**TRIPLE THERAPY FOR COPD**

**Generic (Trade Name):** Tiotropium bromide (Spiriva®); fluticasone propionate/salmeterol xinafoate (Advair®); budesonide/formoterol fumarate (Symbicort®)

**Manufacturer:** Boehringer Ingelheim (Spivira®); GlaxoSmithKline (Advair®); AstraZeneca (Symbicort®)

**Indication:** Adding combination therapy with an inhaled corticosteroid (ICS) and a long-acting beta-adrenergic receptor (β2) agonist (LABA) to chronic therapy with tiotropium is being studied in patients with stable chronic obstructive pulmonary disease (COPD).

**Current Regulatory Status:** In Canada, tiotropium is indicated for the maintenance treatment of COPD.¹ Advair® is approved for the maintenance treatment of COPD,² whereas Symbicort® is indicated for asthma.³

**Description:** Tiotropium is a long-acting anticholinergic agent that is delivered via inhalation powder. It works by inhibiting smooth muscle muscarinic receptors in the airways. This leads to bronchodilation. Fluticasone/salmeterol and budesonide/formoterol, which are a combination of an ICS and a LABA, are delivered via inhalation powder. Fluticasone/salmeterol is also available as an inhalation aerosol. Because anticholinergics and β2-agonists work through different mechanisms to cause bronchodilation, there is a potential for both agents to work synergistically and have a greater effect than would be obtained from either drug on its own.⁴

**Current Treatment:** Bronchodilators are the mainstay of pharmacological therapy for COPD. The Canadian Thoracic Society (CTS) guidelines for bronchodilator therapy for COPD are based on symptoms.¹ For patients with intermittent symptoms, the guidelines recommend starting therapy, as required, with a short-acting β2-agonist. For those with persistent symptoms, treatment with a long-acting bronchodilator, such as tiotropium, salmeterol, or formoterol, is recommended. For patients with exercise intolerance and moderate to severe persistent symptoms, the guidelines recommend a combination of tiotropium and a LABA for maximum bronchodilation. For patients who remain breathless despite optimal bronchodilator therapy, the CTS guidelines maintain that a combination ICS and LABA product can be considered for enhanced symptom relief. The more recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines also recommend a stepwise increase in treatment, depending on the severity of the disease.⁶

**Cost:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spivira® (tiotropium)</td>
<td>18 μg</td>
<td>$2.10/capsule</td>
</tr>
<tr>
<td>Advair® Diskus® (fluticasone/salmeterol)</td>
<td>50 μg/100 μg</td>
<td>$73.82 (60 doses/unit)</td>
</tr>
<tr>
<td></td>
<td>50 μg/250 μg</td>
<td>$88.37 (60 doses/unit)</td>
</tr>
<tr>
<td></td>
<td>50 μg/500 μg</td>
<td>$125.45 (60 doses/unit)</td>
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<tr>
<td></td>
<td>25 μg/125 μg</td>
<td>$88.37 (120 doses/unit)</td>
</tr>
<tr>
<td></td>
<td>25 μg/250 μg</td>
<td>$125.45 (120 doses/unit)</td>
</tr>
<tr>
<td>Advair® Metered Dose Inhaler®</td>
<td>100 μg/6 μg</td>
<td>$60.00 (120 doses/unit)</td>
</tr>
<tr>
<td></td>
<td>200 μg/6 μg</td>
<td>$78.00 (120 doses/unit)</td>
</tr>
<tr>
<td>Symbicort® (budesonide/formoterol)</td>
<td></td>
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**The Canadian Coordinating Office for Health Technology Assessment (CCOHTA)**
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**Evidence:**

The SPRUCE (SPiRiva Usual CarE) trial investigated whether tiotropium is effective in patients receiving regular therapy with ICS and LABAs. SPRUCE was a 12-week, double-blind randomized controlled trial (RCT) in which 395 patients with stable COPD were randomized to receive inhaled tiotropium (18 μg once daily) or placebo. Among patients, 63% continued their regular treatment with ICS, and 29% continued concomitant therapy with LABAs. Preliminary data from the study were presented at the American Thoracic Society meetings in May 2005. The group of patients receiving both ICS and LABA therapy showed a statistically significant improvement in trough forced expiratory volume in the first second (FEV₁) and forced expiratory vital capacity (FVC) responses on day 85 for tiotropium compared with placebo.⁹

The Canadian Optimal Therapy of COPD trial is a double-blind, multicentre RCT that is designed to identify which combination of inhaled medications is most effective in patients with moderate to severe COPD.¹⁰ In the trial, 432 patients will be randomized to one of three parallel treatment arms: tiotropium (18 μg) and fluticasone/salmeterol (250 μg/puff plus 25 μg/puff; two puffs, twice daily); tiotropium (18 μg) and salmeterol (25 μg/puff; two puffs, twice daily); or tiotropium (18 μg) and placebo inhaler. The use of salbutamol will be allowed for all trial participants on an as-needed basis. The study is recruiting patients over 18 months, and patients will be followed for 12 months after randomization. The primary outcome measure is the proportion of patients who experience a respiratory exacerbation. Secondary outcomes will include changes in disease-specific quality of life; changes in dyspnea; total number of hospitalizations; and absolute and relative changes in FEV₁ and FVC.

Another RCT, based in the U.K., is a proof of concept study that is evaluating tiotropium as an add-on therapy to inhaled budesonide/formoterol combination therapy in 25 patients with COPD. Although the trial has been completed, results are unavailable.¹¹

**Adverse Effects:**

Increases in adverse drug reactions were not observed when tiotropium was used concomitantly with other drugs commonly used to treat COPD, such as sympathomimetic bronchodilators and inhaled steroids.¹

**Commentary:**

The analysis done in SPRUCE suggests that a benefit may be gained by adding tiotropium to combined ICS and LABA therapy in patients with COPD. However, evidence will need to be provided by the Canadian Optimal Therapy of COPD Trial, which was designed to evaluate this drug combination, before definite conclusions can be drawn about the potential benefit of triple therapy in this population. It will be important to see the impact that this treatment regimen has on clinically meaningful outcomes, such as the frequency of exacerbations and the number of hospital visits, and to see if these correlate with changes in spirometric measures.
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References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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