COPD Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Antimuscarinics – Short-Acting		
ipratropium inhalation solution[1]	generic	For maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema
ipratropium inhalation aerosol MDI (Atrovent® HFA)[2]	Boehringer-Ingelheim	As a bronchodilator for maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema
Antimuscarinics – Long-Acting		
aclidinium bromide (Tudorza® Pressair®)[3]	Circassia	For the maintenance treatment of patients with COPD
glycopyrrolate (Lonhala® Magnair®)[4]	Sunovion	For the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
glycopyrrolate* (Seebri™ Neohaler®)[5]	Sunovion	For the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
revefenacin (Yupelri™)[6]	Mylan	For the maintenance treatment of patients with COPD
tiotropium inhalation powder DPI (Spiriva HandiHaler®)[7]	Boehringer-Ingelheim	For the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema To reduce COPD exacerbations
tiotropium bromide inhalation spray (Spiriva® Respimat®)[8]	Boehringer-Ingelheim	For the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations For the long-term, once-daily, maintenance treatment of asthma in patients ≥ 6 years old
umeclidinium (Incruse® Ellipta®)[9]	GlaxoSmithKline	For the maintenance treatment of patients with COPD
Antimuscarinic/Beta$_2$-Agonist Combinations – Short-Acting		
albuterol/ipratropium inhalation solution*[10]	generic	For the treatment of bronchospasm associated with COPD in patients requiring more than 1 bronchodilator
albuterol/ipratropium MDI CFC-free (Combivent® Respimat®)[11]	Boehringer-Ingelheim	For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and require a second bronchodilator
Antimuscarinic/Beta$_2$-Agonist Combinations – Long-Acting		
aclidinium bromide/formoterol (Duaklir® Pressair®)[12]	AstraZeneca/Circassia	For the maintenance treatment of patients with COPD
glycopyrrolate/formoterol fumarate (Bevespi Aerosphere™)[13]	AstraZeneca	For the maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema
glycopyrrolate/indacaterol* (Utibron® Neohaler®)[14]	Sunovion	For the long-term, maintenance treatment of airflow obstruction in patients with COPD
tiotropium/olodaterol (Stiolto® Respimat®)[15]	Boehringer-Ingelheim	For the long-term, once-daily maintenance treatment of patients with COPD, including bronchitis and/or emphysema
umeclidinium/vilanterol (Anoro® Ellipta®)[16]	GlaxoSmithKline	For the maintenance treatment of patients with COPD

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Phosphodiesterase 4 (PDE4) Inhibitor		
roflumilast (Daliresp®)[17]	AstraZeneca	As a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler

* Sunovion notified the FDA that they have discontinued glycopyrrolate (Seebri Neohaler) and glycopyrrolate/indacaterol (Utibron Neohaler); product may remain until supply is depleted.

OVERVIEW

COPD

The 2020 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) as a common, preventable, and treatable disease in which its pulmonary component is characterized by persistent respiratory symptoms and airflow limitation that is usually progressive and is associated with airway and/or alveolar abnormalities caused by exposure to noxious particles or gases.[18] It is estimated that the number of Americans with a COPD diagnosis is approximately 16 million.[19] However, the US Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults.[20]

Although the precise distinctions between chronic bronchitis and emphysema are a subject of debate, common belief holds that chronic bronchitis is responsible for 85% of COPD.[21] Patients with chronic bronchitis experience intermittent airway inflammation and excessive mucus production that leads to frequent, prolonged episodes of productive cough. In contrast, 15% of patients with COPD suffer primarily from emphysema, in which destruction of the infrastructure of alveoli and distal airspaces that provide gas exchange and elastic recoil occurs.[22] Both chronic bronchitis and emphysema predispose patients to a common collection of symptoms and impairments in respiratory function.

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of COPD guidelines stresses that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and a history of exposure to risk factors specific to the disease. Spirometry is required to effectively establish a clinical diagnosis of COPD.[23] A post-bronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The assessment of FEV_1 alone is a poor descriptor of disease status. Individual assessment of the patient's symptoms, future risks of exacerbations, severity of airflow limitation, and comorbidities is essential in guiding therapy. A COPD exacerbation is defined as an acute event characterized by worsening of the patient's respiratory symptoms that varies from the normal daily variations and requires a change in medication. Hospitalization for a COPD exacerbation signifies a poor diagnosis and increased risk of death. The COPD Assessment Test (CAT; range, 0 to 40) or the Clinical COPD Questionnaire (CCQ) is recommended for a comprehensive assessment of symptoms. The Modified British Medical Research Council questionnaire may be used, but only assesses breathlessness.

Previously, patient groups were classified into an alphabetic (ABCD) classification system based on exacerbation risk and symptoms in combination with airway limitation. However, patients are now

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classified separately by *both* their GOLD severity (e.g., airflow limitation: 1 to 4) *and* exacerbation/symptom assessment (e.g., GOLD grade 4, group D). Therefore, exacerbation risk and symptoms alone are used to define the ABCD classification and more emphasis is given to a patient's symptom burden when evaluating disease severity.[24,25] The definitions of airflow limitation and numerical values for exacerbations/symptoms have *not* changed, and are summarized below:

- **Assessment of Airflow Limitation:**
  - ❒ GOLD 1: mild, $FEV_1 \geq 80\%$ predicted
  - ❒ GOLD 2: moderate, FEV_1 50% to 79% predicted
  - ❒ GOLD 3: severe, FEV_1 30% to 49% predicted
  - ❒ GOLD 4: very severe, $FEV_1 < 30\%$ predicted
- **Assessment of Exacerbation Risk and Symptoms:**
  - ❒ Patient Group A – Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score < 10 or mMRC grade 0 to 1
  - ❒ Patient Group B – Low Risk, More Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score ≥ 10 or mMRC grade ≥ 2
  - ❒ Patient Group C – High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score < 10 or mMRC grade 0 to 1
  - ❒ Patient Group D – High Risk, More Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score ≥ 10 or mMRC grade ≥ 2

The 2011 American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) Guidelines include a fifth category for disease classification, namely "At Risk", which includes asymptomatic patients with mild to moderate airflow obstruction (FEV_1/FVC ratio < 0.7 and $FEV_1 \geq 50\%$ predicted) or without airflow obstruction (FEV_1/FVC ratio ≥ 0.7).[26] These guidelines support the idea that history or physical examinations alone are poor predictors of airflow obstruction. Airway obstruction (post-bronchodilator $FEV_1/FVC < 0.7$) can be expected with the presence of wheezing on auscultation, smoking history greater than 55 pack years, and patient self-report of wheezing. Spirometry was discussed as a key diagnostic tool to determine respiratory disease and the severity of airflow obstruction.

Bronchodilator medications are central to the symptomatic management of COPD.[27,28,29,30] They improve emptying of the lungs, reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance.[31] They are given either on an as-needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting agents.[32] Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects as compared to maximizing the dose of a single bronchodilator. Bronchodilators include $beta_2$-agonists and antimuscarinic agents; antimuscarinics are also referred to as anticholinergics. Short-acting and long-acting formulations of each are available.

In 2020, the American Thoracic Society (ATS) released additional guidelines for the pharmacologic management of COPD.[33] These guidelines focus on addressing specific questions developed by an ATS panel regarding significant COPD management issues, including when to use dual and triple therapy and ICS use in COPD patients with blood eosinophilia. The panel strongly recommends the use of dual long-

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acting beta$_2$-agonist (LABA)/long-acting muscarinic antagonist (LAMA) therapy over LABA or LAMA monotherapy in COPD patients who complain of exercise intolerance or dyspnea based on pooled evidence demonstrating decreased hospital admissions and exacerbations and improvements in patient quality of life and dyspnea. Additionally, the ATS suggests triple therapy (ICS/LABA/LAMA) in COPD patients with a history of ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year who, despite LABA/LAMA dual therapy, complain of exercise intolerance or dyspnea. Further, for patients receiving triple combination therapy who experience no exacerbations over the course of 1 year, they suggest that ICS therapy may be discontinued. The ATS also suggests the addition of ICS therapy in COPD patients with blood eosinophilia (≥ 2% blood eosinophils or ≥ 150 cells/µL) who have experienced ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year. Additional management recommendations regarding treatment approaches outside of this therapeutic class review are detailed in the guidelines.

The 2020 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk and focus on individualized therapy.[34] Bronchodilator medications continue to be central to symptom management in COPD across all groups. While the guidelines review multiple medications and state that bronchodilators are generally effective, GOLD notes that LAMAs, also known as long-acting anticholinergics, have a greater effect on exacerbation reduction and decreased hospitalizations compared to LABAs (Evidence A and B, respectively). Likewise, they generally state that combination treatment with long-acting bronchodilators (e.g., beta$_2$-agonist and anticholinergic) is more effective than bronchodilator monotherapy. In regards to anti-inflammatory therapy, the addition of an ICS to a LABA is more effective than a LABA alone (Evidence A); however, regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (Evidence A). Triple therapy (ICS/LAMA/LABA) is more effective compared to an ICS/LABA, LABA/LAMA, or LAMA monotherapy (Evidence, A). For the treatment of stable COPD with bronchodilators, LABAs and LAMAs are preferred over short-acting agents except in the case of patients with occasional dyspnea (Evidence A). Inhaled therapy is also preferred over oral therapy (Evidence A). Patients may be initiated on either bronchodilator monotherapy or dual bronchodilator therapy (LAMA/LABA); those initiated on monotherapy with persistent symptoms should be escalated to dual bronchodilator therapy (Evidence A). For the treatment of stable COPD with ICS, monotherapy with an ICS is not recommended (Evidence A), but long-term treatment with an ICS may be considered in addition to a LABA in patients with a history of exacerbations despite bronchodilator therapy (Evidence A). For the treatment of acute exacerbations, GOLD recommends the use of a SABA with or without a short-acting anticholinergic agent (Evidence C).

Following these general medication recommendations, GOLD provides a treatment algorithm based on the patient's ABCD exacerbation/symptom assessment.[35] Previously, GOLD had focused on recommendations for preferred and alternative initial therapy. In the revised guidelines, Group A patients should be initiated on a bronchodilator (short- or long-acting). Patients in Group B should be initiated on a LABA or LAMA. Patients in Group C should be initiated on a LAMA, and Group D patients should be initiated on a LAMA + LABA (if symptomatic), LAMA monotherapy, or a LABA + ICS (may be preferred in patients with elevated eosinophils). For follow-up pharmacologic treatment, GOLD bases recommendations on the predominant treatable trait, either dyspnea or exacerbations. For dyspnea in patients on a LABA or LAMA, the next step is a LABA plus LAMA, and if dyspnea persists, a device or drug switch should be considered, along with investigation and treatment of other causes of dyspnea. For those on a LABA plus ICS, escalation to triple therapy can be considered. Likewise, de-escalation of

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the ICS component or a switch to LABA plus LAMA may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia). For targeting exacerbations, those on a LABA or LAMA can have treatment escalated to LABA plus LAMA, and subsequently, triple therapy (LABA/LAMA/ICS) in patients with an elevated eosinophil count (≥ 100 cells/µL). For those on a LABA or LAMA with a select eosinophil count (≥ 300 cells/µL or ≥ 100 cells/µL plus ≥ 2 moderate exacerbations or 1 hospitalization), treatment with a LABA plus ICS is recommended, followed by triple therapy if needed. If further escalation is needed or escalation is needed in those with an eosinophil count < 100 cells/µL, the addition of roflumilast or azithromycin can be considered in select patients. Similar to targeting dyspnea, de-escalation also should be considered, particularly of the ICS component or a switch to LABA plus LAMA in those on triple therapy may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia).

In 2015, ACCP published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.[36] To prevent moderate to severe exacerbations in patients with moderate to severe COPD, they recommend use of a LABA or a LAMA over no therapy (placebo) (Grade 1B and 1A, respectively). In this same group, they recommend the use of a LAMA over a LABA (Grace 1C) and a LAMA over a short-acting muscarinic antagonist (SAMA) (Grade 1A). To prevent mild to moderate exacerbations in patients with moderate to severe COPD, they recommend use of a SAMA over a SABA (Grade 2C) and a SAMA + LABA over a LABA alone (Grade 2C). In patients with moderate to severe COPD, they recommend use of a SAMA + SABA over SABA monotherapy (Grade 2B) to prevent acute moderate exacerbations and use of a LABA over a SAMA to prevent acute exacerbations (Grade 2C). In patients with stable moderate to very severe COPD, ACCP recommends maintenance therapy with an ICS + LABA over placebo, ICS monotherapy, and LABA monotherapy (Grade 1B, 1B, and 1C, respectively) to prevent acute exacerbations. For patients with stable COPD, they recommend either combination LAMA/LABA therapy or LAMA monotherapy as both are effective for exacerbations (Grade 1C). Likewise, in stable patients, either ICS/LABA or LAMA monotherapy is recommended (Grade 1C) and either a LAMA + ICS + LABA or LAMA monotherapy is recommended to prevent exacerbations (Grade 2C).

In 2017, ATS and ERS published joint guidelines on the prevention of COPD exacerbations.[37] They suggest treatment with an oral mucolytic agent to prevent future exacerbations in patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy (conditional recommendation, low quality of evidence). For patients who have COPD with moderate or severe airflow obstruction and a history of at least 1 COPD exacerbations during the previous year, they recommend use of a LAMA over LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence). For patients with severe or very severe airflow obstruction and COPD exacerbations despite optimal inhaled therapy, they suggest a macrolide antibiotic (also for moderate airflow obstruction) or roflumilast (select patients with chronic bronchitis) to prevent future exacerbations (conditional recommendation, low [macrolide] and moderate [roflumilast] quality of evidence).

Devices

With the conversion to required chlorofluorocarbon (CFC)-free inhalers, the CFC-free combination albuterol-ipratropium MDI (Combivent Respimat) has been approved for use in the treatment of COPD. Other agents within this class include an oral agent, roflumilast (Daliresp), inhaled SAMA agents (ipratropium solution, albuterol/ipratropium solution) inhaled LAMA, (tiotropium [Spiriva Respimat,

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Spiriva HandiHaler]), aclidinium (Tudorza Pressair), umeclidinium (Incruse Ellipta), revefenacin (Yupelri) and glycopyrrolate (Seebri Neohaler, Lonhala Magnair), and combination LAMA/LABA agents (aclidinium/formoterol [Duaklir Pressair], glycopyrrolate/ formoterol fumarate [Bevespi Aerosphere], glycopyrrolate/indacaterol [Utibron Neohaler], tiotropium/olodaterol [Stiolto Respimat], and umeclidinium/vilanterol [Anoro Ellipta]), which are all FDA-approved treatment options in COPD management.

The FDA approved fixed-dose combination inhalers for the maintenance treatment of COPD. These include select dual therapies that contain an ICS and LABA. These products are not included in this therapeutic class review.

Asthma

Prevalence of asthma in the United States continues to rise. More than 25 million Americans have asthma, and approximately 6 million of these are children.[38] Further, the National Health Statistics Report shows that asthma appears to disproportionately affect minority groups, females, children, and individuals of low socioeconomic status which can place significant pressure on public health systems.[39] The National Asthma Education and Prevention Program (NAEPP) of the National Heart Lung and Blood Institute (NHLBI) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[40] In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli.

Medications to treat asthma are classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to maintain asthma control. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms.[41]

The mainstay of asthma therapy is the use of inhaled corticosteroids alone or in combination with LABAs as controller medications.[42] While the corticosteroid reduces inflammation, the LABA acts principally to dilate the airways by relaxing airway smooth muscle. These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists (SABAs) for quick relief. Due to the increased risk of severe exacerbations with regular or frequent use, short-acting beta agonist (SABA)-only treatment is no longer recommended.[43] Likewise, LABAs are not to be used as monotherapy for controlling asthma. For most asthma patients, treatment can be initiated with an as-needed low dose ICS-formoterol, daily low dose ICS, or low dose ICS taken whenever SABA is taken.

The 2020 Global Initiative for Asthma (GINA) guidelines offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects.[44] In patients whose asthma is not adequately controlled on a low dose ICS-containing controller despite good adherence and correct technique, a step up in treatment may be added until control is achieved. A combination ICS/LABA product is the preferred step-up treatment for adults and adolescents ≥ 12 years of age currently on a low dose ICS or as needed low dose ICS-formoterol who continue to have persistent symptoms or exacerbations. For children aged 6 to 11 years with persistent symptoms, an increase in ICS dose or a combination low dose ICS/LABA agent is recommended. If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage

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that maintains control. The effect of a LABA or combination LABA/ICS has not been adequately studied in children aged 5 years and younger.[45] Therefore, LABAs cannot be recommended in this patient population. The stepwise approach for asthma control in the GINA guidelines is described below. Notably, reliever therapy can be considered for symptom management of prior to exercise if needed.

Stepwise Approach to Asthma Control* from 2020 GINA Guidelines – Controller Therapy[46]

Step	Age Group	Preferred Controller	Other Controller Options
Step 1: Symptom-driven or regular controller	≥ 12 years	▪ As-needed low dose ICS-formoterol (unlabeled indication)†	▪ Low dose ICS whenever SABA is taken (unlabeled indication)
	6 to 11 years	--	▪ Low dose ICS whenever SABA is taken (unlabeled indication) or daily low dose ICS
Step 2: One controller AND an as-needed reliever medication	≥ 12 years	▪ Low dose ICS or as needed low dose ICS-formoterol (unlabeled indication)†	▪ Leukotriene modifier or low dose ICS whenever SABA is taken (unlabeled indication)
	6 to 11 years	▪ Low dose ICS	▪ Leukotriene modifier or low dose ICS whenever SABA is taken (unlabeled indication)
Step 3: Two controllers and an as-needed reliever medication	≥ 12 years	▪ Low dose ICS/LABA	▪ Medium dose ICS OR low dose ICS + leukotriene modifier ▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and FEV > 70% predicted
	6 to 11 years	▪ Low dose ICS/LABA or medium dose ICS	▪ Low dose ICS + leukotriene modifier
Step 4: Two controllers and an as-needed reliever medication	≥ 12 years	▪ Medium dose ICS/LABA	▪ High dose ICS, add-on tiotropium, or add-on leukotriene modifier ▪ Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis, house dust mite sensitivity, and FEV > 70% predicted
	6 to 11 years	▪ Medium dose ICS/LABA; refer for expert advice	▪ High dose ICS/LABA, add-on tiotropium, or add-on leukotriene modifier
Step 5: Two controllers and an as-needed reliever medication	≥ 12 years	▪ High dose ICS/LABA; refer for phenotypic assessment with or without add-on therapy (e.g., tiotropium, anti-IgE [omalizumab], anti-interleukin-5[IL5]/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab])	▪ Add-on low dose oral corticosteroid, considering adverse effects
	6 to 11 years	▪ Refer for phenotypic assessment with or without add-on therapy (e.g., anti-IgE [omalizumab]	▪ Add-on anti-IL-5 or add-on low dose oral corticosteroid, considering adverse effects

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL-5 = interleukin-5; LABA = long acting beta$_2$-agonist; SABA = short acting beta$_2$-agonist

* Additional recommendations published regarding the assessment and treatment of severe asthma, incorporating other treatment modalities (e.g., tiotropium, anti-IgE [omalizumab], anti-IL5/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab], based on age).

† The data supporting the use of low dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol (a formulation not available in the US).

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Stepwise Approach to Asthma Control* from 2020 GINA Guidelines (continued) – Reliever Therapy[47]

Age Group	Step	Preferred Reliever	Other Reliever Options
≥ 12 years	Steps 1 and 2	▪ As-needed low dose ICS-formoterol (unlabeled indication)†	▪ As needed SABA
	Steps 3 through 5	▪ As-needed low dose ICS-formoterol (unlabeled indication)‡	
6 to 11 years	Steps 1 through 5	▪ As needed SABA	--

ICS = inhaled corticosteroid; SABA = short acting beta$_2$-agonist

* Additional recommendations published regarding the assessment and treatment of severe asthma, incorporating other treatment modalities (e.g., tiotropium, anti-IgE [omalizumab], anti-IL5/5R [mepolizumab, reslizumab, benralizumab], anti-IL4R [dupilumab], based on age).

† The data supporting the use of low dose ICS/formoterol as a reliever medication are primarily derived from budesonide-formoterol (a formulation not available in the US).

‡ Low dose ICS-formoterol is reliever for those prescribed budesonide-formoterol or beclomethasone dipropionate-formoterol maintenance and reliever therapy. GINA does not recommend use of ICS-formoterol as the reliever for patients taking combination ICS/LABA with a different LABA; rather, a SABA should be used in these patients.

In 2007, the National Asthma Education and Prevention Panel (NAEPP) released a summary of the third report of the Expert Panel (EPR-3) and recommend that, for patients over age 5 years with moderate persistent asthma or asthma not controlled by low-dose corticosteroids, consideration be given for use of a combination of ICS and LABAs or for increasing the dose of ICS.[48] LAMA agents, such as tiotropium (Spiriva Respimat), are not addressed for chronic management in these guidelines; however, the guidelines do include dosing of SAMA agents, such as ipratropium for the emergency management of acute asthma exacerbations in combination with albuterol or as an alternative to albuterol.

Tiotropium inhalational spray (Spiriva Respimat) is approved for the treatment of asthma in patients ≥ 6 years of age. Multiple other medications are indicated for the treatment of asthma and information can be found in other class reviews. In the 2020 GINA guidelines, for children 6 to 11 years of age, tiotropium is an option as add-on to high dose ICS in patients requiring 2 or more controllers and an as-needed reliever medication (Step 4).

PHARMACOLOGY[49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]

The antimuscarinic agents, also known as anticholinergic agents, aclidinium (Duaklir Pressair, Tudorza Pressair), ipratropium (Atrovent), revefenacin (Yupelri), tiotropium (Spiriva HandiHaler, Spiriva Respimat, Stiolto Respimat), glycopyrrolate (Bevespi Aerosphere, Lonhala Magnair, Seebri Neohaler, Utibron Neohaler), and umeclidinium (Incruse Ellipta, Anoro Ellipta) antagonize the action of acetylcholine released from the vagus nerve. Inhibition of the muscarinic receptors blocks the cholinergic neurotransmission causing bronchodilation.

Aclidinium, glycopyrrolate, revefenacin, tiotropium, and umeclidinium have similar affinity to the muscarinic receptor subtypes M1 to M5.[66,67] However, in the airways, they exhibit pharmacological effects through inhibition of M3-receptors at the smooth muscle. This functional selectivity for M3 receptors is due to their ability to dissociate significantly faster from M2 receptors than from M3 receptors, unlike ipratropium.[68] Aclidinium association rate for the M3 receptor was similar to ipratropium and 2.6 times faster than tiotropium.

Roflumilast (Daliresp) and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). This action leads to the accumulation of cyclic adenosine monophosphate

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(cAMP) in lung tissue. Although, the specific mechanism by which roflumilast exerts its therapeutic action in patients with COPD is not well-defined, it is believed to reduce inflammation by increasing cAMP.[69]

Albuterol is a short-acting beta$_2$-agonist (SABA). The combination of albuterol and ipratropium (Combivent Respimat) enables simultaneous administration to produce greater bronchodilator effect than possible with either drug alone. Both ingredients exert a local effect on the muscarinic and beta$_2$ receptors in the lung.

The combination of an antimuscarinic and LABA works simultaneously to produce bronchodilation. LABAs, such as vilanterol (Anoro Ellipta), olodaterol (Stiolto Respimat), formoterol fumarate (Bevespi Aerosphere, Duaklir Pressair), and indacaterol (Utibron Neohaler), selective agonists at beta-$_2$ receptors, exert their effects by increasing activity of adenyl cyclase, an intracellular enzyme responsible for the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP) thus producing bronchodilation and a resultant increase in bronchial airflow.

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PHARMACOKINETICS[70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86]

Drug	Onset of Action 15% or more increase in FEV_1 (hours)	Time to Peak FEV_1 (hours)	Duration of Action (hours)
Antimuscarinics – Short-Acting			
ipratropium inhalation solution (Atrovent)	0.25–0.5	1–2	4–5; up to 7–8 in some patients
ipratropium inhalation aerosol MDI (Atrovent HFA)	0.25	1–2	2–4
Antimuscarinics – Long-Acting			
aclidinium bromide inhalation powder (Tudorza Pressair)	0.5	2–3	12
glycopyrrolate (Lonhala Magnair)	nr	1-2	nr
glycopyrrolate (Seebri Neohaler)	nr	1–2	nr
revefenacin (Yupelri)	nr	nr	nr
tiotropium inhalation powder (Spiriva HandiHaler)	0.5 (13% increase in FEV_1)	1–4	24
tiotropium inhalation spray (Spiriva Respimat)	nr	nr	24
Antimuscarinics – Long-Acting			
umeclidinium inhalation powder (Incruse Ellipta)	nr	nr	24
Antimuscarinic /Beta$_2$-Agonist Combinations – Short-Acting			
albuterol/ipratropium inhalation solution	nr	1.5	4.3–5
albuterol/ipratropium MDI (Combivent Respimat)	0.25	1	4–5
Antimuscarinic/Beta$_2$-Agonist Combinations – Long-Acting			
aclidinium bromide/formoterol (Duaklir Pressair)	nr	nr	nr
glycopyrrolate/formoterol fumarate (Bevespi Aerosphere)	nr	nr	nr
glycopyrrolate/indacaterol (Utibron Neohaler)	nr	1–4	nr
tiotropium/olodaterol (Stiolto Respimat)	nr	2	nr
umeclidinium/vilanterol inhalation powder (Anoro Ellipta)	0.25	3	24
Phosphodiesterase 4 (PDE4) Inhibitor			
roflumilast (Daliresp)	nr	nr	nr

nr = not reported

Bronchodilation following inhalation of these agents is a local, site-specific effect. It is important to note that roflumilast (Daliresp) is not a bronchodilator.

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Although much of an administered dose of aclidinium (Tudorza Pressair), ipratropium (Atrovent), and tiotropium (Spiriva HandiHaler) is swallowed, since they are quaternary amines, minimal drug absorption from the gastrointestinal (GI) tract is expected. Ipratropium is poorly absorbed from the lungs while tiotropium is highly bioavailable from the lung surface (19.5% absolute bioavailability). Following inhalation of tiotropium solution (Spiriva Respimat), urinary excretion data suggest that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3% but, given the mode of administration, suggest there should be substantially higher concentrations in the lung.

Fourteen percent of an inhaled dose of tiotropium is excreted unchanged in the urine. Renal impairment is associated with increased tiotropium concentrations after dry powder inhalation. Approximately 25% of an absorbed tiotropium dose is metabolized via the cytochrome P450 system. Inhibitors of CYP450 3A4 or 2D6, such as ketoconazole or quinidine, may impact tiotropium metabolism. The terminal elimination half-life of tiotropium is between 5 and 6 days and, after once daily inhalation by COPD patients, steady state was reached after 2 to 3 weeks.

The absolute bioavailability of aclidinium bromide is approximately 6% in healthy volunteers. It is extensively metabolized, via hydrolysis, with only 1% excreted as unchanged aclidinium. Approximately 54% to 65% of the radioactivity was excreted in urine and 20% to 33% of the dose was excreted in feces. The estimated effective half-life is 5 to 8 hours.

Following twice-daily oral inhalation of aclidinium/formoterol (Duaklir Pressair), the mean maximum concentrations of both components were reached within 5 minutes. Steady state occurred within 5 days.

In vitro and *in vivo* data showed that revefenacin is rapidly and primarily metabolized via hydrolysis to an active metabolite with activity that is approximately one-third to one-tenth of revefenacin's but the metabolite plasma exposure is 4- to 6-fold higher than revefenacin. Following inhaled administration, revefenacin and its active metabolite were detected within about 14 to 41 minutes in healthy and COPD patients. Revefenacin is extensively distributed to tissues. Revefenacin reaches steady state within 8 days and has a terminal half-life (parent and active metabolite) of 22 to 70 hours in COPD patients.

The absolute bioavailability of roflumilast following a 500 microgram oral dose is approximately 80%. Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Following an oral dose, the median plasma half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing.

In vitro clinical data showed that umeclidinium (Incruse Ellipta) was mostly absorbed from the lung after inhaled doses with minimum contribution from oral absorption. Umeclidinium is primarily metabolized by CYP2D6 and is a P-gp substrate; metabolites have either low or no pharmacological activity. Following oral dosing to healthy male subjects, 92% of the total dose was recovered in feces, and in urine recovery was less than 1% of the total dose. The effective half-life after once-daily inhalation dosing is 11 hours.

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Following inhalation of umeclidinium/vilanterol (Anoro Ellipta), maximum concentration is reached in 5 to 15 minutes and is mostly absorbed from the lung with minimum contribution from oral absorption. *In vitro* data indicates umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6). The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation). The metabolites formed have low or no pharmacological activity. Approximately 92% of the drug is excreted via feces with 1% via urine. Metabolism of vilanterol primarily occurs via hepatic CYP3A4 with the metabolites having significantly reduced $beta_1$- and $beta_2$-agonist activity. Both umeclidinium and vilanterol are a substrate for the P-glycoprotein (P-gp) transporter. Following oral administration, vilanterol metabolites are excreted mainly via urine (70%) and feces (30%).

Data on the tiotropium component of tiotropium/olodaterol (Stiolto Respimat) are comparable to those for tiotropium solutions described above. Olodaterol reaches maximum plasma concentrations within 10 to 20 minutes following inhalation, and inhaled bioavailability is 30% (oral bioavailability is negligible). Olodaterol is metabolized by direct glucuronidation, O-demethylation, and conjugation via CYP2C9 and CYP2C8. Metabolites have little to no clinical activity. The half-life of olodaterol is approximately 7.5 hours, with 38% excreted in the urine and 58% in the feces.

Following inhalation, the median time to reach peak plasma concentrations is 5 minutes for glycopyrrolate (Bevespi Aerosphere, Seebri Neohaler, Utibron Neohaler), 15 minutes for indacaterol (Utibron Neohaler), < 20 minutes for glycopyrrolate (Lonhala Magnair), and 20 to 60 minutes for formoterol fumarate (Bevespi Aerosphere). Absolute bioavailability of glycopyrrolate and indacaterol are 40% and 43% to 45%, respectively, when inhaled, and both agents have minimal gastrointestinal absorption. Bioavailability is not reported in the prescribing information for glycopyrrolate/formoterol fumarate (Bevespi Aerosphere).

Glycopyrrolate (Bevespi Aerosphere, Lonhala Magnair, Seebri Neohaler, Utibron Neohaler) is metabolized via oxidation and hydrolysis by multiple CYP isoenzymes, while indacaterol (Utibron Neohaler) is metabolized by UGT1A1 and CYP3A4. Glycopyrrolate is eliminated primarily renally (60% to 85%) and has a terminal half-life of 33 to 53 hours. Renal clearance plays a very small role in the elimination of indacaterol but plays a role in the clearance of formoterol (62%); 54% of indacaterol is eliminated via the feces. The half-life of indacaterol is 40 to 56 hours. The elimination half-life of glycopyrrolate/formoterol fumarate is 11.8 hours.

CONTRAINDICATIONS/WARNINGS[87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104]

Patients with a history of hypersensitivity to atropine or any of its derivatives (e.g., ipratropium) should not use products containing ipratropium (Atrovent, Combivent Respimat) or tiotropium (Spiriva, Spiriva Respimat, Stiolto Respimat). Immediate hypersensitivity reactions, including angioedema, anaphylaxis, urticaria, rash, bronchospasm, or itching, may occur after administration of aclidinium (Duaklir Pressair, Tudorza Pressair), tiotropium, umeclidinium (Anoro Ellipta, Incruse Ellipta), or roflumilast (Daliresp). If such a reaction occurs, therapy should be stopped at once, and alternative treatments should be considered. Aclidinium and umeclidinium are contraindicated in patients who have a severe hypersensitivity to milk proteins or any other ingredient contained in the product. Patients with a hypersensitivity to the active ingredient(s) or any component of the product should not use glycopyrrolate (Lonhala Magnair), glycopyrrolate/formoterol fumarate (Bevespi Aerosphere), or revefenacin (Yupelri).

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Aclidinium and tiotropium inhalation powders, aclidinium/formoterol (Duaklir Pressair), glycopyrrolate/formoterol fumarate (Bevespi Aerosphere), glycopyrrolate (Lonhala Magnair, Seebri Neohaler), glycopyrrolate/indacaterol (Utibron Neohaler), revefenacin (Yupelri), tiotropium/olodaterol (Stiolto Respimat), umeclidinium (Incruse Ellipta), umeclidinium/vilanterol (Anoro Ellipta), and roflumilast (Daliresp) are not indicated for the initial treatment of acute episodes of bronchospasm or acute deterioration of COPD (e.g., rescue therapy). Avoid using these agents to relieve sudden breathing problems and avoid taking extra doses.

All LABAs were previously contraindicated and carried a boxed warning in patients with asthma without use of a long-term asthma control medication due to the risk of asthma related death. However, in December 2017, the FDA released a communication based on 4 large clinical safety trials. The FDA determined that treatment of asthma with a LABA in combination with an ICS does not lead to significantly more serious asthma-related adverse effects than treatment with an ICS alone. As a result, the boxed warning regarding asthma-related death was removed from ICS and LABA labeling (including combination products). The boxed warning regarding increase risk of asthma-related death with use of LABAs alone to treat asthma will remain in labels for single component LABAs.

Roflumilast is contraindicated for use in patients with moderate to severe liver impairment (Child-Pugh B or C). Psychiatric adverse events (insomnia, depression, and anxiety) were twice as frequent in patients taking roflumilast in controlled trials as compared to placebo. One completed suicide and 2 suicide attempts were reported in clinical trials; post-marketing has produced reports of suicidal ideation in patients with and without a history of depression and the postmarket RESPOND study reported 1 completed suicide. All patients should be monitored for signs of suicidal ideation. For patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits before use. Moderate (5% to 10% of body weight) and severe (> 10% of body weight) weight loss have been reported with roflumilast therapy. Weight was regained after discontinuation of therapy.

Inhaled medicines may cause paradoxical bronchospasm, which may be life-threatening. If this occurs, treatment with any of these products should be stopped and other alternatives considered.

Aclidinium, glycopyrrolate, ipratropium, revefenacin, tiotropium, and umeclidinium should be used with caution in patients with narrow-angle glaucoma or urinary retention. Patients should consult with a physician immediately if symptoms of prostatic hyperplasia or bladder-neck obstruction occur.

Clinically significant cardiac effects, including electrocardiogram (ECG) effects, may occur with excessive LABA use; do not use at doses higher than recommended. Dose may need to be decreased if these effects occur when using the recommended dose. Similarly, beta-agonists may cause hypokalemia, potentially adding to cardiac concerns. Cardiovascular effects and fatalities have been reported in association with overuse of inhaled sympathomimetic medications. When using these medications other LABAs should not be used.

Sympathomimetic agents, including albuterol and LABAs, should be used cautiously in patients with convulsive disorders, thyrotoxicosis, suspected QT prolongation, and those with known sympathomimetic sensitivity. These agents may also cause hyperglycemia.

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DRUG INTERACTIONS[105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121]

Monoamine oxidase (MAO) inhibitors and tricyclic antidepressants should be used cautiously with albuterol-containing products, such as albuterol/ipratropium inhalation solution, and albuterol/ipratropium CFC-free MDI due to the potentiation of cardiovascular effects. A 2-week discontinuation period of the MAO inhibitors and tricyclic antidepressants is suggested prior to initiating therapy with an albuterol-containing product.

Due to their sympathomimetic effects, LABAs should be used cautiously with adrenergic drugs, other sympathomimetic, xanthine derivatives, steroids, MAO inhibitors, tricyclic antidepressants, beta-blockers, and agents that prolong the QT interval. If co-administration is necessary due to lack of an acceptable alternative therapy, a cardioselective beta-blocker could be utilized to limit severe bronchospasm.

Due to the potential for hypokalemia, LABAs should be used cautiously with diuretics, xanthine derivatives, or steroids.

Avoid use of antimuscarinic agents within this class with other antimuscarinic medications.

Coadministration of revefenacin (Yupelri) with OATP1B1 and OATP1B3 inhibitors (e.g., cyclosporine, rifampicin) could lead to an increase in systemic exposure of revefenacin's active metabolite therefore coadministration is not recommended.

Use with inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, cimetidine) will increase roflumilast (Daliresp) systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit.

Caution is advised when considering the co-administration of umeclidinium/vilanterol with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, voriconazole) due to increased risk of adverse effects, including cardiovascular (e.g., QT prolongation).

Tiotropium/olodaterol (Stiolto Respimat) and glycopyrrolate/indacaterol (Utibron Neohaler) should be used cautiously with dual inhibitors of CYP and P-glycoprotein (P-gp), but no dose adjustment is needed.

No formal drug interaction studies have been performed with glycopyrrolate/formoterol fumarate (Bevespi Aerosphere).

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ADVERSE EFFECTS[122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138]

Drug	Dry Mouth	Headache	Nausea / Vomiting	Nervousness	Palpitation / Chest Pain	Tremor
Antimuscarinics – Short-Acting						
ipratropium inhalation solution (Atrovent)	3.2	6.4	4.1	0.5	reported	0.9
ipratropium inhalation aerosol MDI (Atrovent HFA)	2–4	6–7	4	nr	reported	nr
Antimuscarinics – Long-Acting						
aclidinium bromide inhalation powder (Tudorza Pressair)	< 1	6.6	1.1	nr	nr	nr
glycopyrrolate (Lonhala Magnair)	nr	≥ 2	nr	nr	nr	nr
glycopyrrolate (Seebri Neohaler)	nr	nr	< 1	nr	nr	nr
revefenacin (Yupelri)	nr	4	nr	nr	nr	nr
tiotropium inhalation powder DPI (Spiriva)	12–16	nr	1–4	nr	5–7	nr
tiotropium inhalation spray (Spiriva Respimat)	4.1	nr	nr	nr	nr	nr
umeclidinium inhalation powder (Incruse Ellipta)	nr	≥ 1	≥ 1	nr	nr	nr
Antimuscarinic/Beta$_2$-Agonist Combinations – Short-Acting						
albuterol/ipratropium inhalation solution	nr	nr	1.4	nr	2.6	nr
albuterol/ipratropium CFC-free MDI (Combivent Respimat)	< 2	3	< 2	nr	< 2	< 2
Antimuscarinic/Beta$_2$-Agonist Combinations – Long-Acting						
aclidinium bromide/formoterol (Duaklir Pressair)	1-3	6.3	nr	nr	nr	nr
glycopyrrolate/formoterol fumarate (Bevespi Aerosphere)	1–2	1–2	1–2	1–2	1–2	reported
glycopyrrolate/indacaterol (Utibron Neohaler)	nr	nr	nr	nr	< 1	nr
tiotropium/olodaterol (Stiolto Respimat)	reported	nr	nr	nr	reported	nr
umeclidinium/vilanterol inhalation powder DPI (Anoro Ellipta)	< 1	nr	< 1	nr	1	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported.

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Adverse Effects (continued)

Drug	Dry Mouth	Headache	Nausea / Vomiting	Nervousness	Palpitation / Chest Pain	Tremor
Phosphodiesterase 4 (PDE4) Inhibitor						
roflumilast (Daliresp)	nr	4.4	4.7	nr	reported	1–2

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported.

Common adverse reactions associated with aclidinium, when compared to placebo, include nasopharyngitis (5.5%), cough (3%), and dry mouth (< 1%).

The most common adverse effects with an incidence ≥ 1% for glycopyrrolate (Seebri Neohaler) include upper respiratory tract infections, urinary tract infections, oropharyngeal pain, nasopharyngitis, and sinusitis. Additionally, dysphonia was reported as an adverse event in post-marketing studies.

The most common adverse effects with an incidence ≥ 2% for glycopyrrolate (Lonhala Magnair) include dyspnea and urinary tract infections.

The most common adverse event reported with tiotropium was dry mouth (16%). Additionally, use of tiotropium inhalation spray (Spiriva Respimat) has been associated with pharyngitis, cough, and sinusitis. Other reports of adverse events with tiotropium are consistent with anticholinergic effects, including constipation (4%) and blurred vision.

In a single trial that enrolled 198 COPD patients, the number of patients with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the tiotropium-treated group (range, 16% to 20%) as compared to the placebo group (range, 1% to 12%) depending on QT correction method used. Other clinical studies did not detect a drug effect on QTc intervals.

In 2008, the FDA issued a MedWatch related to of the potential for tiotropium to increase the risk of stroke in patients.[139] However, in 2010, the FDA completed its review and issued a statement that the available data did not support the association between tiotropium use and an increase risk for stroke, myocardial infarction, or death from a cardiovascular event.[140]

Common adverse events (incidence ≥ 2% and more common than placebo) associated with the use of umeclidinium (Incruse Ellipta) include nasopharyngitis, upper respiratory tract infection, cough, and arthralgia. Additional postmarketing adverse events include eye pain, glaucoma, blurred vision, and urinary retention.

The most common adverse reactions (incidence ≥ 2%) reported in clinical trials of revefenacin (Yupelri) were cough (4% versus 4% with placebo), nasopharyngitis (4% versus 2% with placebo), upper respiratory tract infection (3% versus 2% with placebo), headache (4% versus 3% with placebo) and back pain (2% versus 1% with placebo).

Other common adverse reactions reported with aclidinium/formoterol (Duaklir Pressair) and at higher rates than placebo, respectively, were upper respiratory tract infection (8.9%and 6.3%) and back pain (3.8% and 3.4%)

Additional adverse effects reported with glycopyrrolate/indacaterol (Utibron Neohaler) include hypertension, back pain and dysphonia.

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The most common adverse reactions reported in ≥ 3% of patients using tiotropium/olodaterol (Stiolto Respimat) in clinical trials were nasopharyngitis, cough, and back pain.

The most common adverse reactions occurring in more than 1% of umeclidinium/vilanterol (Anoro Ellipta) patients were pharyngitis (2%), diarrhea (2%), and extremity pain (2%). Sinusitis, constipation, lower respiratory tract infection, muscle spasms, neck pain, and dysphonia have also been reported. Paradoxical bronchospasm caused by umeclidinium/vilanterol is a rare, but life-threatening event, reported in post-marketing studies.

The 2 most common adverse events reported with roflumilast (Daliresp) were diarrhea (9.5%) and weight loss (7.5%).

SPECIAL POPULATIONS[141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157]

Pediatrics

COPD is a disease that does not normally occur in children. Safety and effectiveness of ipratropium (Atrovent), albuterol/ipratropium inhalation solution, albuterol/ipratropium CFC-free MDI (Combivent Respimat), aclidinium DPI (Tudorza Pressair), aclidinium/formoterol (Duaklir Pressair), glycopyrrolate (Lonhala Magnair, Seebri Neohaler), glycopyrrolate/formoterol fumarate (Bevespi Aerosphere), glycopyrrolate/indacaterol (Utibron Neohaler), revefenacin (Yupelri), roflumilast (Daliresp), tiotropium (Spiriva HandiHaler), tiotropium/olodaterol (Stiolto Respimat), umeclidinium (Incruse Ellipta), and umeclidinium/vilanterol (Anoro Ellipta) in pediatric patients have not been established.

The efficacy of tiotropium inhalational spray (Spiriva Respimat) has not been demonstrated in patients < 18 years old with COPD; however, efficacy in patients ≥ 6years of age has been established in patients with asthma.

Geriatrics

Dose adjustments are not required in geriatric patients.

Pregnancy

Albuterol, albuterol/ipratropium inhalation solution, glycopyrrolate (Seebri Neohaler), glycopyrrolate/formoterol fumarate, glycopyrrolate/indacaterol, and umeclidinium/vilanterol are Pregnancy Category C. Previously a Pregnancy Category C product, roflumilast (Daliresp) and albuterol/ipratropium CFC-free MDI (Combivent Respimat) labeling has been updated to comply with Pregnancy and Lactation Labeling Rule (PLLR) and instructs that there are no randomized clinical trials of the product in pregnant women. Previously a Pregnancy Category B product, ipratropium (Atrovent HFA) labeling has been updated and states maternal use is not expected to result in fetal exposure due to the minimal systemic absorption following oral inhalation. Labeling for tiotropium (Spiriva, Spiriva Respimat), tiotropium/olodaterol (Stiolto Respimat), and umeclidinium (Incruse Ellipta) were also revised to comply with the PLLR and state that data are insufficient to inform of drug-associated risks if used during pregnancy. Also, in compliance with the PLLR, the labeling for aclidinium bromide (Tudorza Pressair), aclidinium/formoterol (Duaklir Pressair), and glycopyrrolate (Lonhala Magnair) does not include a pregnancy category, but rather, states there are no adequate and well-controlled studies in pregnant women.

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Hepatic Impairment

The pharmacokinetics of ipratropium have not been studied in patients with hepatic insufficiency.

No dosage adjustment of aclidinium (Tudorza Pressair) is needed for patients with hepatic impairment.

No dose adjustment of tiotropium/olodaterol is required in patients with mild to moderate hepatic impairment, but this agent has not been studied in severe hepatic impairment.

Umeclidinium (Incruse Ellipta) showed no relevant increases in exposure in patients with moderate hepatic impairment. No dosage adjustment of umeclidinium/vilanterol (Anoro Ellipta) is required for patients with moderate hepatic impairment.

No dose adjustment of glycopyrrolate or glycopyrrolate/indacaterol is required in patients with mild to moderate hepatic impairment. Neither agent has been studied in severe hepatic impairment.

No formal studies of aclidinium/formoterol (Duaklir Pressair) have been performed in patients with hepatic impairment. The need for dosage adjustment in this population is not anticipated based on available data for aclidinium and formoterol.

No formal studies of glycopyrrolate/formoterol fumarate have been conducted in patients with hepatic failure. However, formoterol fumarate is primarily cleared by hepatic metabolism and impairment might lead to accumulation of formoterol fumarate. Monitoring is recommended.

Roflumilast is not recommended for use in patients with moderate to severe hepatic impairment.

The safety of revefenacin in mild to severe hepatic impairment has not been evaluated. It is not recommended for use in patients with any degree of hepatic impairment.

Renal Impairment

The pharmacokinetics of ipratropium have not been studied in patients with renal insufficiency.

No dosage adjustment of aclidinium (Tudorza Pressair) is needed for patients with renal impairment.

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance. Patients with moderate to severe renal impairment (creatinine clearance [CrCl] of ≤ 50 mL/min or < 60 mL/min for tiotropium solution) should be monitored closely for anticholinergic side effects when treated with tiotropium or tiotropium-containing products.

No dose adjustment of umeclidinium (Incruse Ellipta) OR umeclidinium/vilanterol (Anoro Ellipta) is required in patients with renal impairment.

No dose adjustment of glycopyrrolate or glycopyrrolate/indacaterol is required in patients with mild to moderate renal impairment. Use of these agents in severe renal impairment should only be when the benefits clearly outweigh the risks of increased exposure.

No formal studies of aclidinium/formoterol (Duaklir Pressair) have been performed in patients with renal impairment. The need for dosage adjustment in this population is not anticipated based on available data for aclidinium and formoterol.

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No formal studies of glycopyrrolate/formoterol fumarate have been conducted in patients with renal failure. In patients with severe renal impairment (CrCl ≤ 30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, the medication should be used only when benefits outweigh the risk.

No dosage adjustment of roflumilast is necessary in patients with renal impairment.

No dose adjustment of revefenacin (Yupelri) is required in patients with renal impairment, however, patients with severe renal impairment should be monitored for systemic antimuscarinic side effects.

DOSAGES[158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174]

Drug	Adult Dose	Availability
Antimuscarinics – Short-Acting		
ipratropium bromide inhalation solution (Atrovent)	2.5 mL 3 to 4 times daily	500 mcg per 2.5 mL (0.02%)
ipratropium inhalation aerosol MDI (Atrovent HFA)	2 inhalations 4 times daily (do not exceed 12 inhalations in 24 hours)	17 mcg per actuation; 200 inhalations per package
Antimuscarinics – Long-Acting		
aclidinium bromide inhalation powder DPI (Tudorza Pressair)	1 inhalation twice daily	400 mcg per actuation; 30 and 60 actuations/package Breath activated device
glycopyrrolate inhalation solution (Lonhala Magnair)	1 mL twice daily	25 mcg per 1 mL starter kit containing 60 unit-dose vials and 1 Magnair nebulizer or refill kit containing 60 unit-dose vials and a Magnair handset refill
glycopyrrolate inhalation powder DPI (Seebri Neohaler)	1 inhalation twice daily	15.6 mcg per capsule; 60 capsules/package Breath activated device
revefenacin inhalation solution (Yupelri)	3 mL once daily via nebulizer	175 mcg per 3 mL unit-dose vial
tiotropium inhalation powder DPI (Spiriva HandiHaler)	1 inhalation daily (do not swallow capsules)	18 mcg per capsule; 30 or 90 capsules/package Breath activated device
tiotropium inhalation spray ISI (Spiriva Respimat)	COPD: 2 inhalations of 2.5 mcg/actuation once daily Asthma (adults and children ≥ 6 years old): 2 inhalations of 1.25 mcg/ actuation once daily (maximum benefits may take up to 4 to 8 weeks)	1.25, 2.5 mcg tiotropium per actuation; 60 actuations per package
umeclidinium inhalation powder DPI (Incruse Ellipta)	1 inhalation once daily	62.5 mcg per actuation; 30 actuations/package Breath activated device
Antimuscarinic/Beta$_2$-Agonist Combination – Short-Acting		
albuterol sulfate /ipratropium bromide inhalation solution	3 mL 4 times daily (up to 2 additional 3 mL doses per day)	3 mg/0.5 mg per 3 mL
albuterol/ipratropium bromide MDI CFC-free (Combivent Respimat)	1 inhalation (spray) 4 times daily (do not exceed 6 inhalations in 24 hours)	100/20 mcg per actuation; 120 actuations/package

CFC=chlorofluorocarbon; DPI=dry powder inhaler; HFA=hydrofluoroalkane; ISI=inhalation spray inhaler; MDI=metered-dose inhaler

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Dosages (continued)

Drug	Adult Dose	Availability
Antimuscarinic/Beta$_2$-Agonist Combination – Long-Acting		
aclidinium bromide/formoterol DPI (Duaklir Pressair)	1 inhalation twice daily	400/12 mcg per actuation; 30 and 60 actuations/package Breath activated device
glycopyrrolate/formoterol fumarate inhalation aerosol MDI (Bevespi Aerosphere)	2 inhalations twice daily	9/4.8 mcg per actuation; 28 and 120 actuations/canister
glycopyrrolate/indacaterol inhalation powder DPI (Utibron Neohaler)	1 inhalation twice daily	15.6/27.5 mcg per capsule; 60 capsules/package Breath activated device
tiotropium/olodaterol inhalation spray ISI (Stiolto Respimat)	2 inhalations once daily	2.5/2.5 mcg per actuation; 60 actuations/package
umeclidinium/vilanterol inhalation powder DPI (Anoro Ellipta)	1 inhalation daily (administered at the same time every day)	62.5 mg umeclidinium and 25 mcg vilanterol capsules; 30 capsules each of umeclidinium and vilanterol per package (1 capsule of each provides 1 dose) Breath activated device
Phosphodiesterase 4 (PDE4) Inhibitors		
roflumilast (Daliresp)	1 tablet (500 micrograms) daily, with or without food May initiate with 250 mcg once daily for 4 weeks, then increase to 500 mcg once daily thereafter, to reduce the rate of treatment discontinuation in some patients; 250 mcg is not an effective therapeutic dose	Oral tablets: 250 mcg, 500 mcg

CFC=chlorofluorocarbon; DPI=dry powder inhaler; HFA=hydrofluoroalkane; ISI=inhalation spray inhaler; MDI=metered-dose inhaler

Proper use of dry powder inhalers (DPIs) require the patient to perform rapid, deep inhalation, while metered-dose inhalers (MDIs) require hand-breath coordination.175 Inhalation spray inhalers (ISIs) do not depend on the strength of inhalation for proper drug delivery to the lungs.

The inhalation powders for glycopyrrolate (Seebri Neohaler), glycopyrrolate/indacaterol (Utibron Neohaler), and tiotropium (Spiriva HandiHaler), are dispensed as capsules in a blister pack. The capsule placed into the respective Neohaler or HandiHaler device, which pierces the capsule to allow for the powder to be delivered upon oral inhalation. The inhalation powder capsules should only be used with the respective Neohaler or HandiHaler devices and must not be swallowed.

The solution for inhalation for glycopyrrolate (Lonhala Magnair), is available as a unit-dose, single-use 1 mL vial (each vial contains 25 mcg of glycopyrrolate) in either a Starter Kit, which contains 60 unit-dose vials and 1 Magnair nebulizer system, or a Refill Kit, which contains 60 unit-dose vials and a Magnair handset refill (contains only medication cap, handset body, mouthpiece, and aerosol head). For the maintenance treatment of COPD, the recommended dose is inhalation of the contents of 1 vial twice daily using the Magnair nebulizer system. Each treatment should take approximately 2 to 3 minutes.

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The solution for inhalation for revefenacin (Yupelri) is available as a unit-dose vial and should only be removed from the foil pouch and opened immediately prior to use. It should not be mixed with other drugs in the nebulizer as the compatibility, efficacy, and safety of revefenacin have not been established when used with other drugs in the nebulizer.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

COPD

aclidinium (Tudorza Pressair) versus placebo

Three randomized, double-blind, placebo-controlled trials, compared aclidinium dry powder for inhalation 400 mcg or 200 mcg twice daily and placebo in patients (n=1,919) with stable, moderate to severe COPD. Two trials were 12 weeks in duration and one was 24 weeks. The primary efficacy endpoint was change from baseline in morning trough FEV_1 at study's end. Other efficacy variables included peak FEV_1 and St. George's Respiratory Questionnaire (SGRQ), rescue medication usage, and COPD exacerbations. The SGRQ measures the impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.[176] It is also designed with a responder rate threshold of an improved score of 4 or more. The effect size for aclidinium 400 mcg ranged from 72 mL to 124 mL across the 3 trials at Week 12, and the treatment effect persisted at Week 24 ($p<0.001$ for all trials).[177,178] Aclidinium 200 mcg also demonstrated a statistically significant difference in spirometry from placebo, although the magnitude of the treatment difference (51 to 86 mL) was smaller than the effect size observed for the 400 mcg dose. In addition, lack of efficacy was cited more frequently as a reason for discontinuation in the placebo and aclidinium 200 mcg arms compared to aclidinium 400 mcg. Greater decreases in total SGRQ scores were observed for aclidinium compared to placebo ($p<0.001$). Six- and 12-month extension studies suggested a decrease in rate of exacerbations with aclidinium. Results from the 6-month study were less consistent, although this variability may be due in part to a low background rate of exacerbations overall. Use of daily rescue medication changed by as much as -1.2 puffs/day in the aclidinium 400 mcg arm, compared to -0.3 puffs/day in the placebo group. The 200 mcg dosage was not FDA approved.

In a phase 3 efficacy and safety trial (ACCORD I), 561 patients were randomized (1:1:1) to twice daily aclidinium 200 mcg, 400 mcg, or placebo.[179] Primary endpoint was change from baseline in trough

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FEV_1; secondary endpoint was peak FEV_1. Both were measured at Week 12. Additional factors evaluated included the St. George's Respiratory Questionnaire (SGRQ) for health status, twice daily COPD symptoms assessment (assessed via the Transitional Dyspnea Index [TDI]), and safety. Both aclidinium arms showed a statistically significant improvement in trough FEV_1 over the baseline of 1.36 ± 0.54 L. The magnitude of improvement with the 200 mcg dose arm was 86 mL (95% confidence interval [CI], 45 to 127) and 124 mL (95% CI, 83 to 164) in the 400 mcg dose arm (p=0.0001 for both). Peak FEV_1 demonstrated 146 mL (95% CI, 101 to 190) and 192 mL (95% CI, 148 to 236) improvements in the 200 mcg and 400 mcg arms, respectively (p≤0.001 for both). Aclidinium improved SGRQ, TDI, and COPD symptom scores over placebo in both arms (p<0.05). Adverse events were similar across all groups; dry mouth and constipation (both < 2%) were the most commonly reported. Both aclidinium 200 mcg and 400 mcg demonstrated improved efficacy over placebo with similar adverse event profiles.

aclidinium (Tudorza Pressair) versus placebo on cardiovascular outcomes

In the ASCENT randomized, double-blind, placebo-controlled trial patients were evaluated over 36 months for the long-term cardiovascular safety in addition to exacerbations (n=3,630).[180] The trial compared aclidinium (n=1,791) versus placebo (n=1,798). The primary endpoints were the time to first occurrence of a major adverse cardiovascular event (MACE) and the rate of moderate to severe exacerbations during the first year of treatment. Of the patients on aclidinium, 3.9% were reported with at least one MACE compared to 4.2% in the placebo group. The incidence rate of MACE resulted in 2.4 per 100 patient years on aclidinium compared to 2.8 per 100 patient years on placebo (HR, 0.89 [95% CI, 0.64 to 1.23]. There was a 17% reduction in the rate of moderate to severe exacerbations on aclidinium compared to placebo (rate ratio [RR], 0.83 [95% CI, 0.73 to 0.94]; p=0.003). There was a 28% reduction in the rate of hospitalizations due to COPD exacerbation for aclidinium compared to placebo (RR, 0.72 [95% CI, 0.55 to 0.99], p=0.02].

albuterol MDI (Proventil, Ventolin) + ipratropium MDI (Atrovent) versus formoterol (Foradil) + ipratropium MDI (Atrovent)

A large, randomized, double-blind, double-dummy, 2-period crossover study of 172 patients with COPD investigated the effects of the addition of either formoterol or albuterol to ipratropium in patients whose symptoms were not optimally controlled by ipratropium alone.[181] In addition to ipratropium MDI 40 mcg 4 times daily, patients received, in random order, formoterol DPI 12 mcg twice daily for 3 weeks followed by albuterol MDI 200 mcg 4 times daily for 3 weeks, or vice versa. Morning peak expiratory flow rate (PEFR) and FEV_1 were significantly better with the formoterol-ipratropium combination than with the albuterol-ipratropium combination (p=0.0003 and p<0.0001 for PEFR and FEV_1, respectively). Similar findings were noted for FVC. On average, all mean individual symptom scores were lower for patients receiving the formoterol-ipratropium combination than for those receiving the albuterol-ipratropium combination (p=0.0042). There were no significant differences between the formoterol and albuterol groups in mean percentage of days with no rescue drug (72.3% and 68.8%, respectively), the number of patients with no COPD exacerbations (34.6% and 30.8%, respectively), or the percentage of patients experiencing "bad days" during the trial (65% and 69%, respectively).

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aclidinium/formoterol (Duaklir Pressair) versus aclidinium (Tudorza Pressair) versus formoterol fumarate inhalation versus tiotropium (Spiriva)

The AMPLIFY (NTCT02796677) trial was a 24-week, randomized, parallel-group, double-blind, double-dummy, active-controlled that compared aclidinium/formoterol 12/400 mcg twice daily to aclidinium 400 mcg twice daily, formoterol fumarate 12 mcg twice daily, and tiotropium 18 mcg once daily in patients with stable, moderate-to-severe COPD.[182] The fixed-dose combination product resulted in significantly greater improvements in 1-hour post-dose FEV_1 compared with aclidinium (84 mL; p<0.0001), formoterol fumarate (84 mL; p<0.0001), and tiotropium (92 mL; p<0.0001). Significantly greater improvements in change from baseline in trough FEV_1 for the combination compared to formoterol fumarate (55 mL; p<0.001) was also seen; however, the improvements for the combination product compared with aclidinium (14 mL) and tiotropium (19 mL) were not statistically significant. Two additional studies (NCT01492942, NCT01437397) comparing fixed-dose aclidinium/formoterol with aclidinium and with formoterol fumarate reported similar findings in the differences in change in 1-hour post-dose FEV_1 and trough FEV_1.[183]

glycopyrrolate/formoterol fumarate (Bevespi Aerosphere) versus placebo

The safety and efficacy of glycopyrrolate/formoterol fumarate were assessed in 2 placebo-controlled lung function trials of 24 weeks.[184,185,186] Trial 1 and Trial 2, 24 week, randomized, double-blind, placebo-controlled, parallel-group confirmatory trials, were conducted in patients with moderate to very severe COPD (n=3,699; ages 40 to 80 years old; history of smoking ≥ 10 pack-years; post-albuterol FEV_1 < 80% of predicted normal values; FEV_1/FVC ratio < 0.7).[187] Trial 1 and Trial 2 evaluated glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, and placebo twice daily. Trial 1 also had an open-label active control. In both trials glycopyrrolate/formoterol fumarate showed a larger increase in mean change from baseline in trough FEV_1 at week 24 compared to placebo (150 mL and 103 mL, respectively), glycopyrrolate (59 mL and 54 mL, respectively), and formoterol fumarate (64 mL and 56 mL, respectively), the primary endpoint. In Trial 1 and Trial 2, the mean peak FEV_1 improvement from baseline compared to placebo at week 24 was 291 mL (95% CI, 252 to 331) and 267 mL (95% CI, 226 to 308), respectively. Glycopyrrolate/formoterol fumarate also showed an onset of bronchodilatory effect at 5 minutes after the first dose based on a mean increase in FEV_1 compared to placebo in both trials. In Trial 1, the SGRQ responder rate (defined as an improvement in score of ≥ 4) was 37%, 30%, 35%, and 28% for glycopyrrolate/formoterol fumarate, glycopyrrolate, formoterol fumarate, and placebo, respectively, with odds ratios of 1.4 (95% CI, 1.1 to 1.8), 1.1 (95% CI, 0.9 to 1.5), and 1.5 (95% CI, 1.1 to 2.1) for glycopyrrolate/formoterol fumarate versus glycopyrrolate, glycopyrrolate/formoterol fumarate versus formoterol fumarate, and glycopyrrolate/formoterol fumarate versus placebo, respectively. Trends were similar in Trial 2 with odds ratios of 1.2 (95% CI, 0.9 to 1.6), 1.3 (95% CI, 1.9 to 1.7), and 1.3 (95% CI, 0.9 to 1.8) for glycopyrrolate/formoterol fumarate versus glycopyrrolate, glycopyrrolate/formoterol fumarate versus formoterol, and glycopyrrolate/formoterol fumarate versus placebo, respectively. Consistent improvements were also observed in trough FEV_1 with respect to age, gender, degree of airflow limitation, GOLD stage, smoking status, or inhaled corticosteroid (ICS). Decreased use of daily rescue albuterol with glycopyrrolate/formoterol fumarate was observed in both trials compared to placebo. Safety and efficacy was confirmed at 52 weeks in long-term trials.[188]

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glycopyrrolate/formoterol fumarate (Bevespi Aerosphere) versus umeclidinium/vilanterol (Anoro Ellipta)

In a double-blind, double-dummy, 24-week study, patients with COPD received glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg MDI 2 inhalations per dose, twice-daily (n=559) or umeclidinium 62.5 mcg/vilanterol 25 ~~mcgDPI~~mcg DPI one inhalation, once-daily (n=560).[189,190] Primary endpoints were change from baseline in morning pre-dose trough FEV_1 and peak change from baseline in FEV_1 within 2 hours post-dose. Glycopyrrolate/formoterol fumarate was non-inferior to umeclidinium/vilanterol for peak FEV_1 (LSM difference of - 3.4 mL, 97.5% CI, - 32.8 to 25.9) but not for trough FEV_1 (LSM difference of - 87.2 mL; 97.5% CI, - 117 to - 57.4). Glycopyrrolate/formoterol fumarate was nominally superior to umeclidinium/vilanterol for onset of action ($p < 0.0001$). Exacerbation and safety measures were similar between the treatments.

glycopyrrolate (Lonhala Magnair) versus placebo

Approval of glycopyrrolate (Lonhala Magnair) is based on the GOLDEN (Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer) trials, which included 2 dose-ranging studies (n=378), two 12-week placebo-controlled confirmatory studies (n=1,294), and one 48 week safety study.[191] GOLDEN-3 and GOLDEN-4 were phase 3, randomized, double-blinded, placebo-controlled, confirmatory trials in patients with moderate to very severe COPD. Patients were randomized to receive glycopyrrolate 25 mcg, 50 mcg, or placebo twice daily. The primary endpoint was the change from baseline in trough FEV_1 at 12 weeks compared with placebo. Patients receiving glycopyrrolate 25 mcg or 50 mcg twice daily had statistically significant changes from baseline in trough FEV_1, as compared with placebo (GOLDEN-3: 0.105 L and 0.126 L [25 and 50 mcg glycopyrrolate, respectively]; $p \leq 0.0001$; GOLDEN-4: 0.084 L and 0.082 L [25 and 50 mcg glycopyrrolate, respectively); $p \leq 0.0001$]). There was not a sufficient increase in benefit seen to support use of the 50 mcg dose over the 25 mcg dose.

glycopyrrolate (Seebri Neohaler) versus placebo

Safety and efficacy of glycopyrrolate were evaluated in 2 dose ranging, four 12-week, placebo-controlled trials (2 of which were to support the approval of glycopyrrolate/indacaterol fixed dose combination; GEM1 and GEM2), and a 52-week safety trial. Efficacy of glycopyrrolate is based on these 2 dose ranging trials of 471 COPD patients and 2 placebo-controlled confirmatory trials in 867 COPD patients.[192,193] Two of the 12-week, randomized, double-blind, placebo-controlled, parallel group confirmatory trials evaluated the efficacy of glycopyrrolate on lung function in 867 COPD patients. The primary endpoint was to evaluate change from baseline in FEV_1 $AUC_{(0\text{-}12h)}$ after the day 85 morning dose of the 15.6 mcg twice daily dose versus placebo. Both trials demonstrated a greater increase in least squares mean change from baseline in FEV_1 $AUC_{(0\text{-}12h)}$ versus placebo (Trial 1: difference, 0.139 L; 95% CI, 0.095 to 0.184; and Trial 2: difference, 0.123 L; 95% CI, 0.081 to 0.165). The SGRQ was assessed in Trials 1 and 2. In Trial 1, the responder rate for the glycopyrrolate treatment arm was 49% compared to 41% for placebo (odds ratio [OR], 1.43; 95% CI, 0.95 to 2.15). In Trial 2, the SGRQ responder rate for the glycopyrrolate treatment arm was 55% compared to 42% for placebo (OD, 1.78; 95% CI, 1.17 to 2.71).

glycopyrrolate/indacaterol (Utibron Neohaler) versus placebo

The safety and efficacy of glycopyrrolate/indacaterol were evaluated in 2 placebo-controlled confirmatory trials (FLIGHT1 and FLIGHT2), and a 12-month long-term safety trial in COPD patients

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(n=615). [194,195] The efficacy is based on the dose ranging trials which included 562 COPD or asthma patients and the confirmatory trials of 2,038 patients. In the confirmatory trials, the active-controls in these trials were the individual components of the product, indacaterol 27.5 mcg twice daily and glycopyrrolate twice daily, and were included to approximate the contribution each product makes in improved FEV_1. The primary endpoint of the 12-week, randomized, double-blind, placebo- and active-controlled, parallel group confirmatory trials was the least squares mean change from baseline in FEV_1 $AUC_{(0\text{-}12h)}$ following the morning dose of glycopyrrolate/indacaterol (27.5/15.6 mcg) at day 85 compared to placebo. The combination therapy of glycopyrrolate/indacaterol demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{(0\text{-}12h)}$ versus placebo (Trial 1 [n=996]: difference, 0.262 L; 95% CI, 0.224 to 0.3; and Trial 2 [n=1,039]: difference, 0.231 L; 95% CI, 0.192 to 0.271). The combination therapy of glycopyrrolate/indacaterol demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{(0\text{-}12h)}$ versus indacaterol (Trial 1: difference, 0.112 L; 95% CI, 0.075 to 0.149; and Trial 2: difference, 0.094 L; 95% CI, 0.055 to 0.133) and glycopyrrolate (Trial 1: difference, 0.079 L; 95% CI, 0.042 to 0.116; and Trial 2: difference, 0.098 L; 95% CI, 0.059 to 0.137). In both trials, patients used less daily rescue medication (albuterol) compared to patients receiving placebo. In Trial 1, improvement in SGRQ score was higher with glycopyrrolate/indacaterol than with comparators: odds ratios [OR] of 1.4 (95% CI, 1 to 2), 1.1 (95% CI, 0.8 to 1.7), and 2.9 (95% CI, 1.9 to 4.2), for glycopyrrolate/indacaterol versus glycopyrrolate, glycopyrrolate/indacaterol versus indacaterol, and glycopyrrolate/indacaterol versus placebo, respectively. In Trial 2, the SGRQ responder rate was 57%, 46%, 48%, and 39%, for glycopyrrolate/indacaterol, glycopyrrolate, indacaterol, and placebo, respectively, with ORs for glycopyrrolate/indacaterol versus glycopyrrolate of 1.6 (95% CI, 1.1 to 2.3), glycopyrrolate/indacaterol versus indacaterol of 1.5 (95% CI, 1.1 to 2.2), and glycopyrrolate/indacaterol versus placebo of 2.2 (95% CI, 1.5 to 3.2), respectively.

glycopyrrolate/indacaterol (Utibron Neohaler) versus umeclidinium/vilanterol (Anoro Ellipta)

Two replicate, randomized, double-blind, double-dummy, active-controlled, crossover studies compared the efficacy of glycopyrrolate/indacaterol to umeclidinium/vilanterol in patients with moderate to severe COPD (n=357 in study 1 and n=355 in study 2).[196,197,198] Patients were randomized 1:1 to sequential treatments of glycopyrrolate/indacaterol 27.5/15.6 mcg twice daily or umeclidinium/vilanterol 62.5/25 mcg once daily for 12 weeks each, separated by a 3-week washout period. The primary outcome was noninferiority of glycopyrrolate/indacaterol based on 24 hour FEV_1 at week 12 (FEV_1 $AUC_{[0\text{-}24h]}$), and noninferiority was defined as a lower bound margin of the confidence interval of -20 mL. At week 12, the FEV_1 $AUC_{[0\text{-}24h)}$ was 232 mL and 244 mL for glycopyrrolate/indacaterol and umeclidinium/vilanterol, respectively, in study 1 and 185 mL and 203 mL for glycopyrrolate/indacaterol and umeclidinium/vilanterol, respectively, in study 2. In both studies, indacaterol did not meet noninferiority, as the lower bound was -26.9 mL in study 1 and -34.2 in study 2. Despite this lack of statistical noninferiority, the authors concluded that the potential between-group difference was not clinically significant. This study was funded by Sunovion/Novartis.

revefenacin (Yupelri) versus placebo

The safety and efficacy of revefenacin were evaluated in two 12-week, double-blind, placebo-controlled, randomized, parallel-group clinical trials (Trial 1 [NCT02459080], n=619; Trial 2 [NCT02512510], n=645) in patients with moderate to severe COPD.[199,200,201] Patients were randomized to 88 mcg or 175 mcg of revefenacin or to placebo administered once daily via a standard jet nebulizer (PARI LC® Sprint Reusable Nebulizer). The primary endpoint in both trials was the change from baseline

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in predose, or trough, FEV_1 at day 85, following 12 weeks of therapy, in the intent-to-treat (ITT) population. In Trial 1, the least squares mean change in baseline trough FEV_1 was -19 mL in the placebo group compared to 127 mL in the 175 mcg revefenacin group (difference, 146 mL; 95% CI, 103.7 to 188.8). In Trial 2, the least squares mean change in baseline trough FEV_1 was -45 mL in the placebo group compared to 102 mL in the 175 mcg revefenacin group (difference, 147mL; 95% CI, 97 to 197.1). Improvement in mean peak FEV_1, defined as the highest post-dose FEV_1 within the first 2 hours after dosing, on day 1 relative to placebo was 133 mL and 129 mL in Trials 1 and 2, respectively. The SGRQ responder rate (defined as a score improvement ≥ 4) for the 175 mcg treatment group on day 85 was 49% versus 34% with placebo (odds ratio [OR], 2.11; 95% CI, 1.14 to 3.92) in Trial 1 and 45% versus 39%, respectively (OR, 1.31; 95% CI, 0.72 to 2.38) in Trial 2. As only the 175 mcg dose is FDA-approved, available results focus on results with this dose.

roflumilast (Daliresp) versus placebo

Multiple clinical trials comparing roflumilast to placebo have demonstrated its efficacy in COPD patients.[202]

A phase 3, multicenter, double-blind, randomized, placebo-controlled study assigned 1,411 patients with COPD to roflumilast 250 mcg (n=576), roflumilast 500 mcg (n=555), or placebo (n=280) given once daily for 24 weeks.[203] Primary outcomes were post-bronchodilator FEV_1 and health-related quality of life. Secondary outcomes included other lung function parameters and COPD exacerbations. Post-bronchodilator FEV_1 at the end of treatment significantly improved with roflumilast 250 mcg (+74 mL) and roflumilast 500 mcg (+97 mL) compared with placebo ($p<0.0001$). Improvement in health-related quality of life was greater with roflumilast 250 mcg (-3.4 units) and roflumilast 500 mcg (-3.5 units) than with placebo (-1.8 units), but the differences were not significant. The mean numbers of exacerbations per patient were 1.13, 1.03, and 0.75 with placebo, roflumilast 250 mcg, and roflumilast 500 mcg, respectively. Most adverse events were mild to moderate in intensity.

Two double-blind, multicenter trials studied patients older than 40 years with moderate-to-severe COPD who were randomly assigned to roflumilast 500 mcg or placebo once daily for 24 weeks in addition to salmeterol or tiotropium.[204] The primary endpoint was change in pre-bronchodilator FEV_1. In the salmeterol/roflumilast trial, 466 patients were assigned to and treated with roflumilast and 467 with placebo; in the tiotropium/roflumilast trial, 371 patients were assigned to and treated with roflumilast and 372 with placebo. Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV_1 by 49 mL ($p<0.0001$) in patients treated with salmeterol, and 80 mL ($p<0.0001$) in those treated with tiotropium. Similar improvement in post-bronchodilator FEV_1 was noted in both groups. Roflumilast had beneficial effects on other lung function measurements in both groups. Nausea, diarrhea, weight loss, and headache were more frequent in roflumilast patients.

In 2 placebo-controlled, double-blind, multicenter trials, patients with COPD older than 40 years with severe airflow limitation, bronchitis symptoms, and a history of exacerbations were randomly assigned to roflumilast 500 mcg daily or placebo for 52 weeks.[205] Primary endpoints were change in pre-bronchodilator FEV_1 and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Patients were assigned to treatment, stratified according to smoking status and treatment with long-acting beta agonists (LABA), and given roflumilast (n=1,537) or placebo (n=1,554). In both studies, the primary endpoints were achieved and were similar in magnitude. In a pooled analysis, pre-bronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo ($p<0.0001$). The rate

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of exacerbations that were moderate or severe per patient per year was 1.14 with roflumilast and 1.37 with placebo (reduction 17%; p<0.0003). Adverse events were more common with roflumilast. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was -2.17 kg. No trials have been conducted to assess the effects of roflumilast on COPD exacerbations when added to a fixed-dose combination product containing a LABA and ICS.[206]

A 12-week, randomized, double-blind, parallel-group trial assessed roflumilast dose titration in patients with severe COPD associated with chronic bronchitis and ≥ 1 exacerbation within the last year (n=1,323).[207] Patients were randomized to roflumilast 500 mcg once daily for 12 weeks, roflumilast 500 mcg every other day for 4 weeks then 500 mcg once daily for 8 weeks, or roflumilast 250 mcg once daily for 4 weeks followed by 500 mcg once daily for 8 weeks. Discontinuation was found to be lower in those assigned the initial 250 mcg dose compared to those assigned an initial 500 mcg once daily dose (OR, 0.66; 95% CI, 0.47 to 0.93; p=0.017).

tiotropium (Spiriva) versus placebo

The Understanding the Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial was a large, randomized, double-blind, placebo-controlled trial that compared 4 years of therapy with either tiotropium or placebo in 5,993 patients with COPD who were permitted to use all respiratory medications except inhaled antimuscarinic drugs.[208] The patients were at least 40 years of age with an FEV_1 of 70% or less after bronchodilation and a ratio of FEV_1/FVC of 70% or less. The objective of the study was to determine whether treatment with tiotropium 18 mcg reduced the rate of decline of FEV_1 over time in patients with COPD. The 2 co-primary endpoints were the yearly rate of decline in the mean FEV_1 before the use of a study drug and short-acting bronchodilators in the morning (pre-bronchodilator) and after the use of a study drug (post-bronchodilator) from day 30 (steady state) until completion of double-blind treatment. Secondary endpoints included measures of rates of mean decline for both FVC and slow vital capacity (SVC), health-related quality of life as measured by the total score on SGRQ, exacerbations of COPD, and mortality. Patients were randomly assigned to the tiotropium group (n=2,987) or to the placebo group (n=3,006). Mean absolute improvements in FEV_1 in the tiotropium group were maintained throughout the trial (ranging from 87 to 103 mL before bronchodilation and from 47 to 65 mL after bronchodilation), as compared with the placebo group (p<0.001). After day 30, the differences between the 2 groups in the rate of decline in the mean FEV_1 at any time point were not significant. The mean absolute total score on the SGRQ was lower, indicating improvement, in the tiotropium group compared with the placebo group at each time point throughout the 4-year period (p<0.001). At 4 years and 30 days, tiotropium treatment was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure, but tiotropium did not significantly reduce the rate of decline in FEV_1.

In a subgroup analysis of the UPLIFT trial, data from 2,739 participants diagnosed with COPD (GOLD stage 2) were examined.[209] The tiotropium group had a statistically insignificant lower decline of pre-bronchodilator FEV1 than the control group (35 mL per year versus 37 mL per year, p=0.38) and lower post-bronchodilator FEV1 (43 mL per year versus 49 mL per year, p=0.024). SGRQ scores were lower in the tiotropium group than the control group (p≤0.006 for all time points), indicating a statistically significant improved health status. Mean number of exacerbations was lower in the tiotropium group than the control group (0.56 per patient-year versus 0.70 per patient-year, p<0.0001). The results of this subgroup analysis provided further support for the rationale of starting a long-acting antimuscarinic (LAMA) in patients with moderate COPD.

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tiotropium (Spiriva) versus ipratropium (Atrovent)

The Dutch Tiotropium Group evaluated and compared the efficacy and safety of tiotropium and ipratropium during long-term treatment of patients with stable COPD.[210] Two-hundred eighty-eight patients with mean age 65 years and mean FEV_1 41% of predicted value participated in a 14-center, double-blind, double-dummy, parallel group study. Patients were randomized to receive either tiotropium 18 mcg once daily from a dry powder inhaler (HandiHaler; two thirds of patients) or ipratropium 40 mcg 4 times daily from a metered dose inhaler (one third of patients) for 13 weeks. Outcome measures were lung function, daily records of PEF, and the use of concomitant albuterol. During treatment, tiotropium achieved a significantly greater improvement than ipratropium in trough, average, and peak FEV_1 levels, trough and average FVC levels, and weekly mean morning and evening PEF. The use of concomitant albuterol was also significantly lower in the tiotropium group ($p<0.05$). The only drug related adverse event was dry mouth (tiotropium 14.7% versus ipratropium 10.3%).

Two, 1-year, randomized, double-blind, double-dummy studies evaluated tiotropium 18 mcg once daily (n=356) with ipratropium 40 mcg 4 times daily (n=179).[211] Mean baseline FEV_1 values were 41.9% of predicted value for tiotropium and 39.4% of predicted value for ipratropium. Trough FEV_1 at 1 year improved by 0.12 +/- 0.01 L with tiotropium and declined by 0.03 +/- 0.02 L with ipratropium ($p<0.001$). Tiotropium reduced the number of exacerbations by 24% ($p<0.01$), increased time to first exacerbation ($p<0.01$), and the time to first hospitalization for a COPD exacerbation ($p<0.05$) compared with ipratropium. Apart from an increased incidence of dry mouth in the tiotropium group, adverse events were similar between treatments.

tiotropium (Spiriva) versus salmeterol (Serevent)

A 6-month, randomized, placebo-controlled, double-blind, double-dummy, parallel-group study in 623 patients (tiotropium, n=209; salmeterol, n=213; and placebo, n=201) evaluated tiotropium 18 mcg once daily via dry-powder inhaler compared with salmeterol 50 mcg twice daily via metered dose inhaler. The study was conducted in patients with a baseline mean FEV_1 40% of predicted value and a mean age of 65 years.[212] Compared with placebo treatment, the mean pre-dose morning FEV_1 following 6 months of therapy increased significantly more for the tiotropium group (0.14 L) than the salmeterol group (0.09 L) ($p<0.01$). The difference between tiotropium and salmeterol was statistically significant (0.05 L; $p<0.01$). At study end, trough FVC had improved significantly above placebo at 0.25 L for tiotropium ($p<0.001$) and 0.13 L for salmeterol ($p<0.001$). The difference between tiotropium and salmeterol was 0.11 L ($p<0.01$). Both active drugs significantly reduced the need for rescue albuterol. Tiotropium patients also achieved meaningful changes in health-related quality of life compared to salmeterol patients.

Patients with COPD (tiotropium, n=402; salmeterol, n=405; placebo, n=400) were enrolled in two, 6-month, randomized, placebo controlled, double-blind, double-dummy studies of tiotropium 18 mcg once daily via HandiHaler or salmeterol 50 mcg twice daily via a metered dose inhaler.[213] The 2 trials were combined for analysis of health outcomes consisting of exacerbations, health resource use, dyspnea (assessed by the transitional dyspnea index, TDI), health-related quality of life (assessed by SGRQ), and spirometry. Compared with placebo, tiotropium, but not salmeterol, was associated with a significant delay in the time to onset of the first exacerbation. Fewer COPD exacerbations per patient year occurred in the tiotropium group (1.07 events/year), than in the salmeterol group (1.23 events/year; $p=0.222$) or in the placebo group (1.49 events/year; $p<0.05$). The tiotropium group had

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0.1 hospital admissions per patient year for COPD exacerbations compared with 0.17 for salmeterol and 0.15 for placebo (p=NS). SGRQ total scores improved by 4.2, 2.8, and 1.5 units during the 6-month trial for the tiotropium, salmeterol, and placebo groups, respectively (p<0.01 tiotropium versus placebo). Compared with placebo, TDI focal score improved in both the tiotropium group (1.1 units, p<0.001) and the salmeterol group (0.7 units, p<0.05). The difference between tiotropium and salmeterol was not significant (p=0.17).

tiotropium (Spiriva) + placebo versus tiotropium (Spiriva) + salmeterol (Serevent) OR fluticasone/salmeterol (Advair®)

A randomized, double-blind, placebo-controlled trial was conducted in Canada with 449 patients with moderate to severe COPD who had 1 year of treatment with tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol.[214] The proportion of patients in the tiotropium plus placebo group who had episodes of an exacerbation (62.8%) was not different from that in the tiotropium plus salmeterol group (64.8%; 95% CI, –12.8 to 8.8) or in the tiotropium plus fluticasone/salmeterol group (60%; 95% CI, –8.2 to 13.8). Tiotropium plus fluticasone/salmeterol improved lung function as measured by FEV_1 (p=0.049) and disease-specific quality of life (p=0.01), reduced the number of hospitalizations for COPD exacerbation (incidence rate ratio, 0.53; 95% CI, 0.33 to 0.86), as well as all-cause hospitalizations (incidence rate ratio, 0.67; 95% CI, 0.45 to 0.99), compared with tiotropium plus placebo. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo. It is noteworthy that more than 40% of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label ICSs or LABA. The authors concluded that the addition of fluticasone/salmeterol to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.

tiotropium (Spiriva) versus tiotropium (Spiriva) + formoterol (Foradil)

In a 12-week active-controlled, double-blind, multicenter trial, a total of 255 subjects with COPD were randomized to either a combination of formoterol 12 mcg twice daily plus tiotropium 18 mcg once daily in the morning or monotherapy with tiotropium 18 mcg once daily in the morning.[215] The primary efficacy variable was the area under the curve for FEV_1measured 0 to 4 hours after the morning dosing (FEV_1 $AUC_{(0\text{-}4h)}$). Significantly greater improvements in the FEV_1 $AUC_{(0\text{-}4h)}$ were seen with formoterol plus tiotropium versus tiotropium alone at all time points. At endpoint, FEV_1 $AUC_{(0\text{-}4h)}$ increased 340 mL with formoterol plus tiotropium versus 170 mL with tiotropium alone (p<0.001). Improvements in trough FEV_1 with formoterol plus tiotropium versus tiotropium alone were 180 mL and 100 mL, respectively (p<0.01). Significantly greater reductions from baseline in symptom scores (p<0.05) and daytime albuterol use (p<0.04) were seen at endpoint with combination formoterol plus tiotropium versus tiotropium monotherapy. Both treatments were well tolerated.

tiotropium inhalation spray (Spiriva Respimat) versus placebo

Five confirmatory trials of tiotropium inhalation spray were conducted that involved a total of 6,614 patients (Spiriva Respimat, n=2,801; placebo, n=2,798). Trials 1 and 2 were 12-week, randomized, double-blind, placebo- and active- (ipratropium) controlled trials that evaluated bronchodilation.[216] Trials 3 through 5 were 48-week, randomized, double-blind, placebo-controlled, trials that evaluated bronchodilation and effects on COPD exacerbations. The 5 trials enrolled patients who were 40 years

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of age or older with a clinical diagnosis of COPD, a history of smoking greater than 10 pack-years, 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. Trials 1 through 4 utilized tiotropium inhalation spray 5 mcg and 10 mcg doses. Trial 5 only included the 5 mcg dose. The change from baseline in trough FEV_1 was the primary endpoint in all trials. Trials 3 through 5 included COPD exacerbations as primary endpoints.

Tiotropium inhalation spray exhibited significant improvement in trough FEV_1 compared to placebo in all 5 trials. The difference from placebo in trough FEV_1 at the end of treatment (95% CI) was as follows: Trial 1 was 0.11 L, Trial 2 was 0.13 L, Trial 3 was 0.14 L, Trial 4 was 0.11 L, and Trial 5 was 0.1 L. For Trials 3 and 4, the pooled analysis of exacerbation rate per patient year was specified as a primary endpoint, while the primary endpoint for Trial 5 was time to first exacerbation, but included exacerbation rate per patient year as secondary endpoint. Exacerbations were defined as respiratory events/symptoms with a duration of ≥ 3 days with ≥ 2 of the following symptoms or new onset: shortness of breath/dyspnea/shallow rapid breathing, sputum production (volume), occurrence of purulent sputum, cough, wheezing, and chest tightness. In the analysis, Trials 3 and 4, tiotropium inhalation spray 5 mcg significantly reduced the number of COPD exacerbations compared to placebo with 0.78 exacerbations per patient year versus 1 exacerbation per patient year, respectively (RR, 0.78; 95% CI 0.67, 0.92). In Trial 5, treatment with tiotropium inhalation spray) delayed the time the time to first COPD compared to placebo (HR, 0.69; 95% CI, 0.63, 0.77); additionally, the exacerbation rate was also lower in tiotropium inhalation spray compared to placebo. In Trials 3 and 4, patients treated with tiotropium inhalation spray also used less rescue medication compared to patients on placebo.

In a sixth trial, a long-term, randomized, double-blind, double dummy, active-controlled trial that observed patients up to 3 years evaluated the risk of all-cause mortality associated with tiotropium inhalation spray (Spiriva Respimat, n=5,711) compared to tiotropium inhalation powder (Spiriva, n=5,694). The mean age was 65 years and approximately 70% of the subjects were male with the majority of the patients with GOLD 2 or GOLD 3 status (48% and 40% respectively). The mean post-bronchodilator was FEV_1 1.34 L with a mean FEV_1/FVC ratio of 50%. Both treatment groups had a median exposure to treatment for 835 days. The all-cause mortality was found to be similar between both groups (HR, 0.96; 95% CI, 0.84 to 1.09).

tiotropium/olodaterol (Stiolto Respimat) versus tiotropium or olodaterol

The efficacy of Stiolto Respimat is based on two 4-week dose-ranging trials (n=592) and 2 multicenter, phase 3, replicate, randomized, 52-week, double-blind active-controlled trials (n=5,162; Study 1, n=2,624; Study 2, n=2,538) in patients with COPD.[217,218] Dose selection in the confirmatory trials was based on trials for the individual components of the drug, tiotropium and olodaterol. Patients were assigned to tiotropium/olodaterol (fixed combination) 2.5/5 mcg or 5/5 mcg, tiotropium 2.5 or 5 mcg, or olodaterol 5 mcg once daily via the Respimat inhaler for 52 weeks. Most patients were considered GOLD stage 2/3 (88.6%) and approximately one-third of patients were current smokers. The primary endpoint, FEV_1 $AUC_{(0\text{-}3h)}$ at 24 weeks, was 241, 256, 139, and 133 mL in the tiotropium/olodaterol 2.5/5 mcg, tiotropium/olodaterol 5/5 mcg, tiotropium 2.5 mcg, tiotropium 5 mcg, and olodaterol 5 mcg groups, respectively ($p<0.0001$ for tiotropium/olodaterol 5/5 mcg compared single components). Significant differences between the 5/5 mcg fixed combination and the individual components were also seen in the SGRQ score at 24 weeks ($p<0.05$ for both comparisons). Adverse effects were comparable between groups.

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umeclidinium (Incruse Ellipta) versus placebo

Two randomized double-blind, placebo-controlled, parallel-group studies (Study 1 = 24 weeks; Study 2 =12 weeks) were performed in patients with COPD to establish the efficacy of umeclidinium bromide on lung function.[219] Each study enrolled patients with COPD, 40 years of age and older, with a smoking history of 10 pack-years or more, had a post-albuterol FEV_1 ≤ 70% of predicted normal values, with a Modified Medical Research Council (mMRC) score of ≥ 2, and with a ratio of FEV_1/FVC of < 0.7. At the Study 1 screening, the mean post-bronchodilator percent predicted FEV_1 was 47%, patients had a mean post-bronchodilator FEV_1/FVC ratio of 0.47, and the mean percent reversibility was 15%. During Study 1, patients' received either umeclidinium bromide (62.5 mcg) or placebo. The primary endpoint was change from baseline in trough (pre-dose) FEV_1 at day 169 compared to placebo. The study concluded that umeclidinium bromide resulted in a larger increase in mean change from baseline in trough (pre-dose) FEV_1 compared to placebo (95% CI). Results from Study 2 were similar. SGRQ was used to measure patient health-related quality of life. Umeclidinium bromide showed an improvement in mean SGRQ total score compared with placebo at day 168 (-4.69; 95% CI, -7.07 to -2.31).

umeclidinium (Incruse Ellipta) versus tiotropium (Spiriva HandiHaler)

A 12-week, multicenter, randomized, blinded, double-dummy, parallel-group study was conducted in patients 40 years or older with symptomatic moderate to severe COPD (as defined by the ATS/ERS) and a smoking history of ≥ 10 pack-years, a pre-/post-albuterol/salbutamol FEV1/FVC ratio of < 0.7, a post-albuterol/ salbutamol FEV1 of 30% to 70% predicted normal, and a dyspnea score of ≥ 2 on the modified Medical Research Council Dyspnea Scale.220 After the 7 to 14 day run-in period, patients (n=1,017) were randomized 1:1 to receive once daily umeclidinium 62.5 mcg (delivering 55 mcg) administered via the Ellipta DPI plus placebo administered via the HandiHaler, or once daily tiotropium 18 mcg (delivering 10 mcg administered via the HandiHaler plus placebo administered via the Ellipta DPI. Patients requiring long-term oxygen (> 12 hours/day), other maintenance COPD medications (excluding ICSs), and other select medications based on timeframe (e.g., systemic corticosteroids) were excluded; however, use of rescue albuterol/salmeterol was permitted during the trial. Active and placebo inhalers were identical in appearance. The primary endpoint was the trough FEV_1 at day 85 with a noninferiority margin set at -50 mL in the per-protocol (PP) population (n=976). Other outcomes evaluated included other respiratory endpoints in the intent-to-treat population, select patient reported outcomes (e.g., St. George's Respiratory Questionnaire [SGRQ], COPD Assessment Test [CAT], rescue medication use), and safety endpoints. The mean change from baseline in trough FEV_1 was greater with umeclidinium than with tiotropium at day 85 in the per-protocol population with a difference of 59 mL (95% CI, 29 to 88, p<0.001). Similar results were observed in the analysis of trough FEV_1 at day 85 for the intent to treat population (n=1,017) (difference, 53 mL; 95% CI, 25 to 81, p<0.001). Umeclidinium demonstrated superior efficacy compared to tiotropium on the primary end point of trough FEV_1 at day 85. No differences were found in patient-reported outcomes, and adverse events were similar between the 2 group (occurring in 32% of patients treated with umeclidinium and 30% treated with tiotropium).

umeclidinium (Incruse Ellipta) versus placebo with background fluticasone furoate/vilanterol (Breo Ellipta) therapy

Two replicate, 12-week, double-blind, placebo-controlled, parallel-group multicenter trials assessed the efficacy of umeclidinium in 1,238 patients with COPD.[221] Patients were randomized 1:1:1 to

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umeclidinium 62.5 mcg, umeclidinium 113 mcg, or placebo with open-label fluticasone/vilanterol background therapy. The primary endpoint was trough FEV1 on day 85 and was significantly improved with the addition of umeclidinium compared to placebo (Study 1: 0.124 L with umeclidinium 62.5 mcg [95% CI, 0.093 to 0.154] and 0.128 L with umeclidinium 125 mcg [95% CI, 0.098 to 0.159]; Study 2: 0.122 L with umeclidinium 62.5 mcg [95% CI, 0.091 to 0.152] and 0.111 L with umeclidinium 125 mcg [95% CI, 0.081 to 0.141]. The 0 to 6 hour weighted mean FEV_1 values on day 84 compared to placebo were also significant. Results with the SGRQ were inconsistent; a difference was found in both studies with the 62.5 mcg dose but differed between studies using the 125 mcg dose. Adverse effects among groups were similar.

umeclidinium/vilanterol (Anoro Ellipta) versus umeclidinium versus vilanterol versus placebo

Two 6-month randomized, double-blinded, placebo-controlled, parallel-group clinical trials were performed to evaluate the efficacy of umeclidinium/vilanterol on lung function in patients with COPD.[222,223] In Trial 1, a total of 1,532 patients were randomized 3:3:3:2 to umeclidinium/vilanterol 62.5 mcg/25 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo once daily using a DPI. Primary endpoint was change from baseline in trough FEV_1 at day 169 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on day 168) compared with placebo and the individual components. All active treatments produced statistically significant improvement in trough FEV_1 compared with placebo on day 169 (0.072 to 0.167 L; all $p<0.001$). FEV_1 increases were significantly greater than the individual components (0.052 to 0.095 L; $p\leq0.004$). Trial 2 results were similar to those observed in Trial 1 but were not included as it evaluated umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium 125 mcg which are not currently FDA-approved strengths.

umeclidinium/vilanterol (Anoro Ellipta) versus tiotropium (Spiriva HandiHaler), vilanterol, or umeclidinium

Two randomized, blinded, double-dummy, parallel-group, active-controlled, multicenter trials compared the efficacy and safety of once-daily umeclidinium 125 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg/vilanterol 25 mcg with tiotropium 18 mcg monotherapy, and either vilanterol 25 mcg monotherapy (Study 1; n=1,114) or umeclidinium 125 mcg monotherapy (Study 2; n=1,191) for 24 weeks in patients with moderate to very severe COPD.[224] The primary efficacy endpoint of both studies was trough FEV_1 on day 169, as analyzed in the intention-to-treat population. In both studies, on day 169 there were improvements in trough FEV_1 for both doses of umeclidinium/vilanterol compared with tiotropium monotherapy (Study 1, umeclidinium 125 mcg/vilanterol 25 mcg: 0.088 L [95% CI, 0.036 to 0.14; p=0.001]; Study 1, umeclidinium 62.5 mcg/vilanterol 25 mcg: 0.09 L [95% CI, 0.039 to 0.141; p=0.0006]; Study 2, umeclidinium 125 mcg/vilanterol 25 mcg: 0.074 L [95% CI, 0.025 to 0.123; p=0.0031]; Study 2, umeclidinium 62.5 mcg/vilanterol 25 mcg: 0.06 L [95% CI, 0.01 to 0.109; p=0.0182]). Both doses of umeclidinium/vilanterol also improved trough FEV_1 compared with vilanterol monotherapy (umeclidinium 125 mcg/vilanterol 25 mcg: 0.088 L [95% CI, 0.036 to 0.14; p=0.001]; umeclidinium 62.5 mcg/vilanterol 25 mcg: 0.09 L [95% CI, 0.039 to 0.142; p=0.0006], but not compared with umeclidinium 125 mcg monotherapy (umeclidinium 125 mcg/vilanterol 25 mcg: 0.037 L [95% CI, −0.012 to 0.087; p=0.14]; umeclidinium 62.5 mcg/vilanterol 25 mcg: 0.022 L [95% CI, −0.027 to 0.072; p=0.38]). All treatments produced improvements in dyspnea and health-related quality of life. There were no significant differences in symptoms, health status, or risk of exacerbation between umeclidinium/vilanterol and tiotropium. The most common on-treatment, adverse event with severe intensity in both studies was acute exacerbation of COPD (1 to 4 patients across treatment groups in

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Study 1 and 1 to 6 patients in Study 2). There were 15 on-treatment serious adverse events across treatment groups in Study 1, and 9 to 22 in Study 2. Umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium 125 mcg are not FDA-approved strengths.

umeclidinium/vilanterol (Anoro Ellipta) versus tiotropium (Spiriva HandiHaler)

A 24-week, multicenter, multinational, double-blind, double-dummy, parallel-group, randomized controlled trial compared the efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg once daily and tiotropium 18 mcg once daily in patients ≥ 40 years with moderate to severe COPD (n=905).[225] Patients with pneumonia or hospitalization within the past 12 weeks were excluded. Rescue medication (albuterol) and consistently dosed ICSs were allowed. At Day 169, umeclidinium/vilanterol was superior to tiotropium in the primary outcome, trough FEV_1 measured at Day 169 (treatment difference, 0.112 L; 95% CI, 0.081 to 0.144; p<0.001). Umeclidinium/vilanterol also demonstrated superiority in the weighted mean FEV_1 over 0 to 6 hours following the dose on Day 168 (treatment difference, 0.105 L; 95% CI, 0.071 to 0.14; p<0.001) and in the following other endpoints: time to onset of action on Day 1, trough FVC on Day 169, percentage of patients achieving a ≥ 12% and ≥ 0.2 L increase in FEV_1 over baseline during Day 1, percentage of patients achieving a ≥ 0.1 L increase in FEV_1 over baseline on Day 169, and the peak FEV_1 on Day 168 (p<0.001 for all). Patients assigned umeclidinium/vilanterol used less rescue medication than those assigned tiotropium (p<0.001). The overall incidences of adverse effects were similar between groups.

umeclidinium/vilanterol (Anoro Ellipta) versus fluticasone propionate/salmeterol (Advair)

Two 12-week, multicenter, double-blind, parallel-group, double-dummy, randomized trials compared the efficacy of umeclidinium/vilanterol to fluticasone/salmeterol in patients with moderate to severe COPD (Study 1, n=706; Study 2, n=697).[226] Patients with infrequent exacerbations were randomized 1:1 to once-daily umeclidinium/vilanterol 62.5/25 mcg or twice-daily fluticasone/salmeterol 250/50 mcg. Key endpoints included 0 to 24 hour mean FEV_1 on Day 84 (primary), trough FEV_1 on day 85, dyspnea, and change in SGRQ score. Umeclidinium/vilanterol demonstrated significant improvement in lung function compared to fluticasone/salmeterol; the difference in $FEV_{1(0\text{-}24)}$ on day 84 was 74 mL (95% CI, 38 to 110) in Study 1 and 101 mL (95% CI, 63 to 139 in Study 2; p<0.001 for both). Trough FEV_1 values were also superior with umeclidinium/vilanterol in both trials; however, no difference was seen between groups in dyspnea ratings or SGRQ improvement. Adverse event rates were similar between groups.

umeclidinium/fluticasone furoate/vilanterol (Trelegy Ellipta) versus fluticasone furoate/vilanterol (Breo Ellipta) versus umeclidinium/vilanterol (Anoro Ellipta)

The 52-week, double-blind, parallel-group IMPACT trial assessed rate of exacerbations in 10,355 patients ages ≥ 40 years with COPD.[227,228] Patients were randomized 2:2:1 to umeclidinium 62.5 mcg/fluticasone furoate 100 mcg/vilanterol 25 mcg (n=4,145) or fluticasone furoate 100 mcg/vilanterol 25 mcg (n=4,133) or umeclidinium 62.5 mcg/vilanterol 25mcg (n=2,069). Eligible patients had FEV_1 < 50% predicted normal value and a history of 1 or more moderate or severe exacerbations in the prior 12 months, or an FEV_1 of 50% to 80% of predicted normal value. The primary endpoint of annual rate of moderate and severe exacerbations was 0.91/year for triple therapy, 1.07/year for fluticasone/vilanterol, and 1.21/year for umeclidinium/vilanterol; there was a 15% reduction with triple therapy compared to fluticasone/vilanterol [95% CI, 0.8 to 0.9, p<0.001]. Significant differences between triple therapy and fluticasone/vilanterol and umeclidinium/vilanterol were reported for the

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secondary endpoint of mean change from baseline in trough FEV1, (difference of 97 mL [95% CI, 85 to 109] and 54 mL [95% CI, 39 to 69]; p<0.001 for both).

Asthma

tiotropium bromide inhalational spray (Spiriva Respimat) versus placebo (with background ICS therapy and with or without active comparator)

Efficacy of tiotropium bromide inhalation spray is based on 5 confirmatory trials in non-smoking adults (n=3,476) and 2 trials in adolescents aged 12 to 17 years.[229] The adult (mean age = 46 years) trials consisted of one 12-week (Trial 1), 2 replicate 24-week (Trials 2 and 3), and 2 replicate 48-week (Trials 4 and 5) randomized, double-blind, placebo-controlled trials in adults with asthma. All trials included ICS background therapy (additional asthma treatments were also allowed) and rescue therapy.

Trial 1 compared once daily tiotropium 2.5 mcg, tiotropium 5 mcg, and placebo (n=309).[230] After 12 weeks, the mean difference in peak (primary endpoint) and trough FEV_1 of 2.5 mcg compared to placebo were 0.16 L (95% CI, 0.09 to 0.23) and 0.11 L (95% CI, 0.04 to 0.18), respectively (p-values not reported). The FEV_1 improvement in the 5 mcg group was generally lower than improvement in the 2.5 mcg (peak data reported only as a composite with other trials; trough FEV_1 increased by 11% in this trial, but was decreased in subsequent trials).

Trials 2 and 3 compared tiotropium 2.5 mcg once daily, tiotropium 5 mcg once daily, salmeterol 50 mcg twice daily, and placebo (Trial 2, n=524; Trial 3, n=509).[231] Patients included had a FEV_1 of 60% to 90% the predicted value. The primary outcomes were peak FEV_1 and trough FEV_1 at Week 24. Peak FEV_1 responses were greater with both tiotropium doses and salmeterol compared to placebo in the pooled analysis (tiotropium 5 mcg versus placebo difference, 185 mL [95% CI, 146 to 223]; tiotropium 2.5 mcg versus placebo difference, 223 mL [95% CI, 185 to 262], and salmeterol versus placebo difference, 196 mL [95% CI, 158 to 234]; all p<0.0001 versus placebo). Trough FEV_1 responses were greater with both tiotropium doses and salmeterol compared to placebo in the pooled analysis (tiotropium 5 mcg versus placebo difference, 146 mL [95% CI, 105 to 188]; tiotropium 2.5 mcg versus placebo difference, 180 mL [95% CI, 138 to 221], and salmeterol versus placebo difference, 114 mL [95% CI, 73 to 155]; all p<0.0001 versus placebo). Seven-question Asthma Control Questionnaire (ACQ-7) response was higher with all 3 active treatments compared to placebo (tiotropium 5 mcg OR, 1.32 [95% CI, 1.02 to 1.71; p=0.035]; tiotropium 2.5 mcg OR, 1.33 [95% CI, 1.03 to 1.72; p=0.031]; and salmeterol OR, 1.46 [95% CI, 1.13 to 1.89; p<0.0039]). Adverse effects were similar between groups.

Trials 4 and 5 compared tiotropium 5 mcg (2 puffs of 2.5 mcg) once daily to placebo once daily in 912 patients with airway obstruction that was not fully reversible (post-bronchodilator $FEV_1 \leq 80\%$).[232] The primary outcomes were peak FEV_1 and trough FEV_1 at week 24 and time to first asthma exacerbation at week 48. Peak FEV_1 response was greater with tiotropium compared to placebo in both trials (Trial 4 difference, 86 mL [95% CI, 20 to 152; p<0.05]; Trial 5 difference, 154 mL [95% CI, 91 to 217; p<0.001]). Trough FEV_1 response was also greater with tiotropium compared to placebo in both trials (Trial 4 difference, 88 mL [95% CI, 27 to 149; p<0.01]; Trial 5 difference, 111 mL [95% CI, 53 to 169; p<0.001]). Significant differences were also seen in peak FEV_1 in both trials and trough FEV_1 in Trial 5 (not significant in Trial 4) at 48 weeks (p<0.01 for all). Significant differences favoring tiotropium were also seen in peak and trough FVC and peak expiratory flow in the morning and evening at both 24 and 48 weeks (p<0.05 for all comparisons of tiotropium versus placebo). Adverse effects were similar between groups.

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Efficacy in adolescents aged 12 to 17 years was evaluated in one 12-week (Trial 1) and one 48-week (Trial 2) randomized, double-blind, placebo-controlled parallel arm trials (n=789).[233] Patients were assigned to tiotropium 2.5 mcg once daily, 5 mcg once daily, or placebo in addition to background therapy consisting of at least an ICS (Trial 1) or an ICS with ≥ 1 other controller medication (Trial 2). Trial 1 consisted of patients with severe asthma while Trial 2 consisted of patients with moderate asthma (mean age = 14.3 years). The primary endpoint, change in peak FEV_1 at 12 weeks (Trial 1) or 24 weeks (Trial 2), was 0.11 L (95% CI, 0.002 to 0.22) in Trial 1 and 0.13 L (95% CI, 0.03 to 0.23) in Trial 2.

Two double-blind, placebo-controlled trials of 12 and 48 weeks duration evaluated the safety and efficacy of tiotropium in a total of 801 asthma patients 6 to 11 years of age (mean age, 9 years). Patients were randomized to once-daily doses of tiotropium 2.5 mcg (n=271), tiotropium 5 mcg (n=265), or placebo (n=265).[234] The 12-week trial enrolled patients with severe asthma who were on background treatment of ICS plus at least 1 other controller medication. The 48-week trial enrolled patients with moderate asthma on background treatment of ICS with or without another medication. The primary efficacy endpoint in both trials was change from baseline in peak $FEV1_{0\text{-}3hr}$. Patients were assessed at trial end in the 12-week trial and at week 24 in the 48-week trial. Tiotropium 2.5 mcg had a significant effect on the primary endpoint compared to placebo in the 48 week, but not the 12 week trial; mean differences in peak $FEV1_{0\text{-}3hr}$ compared to placebo was 0.17 L (95% CI 0.11, 0.23) in the 48-week study and 0.04 L (95% CI -0.03, 0.10) in the 12-week trial. The tiotropium daily dose of 5 mcg is not approved in the U.S.

META-ANALYSES

COPD

A 2012 meta-analysis of 7 randomized controlled trials representing 12,223 patients was performed. The trials were identified from the Cochrane Airways Group Specialized Register (through February 2012) and other clinical trial registers. Studies were not omitted if standard COPD therapy co-administration was allowed, including stable dose ICSs. The following therapies were compared against tiotropium (via HandiHaler): salmeterol (4 studies), formoterol (1 study), and indacaterol (2 studies). Baseline characteristics matched well across the study treatment groups. Tiotropium demonstrated a statistically significant difference in the number of patients who experienced one or more exacerbations as compared to LABA (OR, 0.86; 95% CI, 0.79 to 0.93). SGRQ data was not pooled for the analysis due to heterogeneity amongst the studies; however, a subgroup analysis evaluating the type of LABA used showed indacaterol slightly favored over tiotropium for improvements to quality of life and tiotropium favored over salmeterol in reducing SGRQ deteriorations. When looking at secondary outcomes, tiotropium showed fewer hospitalizations related to COPD exacerbations as compared to LABA (OR, 0.87; 95% CI, 0.77 to 0.99); all-cause hospitalizations showed no difference. Non-fatal serious adverse events (OR, 0.88; 95% CI, 0.78 to 0.99) and study withdrawals (OR, 0.89; 95% CI, 0.81 to 0.99) were lower in the tiotropium group but were near parity. No statistical difference was seen between tiotropium and LABA with respect to mortality, FEV_1, and symptom score as measured by the Transitional Dyspnea Index (TDI).

A 2008 meta-analysis of 17 randomized, controlled trials of 14,783 patients was conducted to ascertain the cardiovascular risks including cardiovascular death, myocardial infarction (MI), and stroke of inhaled antimuscarinics (tiotropium or ipratropium bromide) versus control therapy (inhaled salmeterol, inhaled salmeterol/fluticasone, inhaled albuterol, or placebo).[235] The study selection included trials of at least 30 days duration and reported on cardiovascular events. The primary

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outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The authors state that cardiovascular death is a more frequent cause of death in patients with COPD than respiratory causes. Based on the results, inhaled antimuscarinics significantly increased the risk of the composite outcome of cardiovascular death, MI, or stroke (1.8% versus 1.2% for control; p<0.001). Further delineation for individual primary outcomes were also assessed and showed inhaled antimuscarinics significantly increased the risk of MI (1.2% versus 0.8%, p=0.03) based on 11 trials involving 10,598 patients. Risk of cardiovascular death was significantly increased by inhaled antimuscarinics (0.9% versus 0.5%, p=0.008) in 12 trials of 12,376 patients. On the other hand, inhaled antimuscarinics did not significantly increase the risk of stroke (0.5% versus 0.4% for control, p=0.2). Inhaled antimuscarinics also did not significantly increase the risk of all-cause mortality (2% versus 1.6%; p=0.06). Important to note in the meta-analysis is that many of the trials included were small and short-term, none of them were specifically designed to monitor risk of cardiovascular events, and some of the reporting of cardiovascular outcomes may have been incomplete. Further prospective studies that are adequately powered are needed to assess the cardiovascular safety of the inhaled antimuscarinics. In the meantime, the risks of adverse events (e.g., MI or cardiovascular death) versus benefits of symptomatic improvement (e.g., increase in exercise capacity, reduced COPD exacerbations and hospitalizations, and improved dyspnea) must be weighed when using the inhaled antimuscarinics. Unfortunately, alternative therapeutic options are limited for patients with COPD due to their differing adverse effect profiles.

Results from a systematic search including studies from MEDLINE and the Cochrane databases between 1966 and March 2007 on inhaled therapies and disease management were used to determine the effectiveness of management strategies for COPD (including inhaled therapies) in regards to exacerbations, hospitalization, deaths, and adverse effects.[236] Treatment was recommended for patients with stable COPD who have respiratory symptoms and FEV_1 < 60%. Treatment should consist of one of the following: inhaled LABA, LAMA, or ICS. There was insufficient documentation to recommend 1 monotherapy over another since they had similar effectiveness although different adverse effects, reductions in deaths, and hospitalizations were observed. Studies of combination therapies do not consistently show benefits of combination therapy over monotherapy.

More questions will be generated as a result of a meta-analysis of 22 randomized, double-blind, placebo or active-controlled trials with 15,276 patients.[237] The meta-analysis evaluated the safety and efficacy of antimuscarinics (ipratropium and tiotropium) and $beta_2$ agonists (albuterol, metaproterenol, formoterol, and salmeterol) in COPD. Antimuscarinics significantly reduced severe COPD exacerbations compared to placebo, as well as reduced respiratory deaths. On the contrary, $beta_2$ agonists did not affect severe COPD exacerbations and actually increased the rate of respiratory deaths compared with placebo.

A meta-analysis of 28 trials (n=14,909) comparing tiotropium (Spiriva HandiHaler or Spiriva Respimat) to placebo found a lower risk of adverse effects (rate ratio [RR], 0.9; 95% CI, 0.87 to 0.93), serious adverse effects (RR, 0.94; 95% CI, 0.89 to 0.99), and fatal adverse effects (RR, 0.9; 95% CI, 0.79 to 1.01) compared to placebo.[238] Likewise, a meta-analysis of 12 randomized controlled trials evaluating the efficacy of aclidinium in 9,547 patients with COPD also found a benefit with this agent compared to placebo.[239] Aclidinium lowered the SGRQ total score (improved quality of life) by mean difference of -2.34 (95% CI, -3.18 to -1.51; 7 trials, 4,442 participants) when compared to placebo. Aclidinium also

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significantly improved pre-dose FEV_1 compared to placebo (mean difference, 0.09 L; 95% CI, 0.08 to 0.1; 9 trials, 4,963 participants). However, no difference was found in all-cause mortality.

A meta-analysis of 27 randomized controlled trials (≥ 12 weeks duration) assessed the efficacy of long-acting anticholinergics (e.g., tiotropium, aclidinium, or glycopyrronium [comparable to glycopyrrolate]) in 48,140 patients with COPD.[240] All products were found to be superior to placebo in number of moderate-to-severe asthma exacerbations (tiotropium inhaled powder hazard ratio [HR], 0.75 for [95% CI, 0.68 to 0.84]; tiotropium inhalation spray HR, 0.67 [95%, 0.54 to 0.84]; aclidinium HR, 0.79 [95% CI, 0.63 to 0.98]; and glycopyrronium HR, 0.72 [95% CI, 0.59 to 0.88]), but no differences were found between agents. In studies of at least 6 months durations, aclidinium appeared to have the greatest efficacy and glycopyrronium had the least efficacy among the agents. A similar meta-analysis of 24 trials (n=21,311) included the above agents in addition to umeclidinium.[241] Compared to placebo, aclidinium, glycopyrronium, tiotropium, and umeclidinium demonstrated a change in 24-week trough FEV_1 of 128.1 mL (95% CI, 84.1 to 172); 135.8 mL (95% CI, 123.1 to 148.3); 106.4 mL (95% CI, 95.45 to 117.3); and 115 mL (95% CI, 74.51 to 155.3), respectively. Significant differences were also seen with each agent compared to placebo in SGRQ improvement and rescue medication use; however, no significant differences were found between agents.

A meta-analysis of 27 trials (n=30,361) comparing efficacy of fixed-dose combinations of LABAs and LAMA agents (e.g., aclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, and umeclidinium/vilanterol) found that all agents have similar efficacy.[242] A Cochrane review compared the efficacy of the combination of a LABA/ICS and tiotropium to either LABA/ICS or tiotropium alone.[243] Data were limited and the authors could not compare tiotropium plus LABA/ICS to LABA/ICS alone, but they were able to make comparisons for tiotropium plus LABA/ICS to tiotropium alone based on date from 6 trials (n=1,902). They found no differences with the addition of a LABA/ICS to tiotropium in mortality (OR, 1.8; 95% CI, 0.55 to 5.91) but did find a difference in all-cause hospitalizations (OR, 0.61; 95% CI, 0.4 to 0.92) and quality of life as measured by the SGRQ (mean difference, -3.46; 95% CI, -5.05 to -1.87) favoring the combination.

Asthma

Meta-analyses in asthma patients have also demonstrated superiority of tiotropium compared to placebo in adults and adolescents. A meta-analysis of 13 studies in 4,966 COPD patients ≥ 12 years of age found a significant improvement in asthma control with tiotropium (multiple formulations; as add-on therapy) compared to placebo (peak expiratory flow, 22 to 24 L/min; FEV_1, 140 to 150 mL; NNT for decreased exacerbations, 36).[244] A similar meta-analysis of 3 studies in adolescents (ages) found significant improvements in change in FEV_1 peak (mean difference, 120 mL; $p<0.001$) and trough (mean difference, 100 mL; $p<0.001$) with tiotropium (Spiriva Respimat) compared to placebo.[245] A significant difference was also seen in the percentage of patients who experienced an ACQ-7 worsening episode (defined as a change of ≥ 0.5) with tiotropium compared with placebo (2.1% versus 4.8%; number needed to treat [NNT]=38). Tiotropium also significantly decreased in the number of patients with at least 1 exacerbation compared with placebo (17.6% versus 23.8%, NNT=16). No significant differences in rescue medication use, withdrawals, withdrawals due to adverse events, and serious adverse effects were identified. A Cochrane review of 3 double-blind, randomized controlled trials comparing the addition of LAMAs (only tiotropium trials were included) to LABA/ICS therapy to LABA/ICS therapy alone in adults with asthma did not find a statistically significant difference in exacerbations (OR, 0.76; 95% CI, 0.57 to 1.02).[246] However, the authors noted that there was a trend toward significance and

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data were limited to rule out a possible benefit. No clinical difference was seen in quality of life, as measured by the Asthma Quality of Life Questionnaire and defined as a change ≥ 0.5 (mean difference, 0.09; 95% CI, 0.24 to 1.47), or serious adverse effects.

SUMMARY

The combined COPD assessment illustrated in the 2020 updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines incorporates spirometric abnormality, as well as symptoms, exacerbation/hospitalization history, and comorbidities to help guide intervention, assigning patients to mixed severity-risk stratification groupings. Consequently, more focus can be placed on the goals of treatment, which are to reduce symptoms and risks while minimizing adverse effects. Treatment initiation may begin with the use of as-needed, short-acting bronchodilators followed by routine long-acting bronchodilators, inhaled corticosteroids (ICS), phosphodiesterase-4 (PDE4) inhibitors, long-term oxygen therapy, and even surgery. Regular use of long-acting beta$_2$-agonists or short- or long-acting antimuscarinics has been shown to improve health status.

Albuterol is available in combination with ipratropium in a CFC-free MDI (Combivent Respimat) and as an inhalation solution for the treatment of COPD. The combination CFC-free MDI may be beneficial in reducing the number of puffs per day required as compared to treatment with the individual components.

Umeclidinium/vilanterol (Anoro Ellipta), aclidinium/formoterol (Duaklir Pressair), glycopyrrolate/formoterol fumarate (Bevespi Aerosphere), glycopyrrolate/indacaterol (Utibron Neohaler), and tiotropium/olodaterol (Stiolto Respimat), once- or twice-daily antimuscarinic/LABA combinations, offer another option for the long-term maintenance treatment of COPD, for patients inadequately controlled with a single long-acting bronchodilator. For patients with moderate to severe airflow obstruction and chronic symptoms, the guidelines recommend maintenance treatment with an inhaled long-acting bronchodilator, either alone or in combination with other agents depending on disease severity. The single-agent antimuscarinic options in this class are ipratropium (Atrovent), aclidinium (Tudorza Pressair), glycopyrrolate (Lonhala Magnair, Seebri Neohaler), revefenacin (Yupelri), tiotropium (Spiriva, Spiriva Respimat), and umeclidinium (Incruse Ellipta). The long-acting, revefenacin, and tiotropium- and umeclidinium-containing agents are dosed once daily with a duration of action of 24 hours or greater. Aclidinium and glycopyrrolate-containing formulations, also long-acting, are dosed twice daily. Ipratropium requires up to 4 administrations daily. All of these agents have been shown to improve bronchodilation, dyspnea, exacerbation rates, and health-related quality of life. Adverse effects for antimuscarinic agents are limited primarily to dry mouth that appears to resolve with continued use. The inhalation solutions of glycopyrrolate (Lonhala Magnair) and revefenacin (Yupelri) are nebulized and provide another treatment administration option for patients with COPD, particularly for patients who have difficulty inhaling medication from other devices. The GOLD guidelines do not recommend one antimuscarinic agent or combination product over another and therapy should be individualized based on the patient's limitation of airflow, symptoms, exacerbations, and comorbidities.

Roflumilast (Daliresp) is the only selective phosphodiesterase-4 (PDE4) inhibitor approved as a treatment option in COPD management. Unlike the other inhaled treatment options currently available, roflumilast is an oral tablet formulation taken once daily. Roflumilast is not a bronchodilator; it acts on the underlying inflammation and is not indicated for the relief of acute bronchospasm.

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Roflumilast's modest benefit appears primarily to be demonstrated in patients with chronic bronchitis and frequent exacerbations.

In addition to its COPD indication, tiotropium inhalation spray (Spiriva Respimat) also carries an indication for asthma in patients ≥ 6 years of age. Efficacy has been demonstrated as add-on therapy to an ICS (with or without other background therapies) in patients with asthma who are not controlled on their current regimen. Its serves as a treatment option in latter stages of step-wise therapy in clinical practice guidelines.

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