**TITLE:** Tiotropium Compared with Ipratropium for Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease: A Review of the Clinical Effectiveness

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**CONTEXT AND POLICY ISSUES:**

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in Canada. It is a common respiratory disorder, affecting over 700,000 adults in Canada and is largely related to smoking. COPD is characterized by partially reversible obstruction of the airways and lung hyperinflation. The airways, tissue, and vasculature of the lungs are constantly inflamed and patients with COPD experience shortness of breath, wheezing, persistent cough, and chest tightness. This disease tends to be progressive. COPD can be classified according to the level of impairment in lung function. A forced expiratory volume in 1 second (FEV₁) that is between 50% and 80% of predicted volume is considered moderate COPD and between 30% and 50% of predicted is considered severe COPD.

The progressive decline in lung function that is characteristic of COPD is largely unaffected by the pharmacological agents that are used to manage the condition. Symptomatic relief is an important treatment goal and is accomplished using a step-wise approach to management, the cornerstone of which is bronchodilator therapy. Inhaled anticholinergics and β₂ agonists are effective in improving shortness of breath, exercise tolerance, and lung function in moderate to severe COPD. Anticholinergics decrease bronchoconstriction and glandular mucus secretion that are associated with COPD. Two inhaled anticholinergics are available in Canada, ipratropium, a short-acting agent, and tiotropium, a derivative of ipratropium and long-acting agent. Ipratropium is administered three to four times daily as an inhalation aerosol (metered dose inhaler; MDI) or as a liquid for inhalation via a nebulizer, whereas tiotropium is administered once daily as a capsule, the contents of which are inhaled using a device called a HandiHaler.

While both ipratropium and tiotropium have been shown to provide symptomatic relief in patients with moderate to severe COPD, Canadian guidelines recommend tiotropium over ipratropium. Reviewing the evidence of clinical effectiveness involving head to head comparisons of these agents in this patient population may help to clarify the strength of...
evidence upon which such a recommendation could be made. This could help in policy decisions regarding coverage of these agents in COPD.

RESEARCH QUESTION:

What is the clinical effectiveness of tiotropium compared with ipratropium for the treatment of patients with moderate to severe chronic obstructive pulmonary disease?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2003 and November 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials.

Articles were included if the population was specific to moderate to severe COPD, directly compared tiotropium to ipratropium and the article was published in full.

SUMMARY OF FINDINGS:

Two relevant RCTs were identified in which tiotropium was compared to ipratropium in patients with moderate to severe COPD. No health technology assessments, systematic reviews or meta-analyses were identified which limited the population to moderate to severe COPD. Other studies that did not limit to patients with moderate to severe COPD were excluded. One systematic review was identified that presented conclusions in its abstract about the efficacy of tiotropium relative to ipratropium in moderate to severe COPD. However, after the full article was reviewed it was apparent that the study population included all patients with COPD.

Randomized controlled trials

In 2008, Voshaar et al. published combined results of two identical, 12-week double-blinded RCTs in which the safety and efficacy of tiotropium and ipratropium were evaluated in patients with COPD. Both studies were sponsored by the manufacturer of the two drugs. Patients were included if they were age 40 years or over, had a diagnosis of COPD with moderate to severe airway obstruction (defined as a FEV₁ that was 60% or lower of predicted and a FEV₁/forced vital capacity that was 70% or lower), and a ten or more pack per year history of smoking. Patients were excluded if they had a history of asthma, allergic rhinitis, any other significant respiratory illness, had known hypersensitivity to anticholinergics, prior use of tiotropium, regular use of daytime oxygen therapy, significant alcohol or drug abuse, or participation in another study. One of the two studies was conducted in 39 centres in Germany, Italy, South Africa, and Switzerland and the other was conducted in 25 centres in the United States and Canada. It was not clear whether this was an inpatient or outpatient study. Patients were randomly assigned to receive tiotropium (5 or 10 µg daily) delivered via the Respimat Soft Mist™ Inhaler (SMI), a propellant-free inhaler; ipratropium (36 µg four times daily) administered via a pressurized metered-dose inhaler; or placebo. A double-dummy feature was used to prevent investigators and patients from distinguishing active drug from placebo based upon the administration device.
Oral and inhaled corticosteroids, theophyllines, and mucolytics were allowed if the dosages were stable for at least 6 weeks prior to and throughout the study. The studies’ primary endpoint was the mean trough FEV1 response after 12 weeks of treatment and secondary endpoints included other spirometry measures and use of rescue medication. The efficacy analysis was not performed according to the intention to treat principle.

About 69% of study participants were male, with an average age of 64 ± 9 years and average duration of COPD of 10 ± 8 years. Between the two studies, 719 patients were randomized to tiotropium 5 μg (n=180), tiotropium 10 μg (n=180), ipratropium (n=178), or placebo (n=181). Of the 719 patients, 689 had data available for the primary outcome measure. The increase in trough FEV1 was significantly larger with both doses of tiotropium compared to ipratropium after 12 weeks of treatment. For the secondary spirometry outcome measures, the differences between tiotropium and ipratropium were not statistically significant for peak FEV1, FEV1 area under the curve from baseline to six hours post-dose (AUC(0–6h)), and peak forced vital capacity (FVC - the maximum volume of air that can be forcibly expired). For FVC AUC(0–6h) (both tiotropium doses) and trough FVC (tiotropium 10 μg dose only), increases were significantly larger for tiotropium compared with ipratropium. Tiotropium 10 μg was statistically superior to ipratropium in reducing the use of rescue medications. There was little difference between the two active treatments in terms of relief of symptoms of COPD. The authors concluded that tiotropium 5 μg and 10 μg daily, delivered via Respimat Soft Mist™ SMI, significantly improved lung function compared with ipratropium MDI.

This study could be limited by its 12-week duration and failure to use an intention to treat analysis for the efficacy outcomes. As well, tiotropium was administered via the Respimat Soft Mist™, a device which is not yet available in Canada. Further, it is unclear how the dosage of tiotropium that was administered in this study via the Respimat Soft Mist™ compares to the dosage that is administered with the HandiHaler® (the device that is used in Canada) since the two devices could potentially deliver different amounts of the drug to the lung. These factors could limit the generalizability of the results to the Canadian population with moderate to severe COPD. As well, the generalizability could be limited by the level of device training that study participants received, which may or may not be replicated in a real world setting. Finally, approximately 88% of patients enrolled had moderate to severe COPD according the definition used in the Canadian COPD guidelines. The study’s inclusion criteria also permitted the enrolment of patients with very severe COPD. This could potentially impact the generalizability of the results as well.

In 2006, Hsu et al. published the results of a double-blind RCT that had the objective of comparing the efficacy and safety of tiotropium and ipratropium in patients with COPD. The study was conducted in six hospitals in Taiwan. Patients were included if they were age 40 years and over with a ten or more pack per year history of smoking and a diagnosis of COPD with an FEV1 of 65% or lower of the predicted value and FEV1/FVC of 70% or lower. Patients were excluded if they had arrhythmias, allergic rhinitis, active tuberculosis, any significant laboratory abnormalities or other serious medical problems, required regular use of daytime oxygen, or had a contraindication to anticholinergic agents. In total, 132 patients were randomized to receive tiotropium18 μg once daily administered via the HandiHaler® device (n=67) or two puffs of ipratropium 20 μg four times daily administered via MDI (n=65). Placebo devices were used to blind the treatment groups. The primary outcome was the change in trough FEV1 from baseline to week 4. The secondary outcome measures were trough FVC
response, FEV₁, and FVC responses at 2 hours post-inhalation. Use of rescue medication and symptoms were also assessed in a patient evaluation questionnaire. An intention to treat analysis was used for the efficacy endpoints.

Approximately 98% of the study population was male. The average age was not reported but the range was from 54.6 to 89.6 years. Duration of COPD was not reported. After four weeks of treatment, the change in trough FEV₁ from baseline was significantly larger in the tiotropium group (61.7 ± 25.3 mL) than in the ipratropium group (16.4 ± 27.9mL; p<0.05). At week four, the mean trough FVC increased by 137.2 ± 49.3 mL in the tiotropium group and was decreased by 84.5 ± 54.5 mL in the ipratropium group (p = 0.001). The FEV₁ and FVC responses at 2 hours post-dose did not differ between the two groups, nor did the use of rescue medications. The score on the patient evaluation questionnaire decreased 1.98 ± 0.42 points in the tiotropium group and by 2.05 ± 0.46 in ipratropium group. The difference between groups was not statistically significant. From these results, the authors concluded that tiotropium demonstrated greater benefit than ipratropium in patients with COPD and that tiotropium might be considered to be a first-line single anticholinergic agent for the treatment of stable stage II moderate to stage IV very severe COPD.

On limitation of this study was its four week duration, which would limit the ability to compare long-term outcomes in the two treatment groups. Another limitation to this study was the sample size of 132, which could potentially impact the generalizability of the results. Further, it is not clear whether the results would be generalizable to females with moderate to severe COPD. As with Voshaar et al. the study also permitted the enrolment of patients with very severe COPD. This could potentially impact the generalizability of the results as well. Finally, it is not clear if the results could be generalized to the outpatient setting.

Limitations

Two RCTs were identified that compared tiotropium to ipratropium in patients with moderate to severe COPD; however, in both studies patients with very severe COPD were also included. In one of the two studies, the device used to administer the medication is not available in Canada at present, so it is unclear whether its findings would be generalizable to the Canadian healthcare system. The two studies assessed short-term outcomes and focused on measures of lung function, rather than patient-centered outcomes like quality of life, functional capacity, or mortality. Such outcomes may be more relevant from the patient’s perspective. While symptoms were assessed, the questionnaires that were used do not appear to be validated, standardized measures and in one study were assessed from the point of view of the physician instead of the patient. Moreover, given that the longest trial was 12 weeks, it is unclear whether any observed differences between tiotropium and ipratropium would be sustained over a longer duration of follow-up. One important limitation to the two included RCTs was that the level of education on administration of the medications and correct device technique could have been superior to what would be observed outside of an RCT. Because of this, it is not clear whether similar results could be expected with either medication or device in real-world settings.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In two RCTs,\textsuperscript{4,5} patients with moderate to severe COPD who were treated with tiotropium experienced larger increases in FEV\textsubscript{1} than patients treated with ipratropium after four to twelve weeks of treatment. However, other spirometry measures typically did not differ between treatments over this time period. Further, symptoms of COPD did not differ between tiotropium and ipratropium and other important outcomes such as functional capacity and quality of life were not assessed. Thus, it is unclear whether the larger gain in FEV\textsubscript{1} that was experienced by patients treated with tiotropium was clinically important or significant from a patient perspective. As such, other factors such as ease of administration, dosing frequency, and cost may be important points to consider when making policy decisions about coverage for these two agents.

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