trials evaluating this outcome (RR, 2.05; 95% CI, 1.06 to 3.99; *P*=0.03).
Karner et al[34] Tiotropium and ICS/LABA vs tiotropium vs ICS/LABA	MA 3 RCT's of participants 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 and SGRQ scores Secondary: Symptoms, FEV_1, non-fatal serious adverse events, adverse events and withdrawals	Primary: There was no significant 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 reported 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). 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).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: The addition of tiotropium to LABA/ICS significantly increased FEV_1 (difference, 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 statistically 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[35] Salmeterol 50 µg BID vs tiotropium 18 µg QD Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment	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 ≤70% of the predicted value, a FEV_1/FVC ratio ≤70%, and a documented history of ≥1 exacerbation leading to treatment	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

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the double-blind treatment phase.	with systemic glucocorticoids or antibiotics or hospitalization within the previous year			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 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 an 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[36] Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, DD, PC, RCT Patients ≥40 years of age with COPD, a 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 and adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared to 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 to 11.1 days in the salmeterol group and 10.9 days in the placebo group (*P*<0.05).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 compared to placebo (*P*<0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared to the placebo group (*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[37] Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable COPD, FEV_1 ≤60% of predicted normal and FEV_1/FVC ≤70%	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI and 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).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Kurashima et al[38] 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 to 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[39] 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 of age with ≥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 <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	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 compared to tiotropium plus placebo (*P*=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8) for tiotropium plus fluticasone/salmeterol compared to the tiotropium plus placebo group (*P*=0.62). The unadjusted OR risk for exacerbations was 1.03 (95% CI, 0.63 to 1.67) with tiotropium plus salmeterol compared to tiotropium plus placebo and 0.85 (95% CI, 0.52 to 1.38) for tiotropium plus fluticasone/salmeterol compared to tiotropium plus placebo.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			visits to a health care practitioner or emergency room, number of hospitalizations for COPD, total number of hospitalizations for all causes, changes in HRQL, dyspnea and lung function	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 to tiotropium plus placebo (*P*=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol compared to tiotropium and tiotropium plus placebo (*P*=0.24). 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 to 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 to 0.086 L in the tiotropium plus fluticasone/salmeterol group (*P*=0.049). In addition, the percent predicted FEV_1 increased by 1.3% in the tiotropium plus placebo group compared to 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[40] Tiotropium 18 µg QD	DB, MC, PG, RCT Patients ≥40 years of	N=605 6 weeks	Primary: FEV_1 $AUC_{0\text{-}12}$, peak FEV_1	Primary: After six weeks, the FEV_1 $AUC_{0\text{-}12}$ mean difference was 78 mL higher (95% CI, 34 to 122) with treatment with tiotropium plus formoterol compared to

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus formoterol 12 µg BID vs fluticasone 500 µg BID plus salmeterol 50 µg BID	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 two		Secondary: Morning predose FEV_1	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).
Ikeda et al[41] Ipratropium 40 µg via MDI vs ipratropium 80 µg via MDI vs ipratropium 40 µg via MDI and albuterol 200 µg via MDI vs ipratropium 80 µg via MDI and albuterol 400 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 <70%, 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 to the placebo group 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 and *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[42]	DB, MC, PG, PRO, RCT	N=534	Primary: Peak change from	Primary: Compared to the individual components, the mean peak response in FEV_1

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Albuterol 100 µg QID via MDI vs ipratropium 21 µg QID via MDI vs ipratropium/albuterol 21/100 µg QID via MDI	Patients ≥40 years of age diagnosed with COPD with stable disease, relative stable, moderately severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio ≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents for COPD control	85 days	baseline in FEV_1, response AUC, symptom score and safety Secondary: Not reported	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 to 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 terms of adverse effects or safety (*P* value not reported). Secondary: Not reported
Dorinsky et al[43] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of ipratropium/albuterol via MDI	DB, MC, PG, RETRO, RCT Patients ≥40 years of age 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 ≤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 ipratropium/albuterol 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 one and two (*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 two to eight percent (*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 ipratropium/albuterol group compared to the individual treatment groups (*P*<0.05). Secondary: Not reported
Friedman et al[44] Albuterol 180 µg QID via MDI	DB, MC, PG, RETRO, RCT Patients ≥40 years of	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 $AUC_{0\text{-}4h}$, total health	Primary: A statistically significant improvement in FEV_1 in the ipratropium/albuterol group was observed compared to other treatment groups on all test days (*P*<0.01).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ipratropium 36 µg QID via MDI vs equivalent dose of ipratropium/albuterol via MDI	age diagnosed with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during three months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤70%		care expenditures and cost effectiveness ratios Secondary: Not reported	A significantly higher FEV_1 AUC_{0-4} in the ipratropium/albuterol group compared to the other treatment groups was observed on all test days ($P \leq 0.008$). The total cost of treating patients in the ipratropium group and the ipratropium/albuterol group was significantly less than the albuterol group (no *P* value reported). No statistical difference was observed between total costs in the ipratropium group and the ipratropium/albuterol group (*P* value not reported). A significantly greater cost effectiveness was observed in the ipratropium and ipratropium/albuterol groups compared to albuterol group ($P<0.05$). Secondary: Not reported
Tashkin et al[45] Ipratropium/albuterol solution for nebulization QID vs ipratropium/albuterol 2 inhalations QID via MDI vs ipratropium/albuterol solution for nebulization administered in the morning and	MC, PG, RCT Patients ≥50 years of age with COPD, 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 ≤70%	N=140 12 weeks	Primary: SGRQ 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	Primary: After six weeks of treatment, the change from baseline in the SGRQ score was clinically (≥4-unit change) 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).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ipratropium/albuterol MDI administered in the afternoon and evening			reported disease exacerbations)	Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the symptom sub-score (*P*=0.0186 and *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. 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[46]	AC, DB, DD, MC, NI, PG, RCT	N=1,480	Primary: FEV_1 change from	Primary: On day 85, ipratropium/albuterol Respimat® inhaler was NI to

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ipratropium/albuterol 20/100 µg QID, administered via Respimat® inhaler vs ipratropium/albuterol 36/206 µg QID, administered via aerosol MDI (Combivent®) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a two week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.	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	12 weeks	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 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_{0-6}, $_{0-4}$ and $_{4-6}$; peak FVC response on day one, 29, 57 and 85 and safety	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 NI 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: 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.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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[47] 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,	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% of patients receiving inhaled antimuscarinics and 1.2% 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).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	including myocardial infarction, stroke, or cardiovascular death			
Lee et al[13] Exposure to ICS, ipratropium, LABA, 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 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA 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 in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (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 ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this 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 ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABA (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 RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 ICS 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, ICS 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.

Drug regimen abbreviations: BID=two times daily, QD=once daily, QID=four times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, BDI=baseline dyspnea index, COPD=chronic obstructive pulmonary disease, ECG=electrocardiogram, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease, HRQL=health related quality of life, IC=inspiratory capacity, ICS=inhaled corticosteroid, LABA=long acting β2 agonist, MDI=metered dose inhaler, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PR=pulmonary rehabilitation, 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

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Special Populations

Table 5. Special Populations[2-7,16]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Aclidinium	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	Probable; use caution.
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 adverse events 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[2-7,16]

Adverse Event(s)	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Cardiovascular				
Angina	-	-	1 to 3	<2
Arrhythmia	-	-	<1	<2

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Adverse Event(s)	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Chest pain	-	-	5 to 7	0.3 to 2.6
Diastolic blood pressure increased	-	-	-	✔
Elevated heart rate	-	-	-	✔
First degree atrioventricular block	<1	-	-	-
Heart failure	<1	-	-	-
Hypertension	-	-	-	<2
Hypotension	-	✔	-	✔
Myocardial ischemia	-	-	-	✔
Palpitations	-	✔	✔	<2
Tachycardia	-	✔	-	<2
Central Nervous System				
Asthenia	-	-	-	✔
Central nervous system stimulation	-	-	-	✔
Coordination difficulty	-	-	-	✔
Depression	-	-	1.0 to 4.4	-
Dizziness	-	3	✔	✔
Drowsiness	-	-	-	✔
Fatigue	-	-	-	✔
Flushing	-	-	-	✔
Headache	6.6	6 to 7	5.7	✔
Insomnia	-	-	4.4	✔
Mental disorder	-	-	-	✔
Nervousness	-	-	-	✔
Paresthesia	-	-	1 to 3	✔
Tremor	-	-	-	✔
Weakness	-	-	-	✔
Dermatological				
Allergic skin reactions	-	✔	2 to 4	-
Angioedema	-	✔	<1	0.3
Dry skin	-	-	✔	-
Pruritus	-	✔	✔	0.3
Skin infection	-	-	✔	-
Skin rash	-	✔	2 to 4	0.3
Skin ulcer	-	-	✔	-
Urticaria	-	✔	✔	0.3
Endocrine and Metabolic				
Diabetes mellitus	<1	-	-	-
Edema	-	-	3 to 5	-
Hypercholesterolemia	-	-	1 to 3	-
Hyperglycemia	-	-	1 to 3	-
Gastrointestinal				
Abdominal pain	-	5 to 6	-	-
Constipation	-	✔	1.0 to 5.1	>1
Diarrhea	2.7	✔	-	<2
Dyspepsia	-	1 to 5	1 to 6	<2
Gastrointestinal disease	-	-	-	✔
Gastroesophageal reflux	-	-	1 to 3	-

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Adverse Event(s)	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Gastrointestinal pain	-	-	3 to 6	-
Heartburn	-	-	-	✔
Intestinal obstruction	-	-	✔	-
Motility disorder	-	-	-	✔
Nausea	-	4	-	<2
Sore throat	-	-	-	✔
Taste perversion	-	-	-	<2
Vomiting	1.1	-	1 to 4	<2
Genitourinary				
Urinary difficulty	-	-	-	✔
Urinary retention	-	✔	<1	-
Urinary tract infection	-	2 to 10	4 to 7	<2
Musculoskeletal				
Arthralgia	-	-	4.2	<2
Arthritis	-	-	≥3	-
Back pain	-	-	-	<2
Joint swelling	-	-	✔	-
Leg cramps	-	-	-	1.4
Leg pain	-	-	1 to 3	-
Muscle spasms	-	-	-	✔
Myalgia	-	-	4	✔
Pain	-	-	-	1.2 to 2.5
Skeletal pain	-	-	1 to 3	-
Respiratory				
Bronchitis	-	10 to 23	-	1.7 to 12.3
Bronchospasm	-	✔	-	0.3
Cardiorespiratory arrest	<1	-	-	-
Chronic obstructive pulmonary disease exacerbation	-	8 to 23	-	✔
Coughing	3	✔	≥3	4.2
Drying of secretions	-	-	-	✔
Dyspnea	-	7 to 8	-	4.5
Hoarseness	-	-	-	✔
Increased sputum	-	-	-	<2
Influenza	-	-	-	1.4
Irritation of aerosol	-	-	-	✔
Lung disease	-	-	-	6.4
Nasal congestion	-	-	-	✔
Nasopharyngitis	5.5	-	-	-
Pharyngitis	-	-	7.0 to 12.5	2.2 to 4.4
Pneumonia	-	-	-	1.3 to 1.4
Respiratory disorder	-	-	-	2.5
Rhinitis	1.6	≥3	3 to 6	1.1
Sinusitis	1.7	1 to 11	3 to 11	<2.3
Upper respiratory tract infection	-	≥3	43 to 41	10.9
Voice alterations	-	-	-	>1
Wheezing	-	-	-	✔
Other				
Accidents	-	-	5 to 13	-

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Adverse Event(s)	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Alopecia	-	-	-	-
Anaphylaxis	-	✔	-	✔
Back pain	-	2 to 7	-	-
Blurred vision	-	✔	-	✔
Cataract	-	-	1 to 3	-
Conjunctival hyperaemia	-	✔	-	✔
Corneal edema	-	✔	-	✔
Dehydration	-	-	✔	-
Dry mouth	≤1	2 to 4	5.1 to 16.0	<2
Dry throat	-	✔	-	✔
Dysphagia	-	-	✔	-
Dysphonia	-	-	1 to 3	-
Edema	-	-	-	✔
Epistaxis	-	-	1 to 4	-
Eye pain	-	✔	-	✔
Falls	1.1	-	-	-
Gingivitis	-	-	✔	-
Glaucoma	-	✔	✔	-
Glaucoma, worsening of narrow-angle	-	✔	-	✔
Halo vision	-	✔	-	✔
Herpes zoster	-	-	1 to 3	-
Hoarseness	-	-	✔	-
Hypersensitivity reaction	-	✔	1 to 3	-
Hyperhidrosis	-	-	-	✔
Hypokalemia	-	-	-	✔
Infection	-	-	1 to 4	-
Influenza-like symptoms	-	4 to 8	≥3	-
Laryngitis	-	-	1 to 3	-
Laryngospasm	-	✔	-	✔
Moniliasis	-	-	3 to 4	-
Mouth edema	-	✔	-	✔
Mucosal ulcers	-	-	-	✔
Mydriasis	-	✔	-	✔
Ocular irritation	-	-	-	✔
Oropharyngeal candidiasis	-	-	✔	-
Osteoarthritis	<1	-	-	-
Stomatitis	-	✔	1 to 3	✔
Taste perversion	-	<1	-	-
Throat irritation	-	✔	✔	-
Toothache	1.1	-	-	-

✔ Percent not specified.
- Event not reported.

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Contraindications

Table 7. Contraindications[2-7,16]

Contraindication	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Hypersensitivity to any component of the product, atropine or its derivatives	-	✔	✔	✔
Hypersensitivity to soya lecithin or related food products including soybeans and peanuts	-	-	-	✔

Warnings/Precautions

Table 8. Warnings and Precautions[2-7,16]

Warning/Precaution	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
Bladder neck obstruction; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	✔	✔	✔	✔
Clinically significant increases in pulse rate, blood pressure, and/or symptoms may occur; use with caution in patients with cardiovascular disorders	-	-	-	✔
Convulsive disorders; use with caution in this patient population	-	-	-	✔
Diabetes; large doses of intravenous albuterol have been 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	-	✔	-	-
Fatalities have been reported in associated with excessive use of inhaled sympathomimetic agents in patients with asthma	-	-	-	✔
Hypersensitivity reactions may occur following administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and anaphylaxis	✔	✔	✔	✔
Hypersensitivity reactions may occur in patients with an allergy to atropine; patients should be monitored for signs of a reaction	✔	-	✔	-
Hypersensitivity reactions may occur in patients with an allergy to	✔	-	✔	-

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Warning/Precaution	Single Entity Agents			Combination Products
	Aclidinium	Ipratropium	Tiotropium	Ipratropium/ Albuterol
milk protein; use with caution in this patient population				
Hyperthyroidism; use with caution in this patient population	-	-	-	✔
Hypokalemia; significant hypokalemia may occur in some patients predisposing them to cardiovascular effects	-	-	-	✔
Indicated for maintenance therapy and should not be used for initial treatment of acute episodes of bronchospasm	✔	✔	✔	-
Narrow-angle glaucoma; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	✔	✔	✔	✔
Paradoxical bronchospasm has been reported; discontinue treatment immediately if paradoxical bronchospasm is suspected	✔	-	-	✔
Prostatic hyperplasia; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported	-	✔	✔	✔
Use with caution in patients who are unusually responsive to sympathomimetic amines	-	-	-	✔

Drug Interactions

Although the inhaled antimuscarinics are minimally absorbed, there is some potential for an additive interaction with concomitantly used antimuscarinic (anticholinergic) medications.[2-7,16]

Dosage and Administration

Table 9. Dosing and Administration[2-7,16]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Aclidinium	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema: Powder for oral inhalation: initial, 400 µg BID	Safety and efficacy in children have not been established.	Powder for oral inhalation: 400 µg
Ipratropium	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema:	Safety and efficacy in children under the age of 12	Aerosol for oral inhalation (Atrovent HFA®):

Generic Name	Adult Dose	Pediatric Dose	Availability
	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	have not been established.	17 µg (200 actuations/ unit) Solution for nebulization (Atrovent®): 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 QID; maximum, 12 inhalations daily Inhalation spray (inhaler): one inhalation QID; maximum, six inhalations a day Solution for nebulization: one vial QID; maximum, six vials daily	Safety and efficacy in children have not been established.	Aerosol for oral inhalation (Combivent®): 21/120 µg* (200 metered inhalations) Inhalation spray (inhaler) (Combivent Respimat®): 20/100 µg* (120 actuations) Solution for nebulization (DuoNeb®): 0.5/3.0 mg (3 mL vials)

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

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 (2011)**[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) <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.

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Clinical Guideline	Recommendations
	• A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the patient's level of symptoms, the severity of the spirometric abnormality and the presence of complications such as respiratory failure, right heart failure, weight loss and arterial hypoxemia. • Chest radiograph may be useful to rule out other diagnoses and to establish the presence of significant comorbidities such as cardiac failure. • Arterial blood gas tension measurements should be considered for all patients with an FEV_1 <35% predicted or clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is <92% arterial blood gases should be assessed. • 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. • 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> • Smoking cessation should be encouraged for all patients, pharmacotherapy and nicotine replacement increase long-term smoking abstinence rates. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • No 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

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Clinical Guideline	Recommendations
	convenient and possibly provide improved drug deposition, although this has not been established in COPD. • Principle bronchodilators include β_2-agonists and anticholinergics and are used as monotherapy or in combination with one another if symptoms are not improved with monotherapy. • 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 long-acting β2 agonists 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. • Based on its relatively low efficacy and adverse event profile, treatment with theophylline is not recommended unless other bronchodilators are unavailable. • The addition of regular treatment with inhaled corticosteroids to bronchodilator treatment is appropriate for patients with severe or very severe COPD with an FEV_1 <60% predicted and repeated exacerbations. • Regular treatment with inhaled corticosteroids has been shown to reduce the frequency of exacerbations and thus improve health status for symptomatic patients with an FEV_1<60% of the predicted value and repeated exacerbations. • Treatment with inhaled corticosteroids increases the likelihood of pneumonia and does not reduce overall mortality. Long-term monotherapy with an inhaled corticosteroids is not recommended. • An inhaled corticosteroid combined with a long-acting β2 agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status. • Combination inhaled corticosteroid/long-acting β2 agonist therapy increases the likelihood of pneumonia. • Addition of an inhaled corticosteroid/long-acting β2 agonist 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. • The phosphodiesterase-4 inhibitor roflumilast may be used to reduce exacerbations in patients with severe and very severe COPD, chronic bronchitis and frequent exacerbations that are not adequately controlled on bronchodilator therapy. • In COPD patients, influenza vaccines can reduce serious illness. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years of age or for patients <65 years of age 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.

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Clinical Guideline	Recommendations
	Management of exacerbations • The most common causes of an exacerbation are tracheobronchial tree infections and air pollution. • Short-acting inhaled β_2-agonists (particularly inhaled β_2-agonists with or without anticholinergics) and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
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)**[15]	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-

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Clinical Guideline	Recommendations
	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. 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)**[48]	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 <60% predicted. The mean FEV_1 was <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 health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile.

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Clinical Guideline	Recommendations
	• 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 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 aclidinium (Tudorza®) ipratropium (Atrovent®, Atrovent® HFA) and tiotropium (Spiriva®). Ipratropium is also available in combination with albuterol, a short-acting β_2 receptor agonist (Combivent®, Combivent Respimat® and DuoNeb®).[2-7] Aclidinium, 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.[2,3,7] Tiotropium is the only agent within the class that is FDA-approved for reducing exacerbations associated with COPD.[3] Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator.[4-6] Aclidinium, ipratropium and tiotropium are all classified as bronchodilators but due to differences in pharmacokinetic parameters, aclidinium and tiotropium are considered long-acting bronchodilators and ipratropium a short-acting bronchodilator. Both aclidinium and tiotropium have a significantly longer duration of action compared to ipratropium and as a result are approved for twice- and once-daily dosing, respectively. Ipratropium has a duration of action of six to eight hours and is administered four times daily.[3,7] All of the 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.[7,31] Meta-analyses have demonstrated significant clinical advantages when tiotropium is used in combination with a bronchodilator from a different pharmacologic class.[32,34,39,40] 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.[29,30] Treatment with aclidinium has demonstrated statistically significant improvements in pulmonary function in patients with COPD compared to placebo; however, head-to-head studies with other antimuscarinics have not been conducted.[17-19]

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 antimuscarinics are preferred compared to four-times-daily

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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.[14]

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