Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class Overview/Summary:
The inhaled 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.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics 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 anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including glycopyrrolate/indacaterol (Utibron Neohaler®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-15] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while glycopyrrolate, tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-15]

Aclidinium, glycopyrrolate, ipratropium and tiotropium, are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD.[4-15]

Table 1. Current Medications Available in the Therapeutic Class[4-16]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza® Pressair)	Bronchospasm associated with COPD, maintenance treatment†	Powder for inhalation: 400 µg	-
Glycopyrrolate (Seebri Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Tiotropium (Spiriva®, Spiriva Respimat®)	Asthma, maintenance treatment (aerosol for inhalation); Bronchospasm associated with COPD, maintenance treatment†, reduce exacerbations in patients with COPD	Aerosol for inhalation (Spiriva Respimat®): 1.25 µg/actuation 2.5 µg/actuation Powder for inhalation (Spiriva HandiHaler®): 18 µg	-
Umeclidinium (Incruse Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment*	Powder for inhalation: 62.5 µg	-
Combination Products			
Glycopyrrolate/indacaterol (Utibron Neohaler®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 15.6 µg/27.5 µg	-
Ipratropium/albuterol* (Combivent Respimat®)	Bronchospasm associated with COPD in patients requiring more than one bronchodilator	Inhalation spray (Combivent Respimat®): 20/100 µg‡ Solution for nebulization (DuoNeb®): 0.5/3.0 mg	a
Tiotropium/olodaterol (Stiolto Respimat®)	Airflow obstruction in patients with COPD, maintenance treatment†	Inhalation Spray 5/5 µg	-
Umeclidinium/vilanterol (Anoro Ellipta®)	Airflow obstruction in patients with COPD, maintenance treatment†	Powder for inhalation: 62.5/25 µg	-

*Generic available in at least one dosage form or strength.
†Long-term maintenance treatment.
‡Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[17-79] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[19,42,43]
- The efficacy of glycopyrrolate is based primarily on the dose-ranging trials in 471 subjects with COPD and two placebo-controlled confirmatory trials in 867 subjects with COPD. The primary efficacy endpoint from the two placebo-controlled confirmatory trials, GEM1 and GEM2, was the change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ following the morning dose at day 85 compared with placebo. In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo.
  - In GEM1, the change from baseline least squares (LS) mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported).
  - For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported).[5,77,78]

- The efficacy of indacaterol/glycopyrrolate was based primarily on the results of two 12-week efficacy studies (FLIGHT1 & 2).[12,79] Both were identical, multicenter, randomized, double-blinded, placebo- and active-controlled, and parallel-group trials in subjects with COPD. A total of 2,038 individuals were randomized to indacaterol/glycopyrrolate 27.5 µg/15.6 µg twice-daily (BID), indacaterol 27.5 µg BID, glycopyrrolate 15.6 mcg BID, or placebo BID. The primary endpoint was the change from baseline in FEV_1 AUC_{0-12h} following the morning dose at Day 85 compared with placebo, glycopyrrolate 15.6 µg BID, and indacaterol 27.5 µg BID.
    - In both trials, Utibron Neohaler® (indacaterol/glycopyrrolate) demonstrated a larger increase in mean change from baseline in FEV_1 AUC_{0-12h} compared to placebo, indacaterol 27.5 µg BID, and glycopyrrolate 15.6 µg BID (treatment difference: 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively, P<0.001). In addition, both indacaterol and glycopyrrolate monotherapies had a statistically greater response than placebo at week 12 in terms of FEV_1 AUC_{0-12h} (treatment difference: 143 mL and 158 mL, respectively, P<0.001).[79]

Key Points within the Medication Class

- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:[1]
    - Inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β2-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 GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.
- According to the National Institute for Clinical Excellence (NICE):[2]
    - 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 anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergics 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 anticholinergic agent.
- Other Key Facts:
    - Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

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Inhaled Anticholinergics

Overview/Summary

The inhaled 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.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics 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 anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including glycopyrrolate/indacaterol (Utibron Neohaler®), umeclidinium/vilanterol (Anoro Ellipta®), tiotropium/olodaterol (Stiolto Respimat®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-15] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while glycopyrrolate, tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Aclidinium, glycopyrrolate, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-15] Aclidinium, glycopyrrolate, ipratropium and tiotropium, are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD.[4-15] Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

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 GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use 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 anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergics 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 anticholinergicagent.[2]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Aclidinium (Tudorza® Pressair)	Inhaled anticholinergic	-
Glycopyrrolate (Seebri Neohaler®)	Inhaled anticholinergic	-
Ipratropium* (Atrovent HFA®)	Inhaled anticholinergic	a
Tiotropium (Spiriva®, Spiriva Respimat®)	Inhaled anticholinergic	-
Umeclidinium (Incruse Ellipta®)	Inhaled anticholinergic	-
Combination Products		
Glycopyrrolate/indacaterol (Utibron Neohaler®)	Inhaled anticholinergic/inhaled	-

Generic Name (Trade name)	Medication Class	Generic Availability
	short-acting β2-adrenegic agonists	
Ipratropium/albuterol* (Combivent Respimat®)	Inhaled anticholinergic/inhaled short-acting β2-adrenegic agonists	a
Tiotropium/olodaterol (Stiolto Respimat®)	Inhaled anticholinergic/inhaled long-acting β2-adrenegic agonists	-
Umeclidinium/vilanterol (Anoro Ellipta®)	Inhaled anticholinergic/inhaled long-acting β2-adrenegic agonists	-

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

Indications

Table 2. Food and Drug Administration-Approved Indications[4-15]

Indication	Single Entity Agents					Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium	Umeclidinium	Glycopyrrolate/ indacaterol	Ipratropium /albuterol	Tiotropium/ olodaterol	Umeclidinium /vilanterol
Asthma, maintenance treatment				a *,†					
Bronchospasm associated with COPD, maintenance treatment	a *		a	a *					
Airflow obstruction in patients with COPD, maintenance treatment		a *			a *	a *		a *	a *
Reduce exacerbations in patients with COPD				a					
Bronchospasm associated with COPD in patients requiring more than one bronchodilator							a		

*Long-term maintenance treatment
†Spiriva Respimat® formulation only
COPD: chronic obstructive pulmonary disease

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 (Spiriva®) has been used off-label in the treatment of patients with asthma.[16]

Pharmacokinetics

Table 3. Pharmacokinetics[4-16]

Generic Name	Onset (minutes)	Duration (hours)	Excretion (%)	Active Metabolites	Half-Life (hours)
Single Entity Agents					
Aclidinium	10	12	Feces (20 to 33) Renal (0.09)	None	5 to 8
Glycopyrrolate	5	Not reported	Feces (not reported) Renal (60 to 70)	Yes (reduced activity)	33 to 53
Ipratropium	15	6 to 8	Feces (48) Renal (3.7 to 5.6)	None	1.6
Tiotropium	60*	24*	Renal (14) Feces (not reported)	None	120 to 144

Generic Name	Onset (minutes)	Duration (hours)	Excretion (%)	Active Metabolites	Half-Life (hours)
Umeclidinium	Not reported	Not reported	Feces (92 [oral]) Renal (<1 [oral])	Yes (reduced activity)	11
Combination Products					
Glycopyrrolate/ indacaterol	5/15	Not reported	Renal (60 to 70)/ Renal (23), Feces (54)	Yes (reduced activity)/ Yes	33 to 53/ 40 to 56
Ipratropium/ albuterol	0.25 to 1.00	3 to 6	Renal (3.7 to 5.6)/ Renal (76 to 100)	none/albuterol 4'-o-sulfate	1.6/5.0
Tiotropium/ olodaterol	60*/ 10 to 20	24*/ Not reported	Renal (14)/ 38 (Renal), 54 (Feces)	None	120 to 144/ 45
Umeclidinium/ vilanterol	27	24	Feces (92 [oral]), Renal (<1 [oral])/Feces (30 [oral]), Renal (70 [oral])	Yes (reduced activity)	11

*Values shown for Spiriva®; values for Spiriva Respimat® not reported

Clinical Trials

Clinical studies demonstrating the safety and efficacy of the inhaled anticholinergics in their respective Food and Drug Administration-approved indications are described in Table 4. In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[17-79] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[19,42,43]

The safety and efficacy of tiotropium/olodaterol were evaluated in a clinical development program that included three dose ranging trials, two active-controlled trials, three active- and placebo-controlled trials, and one placebo-controlled trial.[14] The efficacy of tiotropium/olodaterol is based primarily on two 4-week dose-ranging trials in 592 COPD patients and two confirmatory trials.[14,17] The two confirmatory trials were replicate, randomized, double-blind, active controlled, parallel group trials. They evaluated 1,029 COPD patients who received tiotropium/olodaterol 5/5 µg, 1,033 patients who received olodaterol 5 µg, and 1,033 patients who received tiotropium 5 µg. All agents were administered via the Respimat® inhaler. Patients were 40 years of age or older with a 10-year pack history (current or ex-smoker) and moderate to very severe pulmonary impairment. In both confirmatory trials, tiotropium/olodaterol 5/5 µg showed a significant improvement in forced expiratory volume in one second (FEV_1) area under the curve over three hours $(AUC)_{0\text{-}3hr}$ and trough FEV_1 after 24 weeks compared to the individual components (P<0.0001).[17]

The safety and efficacy of tiotropium soft mist inhaler (Spiriva Respimat®) was approved by the FDA for use in COPD based on one dose-ranging study and five confirmatory trials.[10,16-19] Data was pooled from the confirmatory trials and represents 6,614 COPD patients, of whom 2,801 received tiotropium 5 µg via Respimat® and 2,798 receiving placebo.[9,19-21] The first two trials were 12-week, randomized, double-blind, double-dummy, placebo- and active- (ipratropium) controlled trials that evaluated bronchodilation. The final three trials were 48-week, randomized, double-blind, placebo-controlled, trials that evaluated bronchodilation and effects on COPD exacerbations. All but the fifth trial included both the tiotropium 5 µg and 10 µg doses, whereas the fifth included only the 5 µg dose.[9,19-21] These trials enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60% of predicted and a ratio of FEV_1/FVC of less than or equal to 0.7. All treatments were administered once daily in the morning. Change from baseline in trough FEV_1 was a primary endpoint in all trials. The last three trials also included COPD exacerbations as a primary endpoint.

Tiotropium soft mist inhaler demonstrated significant improvement in trough FEV_1 compared to placebo in all five confirmatory trials (P values not reported for pooled data). Mean change from baseline in trough FEV_1 at end of treatment for trials one and two (12 weeks) were 0.11 L (95% confidence interval [CI], 0.04 to 0.18) and 0.13 L (95% CI, 0.07 to 0.18). Mean change in trough FEV_1 at end of treatment for trials three, four and five (48 weeks) was 0.14 (95% CI, 0.10 to 0.18), 0.11 (95% CI, 0.08 to 0.15), and 0.10 (95% CI, 0.09 to 0.12).[9,19-21] In trials three and four, patients treated with tiotropium soft mist inhaler also used less rescue medication compared to patients on placebo.[9,20] In the pooled analysis of trials three and four, tiotropium soft mist inhaler 5 µg significantly reduced

the number of COPD exacerbations compared to placebo with 0.78 exacerbations per patient year compared to 1.0 exacerbations per patient year, respectively, with a rate ratio of 0.78 (95% CI, 0.67 to 0.92). Time to first exacerbation was also delayed in tiotropium soft mist inhaler patients.[9,20] In trial five, treatment with tiotropium soft mist inhaler delayed the time to first COPD exacerbation compared to treatment with placebo (hazard ratio [HR]=0.69; 95% CI, 0.63 to 0.77).[9,21] Consistent with the pooled analysis of trials three and four, trial five showed that exacerbation rate was lower in tiotropium soft mist inhaler compared to placebo. In addition, tiotropium soft mist inhaler also reduced the risk of COPD exacerbation-related hospitalization compared to placebo (HR=0.73; 95% CI, 0.59 to 0.90).[8,19] Due to an apparent increase in mortality associated with tiotropium soft mist inhaler and to clarify the issue, the manufacturers conducted the TIOSPIR (Tiotropium Respimat Inhaler and the Risk of Death in COPD) study. In total 5,711 patients received tiotropium soft mist inhaler and 5,694 patients received tiotropium dry powder inhaler. All patients were followed for vital status (mortality) at the end of the trial. All-cause mortality was similar between the two tiotropium groups, with an estimated hazard ratio of 0.96 (95% CI, 0.84 to 1.09).[9,22]

Two studies were published reporting an increased risk for mortality and/or cardiovascular events in patients who received tiotropium or other inhaled antimuscarinics.[23-24] 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).[23] However, results from the long-term UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial, it was confirmed that tiotropium did not demonstrate a significant increased risk of stroke or cardiovascular death compared to placebo.[31]

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 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).[23] In the study ACCORD COPD I, 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).[26] Significant improvements persisted through 52 weeks in an extension study.[25] The ACCORD COPD II study was similar in design to the ACCORD COPD I. In ACCORD COPD II, FEV_1 at week 12 was significantly greater for aclidinium 200 and 400 µg versus placebo. The treatment differences over placebo were 51 mL (95% CI, 8 to 94) and 72 mL (95% CI, 29 to 115), respectively (both P<0.05).[28]

The safety and efficacy of umeclidinium was established in two randomized, parallel group, placebo-controlled clinical trials, over 12 and 24 weeks, in patients with COPD (N=835). During these clinical trials patients were allowed to continue concurrent use of rescue albuterol inhalers and maintenance inhaled corticosteroids. Both trials found the mean change from baseline in trough forced expiratory volume in one second (FEV_1) was greater among subjects receiving umeclidinium compared to those receiving placebo (P<0.001). Additionally, both trials found a statistically significant improvement in change from baseline FEV_1 over 0 to six hours post-dose in the umeclidinium treatment group compared to placebo. In the 24-week trial, patients in the umeclidinium treatment group demonstrated a greater improvement in health-related quality of life, based on the mean St. George's Respiratory Questionnaire (SGRQ) score, compared patients treated with placebo.[10,40]

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 AUC over 12 hours (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).[52]

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).[61] When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[64-65] 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.[55] 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).[51] 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).[53] As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[54,55] Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV_1 and FVC in clinical studies when compared to either agent alone.[45-49]

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%).[50]

In a 24-week, randomized, double-blind, placebo-controlled trial study by Donahue et al (N=1,532), umeclidinium/vilanterol 62.5/25 µg once daily was compared to placebo and the single agents, umeclidinium 62.5 µg once daily and vilanterol 25 µg once daily. The primary endpoint of trough FEV_1 on treatment day 169 was significantly improved in all treatment groups compared to placebo (P<0.001 for all). In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively).[75]

In another study, Decramer et al compared tiotropium µg, umeclidinium 125 µg, vilanterol 25 µg, umeclidinium/vilanterol 62.5/25 µg and umeclidinium/vilanterol 125/25 µg. Both strengths of the combination demonstrated significant improvements in trough FEV_1 compared to tiotropium and vilanterol; however, there were no significant differences compared to umeclidinium monotherapy.[76]

The efficacy of glycopyrrolate is based primarily on the dose-ranging trials in 471 subjects with COPD and two placebo-controlled confirmatory trials in 867 subjects with COPD. The primary efficacy endpoint from the two placebo-controlled confirmatory trials, GEM1 and GEM2, was the change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ following the morning dose at day 85 compared with placebo. In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo. In GEM1, the change from baseline least squares (LS) mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported). For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported). In addition, several secondary endpoints were evaluated that showed improvements in COPD symptoms based on the St. George's Respiratory Questionnaire as well as quality of life and medication use in patients with moderate to severe airflow limitation. At the time of this NDR, none of the trials were published and there was no formal product dossier available from the manufacturer.[5,77,78]

The efficacy of indacaterol/glycopyrrolate was based primarily on the results of two 12-week efficacy studies (FLIGHT1 & 2).[12,79] Both were identical, multicenter, randomized, double-blinded, placebo- and active-controlled, and parallel-group trials in subjects with COPD. A total of 2,038 individuals were randomized to indacaterol/glycopyrrolate 27.5 µg/15.6 µg twice-daily (BID), indacaterol 27.5 µg BID, glycopyrrolate 15.6 mcg BID, or placebo BID. The primary endpoint was the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ following the morning dose at Day 85 compared with placebo, glycopyrrolate 15.6 µg BID, and indacaterol 27.5 µg BID. In both trials, Utibron Neohaler® (indacaterol/glycopyrrolate) demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0\text{-}12h}$ compared to placebo, indacaterol 27.5 µg BID, and glycopyrrolate 15.6 µg BID (treatment

difference: 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively, P<0.001). In addition, both indacaterol and glycopyrrolate monotherapies had a statistically greater response than placebo at week 12 in terms of FEV_1 $AUC_{0\text{-}12h}$ (treatment difference: 143 mL and 158 mL, respectively, P<0.001).[79]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Buhl et al[17] Tiotropium/olodaterol 5/5 µg via Respimat® QD vs tiotropium/olodaterol 2.5/5 µg via Respimat® QD vs tiotropium 5 µg via Respimat® QD vs tiotropium 2.5 µg via Respimat® QD vs olodaterol 5 µg via Respimat® QD	Two AC, DB, MC, PG, RCT Patients 40 years of age or older with a diagnosis of COPD (GOLD stage two to four), post-bronchodilator FEV_1 <80%, post-bronchodilator FEV_1/FVC <70% and current or ex-smokers with a smoking history of >10 pack-years	N=5,162 (2, 624 and 2,539 for studies one and two respectively) 52 weeks	Primary: FEV_1 AUC_{0-3h}, trough FEV_1 and SGRQ total score at 24 weeks Secondary: TDI focal score at 24 weeks, rescue medication use,	Primary: FEV_1 $AUC_{0–3}$ responses at week 24 for tiotropium/olodaterol 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 241, 256, 148, 139 and 133 mL, respectively, in the first study. In the second study, FEV_1 $AUC_{0–3}$ responses were 256, 268, 125, 165 and 136 mL, respectively. Improvements in adjusted mean FEV_1 $AUC_{0–3}$ with tiotropium/olodaterol 5/5 µg and 2.5/5 µg compared tothe corresponding individual components in the individual studies and the combined analysis were statistically significant (P<0.0001 for all comparisons). The comparison of tiotropium/olodaterol 2.5/5 µg with tiotropium 5 µg was also statistically significant (P<0.0001 for all analyses). Trough FEV_1 responses after 24 weeks for tiotropium/olodaterol 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 111, 136, 83, 65 and 54 mL, respectively, in the first study. In the second study, trough FEV_1 responses were 125, 145, 62, 96 and 57 mL, respectively. Improvements in the adjusted mean trough FEV_1 with tiotropium/olodaterol 5/5 µg and 2.5/5 µg over the corresponding individual components in both the individual studies and the combined data were statistically significant (P<0.05 for all comparisons). Several subgroup analyses were done for FEV_1 $AUC_{0–3}$ and trough FEV_1 responses. According to the subgroup analysis, there was no influence of sex on either FEV_1 $AUC_{0–3}$ or trough FEV_1 response. Responses were lower in patients with more severe disease severity at baseline (P value not reported). Treatment effect for tiotropium/olodaterol showed a significant improvement for both FEV_1 $AUC_{0–3}$ and trough FEV_1 responses compared to the individual components regardless of inhaled corticosteroid use (P<0.05 for all comparisons). After 24 weeks, tiotropium/olodaterol 5/5 µg showed a significant improvement in adjusted mean SGRQ total score over corresponding individual components (vs olodaterol 5 µg, −1.693 [0.553], P<0.01; vs tiotropium 5 µg, −1.233 [0.551], P<0.05). Tiotropium/olodaterol 2.5/5 µg did not show the same statistically significant improvements compared with its individual components.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Pooled data for both studies showed responder rates for SGRQ total scores after 24 weeks were 57.5% (tiotropium/olodaterol 5/5 µg), 53.2% (tiotropium/olodaterol 2.5/5 µg), 49.6% (tiotropium 2.5 µg), 48.7% (tiotropium 5 µg) and 44.8% (olodaterol 5 µg). The increases in responder rate for tiotropium/olodaterol 5/5 µg over its individual components were statistically significant (nominal P<0.05). Secondary: The pre-specified analysis of the TDI focal score at 24 weeks (combined data set) showed statistically significant improvements for both tiotropium/olodaterol groups compared with their components (P<0.05). Both tiotropium/olodaterol 5/5 µg and 2.5/5 µg provided reductions in adjusted weekly mean daily (24 hour) rescue medication use compared to the monotherapy components throughout the 52-week treatment period (P value not reported). There was a trend for improvement in exacerbations with both combinations versus the monotherapy components (P value not reported). Of the 5,163 patients, 4,368 (84.6%) completed the study. The rates of discontinuation were higher in the monotherapy groups than in the combination treatment groups for both studies.
Caillaud et al[18] Tiotropium 1.25 µg via Respimat inhaler QD vs tiotropium 2.5 µg via Respimat inhaler QD vs	DB, MC, PC, PG, RCT, dose finding Patients 40 years of age or older with a diagnosis of COPD	N=202 3 weeks	Primary: Trough FEV_1 on day 21 Secondary: FVC, PEFR, rescue medication use and safety	Primary: The primary endpoint, trough FEV_1, was statistically significantly improved following treatment with tiotropium 5 µg Respimat®, 20 µg Respimat® and tiotropium 18 µg HandiHaler® compared with placebo (P<0.05). Tiotropium 10 µg Respimat® showed a similar numerical advantage over placebo; however, the difference did not reach statistical significance (P=0.06). Secondary: FVC also improved after treatment with tiotropium Respimat® and HandiHaler® compared with placebo. On day 21, the greatest improvements in FVC were observed with the tiotropium 5 µg and 20 µg Respimat® dose and with tiotropium 18 µg HandiHaler®.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tiotropium 5 µg via Respimat inhaler QD vs tiotropium 10 µg via Respimat inhaler QD vs tiotropium 20 µg via Respimat inhaler QD vs tiotropium 18 µg via HandiHaler QD vs placebo				All active treatments improved morning and evening PEFR on Day 21 compared with placebo (largest: P<0.05). Rescue medication use declined in all active treatment groups, and with the exception of tiotropium 2.5 µg Respimat®, the mean decrease for each treatment group was statistically different from placebo (P<0.05). A trend in favor of active treatment over placebo was observed for nocturnal awakenings. Adverse events were reported in 27.7% (56/202) of randomized patients. The overall incidence of adverse effects as comparable across all active treatment groups and placebo. Dry mouth was more common in the active treatment groups at doses higher than 5 µg. Eight patients withdrew from the study due to adverse effects. Six patients had serious adverse events (only one of which was considered to be study related: hematuria).
Voshaar et al[19] Tiotropium 5 µg via Respimat QD vs tiotropium 10 5 µg via Respimat QD vs ipratropium bromide 36 µg via pMDI QD	AC, DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, moderate-to-severe airway obstruction, FEV_1 ≤60%, FEV_1/FVC ≤70%, smoking history ≥10 pack-years	N=719 12 weeks	Primary: Trough FEV_1 Secondary: FVC, PEFR and the number of patients achieving a 15% increase above baseline FEV_1	Primary: Compared with placebo, there was an increase in trough FEV_1 after treatment with tiotropium Respimat 5 and 10 µg. The mean (SE) trough FEV_1 treatment difference at week 12 in both the 5 and 10 µg tiotropium Respimat groups significantly improved when compared with placebo (5 µg, 0.188 [0.023]; 95% CI, 0.072 to 0.164; P<0.001 and 10 µg, 0.149 [0.023]; 95% CI, 0.103 to 0.195; P<0.001) and when compared to ipratropium pMDI (5 µg, 0.064 [0.023]; 95% CI, 0.018 to 0.110; P<0.01 and 10 µg, 0.095 [0.023]; 95% CI, 0.050 to 0.141; P<0.01). Secondary: Peak FEV_1, FEV_1 $AUC_{(0–6\ h)}$, trough FVC, peak FVC and FVC $AUC_{(0–6\ h)}$ at week 12 for both tiotropium doses (5 and 10 µg) were all significantly improved compared with placebo (P values vary, all <0.01). When compared to ipratropium, tiotropium Respimat provided numerically improved values

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				for FEV_1, FEV_1 $AUC_{(0–6\ h)}$, trough FVC, peak FVC and FVC $AUC_{(0–6\ h)}$ at week 12; however, a significant difference was only observed for FVC $AUC_{(0–6\ h)}$ and trough FVC (tiotropium 10 µg dose only). The weekly morning (trough) and evening PEFR were both higher for the tiotropium Respimat groups than either placebo or ipratropium over 12 weeks of treatment. The between-treatment differences at week 12 were statistically significant (P<0.01, P<0.0001 for the 5 and 10 µg tiotropium groups compared with placebo; P<0.01 for tiotropium 10 µg compared to ipratropium, P value not significant for tiotropium 5 µg compared with ipratropium). A higher proportion of patients in the ipratropium group achieved a 15% increase in FEV_1 during test day one compared with either tiotropium or placebo; however, after 12 weeks of treatment the number of responders in the three active treatments was comparable: tiotropium 5 µg (70%), tiotropium 10 µg (72%), ipratropium 36 µg (69%). All three active treatments reduced the rescue medication use throughout the 12-week study period compared with placebo. The between-treatment differences showed significant reduction in use rescue medication when compared to placebo for tiotropium 5 µg (P=0.0061) and tiotropium 10 µg (P<0.0001), but only tiotropium 10 µg significantly reduced rescue medication use when compared to ipratropium (P=0.04).
Bateman et al[20] Tiotropium 5 µg via Respimat QD vs tiotropium 10 5 µg via Respimat QD vs	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD and an FEV_1 <60% and FEV_1/FVC <70% with a ≥10 pack-years history	N=1,900 48 weeks	Primary: FEV_1, SGRQ score, and Mahler TDI focal score at week 48 and COPD exacerbations per patient-year Secondary: FVC, PEFR, weekly rescue medication use, COPD	Primary: The mean (SEM) differences between the tiotropium Respimat 5 and 10 µg when compared with placebo for combined mean trough FEV_1 response was 127 mL and 150 mL, respectively (P<0.0001 for both). When patients were originally treated with tiotropium 5 µg and switched to 10 µg, there was a slight, non-significant improvement in FEV1 of 23 mL. SGRQ total score for tiotropium 5 µg and 10 µg were significantly improved when compared to placebo. Mean (SEM) treatment differences when compared to placebo were -3.5 (0.7) and -3.8 (0.7) (P<0.0001). Both tiotropium doses were associated with significantly improved Mahler

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			symptom scores, safety	TDI focal score at week 48 when compared to placebo (mean [SEM]=1.05 and 1.08, P<0.0001 for both the tiotropium 5 and 10 µg groups respectively). The mean COPD exacerbation rate (per patient-year) was significantly reduced on treatment with both tiotropium doses and in each of the trials. Odds ratios for tiotropium 5 and 10 µg when compared to placebo were 0.75 (P<0.01) and 0.74 (P<0.001), respectively. Only a small percentage of patients experienced ≥1 COPD exacerbation-related hospitalization, which was lower in both tiotropium groups compared with placebo, but not statistically significant. Secondary: There was also an increase in trough FVC [SEM] of 0.209 L [0.027] and 0.286 L [0.027] for tiotropium 5 and 10 µg compared to placebo; P<0.0001 for both). Morning and evening PEFR were also statistically significantly improved after treatment with both doses of tiotropium compared with placebo (P<0.0001). Over the treatment period, active treatment compared with placebo, on average, provided a reduction of five occasions per week in rescue medication use (P<0.0001). Mean COPD symptom scores at week 48 were also significantly improved compared with placebo (P<0.0001 [P<0.05 for coughing]). Both tiotropium groups were associated with a higher incidence of gastrointestinal disorders than placebo, which was primarily due to dry mouth (7.2%, 14.5% and 2.1% for tiotropium 5 and µg and placebo respectively) and constipation (2.1%, 2.2% and 1.5% for tiotropium 5 and µg and placebo respectively). In addition, urinary tract infections were higher in the tiotropium group (2.5%, 4.2% and 1.1% for tiotropium 5 and µg and placebo respectively).
Bateman et al[21] Tiotropium 5 µg via Respimat QD	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD and an	N=3,991 48 weeks	Primary: FEV_1 response at 48 weeks and time to first COPD exacerbation	Primary: After 48 weeks of treatment, the adjusted mean increase from baseline trough FEV_1 was significantly greater in the tiotropium group (119 mL) than the placebo group (18 mL). The adjusted mean difference between treatments was 102 mL (95% CI, 85 to 118 mL; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	FEV_1 <60% and FEV_1/FVC <70% with a ≥10 pack-years history		Secondary: FEV_1 response at week four and 24 and trough FEV response at week 4, 24 and 48 weeks, number of exacerbations per patients, number of patients with at least one exacerbation, time to first exacerbation that required hospitalization and HRQoL (SGRQ score)	The time to first exacerbation was delayed by treatment with tiotropium. During the treatment period, 685 (35.3%) patients in the tiotropium group and 842 (43.1%) in the placebo group had at least one exacerbation, representing a risk reduction with tiotropium (HR=0.69; 95% CI, 0.63 to 0.77, P<0.0001). Secondary: Trough FEV_1 values at weeks four and 24 were significantly higher in the tiotropium group than in the placebo group, with the differences being 93 and 103 mL respectively (P<0.0001). In addition, trough FVC was significantly higher with tiotropium than with placebo at weeks 4, 24 and 48, with the differences ranging between 151 and 168 mL (P<0.0001). The rate of exacerbations per patient-year was significantly lower with tiotropium during the treatment period than with placebo (0.69 and 0.87 respectively; RR, 0.79; 95% CI, 0.70 to 0.93; P<0.005), as was the rate of exacerbations requiring hospitalization (0.12 and 0.15 respectively; RR, 0.81; 95% CI, 0.7 to 0.93; P<0.005). The time to the first exacerbation requiring hospital treatment was also delayed by treatment with tiotropium. At least one such exacerbation was recorded for 161 (8.3%) patients in the tiotropium group and 198 (10.1%) in the placebo group during the treatment period (HR, 0.73; 95% CI, 0.59 to 0.90; P<0.005). Mean total SGRQ scores fell from baseline in both groups, showing improvement in HRQoL, but the change was significantly greater with tiotropium than placebo. The adjusted mean difference in total scores between tiotropium and placebo was −2.2 units week 24 and -2.9 units at week 48 (P<0.0001 at both time points). Although both these differences were smaller than the minimum clinically important difference for the SGRQ (defined as change of 4 units) the proportion of responders (those whose total score fell by ≥4 units from baseline) was significantly higher in the tiotropium group than the placebo group (P<0.0001 at weeks 24 and 48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of adverse events and serious adverse events reported by patients in the two treatment groups during the on-treatment period (up to the last dose taken 30 days follow-up) was similar. Differences were seen in lower respiratory system disorders (incidence per 100 patient-years [IRs] of 70.5 and 87.0 for tiotropium and placebo respectively; rate ratio, 0.81; 95% CI, 0.74 to 0.89), psychiatric disorders (IRs of 2.92 and 4.27; rate ratio, 0.68, 95% CI, 0.48 to 0.98) and neoplasms (IRs, 2.63 and 1.65; rate ratio; 1.59; 95% CI, 1.00 to 2.53). Most of the frequently-reported adverse events were reported by similar proportions of patients in the two treatment groups. The notable exceptions to this were COPD exacerbation (the most common event reported overall), which was reported by 641 (32.8%) patients in the tiotropium group and 759 (38.6%) patients in the placebo group, and dry mouth, reported by 60 (3.1%) patients and 27 (1.4%) patients, respectively. After COPD exacerbations, the most common adverse events across both groups were balanced between groups, e.g. nasopharyngitis (8.0 and 7.7% respectively), dyspnea (7.0 and 7.7%), upper respiratory tract infection (6.4 and 7.3%) and cough (6.4 and 5.5%). The rate-ratio for all-cause mortality was 1.38 (95% CI, 0.91 to 2.10; P=0.13).
Wise et al[22] TIOSPIR Tiotropium 2.5 µg via Respimat inhaler QD vs tiotropium 5 µg via Respimat inhaler QD vs tiotropium 18 µg via	PC, PG, RCT Patients ≥40 years of age with COPD and an FEV_1/FVC <0.7 and FEV_1 <70% who had ≥10 pack-years history of smoking	N=17,135 time until 1,266 deaths (~3 years)	Primary: Death from any cause (safety), risk of the first COPD exacerbation (efficacy), Secondary: The number of COPD exacerbations, time to the first moderate or severe exacerbation, time	Primary: For risk of death from any cause, tiotropium Respimat 5 µg was non-inferior compared to tiotropium HandiHaler (HR,0.96; 95% CI, 0.84 to 1.09); tiotropium Respimat 2.5 µg was also non-inferior to tiotropium HandiHaler (HR,1.00; 95% CI, 0.87 to 1.14). Death from any cause during the observation period (regardless of if the patient discontinued treatment or not) occurred in 7.7% of patients in the tiotropium Respimat 2.5 µg group, 7.4% in the tiotropium Respimat 5 µg group, and 7.7% in the tiotropium HandiHaler group. Similar results were observed in the as-treated analysis of fatal events of any cause (with 6.3%, 5.7%, and 6.3% of patients in the three groups, respectively). Causes of death were similar across the treatment groups, including death from cardiovascular causes (2.1%, 2.0%, and 1.8% for Respimat 2.5 µg,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HandiHaler inhaler QD			to and number of severe exacerbations, and the time to major adverse cardiovascular events.	Respimat 5 µg, and HandiHaler, respectively). For the risk of the first COPD exacerbation, tiotropium Respimat and tiotropium HandiHaler were not significantly different (HR, 0.98; 95% CI, 0.93 to 1.03; P=0.42). Secondary: The proportions of patients with a COPD exacerbation were 47.9% for the Respimat 5-µg group and 48.9% for the HandiHaler group (median times to the first COPD exacerbation, 756 days and 719 days, respectively).Rates of exacerbations, moderate/severe exacerbations, and severe exacerbations were similar in the three study groups. Relative differences in COPD exacerbations among the study groups across predefined subgroups were consistent. Serious adverse events were reported in 33% of the patients. The highest rates of serious adverse events were lung disorders in all three study groups (17.8%, 16.8%, and 17.0%, for tiotropium Respimat 2.5 and 5 µg and tiotropium HandiHaler, respectively). The overall incidence of major adverse cardiovascular events was 3.9%, 3.9%, and 3.6% in the tiotropium Respimat 2.5 and 5 µg and HandiHaler groups, respectively; the corresponding rates of cardiac arrhythmia were 2.3%, 2.1%, and 2.1%.
Singh et al[23] 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including myocardial infarction, stroke, or cardiovascular death			Secondary: Inhaled antimuscarinics did not significantly increased the risk of all-cause mortality (2.0 vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; P=0.06).
Lee et al[24] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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, 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.
Jones et al[25] 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 (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 (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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[26] (ACCORD COPD I) Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, PC, PG, RCT Patients ≥40 years of age diagnosed with moderate to severe stable COPD and a post-bronchodilator FVC <70% and FEV_1 ≥30% and <80% predicted and who were current or former smokers with a ≥10 pack-years history	N=561 12 Weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Change from baseline in peak FEV_1 at week 12, FEV_1 on day one, trough and peak FEV_1 at weeks one, four and eight, $AUC_{0-3/3h}$ FEV_1, trough, peak and $AUC_{0-3/3h}$ 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	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 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 $AUC_{0-3/3h}$ 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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.
D'Urzo et al (abstract)[27]	DB, ES, PC	N=291	Primary: Long-term safety	Primary: At study end, the percentages of patients who reported a treatment-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	Patients who completed 12 weeks of treatment in Kerwin et al[17] Patients continued the same treatment while patients previously receiving placebo were re-randomized (1:1) to aclidinium 200 µg or 400 µg BID	52 weeks	and tolerability of aclidinium treatment Secondary: Bronchodilation, health status, and rescue medication use	emergent adverse event were similar for both treatments (200 µg, 77.4%; 400 µg, 73.7%). The incidence of anticholinergic treatment-emergent adverse events was low and similar for both treatments, with dry mouth reported in only one patient (400 µg). Cardiac treatment-emergent adverse events were reported in a low percentage of patients (<5% for any event in any group) with no apparent dose dependence. Secondary: Improvements from baseline in lung function were greatest for patients who received continuous aclidinium treatment and those who were re-randomized from placebo to aclidinium 400 µg. These improvements were generally sustained throughout the study. Health status and overall rescue medication use was improved from baseline for both treatments.
Rennard et al[28] (ACCORD COPD II) Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo Albuterol was provided as rescue mediation. Theophylline, inhaled	DB, PC, PG, MC, RCT Patients ≥40 years of age diagnosed with moderate-to-severe stable COPD, post-bronchodilator FEV_1/FVC <70%, FEV_1 ≥30% and <80% predicted, and current or former smokers with a ≥10 pack-years history	N=544 12 weeks	Primary: Trough FEV_1 at week 12 Secondary: Peak FEV_1, trough and peak FEV_1 at day one (peak only) and at weeks 1, 4, 8 and 12, SGRQ scores at weeks 4, 8 and 12, TDI at week 12 and percent of patients who achieved MCID from baseline in SGRQ (≥4 units) or TDI (≥1	Primary: FEV_1 at week 12 were significantly greater for aclidinium 200 µg and 400 µg compared to placebo. LSM treatment differences over placebo were 51 mL (95% CI, 8 to 94) and 72 mL (95% CI, 29 to 115), respectively (both P<0.05). Secondary: Significantly larger changes from baseline in trough FEV_1 with both aclidinium doses compared to placebo were also observed at weeks one, four and eight (all P<0.01), with greater improvements observed with aclidinium 400µ compared to 200 µg. Aclidinium-treated patients showed significantly greater improvements over placebo from baseline in peak FEV_1 (week 12), FEV_1/FVC (week 12), peak FEV_1 (day one) and peak and trough FEV_1 at weeks 4, 8 and 12 (P<0.0001 for both doses and all endpoints).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
corticosteroids, and oral or parenteral corticosteroids were allowed.			unit)	Aclidinium 400 µg consistently provided greater numerical improvements in all lung function outcomes compared to aclidinium 200 µg throughout the study. SGRQ total scores improved from baseline with aclidinium at all study visits. After 12 weeks, a ≥4 unit improvement from baseline in mean SGRQ total scores was achieved with both aclidinium doses; however, no significant differences in SGRQ total scores between aclidinium and placebo were observed. The percentage of patients who achieved the MCID in SGRQ total scores at study end was higher with aclidinium 200 and 400 µg (47.2% and 44.8%, respectively) compared to placebo (38.8%); although, these differences were not significant based on odds ratios (P=0.077 and P=0.260, respectively). Breathlessness, measured by TDI focal scores, was significantly reduced with aclidinium 200 µg and 400 µg at week 12 (both P<0.05). At study end, there were higher percentages of patients who achieved the ≥1 unit clinically meaningful improvement in TDI focal scores in the aclidinium 200 µg (45.6%) and 400 µg (50.7%) groups compared with placebo (34.5%). Only aclidinium 400 µg provided a significant improved compared with placebo based on odds ratios (P=0.01). During the 12-week treatment period, subjects receiving aclidinium 200 µg and 400 µg used less rescue medication than those receiving placebo by 0.17 and 0.31 puffs/day, respectively; although, treatment differences were not statistically significant.
Ogale et al[29] Ipratropium exposure vs no ipratropium exposure	Cohort Veterans with a new diagnosis of COPD	N=82,717 6 years	Primary: Death or hospitalization from cardiovascular events during the period of interest (acute coronary syndrome, heart	Primary: Forty percent of the cohort received no COPD medication during the study. More than 44% were exposed to anticholinergics at some time during the study period. A total of 329,255 prescriptions were dispensed for anticholinergic agents. Only 78 were for tiotropium, while the remaining prescriptions were for ipratropium alone by metered-dose inhaler (55%) or nebulization (7%), or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			failure, or cardiac dysrhythmia) Secondary: Not reported	ipratropium in a fixed-dose combination with albuterol (38%). During the total follow-up period of 274,025 patient-years, there were 6,234 cardiovascular events, for a rate of 2.2 cardiovascular events per 100 patient-years. Nearly 75% of the patients followed had at least one cardiovascular risk factor at study entry. There were 6,234 cardiovascular events (44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia). Compared to subjects not exposed to ipratropium within the past year, any exposure to ipratropium within the past six months was associated with an increased risk of cardiovascular event: ≤4 and ≥4 30-day equivalents (HR, 1.40; 95% CI, 1.30 to 1.51 and HR, 1.23; 95% CI, 1.13 to 1.36, respectively). Overall, exposure to anticholinergics was associated with a 29% higher risk of cardiovascular events relative to no exposure in the past year. Among subjects who received anticholinergics more than six months prior, there did not appear to be an elevated risk of a cardiovascular event. Effect modification by the presence of cardiovascular disease at baseline was statistically significant (P=0.01). Secondary: Not reported
Casaburi et al[30] Tiotropium 18 µg via HandiHaler 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). 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[31] (UPLIFT) Tiotropium 18 µg via HandiHaler 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			any cause and from lower respiratory conditions	score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium (P<0.001). Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (P value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (P value not reported). During the four year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the four year study period plus 30 days included in the intent-to-treat analysis, 941 patients died; 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02).
Decramer et al[32] (UPLIFT) Tiotropium 18 µg via HandiHaler 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			any cause and from lower respiratory conditions	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[33] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo This was a subgroup analysis of patients in the UPLIFT trial who were not on other maintenance treatment at randomization.	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=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: After 30 days of treatment, pre-bronchodilator FEV_1 was significantly larger in the tiotropium group compared to the placebo group (P<0.0001). Trough FEV_1 remained significantly larger in the tiotropium group compared to 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≥0.81). Pre- and post-SVC was significantly higher in the tiotropium group (P≤0.046). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[34] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo This analysis is a more in depth look at the effect of tiotropium and its discontinuation on mortality and its causes.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 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 SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: See previous results by Tashkin et al[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. The most common causes of death included lower respiratory causes, cancer, general disorders, and cardiac disorders.
Singh et al[35] Tiotropium 5 to 10 via Respimat µg vs placebo	MA 5 RCT's of tiotropium solution using a mist inhaler (Respimat® Soft Mist Inhaler) vs placebo for COPD that evaluated mortality as an outcome and had a trial duration of more	N=6,522 Up to 52 weeks	Primary: Mortality from any cause Secondary: Deaths from cardiovascular causes (myocardial infarction, stroke, cardiac death,	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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	than 30 days		and sudden death)	
Celli et al[36] Tiotropium 18 µg via HandiHaler QD vs placebo	MA (30 trials) Patients ≥40 years of age with COPD and smoking history of ≥10 pack-years, and spirometric confirmation of airflow limitation including an FEV_1 ≤70% of FVC	N=19,545 ≥4 weeks	Primary: All-cause mortality and selected cardiovascular events (composite of cardiovascular deaths, nonfatal MI, nonfatal stroke, and the terms sudden death, sudden cardiac death, and cardiac death) Secondary: Not reported	Primary: For all-cause mortality, the incidence rate was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years (RR, 0.88; 95% CI, 0.77 to 0.999). The incidence rate for the cardiovascular endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR, 0.83; 95% CI 0.71 to 0.98). The incidence rate for cardiovascular mortality (excluding nonfatal MI and stroke) was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years (RR, 0.77; 95% CI 0.60 to 0.98). The RRs of total MI, cardiac failure, and stroke were 0.78 (95% CI, 0.59 to 1.02), 0.82 (95% CI, 0.69 to 0.98), and 1.03 (95% CI, 0.79 to 1.35), respectively. Secondary: Not reported
Halpin et al[37] Tiotropium 18 µg via HandiHaler QD vs placebo	Pooled analysis of 9 RCTs Patients ≥40 years of age with stable COPD, FEV_1 ≤65% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=6,171 ≥24 weeks	Primary: Proportion of patients with COPD exacerbation, proportion of patients with hospitalization due to COPD exacerbation, time to first COPD exacerbation, time to first hospitalization for exacerbation Secondary: Not reported	Primary: Tiotropium reduced the risk of COPD exacerbation by 21% compared to placebo (95% CI, 0.729 to 0.862; P<0.0001). Tiotropium reduced the risk of hospitalization associated with COPD exacerbation by 21% compared to placebo (95% CI, 0.65 to 0.96; P=0.015). The cumulative incidence rate of COPD exacerbation at 46 weeks was 42.1% for tiotropium compared to 50.8% for placebo (P<0.001). The cumulative incidence rate of hospitalizations associated with COPD exacerbation at 46 weeks was 8.5% for tiotropium compared to 10.8% for placebo (P=0.015). The protective effect of tiotropium was consistent regardless of age, gender, ICS use, and disease severity. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Kerstjens et al[38] Tiotropium 2.5 µg 2 inhalations QD via Respimat® inhaler vs placebo Individual pretrial maintenance therapy consisting of high dose glucocorticoids and LABAs was maintained throughout the study. Trial looked at two separate replicate trials (trial 1 and trial 2).	DB, PC, PG, RCT Patients 18 and 75 years of age and at least a 5 year history of asthma that was diagnosed before the age of 40 years, with a score of 1.5 on Asthma Control Questionnaire 7, FEV_1 ≤80% than predicted value and FVC ≤70% 30 minutes after inhalation of a short acting beta agonist, despite daily therapy with inhaled glucocorticoids and LABAs	N-912 48 weeks	Primary: Peak and trough FEV_1 at 24 weeks, time to first severe asthma exacerbation Secondary: Peak and trough FEV_1 at each treatment visit, AUC (for three hours after administration of study drug), time to first worsening of asthma, Asthma Control Questionnaire 7	Primary: At 24 weeks, the mean±SE change in peak FEV_1 was significantly greater in the tiotropium group compared to placebo in each trial with a difference of 86±34 mL in trial 1 (P=0.01) and 154±32 mL in trial 2 (P<0.001). The predose trough FEV_1 also significantly improved in each trial in the tiotropium group compared to placebo with a difference of 88±31 mL in trial 1 (P=0.01) and 111±30 mL in trial 2 (P<0.001), respectively. The average time to first severe asthma exacerbation was increased by 56 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 21% (HR, 0.79; P=0.03). Secondary: Improvements in peak FEV_1 were maintained over 48 weeks (P≤0.05 and P≤0.001 in trials 1 and 2, respectively). The mean difference in trough FEV_1 change from 24 to 48 weeks between tiotropium and placebo was 42 (95% CI, -21 to 104) and 92 (95% CI, 32 to 151) in trials 1 and 2, respectively. The median time to first worsening of asthma was increased by 134 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 31% (HR, 0.69; P<0.001). A minimally important difference for the Asthma Control Questionnaire 7 was not achieved in either trial.
Canto et al[39] Tiotropium 18 µg QD via HandiHaler® vs placebo All patients were receiving formoterol 12 µg BID.	DB, PC, PRO, RCT, XO Patients with stable COPD (defined by GOLD) with a long history of smoking (>20 pack-years); patients were randomized to each treatment group for a 2 week treatment	N=38 5 weeks	Primary: Pulmonary function tests (FEV_1, FVC, IC, EELV), inspiratory muscle strength, constant work exercise test Secondary: Not reported	Primary: Treatment with formoterol and tiotropium resulted in a greater numeric improvement in FEV_1 (1.07±0.25 to 1.25±0.32) compared to treatment with formoterol and placebo (1.09±0.21 to 1.21±0.29), although both groups achieved a statistically significant improvement (P<0.05). Similarly, patients treated with formoterol and tiotropium achieved a numerically greater increase in FVC (2.51±0.57 to 2.75±0.91) compared to patients treatment with formoterol and placebo (2.55±0.66 to 2.66±0.98), although a statistically significant improvement was observed in both groups (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	period, followed by a 7 day washout period and then patients XO for a second 2 week period of the alternative regimen			The increase in IC was greater in the formoterol and tiotropium group (1.68±0.41 to 2.16±0.77) compared to the formoterol and placebo group (1.66±0.45 to 2.02±0.49), although both groups achieved a statistically significant improvement (P<0.05). Patients treated with formoterol and tiotropium achieved a greater numeric improvement in EELV (4.35±0.77 to 3.98±0.67) compared to patients treated with formoterol and placebo (4.34±0.59 to 3.85±0.77), although both groups achieved a statistically significant improvement (P<0.05). Treatment with formoterol and tiotropium resulted in a statistically significant improvement in the maximal inspiratory pressure at rest, immediately after exercise and during recovery, while formoterol and placebo improved the maximal inspiratory pressure only at the 10 minute time point during recovery. Treatment with formoterol and tiotropium resulted in significantly larger increments in the maximal inspiratory pressure at all points of comparison. The time to the limit of tolerance was improved following two weeks of intervention in both groups, however, treatment with formoterol and tiotropium resulted in a greater increase compared to treatment with formoterol and placebo (40.7±7.6% vs 84.5±8.2%; P<0.05). Secondary: Not reported
Trivedi et al[40] Umeclidinium 62.5 µg vs umeclidinium 125 µg vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, ≥10 pack-years smoking history, a post-albuterol FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the	N=206 12 weeks	Primary: Trough FEV_1 on treatment day 85 Secondary: Weighted mean FEV_1 over 0 to 6 hours post-dose at days 1, 28, 84; serial FEV_1 days 1 and 84; TDI score;	Primary: Compared to placebo, there were significant improvements in LSM change from baseline at day 85 in trough FEV_1 in the 62.5 µg (127 mL; 95% CI, 52 to 202; P<0.001) and 125 µg (152 mL; 95% CI, 76 to 229; P<0.001) groups. Secondary: Compared to placebo, there were significant improvements in LSM change from baseline in weighted mean FEV_1 over 0 to 6 hours post-dose at days 1 (125 mL; 95% CI, 83 to 166 and 147 mL), 28 (165 mL; 95% CI, 105 to 224 and 196 mL; 95% CI 135 to 256) and 84 (166 mL; 95% CI, 94 to 239 and 191 mL; 95% CI, 117 to 265) in the 62.5 µg and 125 µg groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	MRCDS		proportion of responders based on TDI score improvement; trough FVC; serial FVC, weighted mean FVC, time to onset; rescue albuterol use; SGRQ score	There were significant improvements in serial FEV_1 days 1 and 84 in both treatment groups compared to placebo (P≤0.003). Compared to placebo, there were significant improvements in LSM change from baseline at day 85 in trough FVC in the 62.5 µg (193 mL; 95% CI, 74 to 313; P=0.002) and 125 µg (236 mL; 95% CI, 114 to 358; P<0.001) groups. Compared to placebo, there were significant improvements in LSM change from baseline in weighted mean FVC over 0 to 6 hours post-dose at day 84 in the 62.5 µg (243 mL; 95% CI, 123 to 363; P<0.001) and 125 µg (318 mL; 95% CI, 196 to 439) groups. Fifty-nine percent of patients in the 62.5 µg group and 64% in the 125 µg group had an onset (100 mL increase from baseline in FEV_1) at 1 hour. In the placebo group, 66% of patients did not reach an increase of ≥100 mL from baseline. At day 84, there were significant improvements in LSM TDI score in the 62.5 µg (1.0; 95% CI, 0.0 to 2.0; P=0.05) and 125 µg (1.3; 95% CI, 0.3 to 2.3; P< 0.05) groups compared to placebo. At day 84, there were significantly greater proportion of responders in the 62.5 µg (OR, 3.4; 95% CI, 1.3 to 8.4; P=0.009) and 125 µg (OR, 3.4; 95% CI, 1.4 to 8.6; P=0.009) compared to placebo. Compared to placebo, there was a significant difference in albuterol rescue use in the 62.5 µg group (mean -0.7 puffs per day; 95% CI, -1.3 to -0.1; P=0.025) but not the 125 µg group (mean -0.6 puffs per day; 95% CI, -1.2 to -0.0; P=0.069). On day 84, there were significant differences in the SGRQ score in the 62.5 µg (-7.90; 95% CI, -12.20 to -3.60; P<0.001) and 125 µg (-10.87; 95% CI, -15.25 to -6.49; P<0.001) compared to placebo. The adverse effects were similar across all groups. The most frequent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				medication related effects were dry throat, dyspnea and cough.
Beier et al (abstract)[41] Aclidinium 400 µg BID vs tiotropium 18 µg via HandiHaler QD vs placebo	AC, DB, MC, PC, RCT Patients with moderate-to-severe COPD	N=414 6 weeks	Primary: Mean change from baseline in FEV_1 $AUC_{0–24}$ at six weeks Secondary: Change from baseline in FEV_1 $AUC_{12–24}$, COPD symptom total score and, additional symptoms questionnaire and safety	Primary: Compared to placebo, there was a significant change from baseline in FEV_1 $AUC_{0–24}$ at six weeks with aclidinium (150 mL; P<0.0001) and tiotropium (140 mL; P<0.0001). Secondary: The change from baseline in FEV_1 $AUC_{12–24}$ at six weeks was significantly greater with aclidinium (160 mL; P<0.0001) and tiotropium (123 mL; P<0.0001) compared to placebo. Significant improvements in total symptom scores over six weeks were numerically greater with aclidinium (P<0.0001) than tiotropium (P<0.05) compared to placebo. Only aclidinium significantly reduced the severity of early-morning cough, wheeze, shortness of breath, and phlegm, and of nighttime symptoms compared to placebo (P<0.05). The incidence of adverse events was similar between treatments. Few anticholinergic adverse events (<1.5%) or serious events (<3%) occurred in any group.
Van Noord et al[42] Tiotropium 18 µg via HandiHaler 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[43] Tiotropium 18 µg via HandiHaler QD vs ipratropium 40 µg QID	DB, DD, MC, PG, RCT Patients with COPD ≥40 years of age with an FEV_1 ≤65% of predicted normal value and ≤70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	Primary: By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared 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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; P=0.004). During the one-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30±1.13 on day 364; P<0.05). Quality of life, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last two test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.
Niewoehner et al[44] Tiotropium 18 µg via HandiHaler QD vs ipratropium and albuterol MDI QID (fixed-dose combination product) Concomitant medications allowed throughout the trial included ICSs, theophylline, and stable doses of prednisone (not to exceed 10 mg daily or	Pooled analysis of 2 RCTs Patients ≥40 years of age with COPD, current or former cigarette smoker with lifetime consumption of ≥10 pack-years, postbronchodilator FEV_1 ≤70% of predicted, pre bronchodilator FEV_1 ≤65% of predicted, and FEV1/FVC ≤70% who were receiving ipratropium and albuterol (18 to 103 µg) MDI for	N=676 12 weeks	Primary: Trough FEV_1, FEV_1 $AUC_{0–6}$, and FVC Secondary: PEF, albuterol rescue therapy, total albuterol use, and patient global evaluations	Primary: Mean change in trough FEV_1 was significantly larger in the tiotropium group compared to the ipratropium and albuterol group (difference, 86 mL; 95% CI, 49 to 133 mL; P<0.0001). Mean FEV_1 $AUC_{0–6}$ in the tiotropium arm was statistically non-inferior to the ipratropium and albuterol arm (difference, 17 mL; 95% CI, -21 to 56 mL; P=0.0003), but not statistically superior (P=0.37). Mean peak FEV_1 responses were larger in the ipratropium/albuterol arm compared to the tiotropium arm, with differences ranging from 120 to 134 mL (P<0.001). Differences in FVC responses were similar to those observed with the FEV_1. Mean FVC trough for the tiotropium group was significantly larger on study days 42 and 84 (P<0.01) compared to the ipratropium and albuterol group, but the $AUC_{0–6}$ was not (P>0.5). Secondary: Weekly mean morning PEF and FEV_1 were both significantly larger in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
its equivalent).	≥1 month			tiotropium arm compared to the ipratropium and albuterol arm for morning measurements (P<0.05), but not for evening measurements. No significant treatment-related differences were detected in albuterol rescue therapy, physician global evaluations, or patient reported shortness of breath. Total albuterol use was significantly lower in the tiotropium group compared to the ipratropium/albuterol group (5.3 vs 6.8 puffs per day based on weekly means; P<0.001). Mean patient global evaluations were statistically significantly better (P<0.05) for the tiotropium group on study day 42, but not on study day 84.
Ikeda et al[45] 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	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Bone et al[46] Albuterol 100 µg QID via MDI vs ipratropium 21 µg QID via MDI vs ipratropium/albuterol 21/100 µg QID via MDI	DB, MC, PG, PRO, RCT 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	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score and safety Secondary: Not reported	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (P<0.001 to P=0.015). There was no difference in symptom score between the groups (P value not reported). Compared 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[47] 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Friedman et al[48] 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 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%	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC_{0-4h}, total health care expenditures and cost effectiveness ratios Secondary: Not reported	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). 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≤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[49] Ipratropium/albuterol solution for nebulization QID vs ipratropium/albuterol 2 inhalations QID via MDI vs ipratropium/albuterol	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	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),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
solution for nebulization administered in the morning and ipratropium/albuterol MDI administered in the afternoon and evening			measures (vital signs, changes in physical findings, and investigator reported disease exacerbations)	however results were not statistically significant (P value not reported). At week 12 only the concomitant therapy group approached a clinically significant improvement in total score (-3.5±2.64). Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the symptom sub-score (P=0.0186 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The differences in adverse events were not discussed.
Zuwallack et al[50] 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.	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack-years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium/ albuterol via Respimat® inhaler vs aerosol MDI and ipratropium/ albuterol via Respimat® inhaler vs ipratropium via 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	Primary: On day 85, ipratropium/albuterol Respimat® inhaler was NI to ipratropium/albuterol aerosol MDI at zero to six hours, and was "superior" to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium/albuterol Respimat® inhaler was 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event was lower with ipratropium/albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower 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.
Yohannes et al[51] Tiotropium via HandiHaler vs ipratropium vs LABA (salmeterol or formoterol)	MA 16 RCTs 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(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; 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
Singh et al[52] Aclidinium 100 µg BID vs aclidinium 200 µg BID vs	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	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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aclidinium 400 µg BID vs formoterol 12 µg BID vs placebo	FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history		$AUC_{12–24}$, 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, morning peak FEV_1 on day one and seven, morning trough FVC on day seven, use of relief medication after seven days and safety	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 $AUC_{0–24}$. 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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.
McCrory et al [53] 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
Matera et al[54] Ipratropium 40 µg plus placebo	RCT, SB, XO Male patients ≥40 years of age with COPD and an FEV_1	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in FEV_1	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 50 µg plus placebo vs ipratropium 40 µg plus salmeterol 50 µg vs placebo plus placebo	between 16 and 62% of predicted value		AUC	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[55] Salmeterol 50 µg plus ipratropium matched placebo vs ipratropium 40 µg plus salmeterol 50 µg vs salmeterol-matched placebo plus ipratropium-matched placebo	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: 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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).
Wang et al[56] Tiotropium via HandiHaler and formoterol vs	MA 8 RCT's of patients diagnosed with COPD who had stable disease who were being treated with	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	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;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tiotropium	tiotropium and/or formoterol		TDI scores Secondary: Not reported	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[57] Tiotropium via HandiHaler vs placebo, or ipratropium, or a LABA	MA 9 RCT's with patients diagnosed with COPD, whose disease was stable	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations and mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use and adverse events	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Donohue et al[58] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg via HandiHaler 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≤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 all assessments with both doses of indacaterol and after four, 12 and 16

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.				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[59] INTIME Indacaterol 150 µg QD	DB, DD, PC, RCT, XO Patients ≥40 years of age with moderate to severe COPD,	N=169 12 weeks	Primary: Trough FEV_1 at 14 days Secondary:	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; P<0.001).

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 via HandiHaler 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	smoking history ≥10 pack years, post-bronchodilator FEV_1 30 to <80% predicted and FEV_1/FVC <70%		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	Secondary: Patients receiving indacaterol 150 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
needed.				
Buhl et al[60] INTENSITY Indacaterol 150 µg QD vs tiotropium 18 µg via HandiHaler 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 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be 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).

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).
Vogelmeier et al[61] Salmeterol 50 µg BID vs tiotropium 18 µg via HandiHaler QD Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the DB treatment phase.	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 with systemic glucocorticoids or antibiotics or hospitalization within the previous year	N=7,384 1 year	Primary: Time to the first exacerbation of COPD Secondary: Time-to-event end points, number-of-event end points, serious adverse events, and death	Primary: Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; P<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore, it was not possible to calculate the median time to first exacerbation in this population. Secondary: Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; P<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; P<0.001). Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; P<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; P<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[62] Tiotropium 18 µg via HandiHaler 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). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[63] Tiotropium 18 µg via HandiHaler 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). 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[64] Tiotropium 18 µg via HandiHaler QD vs	OL, RCT, XO Patients ≥40 years of age with COPD and stable airway obstruction with post-bronchodilator	N=78 4 months (2 months/ treatment arm)	Primary: Post-bronchodilator FVC and FEV_1 Secondary: HRQoL 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone 200 µg and salmeterol 50 µg BID	FEV_1/FVC <70%, predicted FEV_1 30 to 80%, and smoking history of >10 pack-years			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[65] Tiotropium 18 µg via HandiHaler QD plus placebo vs tiotropium 18 µg via HandiHaler QD plus salmeterol 50 µg BID vs tiotropium 18 µg via HandiHaler 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 visits to a health care practitioner or emergency room, number of hospitalizations for COPD, total number of hospitalizations for all causes, changes in HRQoL, dyspnea and lung function	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. 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[66] Tiotropium 18 µg via HandiHaler QD plus formoterol 12 µg BID vs fluticasone 500 µg BID plus salmeterol 50 µg BID	DB, MC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC <70% at visit 1, and predose FEV_1 ≤65% predicted at visit two	N=605 6 weeks	Primary: FEV_1 $AUC_{0-12,}$ peak FEV_1 Secondary: Morning predose FEV_1	Primary: After six weeks, the FEV_1 AUC_{0-12} mean difference was 78 mL higher (95% CI, 34 to 122) with treatment with tiotropium plus formoterol compared to treatment with fluticasone plus salmeterol (P=0.0006). The difference in peak FEV_1 was 103 mL (95% CI, 55 to 150) in favor of tiotropium plus formoterol (P<0.0001). Secondary: The difference in predose FVC after six weeks favored tiotropium plus formoterol (95% CI, 11 to 147; P<0.05).
Decramer et al[67] (abstract) Tiotropium via HandiHaler 18 µg	AC, DB, MC, PG Patients ≥40 years of age with COPD and current or former	N=843 (study 1) N=869 (study 2)	Primary: Trough FEV_1 on day 169 Secondary:	Primary: At day 169, there were significant improvements in the umeclidinium/ vilanterol 125/25 µg and 62.5/25 µg groups compared to the tiotropium group in study 1 (0.088 L (95% CI, 0.036 to 0.140; P=0.0010 and 0.090 (95% CI, 0.039 to 0.141; P=0.0006), respectively. Improvements were also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(study 1 and 2) vs umeclidinium 125 µg (study 2) vs vilanterol 25 µg (study 1) vs umeclidinium/ vilanterol 125/25 µg (study 1 and 2) vs umeclidinium/ vilanterol 62.5/25 µg (study 1 and 2)	smokers	24 weeks	Not reported	significant in study 2 in the umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups compared to the tiotropium group (0.074 L (95% CI, 0.025 to 0.123; P=0.0031 and 0.060 (95% CI, 0.010 to 0.109; P=0.0182), respectively. Compared to vilanterol monotherapy, umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups had significant improvements in trough FEV_1 on day 169 (0.088 L; 95% CI, 0.036 to 0.140; P=0.0010 and 0.090 L; 95% CI, 0.039 to 0.142; P=0.0006, respectively. There were no significant improvements in the umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups when compared to umeclidinium monotherapy (0.037 L; 95% CI, -0.012 to 0.087; P=0.14 and 0.022 L; 95% CI, -0.027 to 0.072; P=0.38, respectively). Secondary: Not reported
Karner et al[68] Tiotropium via HandiHaler and ICS/LABA vs tiotropium via HandiHaler vs	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ICS/LABA				(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). 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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.92; 95% CI, 0.46 to 1.83).
Puhan et al[69] Tiotropium via HandiHaler vs LABA monotherapy vs ICS monotherapy vs ICS and LABA combination therapy	MA (35 trials) Patients with stable COPD	N=26,786 ≥4 weeks	Primary: Comparison of treatments by reported COPD exacerbations Secondary: Comparison of treatments by reported COPD exacerbations in patients with FEV_1 ≤40% or FEV_1 >40% predicted	Primary: All regimens significantly reduced exacerbations compared to placebo: tiotropium (OR, 0.41; 95% CI, 0.64 to 0.80), ICS (OR, 0.78; 95% CI, 0.70 to 0.86), LABA (OR, 0.77; 95% CI, 0.64 to 0.84), and ICS and LABA (OR, 0.72; 95% CI, 0.64 to 0.80). Neither tiotropium nor combination therapy reduced exacerbations more than LABA monotherapy (OR, 1.02; 95% CI, 0.90 to 1.16 and OR, 0.93; 95% CI, 0.84 to 1.04, respectively). Combined treatment was not more effective than LABA or tiotropium monotherapy (OR, 0.93; 95% CI, 0.84 to 1.04 and OR, 1.02; 95% CI, 0.90 to 1.16, respectively) Secondary: In patients with FEV_1 ≤40% predicted, tiotropium, ICS, and ICS and LABA significantly reduced exacerbations compared to LABA monotherapy (OR, 0.83; 95% CI, 0.71 to 0.98; OR, 0.75; 95% CI, 0.57 to 1.00, and OR, 0.79; 95% CI, 0.67 to 0.93, respectively). In patients with FEV_1 >40% predicted, there was no difference in COPD exacerbations between treatments.
Dong et al[70] Tiotropium via HandiHaler vs LABA vs ICS	MA (42 trials) Patients with COPD	N=52,516 ≥6 months	Primary: Mortality Secondary: Not reported	Primary: Results indicated that tiotropium Soft Mist Inhaler® was associated with an increased risk of overall death compared to placebo (OR, 1.51; 95% CI, 1.06 to 2.19), tiotropium HandiHaler® (OR, 1.65; 95% CI, 1.13 to 2.43), LABA (OR, 1.63; 95% CI, 1.10 to 2.44), and LABA and ICS combination therapy (OR, 1.90; 95% CI, 1.28 to 2.86). The risk with tiotropium Soft Mist Inhaler® was more evident for cardiovascular death, severe COPD, and at higher daily doses. Among all treatments LABA and ICS combination therapy was associated with the lowest risk of death, while no excess risk was noted for tiotropium HandiHaler® or LABA therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs LABA and ICS combination therapy vs placebo				Secondary: Not reported
Rodrigo et al[71] Tiotropium via HandiHaler vs placebo, LABA, or ICS and LABA	MA (19 trials) Patients >35 years of age with stable COPD	N=18,111 ≥4weeks	Primary: Major cardiovascular events (composite of nonfatal MI, stroke, and cardiovascular death), cardiovascular mortality (includes sudden death), nonfatal MI, and nonfatal stroke (includes transient ischemic attack) Secondary: All-cause mortality	Primary: There was no difference in the incidence of major cardiovascular events among the treatment groups (RR, 0.96; 95% CI, 0.82 to 1.12). There was no difference in cardiovascular deaths among the treatment groups (RR, 0.93; 95% CI, 0.73 to 1.20). There was no difference in nonfatal MI among the treatment groups (RR, 0.84; 95% CI, 0.6 to 1.09). There was no difference in nonfatal stroke among the treatment groups (RR, 1.04; 95% CI, 0.78 to 1.39). Secondary: Tiotropium did not significantly increase the risk of all-cause mortality (RR, 0.97; 95% CI, 0.86 to 1.09).
Baker et al[72] Tiotropium via HandiHaler vs ICS vs	MA (43 trials) Patients with COPD	N=31,020 4 to 60 weeks	Primary: COPD exacerbations, all-cause mortality Secondary: Withdrawal from trial based on drug class	Primary: LABAs, tiotropium, ICSs, and combination ICS and LABA therapy each decreased the odds of having an exacerbation by 16, 31, 15, and 24%, respectively, compared to placebo. Tiotropium reduced the odds of having at least one exacerbation by 18% compared to LABAs and by 19% compared to ICSs alone. Compared to combination therapy, tiotropium reduced exacerbations by 9%. Only combination therapy was associated with a mortality benefit, showing a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LABAs vs combination therapy				29% reduction compared to placebo and a 25% reduction compared to LABAs alone. Compared to combination therapy, tiotropium use non-significantly increased mortality by 4%. Secondary: Each of the four drug classes was associated with a significant reduction in withdrawals (26 to 41%) compared to placebo. Both tiotropium and combination therapy significantly reduced patient withdrawals compared to LABAs or ICSs alone.
Lee et al[73] Tiotropium (via HandiHaler)-containing regimens vs non-tiotropium combination regimens	Cohort Veterans ≥45 years of age with COPD who were switched to regimens containing tiotropium	N=42,090 Death, no prescription refill for 180 days, or 547 days from index date, whichever occurred first	Primary: Difference in all-cause mortality, COPD exacerbations, COPD hospitalizations Secondary: Not reported	Primary: Treatment with tiotropium+ICS+LABA was associated with a 40% reduction in death compared to ICS+LABA (95% CI, 0.45 to 0.79). Treatment with tiotropium+ICS+LABA was associated with a 16% reduction of COPD exacerbations compared to other regimens (95% CI, 0.73 to 0.97). There was no significant difference in exacerbations with tiotropium+ICS+LABA compared to ICS+LABA (HR, 1.03; 95% CI, 0.88 to 1.21). Treatment with tiotropium+ICS+LABA was associated with a 22% reduction of COPD hospitalizations compared to other regimens (95% CI 0.62 to 0.98). There was no significant difference in hospitalizations with tiotropium+ICS+LABA compared to ICS+LABA (HR, 1.15; 95% CI, 0.90 to 1.46). Other three drug combination regimens that included tiotropium and the four drug combination regimens that included tiotropium+ICS+LABA+ ipratropium were associated with increased mortality risk (HR, 1.38; 95% CI, 1.06 to 1.81 and HR, 1.36; 95% CI, 1.05 to 1.76, respectively). Secondary: Not reported
Celli et al[74] Umeclidinium/	DB, MC, PC, PG, RCT Patients ≥40 years of	N=1,489 (3:3:3:2)	Primary: Pre-dose trough FEV_1 on treatment	Primary: Significant improvements in mean change from baseline in trough FEV_1 at day 169 were seen in the umeclidinium/vilanterol (0.238 L; P<0.001),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vilanterol 125/25 µg QD vs umeclidinium 125 µg QD vs vilanterol 25 µg QD vs placebo	age with a diagnosis of COPD, ≥10 pack-years smoking history, a post-albuterol FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the MRCDS	24 weeks	day 169 Secondary: FEV_1 over 0 to six hours post-dose at day 168, TDI score, lung function changes (time to onset of response during 0 to six hours post-dose on day 1, proportion of patients achieving increased FEV_1 ≥12% and ≥0.200 L above baseline at any time during 0 to six hours post-dose on day 1, proportion of patients achieving increase of ≥0.100 L above baseline in trough FEV_1, peak FEV_1, serial FEV_1, and serial and trough FVC) and changes in symptom measures (weekly SOBDA score, rescue albuterol use, HRQoL, time to first exacerbations)	umeclidinium (0.160 L; P<0.001) and vilanterol (0.124 L; P<0.001) groups compared to placebo. In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.079 L; P<0.001 and 0.114 L; P<0.001 respectively). Secondary: There were significantly greater increases in the 0 to six hour weighted mean FEV_1 at day 168 compared to placebo for umeclidinium/vilanterol (0.287 L; P<0.001), umeclidinium (0.178 L; P<0.001) and vilanterol (0.145 L; P<0.001). When compared to umeclidinium and vilanterol monotherapy, the umeclidinium/vilanterol group had significantly greater improvements in the 0 to six hour weighted mean FEV_1 at day 168 (0.109 L; P<0.001 and 0.142 L; P<0.001, respectively). All other lung function outcomes demonstrated significantly greater improvements with umeclidinium/vilanterol compared to placebo and monotherapy (P<0.001 for all). There was significant improvements in TDI score at day 168 in the umeclidinium/vilanterol group compared to placebo (P<0.001) and compared to umeclidinium and vilanterol monotherapy (P<0.01 and P<0.05, respectively). There were significant decreases in albuterol use in the umeclidinium/vilanterol group compared to placebo and monotherapy (P<0.001 for all). Compared to placebo, all treatment groups had a significantly lower risk of COPD exacerbation (P≤0.006 for all). There were significant improvements in all other symptom measures in the umeclidinium/vilanterol group compared to placebo (P≤0.05).
Donahue et al[75] Umeclidinium/ vilanterol 62.5/25 µg	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis	N=1,532 (3:3:3:2) 24 weeks	Primary: Pre-dose trough FEV_1 on treatment day 169	Primary: Significant improvements in mean change from baseline in trough FEV_1 at day 169 were seen in the umeclidinium/vilanterol (0.167 L; P<0.001), umeclidinium (0.115 L; P<0.001) and vilanterol (0.072 L; P<0.001) groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD vs umeclidinium 62.5 µg vs vilanterol 25 µg vs placebo	of COPD, ≥10 pack-years smoking history, a post-albuterol FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the MRCDS		Secondary: FEV_1 over 0 to six hours post-dose at day 168, lung function changes (time to onset of response during 0 to six hours post-dose on day 1, proportion of patients achieving increased FEV_1 ≥12% and ≥0.200 L above baseline at any time during 0 to six hours post-dose on day 1, proportion of patients achieving increase of ≥0.100 L above baseline in trough FEV_1, peak FEV_1, serial FEV_1, and serial and trough FVC) and changes in symptom measures (TDI focal score, weekly SOBDA score, rescue albuterol use, HRQoL, time to first exacerbations)	compared to placebo. In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively). Secondary: There were significantly greater increases in the 0 to six hour weighted mean FEV_1 at day 168 compared to placebo for umeclidinium/vilanterol (0.242 L; P<0.001), umeclidinium (0.150 L; P<0.001) and vilanterol (0.122 L; P<0.001). When compared to umeclidinium and vilanterol monotherapy, the umeclidinium/vilanterol group had significantly greater improvements in the 0 to six hour weighted mean FEV_1 at day 168 (0.092 L; P<0.001 and 0.120 L; P<0.001, respectively). Compared to placebo at day 169, there were significant greater improvements in trough FVC in all treatment groups (0.248 L for umeclidinium/vilanterol, 0.175 L for umeclidinium and 0.105 L for vilanterol P≤0.002 for all). There were significantly greater improvements in the umeclidinium/vilanterol group compared to the umeclidinium and vilanterol monotherapy groups (0.074 L; P=0.012 and 0.143L; P<0.001). At day 168, there were significantly greater increases in TDI focal score in the umeclidinium/vilanterol (2.4; P≤0.001), umeclidinium (2.2; P≤0.001) and vilanterol (2.1; P≤0.001) groups compared to placebo (1.2). There were no significant differences in combination therapy compared to monotherapy. At week 24, there were significantly greater improvements in SOBDA score in the umeclidinium/vilanterol (-0.23; P≤0.001), umeclidinium (-0.16; P<0.05) and vilanterol (-0.21; P≤0.01) groups compared to placebo (-0.06). There were no significant differences in combination therapy compared to monotherapy. Over the 24 week period when compared to placebo (-1.4), there were significantly less albuterol use in the umeclidinium/vilanterol (-2.3; P≤0.001) and vilanterol (-2.4; P≤0.001) groups, but not in the umeclidinium group (-1.7; P value not reported). When combination therapy was compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				monotherapy, there were significant differences between the umeclidinium/vilanterol and umeclidinium groups (P<0.05), but not the umeclidinium/vilanterol and umeclidinium groups (P value not reported). Compared to placebo, there was a lower risk of COPD exacerbations in the umeclidinium/vilanterol and umeclidinium groups (HR, 0.5; P≤0.01 and HR, 0.6; P<0.05, respectively).
Kew et al[76] LABAs (formoterol, indacaterol, salmeterol) vs LAMAs (aclidinium, glycopyrronium, tiotropium) vs ICSs (budesonide, fluticasone, mometasone) vs placebo	MA (71 RCTs) Patients with COPD	N=73,062 ≥ 6 months	Primary: Change from baseline in SGRQ, trough FEV_1 Secondary: Not reported	Primary: At six months, LABA/ICS combination was the highest ranked treatment for change in baseline in SGRQ with a mean improvement of -3.89 compared to placebo (95% CI, -4.70 to -2.97). LAMAs, LABAs and ICSs were ranked second (-2.63; 95% CI, -3.53 to -1.97), third (-2.29; 95% CI, -3.18 to -1.53) and fourth (-2.0; 95% CI, -3.06 to -0.87). At 12 months, LABA/ICS combination was the highest ranked treatment with a mean improvement compared to placebo of -3.60 (95% CI, -4.63 to -2.34). The other treatments were similar at month 12 with improvements compared to placebo between -2.34 and -2.55. At six months, LABA/ICS combination was the highest ranked treatment for trough FEV_1 with a mean improvement of 133.3 mL compared to placebo (95% CI, 100.6 to 164.0). LAMAs, LABAs and ICSs were ranked second (103.5 mL; 95% CI, 81.8 to 124.9), third (99.4 mL; 95% CI, 72.0 to 127.8) and fourth (65.4 mL; 95% CI, 33.1 to 96.9). At 12 months, LABA/ICS combination was the highest ranked treatment with a mean improvement compared to placebo of -100 mL (95% CI, 55.5 to 140.1). The other treatments were similar at month 12. Secondary: Not reported
NCT01709864‡ and NCT01715298‡ [5,77,78] GEM1 and GEM2 Glycopyrrolate 15.6 µg BID	DB, MC, PC, PG, RCT Patients aged ≥ 40 years with stable but symptomatic moderate to severe COPD according to	N=867 12 weeks	Primary: Change from baseline in FEV_1 $AUC_{0\ to\ 12h}$ following the morning dose at day 85 compared with placebo	Primary: In both trials, the glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0\ to\ 12\ h}$ compared to placebo. In GEM1, the change from baseline LS mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (Treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P values not reported). For GEM2, the change from baseline LS mean was 0.115 L in the glycopyrrolate group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	the 2011 GOLD Guidelines, with airflow limitation of ≥ 30% and < 80% of the predicted normal (FEV_1), post-bronchodilator $FEV_1/FVC < 0.70$, current or ex-smokers who had a smoking history of ≥ ten pack years and an mMRC grade ≥ 2		Secondary: Change from baseline in the health status assessed by SGRQ, change from baseline in the percentage of days without rescue medication use, change from baseline in percentage of days able to perform usual daily activities	compared to -0.008 L in the placebo group (Treatment difference LS Mean, 0.123 L; 95% CI, 0.081 to 0.165; P values not reported). Secondary: The SGRQ responder rate (defined as an improvement in score of ≥ 4) was 49% for the glycopyrrolate group compared to 41% for the placebo group in GEM1 (OR: 1.43, 95% CI, 0.95 to 2.15, P values not reported). In GEM2, the SGRQ responder rate was 55% for the glycopyrrolate group compared to 42% for the placebo group (OR, 1.78; 95% CI, 1.17 to 2.71; P values not reported). It was noted that patients in GEM1 and GEM2 treated with glycopyrrolate, received less daily rescue albuterol during the trial compared to patients treated with placebo. In GEM1, the percentage of days without rescue medication use was LS Mean 16.6 for the glycopyrrolate group versus 10.5 for placebo. In GEM2, the percentage of days without rescue medication use was LS Mean 11.4 for the glycopyrrolate group versus 7.0 for placebo (P values not reported). The change from baseline in percentage of days able to perform usual daily activities was reported as LS mean 8.6 for the glycopyrrolate group compared to 1.8 for placebo in GEM1. In GEM2, change from baseline in percentage of days able to perform usual daily activities was reported as LS mean 5.2 for the glycopyrrolate group compared to 0.9 for placebo (P values not reported). Adverse events were comparable for the glycopyrrolate and placebo groups.
Mahler et al[79] FLIGHT1 and FLIGHT2 Indacaterol/glycopyrrolate 27.5/15.6 µg BID vs	AC, DB, MC, PC, PG, RCT Patients aged ≥ 40 years with stable but symptomatic moderate to severe COPD according to the 2011 GOLD	N=2,038 12 weeks	Primary: FEV_1 $AUC_{0\ to\ 12h}$ at week 12 for indacaterol/ glycopyrrolate compared to its monotherapy components	Primary: At week 12, indacaterol/glycopyrrolate was found to have a statistically greater response than placebo in terms of FEV_1 $AUC_{0\text{-}12h}$ compared to its respective monotherapy components in the pooled analysis (treatment difference, 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively; P<0.001 for both). Secondary: Indacaterol/glycopyrrolate treatment also had a statistically greater response

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
indacaterol 27.5 µg BID vs glycopyrrolate 15.6 µg BID vs placebo	Guidelines, with airflow limitation of ≥ 30% and < 80% of the predicted normal (FEV_1), post-bronchodilator $FEV_1/FVC < 0.70$, current or ex-smokers who had a smoking history of ≥ ten pack years and an mMRC grade ≥ 2		Secondary: Changes from baseline in the SGRQ total score (indacaterol/ glycopyrrolate vs placebo) and the percentage of responders at 12 weeks; FEV_1 ($AUC_{0 \text{ to } 12h}$), FEV_1, TDI total score, daily rescue medication use and daily symptoms as reported by patients in their e-diary at week 12 for indacaterol/ glycopyrrolate compared to placebo	than placebo for FEV_1 AUC $_{0\text{-}12h}$ (treatment difference, 246 mL, P<0.001). In addition, both indacaterol and glycopyrrolate treatment had statistically greater responses than placebo at week 12 in terms of FEV_1 AUC $_{0\text{-}12h}$ (treatment differences, 143 mL and 158 mL, respectively; P<0.001 for both). At week 12, patients in the indacaterol/glycopyrrolate group had a statistically and clinically significant improvement in their HRQoL as demonstrated by the SGRQ total score compared with placebo (5.0 unit improvement; P<0.001). SGRQ total score showed a significant reduction with indacaterol/glycopyrrolate when compared with indacaterol (P=0.019) and glycopyrrolate (P=0.033). The proportion of patients in the indacaterol/glycopyrrolate group who achieved the MCID of −4 units was significantly higher than those in the placebo (OR, 2.5; P<0.001), indacaterol (OR, 1.3; P=0.041), and glycopyrrolate (OR, 1.5; P=0.003) groups. Patients treated with [i]ndacaterol/glycopyrrolate had statistically significant improvements (defined as a ≥1 unit increase in TDI total score) in their TDI total score compared with placebo (1.64 unit improvement; P<0.001), indacaterol (0.78 unit improvement; P<0.001), and glycopyrrolate (0.73 unit improvement; P<0.001) at week 12. A statistically significant reduction in mean daily rescue medication use (puffs/day) was observed with indacaterol/glycopyrrolate compared to placebo in both studies (LS mean treatment difference, −1.22 in FLIGHT1 and −1.16 in FLIGHT2; P<0.001 for both), compared to glycopyrrolate in both studies (LS mean treatment difference, −0.58 in FLIGHT1 and −0.41 in FLIGHT2, both P<0.05), and compared to indacaterol in FLIGHT1 (LS mean treatment difference, −0.50; P<0.05). Patients' mean daily symptom scores and CAT scores were also significantly reduced with indacaterol/glycopyrrolate treatment compared with placebo and its monotherapy components after 12 weeks. In both FLIGHT1 and FLIGHT2, patients in all three active treatment arms had statistically significant and clinically meaningful improvements in their

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mean daytime and nighttime total symptom scores (as measured by the patients in a daily e-diary) compared with patients in the placebo arm. After 12 weeks of treatment, mean daytime and nighttime total symptom scores were improved with indacaterol/glycopyrrolate vs placebo (daytime total symptom score, LS mean difference, −0.80 in FLIGHT1 and −0.63 in FLIGHT2; both P<0.001; nighttime total symptom score, LS mean difference, −0.67 in FLIGHT1 and −0.68 in FLIGHT2; both P<0.001). In FLIGHT1, daytime total symptom scores were similarly reduced compared to both indacaterol and glycopyrrolate (indacaterol/glycopyrrolate vs indacaterol (LS mean difference, −0.33; P=0.017 and indacaterol/glycopyrrolate vs glycopyrrolate, LS mean difference, −0.30; P=0.030). The number of adverse events reported within both studies was similar between comparators; adverse events were mostly mild to moderate in severity. Serious adverse events were reported in 3.2% of Indacaterol/glycopyrrolate patients, 3.5% of indacaterol patients, 3.9% of glycopyrrolate patients, and 4.1% in placebo patients. COPD worsening was the most frequently occurring adverse event across all the treatment groups (Indacaterol/glycopyrrolate: 15.2%; indacaterol: 15.5%; glycopyrrolate: 17.4%; placebo: 20.1%).

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, ES=extension study, HR=hazard ratio, IRs=incidence per 100 patient-years, LS=least square, LSM=least square mean, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, SE=standard error, SEM=standard error of the mean, 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, HRQoL=health related quality of life, IC=inspiratory capacity, ICS=inhaled corticosteroid, LABA=long acting β2 agonist, MCID= minimal clinically important differences, MDI=metered dose inhaler, mMRC=Medical Research Council grade MRCDS=medication research council dyspnea scale, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, pMDI=pressurized metered-dose inhaler, PR=pulmonary rehabilitation, SF-36=short form 36, SGRQ=St. George's respiratory questionnaire, SOBDA=shortness of breath with daily activity, SVC=slow vital capacity, TDI=transitional dyspnea index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[4-15]

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.
Glycopyrrolate	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate impairment. Not studied in severe impairment.	C	Unknown; use caution.
Ipratropium	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown; use caution.
Tiotropium	No dosage adjustment required in the elderly. FDA approved for the maintenance treatment of asthma in children 12 years of age and older.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Umeclidinium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Combination Products					
Glycopyrrolate/ indacaterol	No dosage adjustment required in the elderly. FDA approved for the maintenance	No dosage adjustment required.	No dosage adjustment required in mild to moderate impairment. Not studied in	C	Unknown; use caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	treatment of asthma in children 12 years of age and older.		severe impairment.		
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; use caution.
Tiotropium/ olodaterol	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate impairment. Not studied in severe impairment.	C	Unknown; use caution.
Umeclidinium/ vilanterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in moderate impairment. Not studied in severe hepatic dysfunction.	C	Unknown; use caution.

Adverse Drug Events

Table 6. Adverse Drug Events[4-15]

Adverse Event(s)	Single Entity Agents						Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Cardiovascular										
Angina	-	-	-	1 to 3	-	-	-	<2	-	-
Arrhythmia	-	-	-	<1	-	<1	-	<2	-	<1
Chest pain	-	-	-	5 to 7	-	-	-	0.3 to 2.6	-	1
Diastolic blood pressure increased	-	-	-	-	-	-	-	a	-	-
Elevated heart rate	-	-	-	-	-	-	-	a	-	-
First degree atrioventricular block	<1	-	-	-	-	-	-	-	-	-
Heart failure	<1	-	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	1.0 to 2.0	<2	≤3	-
Hypotension	-	-	a	-	-	-	-	a	-	
Myocardial ischemia	-	-	-	-	-	-	-	a	-	<1
Palpitations	-	-	a	a	1 to 3	-	-	<2	≤3	-
Tachycardia	-	-	a	-	-	1	-	<2	≤3	-
Central Nervous System										
Asthenia	-	-	-	-	-	-	-	a	-	<1
Central nervous system stimulation	-	-	-	-	-	-	-	a	-	-
Coordination difficulty	-	-	-	-	-	-	-	a	-	-
Depression	-	-	-	1.0 to 4.4	-	a	-	-	-	-
Dizziness	-	-	3	a	1 to 3	a	-	a	≤3	-
Drowsiness	-	-	-	-	-	-	-	a	-	-
Fatigue	-	-	-	-	-	-	-	a	-	-
Flushing	-	-	-	-	-	-	-	a	-	-
Headache	6.6	-	6 to 7	5.7	-	a	-	a	-	-
Insomnia	-	-	-	4.4	-	-	-	a	≤3	-
Nervousness	-	-	-	-	-	-	-	a	-	-
Paresthesia	-	-	-	1 to 3	-	-	-	a	-	-
Tremor	-	-	-	-	-	-	-	a	-	-
Weakness	-	-	-	-	-	-	-	a	-	-
Dermatological										
Allergic skin reactions	-	-	a	2 to 4	-	-	-	-	≤3	-
Angioedema	-	-	a	<1	<1	-	-	0.3	≤3	-
Dry skin	-	-	-	a	<1	-	-	-	≤3	-
Pruritus	-	-	a	a	1 to 3	-	-	0.3	≤3	<1
Skin infection	-	-	-	a	<1	-	-	-	≤3	
Skin rash	-	-	a	2 to 4	1 to 3	a	-	0.3	≤3	<1
Skin ulcer	-	-	-	a	<1	-	-	-	≤3	-
Urticaria	-	-	a	a	-	-	-	0.3	≤3	-
Endocrine and Metabolic										
Diabetes mellitus	<1	-	-	-	-	-	-	-	-	-

Adverse Event(s)	Single Entity Agents						Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Edema	-	-	-	3 to 5	-	-	-	-	-	-
Hypercholesterolemia	-	-	-	1 to 3	-	-	-	-	-	-
Hyperglycemia	-	-	-	1 to 3	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain	-	-	5 to 6	-	-	1	-	-	-	<1
Constipation	-	-	a	1.0 to 5.1	1 to 3	-	-	>1	≤3	1
Diarrhea	2.7	-	a	-	-	a	-	<2	-	2
Dyspepsia	-	-	1 to 5	1 to 6	-	a	-	<2	-	<1
Gastrointestinal disease	-	-	-	-	-	-	-	a	-	-
Gastroesophageal reflux	-	-	-	1 to 3	1 to 3	-	-	-	≤3	<1
Gastrointestinal pain	-	-	-	3 to 6	-	-	-	-	-	-
Heartburn	-	-	-	-	-	-	-	a	-	-
Intestinal obstruction	-	-	-	a	<1	-	-	-	-	-
Motility disorder	-	-	-	-	-	-	-	a	≤3	-
Nausea	-	-	4	-	-	a	-	<2	-	-
Sore throat	-	-	-	-	-	-	-	a	-	-
Taste perversion	-	-	-	-	-	-	-	<2	-	-
Vomiting	1.1	-	-	1 to 4	-	-	-	<2	-	<1
Genitourinary										
Urinary difficulty	-	-	-	-	<1	-	-	a	≤3	-
Urinary retention	-	-	a	<1	<1	a	-	-	≤3	-
Urinary tract infection	-	1.4	2 to 10	4 to 7	1 to 3	-	-	<2	≤3	-
Musculoskeletal										
Arthralgia	-	-	-	4.2	-	2	-	<2	≤3	-
Arthritis	-	-	-	≥3	-	-	-	-	-	-
Back pain	-	-	2 to 7	-	-	a	1.4 to 1.8	<2	3.6	-
Extremity Pain	-	-	-	-	-	a	-	-	-	2
Joint swelling	-	-	-	a	<1	-	-	-	≤3	-
Leg cramps	-	-	-	-	-	-	-	1.4	-	-
Leg pain	-	-	-	1 to 3	-	-	-	-	-	-
Muscle spasms	-	-	-	-	-	1	-	a	-	1
Myalgia	-	-	-	4	-	-	-	a	-	-
Neck Pain	-	-	-	-	-	a	-	-	-	1
Pain	-	-	-	-	-	-	-	1.2 to 2.5	-	-
Skeletal pain	-	-	-	1 to 3	-	-	-	-	-	-
Respiratory										
Bronchitis	-	-	10 to 23	-	-	-	-	1.7 to 12.3	-	-
Bronchospasm	-	-	a	-	-	-	-	0.3	≤3	-
Cardiorespiratory arrest	<1	-	-	-	-	-	-	-	-	-
Chronic obstructive pulmonary disease exacerbation	-	-	8 to 23	-	-	-	-	a	-	-
Coughing	3	-	a	≥3	5.8	3	-	4.2	-	-

Adverse Event(s)	Single Entity Agents						Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Drying of secretions	-	-	-	-	-	-	-	a	-	-
Dyspnea	-	-	7 to 8	-	-	-	-	4.5	-	-
Hoarseness	-	-	-	a	-	-	-	a	-	-
Increased sputum	-	-	-	-	-	-	-	<2	-	-
Influenza	-	-	-	-	-	-	-	1.4	-	-
Irritation of aerosol	-	-	-	-	-	-	-	a	-	-
Lower respiratory tract infection	-	-	-	-	-	a	-	-	-	1
Lung disease	-	-	-	-	-	-	-	6.4	-	-
Nasal congestion	-	-	-	-	-	-	-	a	-	-
Nasopharyngitis	5.5	2.1	-	-	-	8	2.5 to 4.1	-	12.4	-
Pharyngitis	-	-	-	7.0 to 12.5	11.5	1	-	2.2 to 4.4	≤3	2
Pneumonia	-	-	-	-	-	a	-	1.3 to 1.4	-	-
Productive Cough	-	-	-	-	-	-	-	-	3.9	<1
Respiratory disorder	-	-	-	-	-	-	-	2.5	-	-
Rhinitis	1.6	-	≥3	3 to 6	-	a	-	1.1	-	-
Sinusitis	1.7	1.4	1 to 11	3 to 11	3.1		-	<2.3	≤3	1
Upper respiratory tract infection	-	3.4	≥3	43 to 41	-	5	-	10.9	-	-
Voice alterations	-	-	-	-	-	-	-	>1	-	-
Wheezing	-	-	-	-	-	-	-	a	-	-
Other										
Accidents	-	-	-	5 to 13	-	-	-	-	-	-
Alopecia	-	-	-	-	-	-	-	-	-	-
Anaphylaxis	-	-	a	-	-	-	-	a	-	-
Atrial Fibrillation	-	-	-	-	-	-	-	-	≤3	-
Blurred vision	-	-	a	-	-	-	-	a	≤3	-
Cataract	-	-	-	1 to 3	-	-	-	-	-	-
Conjunctival hyperemia	-	-	a	-	-	-	-	a	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	<1
Contusion	-	-	-	-	-	1	-	-	-	-
Corneal edema	-	-	a	-	-	-	-	a	-	-
Dehydration	-	-	-	a	-	-	-	-	≤3	-
Dry mouth	≤1	-	2 to 4	5.1 to 16.0	4.1	-	-	<2	≤3	<1
Dry throat	-	-	a	-	-	-	-	a	-	-
Dysphagia	-	-	-	a	<1	-	-	-	≤3	-
Dysphonia	-	-	-	1 to 3	1 to 3	-	-	-	≤3	-
Edema	-	-	-	-	-	-	-	a	-	-
Epistaxis	-	-	-	1 to 4	<1	-	-	-	≤3	-
Eye pain	-	-	a	-	-	-	-	a	-	-
Falls	1.1	-	-	-	-	-	-	-	-	-
Gingivitis	-	-	-	a	<1	-	-	-	≤3	-
Glaucoma	-	-	a	a	-	-	-	-	≤3	-
Glaucoma, worsening of narrow-angle	-	-	a	-	-	-	-	a	a	-

Adverse Event(s)	Single Entity Agents						Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Glossitis	-	-	-	-	-	-	-	-	≤3	-
Halo vision	-	-	a	-	-	-	-	a	-	-
Herpes zoster	-	-	-	1 to 3	-	-	-	-	-	-
Hypersensitivity reaction	-	-	a	1 to 3	-	-	-	-	-	-
Hyperhidrosis	-	-	-	-	-	-	-	a	-	-
Hypokalemia	-	-	-	-	-	-	-	a	-	-
Infection	-	-	-	1 to 4	-	-	-	-	-	-
Influenza-like symptoms	-	-	4 to 8	≥3	-	-	-	-	-	-
Intraocular pressure increased	-	-	-	-	-	-	-	-	≤3	-
Laryngitis	-	-	-	1 to 3	<1	-	-	-	≤3	-
Laryngospasm	-	-	a	-	-	-	-	a	-	-
Moniliasis	-	-	-	3 to 4	-	-	-	-	-	-
Mouth edema	-	-	a	-	-	-	-	a	-	-
Mucosal ulcers	-	-	-	-	-	-	-	a	-	-
Mydriasis	-	-	a	-	-	-	-	a	-	-
Oropharyngeal candidiasis	-	-	-	a	1 to 3	-	-	-	≤3	-
Oropharyngeal pain	-	1.8	-	-	-	-	0.8 to 1.6	-	-	-
Osteoarthritis	<1	-	-	-	-	-	-	-	-	-
Stomatitis	-	-	a	1 to 3	-	-	-	a	≤3	-
Taste perversion	-	-	<1	-	-	-	-	-	-	-
Throat irritation	-	-	a	a	-	-	-	-	-	-
Toothache	1.1	-	-	-	-	1	-	-	-	-

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[4-15]

Contraindication	Single Entity Agents					Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Hypersensitivity to any component of the product, atropine or its derivatives.	-	a	a	a *	-	a	a	a *	a
Hypersensitivity to milk proteins.	-	-	-	-	a	-	-	-	a
Hypersensitivity to soya lecithin or related food products including soybeans and peanuts.	-	-	-	-	-	-	a	-	-
Use in asthma without use of a long-term asthma control medication	-	-	-	-	-	a	-	a	-

*Including ipratropium

Black Box Warning for Utibron Neohaler (glycopyrrolate/indacaterol)[12]

WARNING
Long-acting β_2-adrenergic agonists (LABA), increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including indacaterol, one of the active ingredients in Utibron Neohaler. The safety and efficacy of Stiolto Respimat in patients with asthma have not been established. Utibron Neohaler is not indicated for the treatment of asthma.

Black Box Warning for Stiolto Respimat® (tiotropium/olodaterol)[14]

WARNING
Long-acting β_2-adrenergic agonists (LABA), increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including olodaterol, one of the active ingredients in Stiolto Respimat. The safety and efficacy of Stiolto Respimat in patients with asthma have not been established. Stiolto Respimat is not indicated for the treatment of asthma.

Black Box Warning for Anoro Ellipta® (umeclidinium/vilanterol)[15]

WARNING
Long-acting β-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in Anoro Ellipta®. The safety and efficacy of Anoro Ellipta® in patients with asthma have not been established. Anoro Ellipta® is not indicated for the treatment of asthma.

Warnings/Precautions

Table 8. Warnings and Precautions[4-15]

Warning/Precaution	Single-Entity Agents					Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Acutely deteriorating COPD, avoid use.	-	a	-	-	-	a	-	a	-
Asthma-related death; long-acting β-agonists may increase the risk of asthma-related deaths; there is no data to determine if rate of death in patients with chronic obstructive pulmonary disease is increased.	-	-	-	-	-	a	-	a	a
Bladder neck obstruction; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	a	a	a	a	a	a	a	a	a
Clinically significant increases in pulse rate, blood pressure, and/or symptoms may occur; use with caution in patients with cardiovascular disorders.	-	-	-	-	-	a	a	a	a
Convulsive disorders; use with caution in this patient population.	-	-	-	-	-	a	a	a	a
Diabetes; large doses of intravenous albuterol have been reported to aggravate diabetes mellitus and ketoacidosis.	-	-	-	-	-	-	a	a	-
Do not puncture contents of aerosol and do not use or store near heat or an open flame.	-	-	a	-	-		-		-
Excessive use of β_2-adrengeric agents or in conjunction with other long-acting β_2-adrengeric agonists is not recommended and may result in overdose.	-	-	-	-	-	a	-	a	-
Fatalities have been reported in associated with excessive use of inhaled sympathomimetic agents in patients with asthma.	-	-	-	-	-	a	a	a	a
Hypersensitivity reactions may occur immediately following administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and anaphylaxis.	a	a	a	a	-	a	a	a	-
Hypersensitivity reactions may occur in patients with an allergy to atropine; patients should be monitored for signs of a reaction.	a	-	-	a	-	-	-	-	-
Hypersensitivity reactions may occur in patients with an allergy to milk protein; use with caution in this patient population.	a	-	-	a	a	-	-	-	a
Hyperthyroidism; use with caution in this patient population.	-	-	-	-	-	-	a	-	-
Hypokalemia; significant hypokalemia may occur in some patients predisposing them to cardiovascular effects.	-	-	-	-	-	a	a	a	a
Indicated for maintenance therapy and should not be used for initial treatment of acute episodes of bronchospasm.	a	-	a	a	a	-	-	-	a

Warning/Precaution	Single-Entity Agents					Combination Products			
	Aclidinium	Glycopyrrolate	Ipratropium	Tiotropium	Umeclidinium	Glycopyrrolate/ Indacaterol	Ipratropium/ Albuterol	Tiotropium/ Olodaterol	Umeclidinium/ Vilanterol
Narrow-angle glaucoma; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	a	a	a	a	a	a	a	a	a
Paradoxical bronchospasm has been reported; discontinue treatment immediately if paradoxical bronchospasm is suspected.	a	a	-	a *	a	a	a	a	a
Prostatic hyperplasia; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	-	a	a	a	a	a	a	a	a
Renal impairment (mild to moderate), decreased excretion, monitor for increased anticholinergic side effects.	-	-	-	-	-	-	-	a	-
Use with caution in patients who are unusually responsive to sympathomimetic amines.	-	-	-	-	-	a	a	-	-
Urinary retention may worsen.	-	a	-	-	-	a	-	a	-

COPD=chronic obstructive pulmonary disease
*Respimat® dosage form

Drug Interactions

Although the inhaled anticholinergics are minimally absorbed, there is some potential for an additive interaction with concomitantly used anticholinergic medications.[4-15]

Table 9. Drug Interactions[1,4-15]

Generic Name	Interacting Medication or Disease	Potential Result
Glycopyrrolate, Glycopyrrolate/ indacaterol	Potassium	May result in the risk of gastrointestinal lesions.
Glycopyrrolate, Glycopyrrolate/ indacaterol	Anticholinergics	May lead to an increase in anticholinergic adverse effects.
Glycopyrrolate, Glycopyrrolate/ indacaterol	Digoxin	May result in increased plasma concentrations of digoxin.
Glycopyrrolate/ indacaterol	Adrenergic Agents	Sympathetic effects of indacaterol may be potentiated; use with caution.
Glycopyrrolate/ indacaterol	Sympathomimetics, xanthine derivatives, steroids or diuretics	May potentiate any hypokalemic effect of indacaterol.
Glycopyrrolate/ indacaterol	Non-potassium sparing diuretics	Electrocardiogram changes and/or hypokalemia may result can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded; use with caution.
Glycopyrrolate/ indacaterol	Monoamine oxidase inhibitors, tricyclic antidepressants, QTc prolonging agents	Adrenergic agonists may potentiate the cardiovascular system.
Glycopyrrolate/ indacaterol	β-blockers	β-blockers and indacaterol may interfere with the effect of each other when administered concurrently. In certain instances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of β-blockers in patients with COPD. In this setting, cardioselective β-blockers could be considered.
Tiotropium/ olodaterol	Adrenergic drugs	Sympathetic effects of olodaterol may be potentiated.
Tiotropium/ olodaterol	Sympathomimetics, xanthine derivatives, steroids, and Diuretics	May potentiate any hypokalemic effect of olodaterol.
Tiotropium/ olodaterol	Non-potassium sparing diuretics	The ECG changes and/or hypokalemia that may result from non-potassium sparing diuretics can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.
Tiotropium/ olodaterol	Monoamine oxidase inhibitors, tricyclic antidepressants, QTc prolonging drugs	Adrenergic agonists on the cardiovascular system may be potentiated.
Tiotropium/ olodaterol	Beta-blockers	May interfere with the effect of each other when administered concurrently.
Tiotropium/ olodaterol	Anticholinergics	There is potential for an additive interaction.

Umeclidinium/ vilanterol	CYP 450 3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, nefazodone, etc.)	Concomitant administration of a potent CYP-3A4 inhibitor increases the systemic exposure to these agents. Caution should be advised when using these combinations.
Umeclidinium/ vilanterol	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
Umeclidinium/ vilanterol	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
Umeclidinium/ vilanterol	Nonselective β_2-antagonists	β-blockers inhibit the therapeutic effects of β-agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
Umeclidinium/ vilanterol	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β-agonists.

Dosage and Administration

Table 10. Dosing and Administration[4-15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Aclidinium	Bronchospasm associated with COPD, maintenance treatment*: Powder for inhalation: initial, 400 µg twice daily	Safety and efficacy in children have not been established.	Powder for inhalation: 400 µg
Glycopyrrolate	Airflow obstruction in patients with COPD, maintenance treatment*: Powder for inhalation: initial, maintenance, and maximum: One inhalation (15.6 µg) once daily	Safety and efficacy in children have not been established.	Powder for inhalation: 15.6 µg
Ipratropium	Bronchospasm associated with COPD, maintenance treatment: Aerosol for oral inhalation: initial, 34 µg (two inhalations) four times daily; maximum, do not exceed 204 µg (12 inhalations) in 24 hours Solution for nebulization: maintenance, 500 µg four times daily, dose six to eight hours apart	Safety and efficacy in children under the age of 12 have not been established.	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)
Tiotropium	Asthma, maintenance treatment: Aerosol for inhalation: Initial, maintenance, two 1.25 µg inhalations (2.5 µg) once-daily Bronchospasm associated with COPD, maintenance treatment*; reduce exacerbations in patients with COPD: Powder for inhalation: initial, 18 µg once daily Aerosol for inhalation: initial, 2 inhalations (5 µg) once-daily	Asthma (12 years of age or older): Refer to adult dose Safety and efficacy in children have not been established <12 years of age for the treatment of asthma or children <18 years of age for other diagnoses.	Aerosol for inhalation (Spiriva Respimat®): 1.25 µg/actuation 2.5 µg/actuation Powder for inhalation (Spiriva HandiHaler®): 18 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
Umeclidinium	Airflow obstruction in patients with COPD, maintenance treatment*: Powder for inhalation: one inhalation (62.5 µg) once daily	Safety and efficacy in children have not been established.	Powder for inhalation: 62.5 µg
Combination Products			
Glycopyrrolate/ indacaterol	Airflow obstruction in patients with COPD, maintenance treatment*: Powder for inhalation: initial; maintenance; and maximum: One inhalation twice daily	Safety and efficacy in children have not been established.	Powder for inhalation: 15.6 µg/27.5 µg
Ipratropium/ albuterol	Bronchospasm associated with COPD in patients requiring more than one bronchodilator: Inhalation spray (inhaler): one inhalation four times daily; maximum, six inhalations a day Solution for nebulization: one vial four times daily; maximum, six vials daily	Safety and efficacy in children have not been established.	Inhalation spray (Combivent Respimat®): 20/100 µg† Solution for nebulization (DuoNeb®): 0.5/3.0 mg
Tiotropium/ olodaterol	Airflow obstruction in patients with COPD, maintenance treatment*: Inhalation spray: two inhalations once daily at the same time every day; maximum, two inhalations once daily	Safety and efficacy in children have not been established.	Inhalation Spray 5/5 µg
Umeclidinium/ vilanterol	Airflow obstruction in patients with COPD, maintenance treatment*: Powder for inhalation: one inhalation (62.5/25 µg) once daily	Safety and efficacy in children have not been established.	Powder for inhalation: 62.5/25 µg

* Long-term maintenance treatment
† Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Clinical Guidelines

Table 11. 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 (2015)**[1]	Diagnosis · A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. · A diagnosis of COPD should be confirmed by spirometry. · The presence of a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 confirms the presence of persistent airflow limitation and COPD. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. · Chest radiograph may be useful to rule out other diagnoses. · Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment

Clinical Guideline	Recommendations
	· Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. · The management of COPD should be individualized to address severity of symptoms, risk of exacerbations, drug availability and patient's response. · None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and risk of future events complications. · COPD patients should receive a yearly influenza vaccination. · Bronchodilators are central to symptom management. · Inhaled therapy is preferred to oral therapy. · Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. · Choice between β_2-agonists, anticholinergic, theophylline or combination therapy is based on availability and individual patient response. · The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. · Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. · The combination of a short- or long-acting β_2-agonist (LABA) and anticholinergics may be considered if symptoms are not improved with single agents. · Short-term combination therapy using formoterol and tiotropium has been shown to have a bigger impact on FEV_1 than the single components. · Combinations of short-acting β_2-agonists (SABA) and anticholinergics are also superior compared to either medication alone in improving FEV_1 and symptoms. · Combinations of a LABA and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact in patient reported outcomes is limited. There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations. · In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. · Long term monotherapy with oral corticosteroids (OCS) or inhaled corticosteroids (ICS) is not recommended. · Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · Roflumilast may be used to reduce exacerbations for patients with chronic bronchitis, severe airflow limitation and frequent exacerbations not controlled by long-acting bronchodilators. · An ICS combined with a LABA is more effective that either component alone for improving lung function, health status and reducing exacerbations in patients with moderate to very severe COPD. However, this combination is also associated with an increased risk of pneumonia. · Methylxanthines (e.g., theophylline) are less effective and less well-tolerated than inhaled long-acting bronchodilators and are not recommended if those drugs are available.

Clinical Guideline	Recommendations
	· The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. · Pulmonary rehabilitation should be implemented for all COPD patients. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure and severe resting hypoxemia. Management of exacerbations · The most common causes of an exacerbation are respiratory tract infections. · Inhaled SABAs, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. · Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. · Systemic corticosteroids shorten recovery time, improve lung function and arterial hypoxemia, and reduce the risks of early relapse, treatment failure, and length of hospital stay. · Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
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)**[2]	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 (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. · Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic 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 an anticholinergic antagonist. o FEV_1 ≥50% predicted: long acting beta agonist (LABA) or long-acting anticholinergic antagonist. o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist. · In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined.

Clinical Guideline	Recommendations
	· Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. · Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. · In most cases, inhaled bronchodilator therapy is preferred. · Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. · Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. · Pulmonary rehabilitation should be made available to patients. · Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. 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**	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 LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1

Clinical Guideline	Recommendations
Society, and European Respiratory Society (2011)[3]	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. · There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. · ICSs 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, LABA, or ICS) 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 LABA plus ICS. · 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 (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).

Conclusions

The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), glycopyrrolate (Seebri Neohaler®), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®). Ipratropium is available in combination with albuterol, a short-acting β_2-agonist (Combivent Respimat® and DuoNeb®). Umeclidinium/vilanterol was the first combination product containing a long acting muscarinic and long-acting β_2-agonist with the others being glycopyrrolate/indacaterol (Utibron Neohaler®) and tiotropium/olodaterol (Stiolto Respimat®)[4-15] Aclidinium, glycopyrrolate, ipratropium and tiotropium are FDA-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only agent within the class that is FDA-approved for reducing exacerbations associated with COPD. Additionally, tiotropium soft mist inhaler (Spiriva Respimat®) has been approved for the chronic management of asthma. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Glycopyrrolate/indacaterol, umeclidinium, umeclidinium/vilanterol and tiotropium/olodaterol are FDA-approved for the maintenance treatment of airflow obstruction in patients with COPD. [4-15] Aclidinium, ipratropium, tiotropium and umeclidinium are all classified as bronchodilators but due to differences in pharmacokinetic parameters, aclidinium, tiotropium and umeclidinium are considered long-acting bronchodilators and ipratropium a short-acting bronchodilator. Aclidinium, glycopyrrolate, and tiotropium have a significantly longer duration of action compared to ipratropium and as a result are approved for once- or twice-daily dosing. All of the anticholinergic 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.[19,42,43] Meta-analyses have demonstrated significant clinical advantages when tiotropium is used in combination with a bronchodilator from a different pharmacologic class.[56,65,66] 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.[54,55] Treatment with aclidinium has demonstrated statistically significant improvements in pulmonary function in patients with COPD compared to placebo.[26-28] Umeclidinium/vilanterol has demonstrated significant improvements in lung function measures when compared to placebo and the individual agents.[74,75]

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 anticholinergics are preferred compared to four-times-daily short-acting anticholinergics 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 anticholinergic.[2]

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