COPD Inhaled Anticholinergics Monograph
July 2011

Introduction:

Chronic obstructive pulmonary disease (COPD) is a respiratory condition of airflow obstruction due to chronic bronchitis or emphysema. Although obstruction may be reversible, it often worsens with time and is commonly associated with respiratory hyperreactivity.[1] While there is some debate about the distinction between emphysema and chronic bronchitis, 85% of COPD cases are attributed to the latter.[2] Patients with chronic bronchitis present with intermittent airway inflammation and excessive mucus production resulting in episodes of prolonged, productive cough. Patients with emphysema experience destruction of the alveolar and distal airspace structure, resulting in loss of gas exchange, decreased ventilation and decreased perfusion.[1]

COPD is the fourth leading cause of chronic morbidity and mortality in the United States.[1] In 2005, COPD was the underlying cause in about 1 of every 20 deaths. Smoking is estimated to be responsible for at least 75% of COPD deaths. An estimated $6,000 is spent annually on each COPD patient's healthcare.[3] Most recently, it was estimated that 9.9 million (4.4%) Americans were living with chronic bronchitis and 4.9 million (2.2%) with emphysema. Based upon these numbers, approximately $89 billion in direct healthcare costs are spent annually on COPD. COPD mortality rates during the same time were 0.2 and 4.2 per 100,000 people, for chronic bronchitis and emphysema respectively.[4]

From 1980 to 2000, mortality rates resulting from COPD increased 67%. The overall increase resulted in a 13% increase in mortality for men, while the rates tripled for women. The year 2000 was the first that more women died from COPD than men.[5] Between 2000 and 2005, death rates attributable to COPD increased for both men and women at 5% and 11%, respectively.[3]

Despite ranking highest among different ethnic groups with a smoking prevalence rate of 23.1% among ages 12 to 17, the prevalence of COPD in American Indians and Alaskan Natives (AI/AN) is less than in the general American population.[6-7] The lower prevalence of COPD may be due to AI/AN youth being more likely to be light smokers (<15 cigarettes/day). Between 2007 and 2009, it was estimated that 5.1% of American adults were living with COPD, while only 4.6% of AI/ANs had COPD.[8] In 2007, 667 deaths in the United States were caused by chronic bronchitis and 12,790 were attributed to emphysema. AI/ANs made up only 49 of the deaths related to chronic bronchitis, and 2 deaths due to emphysema.[7]

Medications are critical to symptom management. Inhaled bronchodilators are central to the core treatment recommended by numerous guidelines and systematic reviews.[1, 9-10] For example, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[1] recommend a four step approach to pharmacotherapy based on disease severity:

1. Mild → short-acting bronchodilator (SABA) for as needed treatment
2. Moderate → add regular treatment with a long-acting bronchodilator (LABA)
3. Severe → add inhaled corticosteroids (ICS)
4. Very Severe → add long-term oxygen

Other medications, such as methylxanthines and phosphodiesterase-4 inhibitors see limited use, due to toxicities or minimal evidence.

This monograph will focus on two anticholinergic agents found in three formulations: ipratropium alone (Atrovent®), ipratropium and albuterol combined (Duoneb®, Combivent®) and tiotropium (Spiriva®).

Pharmacology/Pharmacokinetics:[11-16]

Mechanism of Action:

Ipratropium

Ipratropium is an anticholinergic agent, which antagonizes the action of acetylcholine in the lungs thereby inhibiting vagally-mediated reflexes and producing bronchodilation. Ipratropium also prevents the increase in intracellular calcium concentration by interfering with acetylcholine's actions on muscarinic receptors on bronchial smooth muscle.

Tiotropium

Anticholinergic agents have affinity to the subtypes of muscarinic receptors M1 to M5. The pharmacological effects of tiotropium in the airways are through inhibition of M3 receptors at the smooth muscle leading to bronchodilation. Tiotropium is a highly potent antimuscarinic. The antagonism of the muscarinic receptors is competitive and reversible, as shown with human and animal origin receptors and isolated organ preparations. Tiotropium demonstrates very slow dissociation from muscarinic receptors which clinically correlates with significant and long lasting bronchodilation in COPD patients.[13, 15, 17]

Table 1. Pharmacokinetic Properties

Drug	Absorption	Distribution	Metabolism	Excretion
Ipratropium bromide	Bioavailability: Inhalation 0.03% to 6.9%; Oral inhalation dose primarily routed to the gastrointestinal (GI) tract (~ 90%) Onset of action: within 15 min Peak effect: 2-5 hours Quaternary amine not readily absorbed into systemic circulation through GI tract or lungs	Approximately 15% of dose reaches lower airways Minimally bound to plasma albumin and α_1-acid glycoprotein (≤ 9%)	Partially hydrolyzed to inactive ester products	Feces: 2.8% Urine: 48% Elimination half-life: 2 to 3.8 hours

Tiotropium bromide (Spiriva®)	F = 19.5% Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation	Volume of distribution = 32 L/Kg (binds extensively to tissues) Protein Binding = 72%	Extent of metabolism is small: 74% is renally excreted unchanged. Metabolites: N-methylscopine, dithienylglycolic acid. CYP 450 2D6 and 3A4 are involved in the metabolic pathways responsible for the small fraction that is metabolized.	Terminal half-life = 5 to 6 days following inhalation. Renal Clearance = 880 ml/min after an intravenous dose in young healthy volunteers.

FDA Approved Indications:[11-16, 18-19]

Ipratropium:

- Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema

Ipratropium/Albuterol:

- COPD, for patients requiring a second bronchodilator

Tiotropium Bromide:

- Long-term, maintenance treatment of bronchospasms associated with COPD, including chronic bronchitis and emphysema.

- To reduce exacerbations in COPD patients.

Current National Core Formulary Alternatives:[20]

SABA: albuterol (Proventil HFA®); ipratropium (Atrovent®)

LABA: salmeterol (Serevent®)

ICS: mometasone (Asmanex®)

ICS/LABA Combination: fluticasone/salmeterol (Advair®)

Dosage and Administration:[11-16, 18-19]

Table 2. Dosage and Administration

Drug	Adult Dose	Special Populations	Hepatic Impairment	Renal Impairment
Ipratropium bromide	Inhalation aerosol: Usual starting dose is 2 inhalations 4 times a day and titrated up as needed not to exceed 12 inhalations in 24 hours Inhalation solution: 500 mcg (1 unit dose vial) via nebulization 3 to 4 times a day about 6 to 8 hours apart	Geriatric patients—follow adult dosing guidelines Pediatrics—safety and effectiveness has not been established <12 years old Pregnancy category B Available data is inadequate/inconclusive for determining infant risk during breastfeeding	Pharmacokinetics of ipratropium have not been studied in hepatic impairment	Pharmacokinetics of ipratropium have not been studied in renal impairment
Ipratropium bromide/Albuterol sulfate	For patients requiring a second bronchodilator: Inhalation aerosol- 2 inhalations 4 times daily and titrated up as needed not to exceed 12 inhalations in 24 hours Inhalation solution- one 3 mL vial via nebulization 4 times daily; max 6 doses in 24 hours	Geriatric patients—follow adult dosing guidelines Pediatrics—safety and effectiveness has not been established <12 years old Pregnancy category C Available data is inadequate-inconclusive for determining infant risk during breastfeeding	Pharmacokinetics of ipratropium have not been studied in hepatic impairment	Pharmacokinetics of ipratropium have not been studied in renal impairment

Tiotropium Bromide	Two inhalations of the powder contents of a tiotropium capsule (18mcg) once daily	Geriatric patients—follow adult dosing guidelines Pediatrics—safety and effectiveness has not been established <12 years old Pregnancy category C Available data is inadequate-inconclusive for determining infant risk during breastfeeding	No dosage adjustment for hepatic impairment	Patients with moderate to severe renal impairment given tiotropium should be monitored closely for anticholinergic effects.

Ipratropium

Ipratropium does not require shaking; however, inhaler should be primed before first use by releasing two sprays into the air. Inhaler will also need primed if it has not been used for more than three days. Use with nebulizer mouthpiece rather than a mask is recommended with inhalation solution to avoid getting into eyes.

Tiotropium

Tiotropium capsules must be stored in the blister. For oral inhalation only, capsules should not be swallowed.

Efficacy:

Ipratropium

Clinical Trials

A small trial evaluated safety and efficacy of ipratropium versus placebo in COPD treatment The trial was a double-blind, randomized, crossover study involving 22 patients with COPD ranging from 18 to 67 years old.[21] It excluded patients with hypersensitivity to atropine or its derivatives, and patients with significant cardiac, renal, hepatic, or metabolic disease. Patients underwent two weeks of treatment with two inhalations of ipratropium 20mcg four times a day. Statistically significant increases in forced expiratory volume (FEV_1) were seen with ipratropium versus placebo. Mean FEV_1 increases stayed above the clinically meaningful level of +15% for at least four hours after administration in patients given ipratropium.

Ipratropium bromide hydrofluoroalkane (HFA) initial efficacy data derived from two randomized, double-blind, controlled clinical study enrolling males and females ≥40 years old, with history of COPD, a smoking history of >10 pack-years, an FEV_1 <65%, and an

FEV_1/forced vital capacity (FVC) <70%. One of the studies was a 12 week, randomized, double-blind, active and placebo controlled study enrolling 505 patients. The patients were randomized to either 42mcg ipratropium HFA (n=124), 84mcg ipratropium HFA (n=126), 42mcg ipratropium chlorofluorocarbons (CFC) (n=127), HFA placebo (n=62), or CFC placebo (n=66). Serial FEV_1 showed that 42mcg of ipratropium HFA produced significantly greater improvement in pulmonary function versus placebo. Mean peak improvement in FEV_1 in six hours immediately post dose, relative to baseline, was 0.295 liters compared to 0.138 liters for placebo on day 1 and 0.295 liters versus 0.140 liters on day 85. Ipratropium HFA was clinically comparable to same dose CFC. The second study was a 12-week, randomized, double-blind, active-controlled, study which found ipratropium HFA to be comparable in regards to safety and efficacy to ipratropium CFC.[11] Similar results were found with a CHEST published study comparing ipratropium HFA to ipratropium CFC.[22]

Head-to-Head

Ipratropium/Albuterol

A retrospective analysis of data from seven clinical trials found the long-term benefits of bronchodilator therapy to differ from the short-term effects.[23] This analysis included seven 90-day trials which evaluated COPD patients of ≥40 years of age and with a smoking history >10 pack-years. The patients had FEV_1 ≤75% of predicted normal with 5 of the 7 trials requiring FEV_1 ≤ 65% of predicted normal. Patients with history of asthma, allergic rhinitis or atopy, on >10mg of prednisone daily, using cromolyn sodium, or with an elevated blood eosinophil count were excluded. Studies included 1,836 patients randomized to receive β-agonist (909) or ipratropium (927). Completion rates were 77% for β-agonist group and 80% for ipratropium group with reasons for dropouts being similar between groups. Most patients responded to short-term administration of ipratropium or albuterol both before and after extended therapy; However after 90 days of therapy there was a decrease in the number of patients who responded acutely for both ipratropium and albuterol. The reduction in responsiveness was significantly less with ipratropium versus albuterol. Improvement in lung function was significantly better with ipratropium (FEV_1 increased 28mL, FVC increased 131mL, $p<0.01$) versus albuterol (FEV_1 increased 1mL, FVC increased 20mL, $p<0.01$). A significant decrease in post-bronchodilator lung function was seen in the albuterol group after extended treatment (FEV_1 decreased 49mL, FVC decreased 74mL, $p<0.0001$). An increase in post-bronchodilator lung function was seen with ipratropium (FEV_1 increased 6mL, FVC increased 44mL, $p>0.2$ and $p<0.01$, respectively); However, only the increase in FVC was significant. Part of the improvement in lung function may be due to the extended duration of ipratropium versus albuterol since treatment was only withheld for 12 hours prior to evaluation and ipratropium may have had some residual effects.[23] Another study showed ipratropium benefit due to the longer duration of ipratropium versus albuterol.[24] Inclusion of ipratropium with or without albuterol was also shown to decrease the number of exacerbations in COPD and resulted in lower total treatment costs.[23]

A 12-week prospective, double-blind, parallel-group evaluation of ipratropium and albuterol combination versus either agent alone was performed. Patients included had a diagnosis of COPD, had a history of more than 10 pack-years, were regularly using at least two prescribed therapeutic agents for COPD control, and were at least 40 years of age. Patients had moderately severe airway obstruction classified as FEV_1 ≤65% of predicted normal and FEV_1≤70% of FVC. Patients with history of asthma, allergic rhinitis or atopy, on >10mg of prednisone daily, or with an elevated blood eosinophil count were excluded. A total of 534

patients were recruited with withdrawal rates similar among the groups. The mean FEV_1 response was clinically significant (≥15% above baseline) and seen in all three groups on all measurements. The mean peak responses to the ipratropium/albuterol combination were significantly greater than the individual agents on all measurements. The mean peak percent increases in FEV_1 over baseline were 31 to 33 % for ipratropium/albuterol combination, 24 to 25% for ipratropium, and 24 to 27% for albuterol.[25] Other studies have shown similar results with inhalation aerosols and solutions.[25-26]

Ipratropium/Salmeterol

A single-blind, balanced, cross-over, randomized study evaluating 12 male patients with COPD evaluated the effect of salmeterol alone versus salmeterol/ipratropium combination.[27] The patients were >40 years of age, had a smoking history of >10 pack-years, had a FEV_1 between 16 and 62% of predicted values after withholding long-acting and short-acting bronchodilator drugs for 24 and 12 hours, respectively. Patients with history of asthma, allergic rhinitis or atopy, or with an elevated eosinophil blood count were excluded. The patients were randomized to salmeterol plus placebo, ipratropium plus placebo, salmeterol plus ipratropium, or placebo plus placebo. Fifteen minutes after drug inhalation the percentage modification caused by ipratropium (19.3±4.6) was greater than that caused by salmeterol (13.5±2.9). No significant difference was found between regimens containing active medications 15 minutes after inhalation, but all regimens containing active medications were significantly better than placebo. Only salmeterol and salmeterol plus ipratropium had a significant spirometric increase over the 12 hour monitoring period. This study shows that ipratropium at the clinical recommended dose does not bring further bronchodilation compared to salmeterol; however, ipratropium may have a faster onset and salmeterol has a longer duration of action.

Another study comparing salmeterol alone versus salmeterol plus ipratropium found benefit in the combination therapy.[28] This randomized, double-blind, double-placebo, parallel group design evaluated 144 patients with COPD, a smoking history equivalent to 10 pack-years, aged 40 to 75 years old, FEV_1 ≤75% of predicted after inhalation of short acting beta agonist, and no change in medications for COPD in the preceding 6 weeks. Patients were excluded if they had history of asthma, allergic rhinitis or atopy, or an elevated eosinophil count. Patients were randomized to salmeterol (47), salmeterol plus ipratropium (47) or placebo (50). The mean FEV_1 and FVC area under the curves (AUC) in the salmeterol alone, and the salmeterol plus ipratropium groups were significantly better than placebo ($p<0.001$). The FEV_1 AUC was significantly greater with salmeterol plus ipratropium versus salmeterol alone ($p<0.05$). No significant difference was found for improvement in symptom control or need for a rescue inhaler between the salmeterol, and the salmeterol plus ipratropium groups.

Patakas and colleagues authored an article on the comparison of effects of ipratropium and salmeterol on exercise performance and breathlessness in patients with COPD.[29] It was a small study performed in a group of 15 patients. The patients were randomized to receive either six puffs of placebo, six puffs of ipratropium, or two puffs of salmeterol. Pulmonary function tests were performed at baseline and 30 minutes after drug inhalation, as well as a progressive incremental exercise test was performed via treadmill. A statistically significant improvement in FVC, FEV_1, and other lung function tests were seen in both the salmeterol and ipratropium groups versus placebo. However, no significant difference was found between the two active groups. The arterial oxygen saturation recovery time was significantly shorter with ipratropium or salmeterol versus placebo, but no significant difference was found between the two groups.

Tiotropium

Clinical Trials

In a randomized, double-blinded, placebo-controlled study of 187 patients, tiotropium was assessed for its effectiveness in reducing lung hyperinflation.[30] Ninety-six patients received 18 mcg of tiotropium while 91 patients received placebo once daily for 42 days. The use of tiotropium, when compared to placebo, was associated with increased vital capacity (0.43+/-0.06), inspiratory capacity (0.24+/-0.06), decreased residual volume (-0.56+/-0.10), and functional residual capacity (-0.45+/-0.10) ($p<0.05$ for all). Tiotropium increased post-dose exercise endurance time by 105 seconds (21%; $p=0.0098$) on day 42. Tidal volume and minute ventilation both increased (0.11+/-0.03 and 3.0+/-0.8, respectively; $p<0.001$ for both), while dyspnea decreased by 0.9+/-0.3 Borg scale units ($p<0.01$). This study showed an association between tiotropium and sustained reductions of lung hyperinflation at rest and during exercise.

A study that took place in 26 Veterans Affairs medical centers prospectively evaluated the effectiveness of tiotropium in reducing COPD exacerbations and exacerbation-related health care utilization.[31] 1,829 patients with moderate to severe COPD were given either 18 mcg of tiotropium once daily or placebo for 6 months. The primary endpoints were the percentage of patients with an exacerbation and the percentage of patients with a COPD related hospitalization. This study found that tiotropium significantly reduced the percentage of patients experiencing at least one exacerbation compared to placebo (27.9% vs. 32.3%, respectively; [95% CI, -10.4 to -1.0 percentage points]; $p=0.037$). Fewer tiotropium patients were hospitalized because of COPD exacerbations, but this difference was not statistically significant, although the results trended in favor of tiotropium (7.0% vs. 9.5%, respectively; [CI, -5.9 to -0.1 percentage points]; $p=0.056$).

In 2008, Tashkin, et al. published data from the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study.[32] A total of 5,993 patients were studied over four years, comparing tiotropium (n = 2987) to placebo (n = 3006). Individuals were included who were over age 40, had FEV_1 70% or less after bronchodilation, and had a FEV_1 to FVC ratio of 70% or less. Patients were allowed to use any other medication besides inhaled anticholinergics. Primary endpoints included rate of decline for both before and after exercise measurements of FEV_1. Secondary endpoints included FVC measurements, exacerbations of COPD, and mortality. Initial measurements were taken on day 30. Tiotropium performed significantly better than placebo for secondary outcomes, but the primary outcomes were not different. Mean number of exacerbations were better with tiotropium than placebo by 14% ($P<0.001$). Mortality rates trended toward a benefit with the study drug, but the differences were not significant (14.9% vs. 16.9%; HR 0.89; 95% CI, 0.79 to 1.02).

In 2009, Decramer, et al. published a subgroup analysis of the UPLIFT study. This was a randomized, double-blind, placebo-controlled trial that recruited 5,993 patients with COPD to receive four years of treatment with either once daily tiotropium 18 mcg or placebo, delivered by inhalation device.[33] Although the primary outcome-lung function decline was negative, long-acting bronchodilators reduced exacerbation rates and improved health status. The subgroup analysis focused on patients with GOLD stage II disease. Primary endpoints were the yearly rates of decline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) and in post-bronchodilator FEV1. The rate of decline of mean pre-bronchodilator FEV1 did not differ between groups (35 mL per year [SE 2] vs. 37 mL per year [SE 2]; $p=0.38$). The rate of

decline of mean post-bronchodilator FEV1 was lower in the tiotropium group than in the control group (43 mL per year [SE 2] vs. 49 mL per year [SE 2], p=0.024.

Head-To-Head Trials:

Tiotropium vs. Salmeterol

In 2005, a study comparing the long-acting anticholinergic tiotropium with the long-acting beta-agonist salmeterol was published. This randomized, double-blind, double-dummy, parallel-group study aimed to specifically compare daytime bronchodilator efficacy of these two medications.[34] Randomization included 653 patients (328 tiotropium 18 mcg once daily, 325 salmeterol 50 mcg twice daily). Primary endpoints were average FEV1 over 12 hours, and peak FEV1 at 12 weeks. After 12 weeks, the average post-dose FEV1 over 12 hours was significantly higher with tiotropium compared with salmeterol (167 vs. 130 mL, respectively, p=0.03), as was peak FEV1 (262 vs. 216 ml, respectively, p=0.01). The average FEV1 responses from 0–6 h and 6–12 h were higher in the tiotropium group compared with salmeterol (p<0.05). Peak and average FVCs were significantly higher with tiotropium compared with salmeterol (p<0.01). Morning pre-dose FEV1 responses were not significantly different; However, tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol (p<0.05).

A 1-year, randomized, double-blind, double dummy, parallel-group trial published in 2011, compared the effect of tiotropium to salmeterol. This study of patients with moderate to very severe COPD and a history of exacerbations in the preceding year looked at the incidence of moderate or severe exacerbations.[35] The tiotropium group had an increased the time to the first exacerbation (187 days vs.145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; p<0.001). Tiotropium increased the time to the first severe exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; p<0.001), reduced the annual number of moderate or severe exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; p=0.002) and reduced the annual number of severe exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; p<0.001). The incidence of serious adverse events was similar in the two study groups. There were 64 deaths (1.7%) in the tiotropium group and 78 (2.1%) in the salmeterol group.

Tiotropium vs. Salmeterol/Fluticasone

A study by Wedzicha, et al. compared the relative efficacy of the combination salmeterol/fluticasone 50/500 mcg twice daily and tiotropium 18 mcg once daily in preventing exacerbations and related outcomes in patients with severe and very severe COPD.[36] Randomization included 1,323 patients in this 2-year, double blind trial. The primary endpoint was health care utilization rate due to exacerbations. Secondary endpoints included health status measured by St. George's Respiratory Questionnaire (SGRQ), mortality, adverse events and study withdrawal. The SGRQ score was statistically lower at 2 years with salmeterol/fluticasone vs. tiotropium (difference 2.1 units; 95% CI, 0.1-4.0; p=0.038). More pneumonias were reported in the salmeterol/fluticasone group (p=0.008). Probability of withdrawing from the study was 29% greater with tiotropium than salmeterol/fluticasone (p=0.005). The modeled annual exacerbation rate was 1.28 in the salmeterol/fluticasone group and 1.32 in the tiotropium group. This difference was not statistically significant (rate ratio, 0.967; [95% CI, 0.836-1.119]; p=0.656).

Tiotropium/Ipratropium

In 2002, the Dutch/Belgium Tiotropium Study Group published the results of a one-year randomized controlled trial comparing health outcomes with use of tiotropium and ipratropium in COPD patients. [37] The primary outcomes were FEV1, peak expiratory flow rate (PEF), dyspnea, short-acting beta-agonist use, health-related quality of life and COPD exacerbations. The tiotropium treatment group consisted of 356 patients, while the ipratropium treatment group had 179 patients. At the end of one year, the trough FEV1 was significantly improved in the tiotropium group. Trough FEV1 improved by 0.12 ± 0.01 L with tiotropium and declined by 0.03 ± 0.02 L with ipratropium ($p<0.001$). Tiotropium was found to reduce exacerbations by 24% ($p<0.01$), as well as reduce the time to first exacerbation ($p<0.01$) and hospitalization ($p<0.05$). Significant improvements were also found in the PEF, health-related quality of life, short-acting beta-agonist use, and dyspnea. The authors concluded that tiotropium was recommended as first-line maintenance treatment of COPD.[38] Another trial comparing tiotropium and ipratropium was published by the Tiotropium Study Group in 2000 prior to this larger trial. The randomized controlled trial looked at similar results over a 13 week period. It was determined that tiotropium was more effective than ipratropium in improving lung function in COPD patients.[28] Both studies concluded that the safety profile of tiotropium and ipratropium were similar. Lastly, a cost-effectiveness study looking at two randomized controlled trials determined that tiotropium decreased exacerbations, hospitalizations, and unscheduled healthcare provider visits. However, this resulted in a slightly higher annual healthcare cost per patient.

Guidelines/Systematic Reviews/Meta-Analysis

Clinical guidelines and systematic reviews evaluating the treatment of stable COPD have all outlined similar treatment strategies. Bronchodilators are the cornerstone of therapy, with long-acting medications being preferred based on efficacy in moderate to very severe COPD patients. Inhaled long-acting beta-agonists and long-acting anticholinergics can both be used as maintenance therapy, with short-acting medications being utilized for exacerbations.

A systematic review of tiotropium evaluated nine randomized-controlled trials comparing the effectiveness to either placebo or ipratropium. The review concluded that tiotropium both reduced exacerbations (OR 0.74; 95% CI 0.66-0.83) and related hospitalizations (OR 0.64; 95% CI 0.51-0.82) compared with placebo and ipratropium. Furthermore, with tiotropium treatment, the number needed to treat was 14 to prevent an exacerbation (95% CI 11-22), and 30 to prevent a hospitalization (95% CI 22-61). Tiotropium not only provides symptomatic relief, but also produces greater increases in FEV1 and FVC from baseline compared to placebo, ipratropium and LABA's.[39]

The GOLD guidelines were updated in 2010 and are seen as a primary resource for guiding pharmacotherapy in the treatment of COPD. Short-acting bronchodilators, including ipratropium, are recommended initially for patients categorized in the mild stage of COPD. This therapy is to be continued on an as needed basis throughout disease progression. Long-acting bronchodilators, including tiotropium, should be added on as maintenance therapy in the moderate stage of COPD. The GOLD guidelines did not recommend the LABA or long-acting anticholinergic over the other as a preferred long-acting bronchodilator. However, it was suggested that the mechanisms of action be different between the short-acting and long-acting bronchodilators in a COPD regimen. [1]

The National Institute for Health and Clinical Excellence (NICE) guideline was also updated in 2010, but primarily to align the diagnostic criteria with the GOLD guideline. The guideline also concluded that LABAs and long-acting anticholinergics used as monotherapy are equally effective in the treatment of COPD. In a cost-effectiveness evaluation of two economic reviews, it was determined that long-acting anticholinergics were favored over short-acting anticholinergics in patients requiring maintenance bronchodilator therapy. Moreover, long-acting anticholinergics were more convenient when considering the once-daily dosing.[9]

The American College of Physicians (ACP) guideline was released in 2007. The recommendations for maintenance therapy for COPD differed slightly from that of GOLD and NICE. For symptomatic patients with a FEV1 less than 60% predicted, patients should be prescribed one of the following as monotherapy: inhaled LABA, long-acting anticholinergic or ICS. This was considered a strong recommendation with high-quality evidence.[40]

A systematic review (and meta-analysis) was conducted in 2008 based upon data from randomized controlled trials of any inhaled anticholinergic for treatment of COPD. A minimum of 30 days of treatment and reports of cardiovascular events were required. The purpose of this review was to assess the cardiovascular risks of these drugs, including cardiovascular death, myocardial infarction (MI) and stroke. The primary outcome was a composite of cardiovascular death, MI or stroke. The secondary outcome was all-cause mortality. A total of 17 trials (14,783 patients) were analyzed. Cardiovascular death, MI or stroke occurred in 135 of 7,472 patients (1.8%) that received inhaled anticholinergics and 86 of 7311 patients (1.2%) that received the control therapy (RR, 1.58 [95% CI 1.21-2.06]; p<0.001). Specifically, patients that received inhaled anticholinergics had a significantly increased risk of MI (RR, 1.53 [95% CI 1.05-2.23]; p=0.03) and cardiovascular death (RR, 1.80 [95% CI, 1.17-2.77]; p=0.008). There was not a statistically significant increase in the risk of stroke (RR, 1.46 [95% CI, 0.81-2.62]; p=0.20). All-cause mortality was reported in 149 (2.0%) patients treated with anticholinergics versus 115 (1.6%) of the control patients (RR, 1.26 [95% CI, 0.99-1.61]; p=0.06). A sensitivity analysis restricted to 5 long-term trials (lasting greater than 6 months) confirmed the significant increased risk of cardiovascular death, MI or stroke (2.9% of patients treated with anticholinergics vs. 1.8% of control patients; RR, 1.73 [95% CI, 1.27-2.36]; p=0.001).[41]

Adverse Events:[11-16, 18-19]

Ipratropium:

- Cardiovascular:
  - Chest pain 3%
  - Atrial fibrillation <1%
  - Cerebrovascular accident <1%
  - Myocardial infarction <1%
  - Tachycardia including supraventricular <1%
- Central nervous system:
  - Headache 6-7%
  - Dizziness 2-3%
- Gastrointestinal:
  - Abnormal taste in mouth 20-30%
  - Nausea 4%
  - Xerostomia 2-4%
  - Dyspepsia 1-5%
- Genitourinary:
  - Urinary tract infection 2-10%

    - Urinary retention <1%
- Neuromuscular and skeletal:
    - Back pain 2-7%
- Ocular effects:
    - Mydriasis <1%
    - Eye pain <1%
    - Increased intraocular pressure <1%
    - Blurred vision <1%
- Respiratory:
    - Upper respiratory tract infection 9-34%
    - Bronchitis 10-23%
    - Sinusitis 1-14%
    - Dyspnea 7-10%
    - Pharyngitis 4%
    - Cough 3-5%
    - Rhinitis 2-6%
    - Paradoxical bronchospasm 2%
    - Sputum increased 1%
- Miscellaneous:
    - Flu-like syndrome 4-8%
    - Hypersensitivity reactions <1%
    - Anaphylactic reaction <1%

Tiotropium

- >10%
    - Gastrointestinal: Xerostomia (5-16%)
    - Respiratory: Upper respiratory tract infection (41%), pharyngitis (9-13%), sinusitis (7-11%)
- 1% to 10%
    - Cardiovascular: Chest pain (1-7%), edema (5%)
    - Central nervous system: Headache (6%), insomnia (4%), depression (1-4%), dysphonia (1-3%)
    - Dermatological: Rash (4%)
    - Endocrine and metabolic: Hypercholesterolemia (1-3%), hyperglycemia (1-3%)
    - Gastrointestinal: Dyspepsia (6%), abdominal pain (5%), constipation (4-5%), vomiting (4%), gastroesophageal reflux (1-3%), stomatitis-including ulcerative (1-3%)
    - Genitourinary: Urinary tract infection (7%)
    - Neuromuscular and skeletal: Arthralgia (4%), myalgia (4%), arthritis (≥3%), leg pain (1-3%), paresthesia (1-3%), skeletal pain (1-3%)
    - Ocular: Cataract (1-3%)
    - Respiratory: Rhinitis (6%), epistaxis (4%), cough (≥3%), laryngitis (1-3%)
    - Miscellaneous: Infection (4%), moniliasis (4%), flu-like syndrome (≥3%), allergic reaction (1-3%), herpes zoster (1-3%)
- <1%
    - Angioedema, application site irritation, atrial fibrillation, blurred vision, candidiasis, dizziness, dehydration, dry skin, dysphagia, hypersensitivity reactions, ileus, intestinal obstruction, intraocular pressure increase, joint swelling, palpitation, paradoxical bronchospasm, pruritis, pupil dilation, skin infection, skin ulcer, supraventricular tachycardia, tachycardia, throat irritation, urinary difficulty, urinary retention, urticaria

Precautions/Contraindications:[11-16, 18-19]

Ipratropium:

Contraindication:

- Hypersensitivity to ipratropium or atropine or any of its derivatives or components of the formulation including peanuts

Precautions:

- Not for use in acute episodes of bronchospasm
- Hypersensitivity reactions including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema may occur
- Life threatening paradoxical bronchospasm may occur
- May increase intraocular pressure resulting in precipitation or worsening of narrow-angle glaucoma
- May cause urinary retention; use caution in patients with prostatic hyperplasia or bladder-neck obstruction

Tiotropium

Contraindication:

- Hypersensitivity to tiotropium or ipratropium, or any component of the formulation (contains lactulose)

Precautions:

- Spiriva capsules for inhalation are for administration via an inhalation device and are not for oral use
- Not for acute use; Not for use as a rescue medication
- Immediate hypersensitivity reactions: Discontinue tiotropium at once and consider alternatives if immediate hypersensitivity reactions occur, including angioedema, and use with caution in patients with severe hypersensitivity to milk proteins
- Paradoxical bronchospasm: Discontinue tiotropium and consider other treatments if paradoxical bronchospasm occurs
- Worsening of narrow-angle glaucoma may occur; use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs
- Worsening of urinary retention may occur; use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs

Look-alike/Sound-alike Error Risk Potential:

Spiriva® may be confused with Inspra® or Serevent®.[13, 42]

Atrovent® may be confused with Serevent®.[18]

The generic names, tiotropium and ipratropium, may be confused for each other.[18-19]

The Institute for Safe Medication Practices (ISMP) does not list either medication on its list of high alert medications nor the list of medications that should not be crushed or chewed.[43-44] ISMP makes no recommendation for these drugs regarding tallman lettering and they are not included on the Beer's list.[45-46]

Aside from risk potential directly regarding the names, there is also error potential regarding the misuse of Spiriva capsules. These capsules are intended for use in the inhalation device only and are not meant to be swallowed.[13]

FDA Risk Evaluation and Mitigation Strategy (REMS):[47]

No applicable REMS is recommended by the Food and Drug Administration.

Drug Interactions:[11-16, 18-19]

Ipratropium

- Acetylcholinesterase inhibitors: anticholinergics may diminish the effects of acetylcholinesterase inhibitors
- Anticholinergics: potential for additive interaction with concomitant use of other anticholinergic medications
- Betel Nut: reduced anticholinergic effect of ipratropium due to betel nut cholinergic effects
- Cannabinoids: anticholinergic agents may enhance tachyarrhythmia effect of cannabinoids
- Cisapride: loss of cisapride efficacy due to counteracting GI motility induced by cisapride
- Potassium chloride: anticholinergics may enhance the ulcerogenic effect of potassium chloride, consider modification of therapeutic agent
- Secretin: anticholinergics may diminish the stimulatory effect of secretin, consider modification of therapeutic agent

Tiotropium

Increased Effect/Toxicity

- Tiotropium may increase the levels/effects of abobotulinumtoxin A, anticholinergics, cannabinoids, onabotulinumtoxin A, potassium chloride, rimabotulinumtoxin B
- Tiotropium levels/effects may be increased by conivaptan, pramlintide

Decreased Effect/Toxicity

- Tiotropium may decrease the levels/effects of anticholinesterase inhibitors, secretin
- Tiotropium levels/effects may be decreased by anticholinesterase inhibitors, peginterferon alfa-2b

Conclusions:

COPD affects approximately 4.6% of American Indians and Alaskan Natives. The prevalence rates and mortality associated with COPD are rising especially in women. COPD not only negatively affects quality of life, but also contributes to ~$6000 in health care costs per patient annually for treatment. For mild COPD, the guidelines recommend a short-acting bronchodilator such as ipratropium or albuterol for initial treatment. Ipratropium and albuterol are both effective for acute bronchodilation; However, ipratropium demonstrates better long-term benefits by improving lung function and decreasing the number of exacerbations thus decreasing costs. The combination of ipratropium/albuterol is more effective than either agent alone and could be considered for patients who require a second bronchodilator. For moderate COPD, addition of a long-acting bronchodilator such as tiotropium or salmeterol is recommended. Tiotropium provides more favorable results on time to first exacerbation, number of exacerbations and severity of exacerbations versus salmeterol. Tiotropium also has more beneficial effects on lung function over salmeterol. For severe COPD, guidelines recommend use of a long-acting bronchodilator plus an ICS for repeated exacerbations. Tiotropium and salmeterol/fluticasone had similar annual exacerbation rates. Salmeterol/fluticasone demonstrated better results on health related quality of life measures. For very severe COPD long term oxygen therapy should be added if respiratory failure. In moderate to very severe COPD treatment

with a long-acting maintenance medication and a short-acting rescue medication may be utilized. In these patients guidelines recommend use of agents with differing mechanisms of action. Anticholinergics have shown to be more effective than beta agonists; however, they also increase risk of MI and cardiovascular death, and may increase risk of stroke.

Recommendations:

Each of the agents discussed have a role in COPD treatment. Ipratropium should remain on the NCF for use in mild COPD and for acute relief in patients in addition to maintenance therapy. A consensus of the guidelines is to use long acting bronchodilators in moderate to very severe COPD. Tiotropium has been found to be superior to salmeterol in patient outcomes; therefore, it would be recommended to add tiotropium to the NCF as a first line agent in moderate to very severe COPD.

Relevant Acronyms:

COPD	Chronic Obstructive Pulmonary Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ISMP	Institute of Safe Medication Practice
NICE	National Institute for Health and Clinical Excellence
AI/AN	American Indians/Alaska Natives
GI	Gastrointestinal
FEV_1	Forced Expiratory Volume
HFA	Hydrofluoroalkane
CFC	Chlorofluorocarbons
FVC	Forced Vital Capacity
AUC	Area Under the Curve
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium
PEF	Peak Expiratory Flow Rate
SGRQ	St. George's Respiratory Questionnaire
ACP	American College of Physicians
ISMP	Institute of Safe Medication Practice
FDA	Food and Drug Administration
REMs	Approved Risk Evaluation and Mitigation Strategies

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