

Bronchodilators, Anticholinergic Review

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Bronchodilators, Anticholinergic Review

FDA-Approved Indications

| Drug | Manufacturer | Indication(s) |
|--|----------------------|---|
| albuterol/ipratropium inhalation solution (Duoneb [®]) ¹ | generic | For the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator |
| albuterol/ipratropium MDI (Combivent [®]) ² | 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 |
| ipratropium inhalation solution (Atrovent [®]) ³ | generic | For maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema |
| ipratropium inhalation aerosol MDI (Atrovent [®] HFA) ^{4,5} | Boehringer-Ingelheim | As a bronchodilator for maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema |
| tiotropium inhalation powder DPI (Spiriva Handihaler [®]) ⁶ | Boehringer-Ingelheim | For the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema |

MDI=metered-dose inhaler

DPI=dry powder inhaler

Overview

In the United States, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of chronic morbidity and mortality.⁷ COPD is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. The airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.⁸

Although the precise distinctions between chronic bronchitis and emphysema are a subject of debate, tradition holds that chronic bronchitis is responsible for 85 percent of COPD.⁹ Patients with chronic bronchitis experience intermittent airway inflammation and excessive mucus production that leads to frequent, prolonged episodes of productive cough. In contrast, 15 percent of patients with COPD suffer primarily from emphysema. Emphysema is a disease in which destruction of the infrastructure of alveoli and distal airspaces, and thus the portion of the lung that provides gas exchange and elastic recoil, occurs.¹⁰ The loss of alveolar walls results in decreased ventilation and a loss of the capillary network essential to perfusion.

Both chronic bronchitis and emphysema predispose patients to a common constellation of symptoms and to a collection of derangements in respiratory function. There are reductions in forced expiratory volume after one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio and forced expiratory flow (FEF_{25-75%}). The 2007 revised Executive Summary of the GOLD (Global Initiative for Chronic Obstructive Lung Disease) COPD guidelines identify four stages of COPD severity based on post-bronchodilator FEV₁: Stage 1 (Mild = FEV₁ ≥ 80%), Stage 2 (Moderate = 50% ≤ FEV₁ < 80%), Stage 3 (Severe = 30% ≤ FEV₁ < 50%), and Stage 4 (Very

Severe = $FEV_1 < 30\%$ or $FEV_1 < 50\%$ plus the presence of chronic respiratory failure).¹¹ The American Thoracic Society/European Respiratory Society (ATS/ERS) Guidelines include a 5th category, namely “At Risk”, which is based on FEV_1 and risk factors including smoking or exposure to pollutants with cough, sputum, or dyspnea; or a family history of respiratory disease.¹²

Bronchodilator medications are central to the symptomatic management of COPD.^{13,14,15,16} They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance.¹⁷ 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.¹⁸ Combining bronchodilators may improve efficacy and decrease the risk of side effects as compared to maximizing the dose of a single bronchodilator.¹⁹

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend a stepwise treatment plan for COPD based on disease severity.²⁰ Bronchodilator medications are central to symptom management in COPD. For mild COPD, a short-acting bronchodilator used on an as-needed basis is recommended. For moderate and severe COPD, regular use of one or more long-acting bronchodilators is recommended. Long-acting inhaled bronchodilators are more effective and convenient, but there is insufficient evidence to recommend one long-acting agent over another. The choice between a beta₂ agonist, anticholinergic, theophylline, or combination therapy depends on individual response in terms of symptom relief and side effects.

In 2008, the updated GOLD guidelines were released and reiterated that beta₂ agonist bronchodilators are among the principal treatments for symptomatic management of COPD.²¹ The guidelines state that patient care should be based on level of disease severity and clinical symptoms. The following medications are identified based on the likely order of introduction in treatment: short-acting beta agonists, long-acting beta agonists, short-acting anticholinergics, long-acting anticholinergics, combination short-acting beta agonist plus anticholinergic in one inhaler, methylxanthines, inhaled glucocorticoids, combination long-acting beta agonists plus glucocorticoids in one inhaler, and systemic glucocorticoids.

The 2004 Standards for the Diagnosis and Treatment of Patients with COPD serves as an update to the COPD position paper published by the ATS and the ERS in 1995.²² The ATS/ERS position paper also recommends a similar stepwise treatment. For intermittent symptoms, an as-needed beta₂ agonist is recommended. For persistent symptoms, regular use of either a long-acting bronchodilator or a short-acting bronchodilator used four times daily, in addition to an as-needed agent (beta₂ agonist), is recommended. If response to these measures is inadequate, consider an alternative class of bronchodilator or combination therapy.

Medications for COPD currently available can reduce or abolish symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. At present, no treatment is shown to modify the rate of decline in lung function.²³

Pharmacology

Anticholinergics produce greater improvement in pulmonary function tests than the beta₂ agonists in COPD patients with fewer systemic effects while maintaining efficacy over years of continuous use.²⁴ Beta₂ agonists relax airway smooth muscle by stimulating beta₂ receptors and inducing bronchodilation.²⁵

The anticholinergic/parasympathetic agents, ipratropium (Atrovent) and tiotropium (Spiriva), antagonize the action of acetylcholine released from the vagus nerve. Inhibition of the muscarinic receptors blocks the cholinergic neurotransmission causing bronchodilation.

Tiotropium has similar affinity to the muscarinic receptor subtypes M1 to M5. Affinity to these receptors is six- to 20-fold greater than ipratropium. In the airways, tiotropium exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle. Tiotropium dissociates rapidly from M2 receptors (blockade of the specific M2 receptor causes an increase in the release of acetylcholine, which is an unwanted effect), but slowly from M1 and M3 receptors, resulting in prolonged bronchodilation.²⁶

Pharmacokinetics

| Drug | Onset of Action 15 percent or more increase in FEV ₁ (hours) | Time to Peak FEV ₁ (hours) | Duration of Action (hours) |
|--|--|--|---------------------------------------|
| albuterol/ipratropium inhalation solution (Duoneb) ²⁷ | nr | 1.5 | 4.3 - 5 |
| albuterol/ipratropium MDI (Combivent) ²⁸ | 0.25 | 1 | 4 - 5 |
| ipratropium inhalation solution (Atrovent) ²⁹ | 0.25 - 0.5 | 1 - 2 | 4 - 5 up to 7 - 8 in some patients |
| ipratropium inhalation aerosol MDI (Atrovent HFA) ³⁰ | 0.25 | 1 - 2 | 2 - 4 |
| tiotropium inhalation powder (Spiriva) ³¹ | 0.5 (13 percent increase in FEV ₁) | over the course of day 1, continued improvement over eight days | 24 |

nr = not reported

Bronchodilation following inhalation of these agents is a local, site-specific effect.

Although much of an administered dose is swallowed, both ipratropium (Atrovent) and tiotropium (Spiriva) are quaternary amines, and minimal drug is absorbed from the gastrointestinal (GI) tract. Ipratropium is poorly absorbed from the lungs while tiotropium is highly bioavailable from the lung surface (19.5 percent absolute bioavailability).^{32,33}

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 percent 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.³⁴

The terminal elimination half-life of tiotropium is between five and six days, and after once daily inhalation by COPD patients, steady state was reached after two to three weeks.³⁵

Contraindications/Warnings^{36,37,38,39,40,41}

Patients with a history of hypersensitivity to atropine or any of its derivatives (e.g. ipratropium) should not use any of these products.

Albuterol/ipratropium MDI (Combivent) is contraindicated in patients with a history of hypersensitivity to soy lecithin or related food products such as soybean or peanut.

Tiotropium inhalation powder (Spiriva) is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy. In addition, immediate hypersensitivity reactions, including angioedema, may occur after administration. If such a reaction occurs, therapy should be stopped at once and alternative treatments should be considered.

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

Drug Interactions^{42,43,44,45,46,47}

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

Adverse Effects

| Drug | Dry Mouth | Head-ache | Nausea / Vomiting | Nervousness | Palpitations / Chest Pain | Tremor |
|--|-----------------------------------|-----------|-------------------|-------------|---------------------------|--------|
| albuterol/ ipratropium inhalation solution (Duoneb) ⁴⁸ | nr | nr | 1.4 | nr | 2.6 | nr |
| albuterol/ ipratropium MDI (Combivent) ⁴⁹ | ≤ 2 | 5.6 | ≤ 2 | < 2 | 0.3 | < 2 |
| ipratropium inhalation solution (Atrovent) ⁵⁰ | 3.2 | 6.4 | 4.1 | 0.5 | reported | 0.9 |
| ipratropium inhalation aerosol MDI (Atrovent HFA) ⁵¹ | 4 | 6 | 4 | nr | nr | nr |
| tiotropium inhalation powder DPI (Spiriva) ⁵² | 16 versus 12 ipratropium | nr | 4 | nr | 7 | nr |

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

The most common adverse event reported with tiotropium was dry mouth (16 percent). Other reports of adverse events with tiotropium are consistent with anticholinergic effects including constipation (four percent), blurred vision, and glaucoma (percentages not reported) and urinary retention or difficulty (less than one percent).

In one trial that enrolled 198 COPD patients, the number of patients with changes from baseline-corrected QT interval of 30 – 60 msec was higher in the tiotropium-treated group (range 16 to 20 percent) as compared to the placebo group (range one to 12 percent) depending on QT correction method used. Other clinical studies did not detect a drug effect on QTc intervals.⁵³

An FDA MedWatch was issued on March 19, 2008 related to an ongoing safety review of tiotropium and its potential to increase the risk of stroke in patients.⁵⁴ The information is based on data submitted by the manufacturer, Boehringer Ingelheim, from a pooled analysis of 29 placebo-controlled trials with 13,500 patients with COPD. The preliminary estimate of eight strokes per 1,000 patients treated annually with tiotropium is higher than the six strokes per 1,000 patients treated annually with placebo. The FDA cautions that it has not yet confirmed these analyses with the manufacturer. Although pooled analyses are useful in highlighting potential safety issues, they have inherent limitations and uncertainty, mandating further investigation with other data sources. The FDA informed healthcare professionals that they have reviewed preliminary data from the UPLIFT trial and confirmed that the preliminary results reported by Boehringer Ingelheim to the FDA showed that there was no increased risk of stroke with tiotropium bromide compared to placebo. Due to the amount of data collected in UPLIFT, a complete review of the results could take several months. The FDA will provide an updated communication with the final results of the UPLIFT analysis, as well as any available data regarding tiotropium and stroke risk.

Monitoring

Anticholinergic drugs may worsen symptoms associated with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction.

Tiotropium is a predominantly renally excreted drug. Patients with moderate-to-severe renal impairment (creatinine clearance less or equal to 50 mL per minute) should be monitored closely.⁵⁵

Special Populations^{56,57,58,59,60,61}

Pediatrics

COPD is a disease that does not normally occur in children. Safety and effectiveness of ipratropium (Atrovent), albuterol/ipratropium MDI (Combivent), albuterol/ipratropium inhalation solution (Duoneb), and tiotropium DPI (Spiriva) in pediatric patients have not been established.

Pregnancy

Albuterol, albuterol/ipratropium MDI, albuterol/ipratropium inhalation solution, and tiotropium are Pregnancy Category C. Ipratropium is Category B.

Other considerations – renal, hepatic, race, etc.

The pharmacokinetics of albuterol/ipratropium (Combivent) have not been studied in patients with renal insufficiency, hepatic insufficiency, or the elderly.

The pharmacokinetics of ipratropium as not been studied in patients with renal or hepatic

insufficiency.

An eight-week, randomized, double-blind, placebo-controlled trial was conducted in 166 African-Americans with COPD to determine the efficacy of once daily inhaled tiotropium versus placebo.⁶² The primary efficacy endpoint was the FEV₁ AUC (0-3) after eight weeks of therapy.

A total of 160 patients were eligible for efficacy evaluation. At the end of the study period, the tiotropium group (n=78) had a FEV₁ AUC (0-3) of 180 mL greater than the placebo group (n=82; p<0.0001). There were no significant differences in use of rescue medications between the two groups. Also, there were no patients in the tiotropium group who experienced a COPD exacerbation while there were 12 patients in the placebo group who did. This study was sponsored and conducted by the manufacturer of tiotropium.

Dosages

| Drug | Adult Dose | Availability |
|---|--|-------------------------------|
| albuterol/ipratropium inhalation solution (Duoneb [®]) ⁶³ | 3 mL four times daily (up to two additional 3 mL doses per day) | 3 mg / 0.5 mg per 3 mL |
| albuterol/ipratropium MDI (Combivent [®]) ⁶⁴ | Two inhalations four times daily (do not exceed 12 inhalations in 24 hours) | 90 mcg / 18 mcg per actuation |
| ipratropium inhalation solution (Atrovent) ⁶⁵ | 2.5 mL three to four times daily | 500 mcg per 2.5 mL |
| ipratropium inhalation aerosol MDI (Atrovent HFA) ⁶⁶ | Two inhalations four times daily (do not exceed 12 inhalations in 24 hours) | 17 mcg per actuation |
| tiotropium inhalation powder DPI (Spiriva Handihaler [®]) ⁶⁷ | One inhalation daily | 18 mcg per capsule |

MDI=metered-dose inhaler

DPI=dry powder inhaler

An FDA Public Health Advisory was issued in March 2008 to highlight the correct use of tiotropium (Spiriva) capsules, which are to be used in the Handihaler device. These capsules should not be swallowed.⁶⁸

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the 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 percent 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/funding must be considered, the studies in this review have also been evaluated for validity and importance.

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

A large, randomized, double-blind, double-dummy, two-period crossover study of 172 COPD patients investigated the effects of the addition of either formoterol or albuterol to ipratropium in patients whose symptoms were not optimally controlled by ipratropium alone.⁶⁹ In addition to ipratropium MDI 40 mcg four times daily, patients received, in random order, formoterol DPI 12 mcg twice daily for three weeks followed by albuterol MDI 200 mcg four times daily for three weeks, or vice versa. Morning peak expiratory flow rate (PEFR) and FEV₁ were significantly better with the formoterol-ipratropium combination than with the albuterol-ipratropium combination (p=0.0003 and p<0.0001 for PEFR and FEV₁, 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 percent, respectively), the number of patients with no COPD exacerbations (34.6 and 30.8 percent, respectively), or the percentage of patients experiencing "bad days" during the trial (65 and 69 percent, respectively).

tiotropium (Spiriva) versus placebo

The UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial was a large, randomized, double-blind, placebo-controlled trial that compared four years of therapy with either tiotropium or placebo in 5,993 patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs.⁷⁰ The patients were at least 40 years of age with an FEV₁ of 70 percent or less after bronchodilation and a ratio of FEV₁ to FVC of 70 percent or less. The two primary endpoints were the rate of decline in the mean FEV₁ before and after bronchodilation beginning on day 30. Secondary endpoints included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality. Patients were randomly assigned to the tiotropium group or to the placebo group. Mean absolute improvements in FEV₁ 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 two groups in the rate of decline at any timepoint were not significant. The mean absolute total score on the SGRQ was lower in the tiotropium group compared with the placebo group at each time point throughout the 4-year period (p<0.001). At four years and 30 days, tiotropium treatment was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure, but did not significantly reduce the rate of decline in FEV₁.

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.⁷¹ Two-hundred eighty-eight patients with mean age 65 years and mean FEV₁ 41 percent 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 four 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 FEV₁ 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 percent versus ipratropium 10.3 percent).

Two, one-year, randomized, double-blind, double-dummy studies evaluated tiotropium 18 mcg once daily (n=356) with ipratropium 40 mcg four times daily (n=179).⁷² Mean baseline FEV₁ values were 41.9 percent of predicted value for tiotropium and 39.4 percent of predicted value for ipratropium. Trough FEV₁ at one 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 percent (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 six-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 COPD patients with a baseline mean FEV₁ 40 percent of predicted value and a mean age of 65 years.⁷³ Compared with placebo treatment, the mean predose morning FEV₁ following six months of therapy increased significantly more for the tiotropium group (0.14 L) than the salmeterol group (0.09 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.

COPD patients (tiotropium, n=402; salmeterol, n=405; placebo, n=400) were enrolled in two, six-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.⁷⁴

The two 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 0.10 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 six-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 with 449 patients with moderate to severe COPD in Canada who had one year of treatment with tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol.⁷⁵ The proportion of patients in the tiotropium plus placebo group who had episodes of an exacerbation (62.8 percent) was not different from that in the tiotropium plus salmeterol group (64.8 percent; difference, -2.0 percentage points [95% CI, -12.8 to 8.8]) or in the tiotropium plus fluticasone/salmeterol group (60 percent; difference, 2.8 percentage points [95% CI, -8.2 to 13.8 percentage points]). Tiotropium plus fluticasone/salmeterol improved lung function ($p=0.049$) 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 percent of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled corticosteroids or long-acting beta-agonists. 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.

Meta-Analyses

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 anticholinergics (tiotropium (Spiriva) or ipratropium bromide (Atrovent)) versus control therapy (inhaled salmeterol (Serevent), inhaled salmeterol/fluticasone (Advair), inhaled albuterol or placebo)).⁷⁶ 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 anticholinergics significantly increased the risk of cardiovascular death, MI or stroke (1.8 percent versus 1.2 percent for control; $p<0.001$). Further delineation for individual primary outcomes were also assessed and showed inhaled anticholinergics significantly increased the risk of MI (1.2 percent versus 0.8 percent, $p=0.03$) based on eleven trials involving 10,598 patients. Risk of cardiovascular death was significantly increased by inhaled anticholinergics (0.9 percent versus 0.5 percent, $p=0.008$) in twelve trials of 12,376 patients. On the other hand, inhaled anticholinergics did not significantly increase the risk of stroke (0.5 percent versus 0.4 percent for control, $p=0.20$). 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 anticholinergics. 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 anticholinergics. 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 and deaths, and adverse effects.⁷⁷ Treatment was recommended for patients with stable COPD who have respiratory symptoms and FEV₁<60. Treatment should consist of one of the following: long-acting inhaled beta-agonist, long-acting inhaled anticholinergic, or inhaled corticosteroid. There was insufficient documentation to recommend one 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.⁷⁸ The meta-analysis evaluated the safety and efficacy of anticholinergics (ipratropium and tiotropium) and beta₂ agonists (albuterol, metaproterenol, formoterol, and salmeterol) in COPD. Anticholinergics significantly reduced severe COPD exacerbations compared to placebo as well as reduced respiratory deaths. On the contrary, beta₂ agonists did not affect severe COPD exacerbations and actually increased the rate of respiratory deaths compared with placebo. This finding is in contrast to the 2006 GOLD COPD guidelines that suggest either long-acting beta agonists or tiotropium be used as monotherapy for COPD.

Summary

COPD is categorized in Stages: I (mild), II (moderate), III (severe), and IV (very severe). Treatment initiation may begin with use of as-needed short-acting bronchodilators followed by routine long-acting bronchodilators, inhaled corticosteroids, long-term oxygen therapy, and even surgery. Regular use of long-acting beta agonists or short- or long-acting anticholinergics has been shown to improve health status.

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

The two anticholinergic options in this class are ipratropium (Atrovent) and tiotropium (Spiriva). Ipratropium. Both are safe and effective drugs; however, the long-acting, anticholinergic agent tiotropium is dosed once daily and has a duration of action greater than 24 hours. Both have been shown to improve bronchodilation, dyspnea, exacerbation rates and health-related quality of life. Adverse reactions are limited primarily to dry mouth that appears to resolve with continued use.

References

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- ² Combivent [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; November 2008.
- ³ Atrovent [package insert], Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; March 2002.
- ⁴ Atrovent [package insert]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals; March 2002.
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