



**TITLE: Combination Inhaled Corticosteroids and Long-Acting Beta2-Agonists for Acute Respiratory Tract Infections and Cough: A Review of the Clinical Effectiveness**

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## **CONTEXT AND POLICY ISSUES**

Currently, there is Health Canada approval for the use of inhaled corticosteroids (ICSs) in combination with long-acting beta2-agonists (LABAs) for the management of asthma and chronic obstructive pulmonary disease (COPD) under given conditions. ICSs are the mainstay of asthma therapy whereas LABAs are an important class of agents for the management of persistent asthma in patients whose asthma is not well controlled with ICS monotherapy.<sup>1</sup> On the other hand, LABAs are effective and convenient for preventing and treating COPD in patients with persistent symptoms, while ICS monotherapy is not recommended in COPD.<sup>2</sup> However, combination ICS and LABA is used for the management of dyspnea for patients with advanced COPD, and in combination with other agents such as inhaled anticholinergics and/or antibiotics to manage COPD exacerbations.<sup>3</sup>

Corticosteroids, including ICSs, have a broad spectrum of anti-inflammatory effects, inhibiting multiple inflammatory mediators to suppress inflammation and reduce the number of inflammatory cells in the airways.<sup>4</sup> LABAs are bronchodilators which act to decrease muscle tone in the airways to increase ventilation. Moreover, the anti-inflammatory activity by LABAs in combination with an ICS indirectly improves mucociliary clearance<sup>5</sup> and has shown greater bronchodilator effects than ICSs alone.<sup>6</sup>

Although ICSs and LABAs reduce airway inflammation and mucus secretion which promotes coughing, there remains uncertainty regarding the use of ICS/LABA combination products in patients with persistent non-asthma or non-COPD coughs. The aim of this review is to summarize evidence of the clinical effectiveness of combination ICSs and LABAs in patients with acute bacterial or viral upper respiratory tract infections, post-infectious or subacute cough, chronic cough, or cough in sarcoidosis to support decision making.

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## RESEARCH QUESTIONS

1. What is the clinical effectiveness of combination inhaled corticosteroids (ICSs) and long-acting beta2-agonists (LABAs) for patients with acute bacterial upper respiratory tract infections?
2. What is the clinical effectiveness of combination ICSs and LABAs for patients with acute viral upper respiratory tract infection?
3. What is the clinical effectiveness of combination ICSs and LABAs for patients with post-infectious or subacute cough?
4. What is the clinical effectiveness of combination ICSs and LABAs for patients with chronic cough?
5. What is the clinical effectiveness of combination ICSs and LABAs for patients with cough in sarcoidosis?

## KEY FINDINGS

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with acute bacterial or viral upper respiratory tract infections, post-infectious or subacute cough, chronic cough, or cough in sarcoidosis.

## METHODS

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were not applied. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and June 3, 2016. Internet links were provided, where available. Rapid Response reports are organized so that the evidence for each research question is presented separately.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Adult and pediatric patients with: Q1: Acute bacterial upper respiratory infections (URTIs) Q2: Acute viral URTIs Q3: Post-infectious or sub-acute cough (3 to 8 weeks) Q4: Chronic cough (> 8 weeks) Q5: Cough in sarcoidosis
<b>Intervention</b>	Combination inhaled corticosteroids (ICSs) and long-acting beta2-agonists (LABAs) with or without antibiotics.
<b>Comparator</b>	Any active comparator, for example: <ul style="list-style-type: none"> <li>• ICSs alone</li> <li>• Antihistamines</li> <li>• Antitussives</li> <li>• Oral and topical decongestants</li> <li>• Short-acting anticholinergics (e.g., Ipratropium)</li> <li>• Short-acting beta2-agonists (e.g., Salbutamol)</li> <li>• Leukotriene antagonists</li> <li>• Oral steroids (e.g., Prednisone)</li> <li>• Antibiotics alone</li> </ul>
<b>Outcomes</b>	Clinical effectiveness (e.g., symptom resolution, symptom scores, exacerbation duration and frequency, lung function [FEV1 or FVC], quality of life, hospitalizations, length of hospital stay, mortality);  Harms (e.g., headache, thrush, local irritation, adrenal insufficiency, cataracts, linear growth)
<b>Study Designs</b>	Health Technology Assessments (HTA); Systematic reviews/Meta-analyses; Randomized controlled trials; and Non-randomized studies

**Exclusion Criteria**

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

A total of 124 citations were identified in the literature search. Following screening of titles and abstracts, 120 citations were excluded and four potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. None of these six potentially relevant articles met the inclusion criteria for this report. Appendix 1 describes the PRISMA flowchart of the study selection.

**Summary of Findings**

*What is the clinical effectiveness of combination inhaled corticosteroids (ICSs) and long-acting beta2-agonists (LABAs) for patients with acute bacterial upper respiratory tract infections?*

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with acute bacterial upper respiratory tract infections.

*What is the clinical effectiveness of combination ICSs and LABAs for patients with acute viral upper respiratory tract infection?*

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with acute viral upper respiratory tract infections.

*What is the clinical effectiveness of combination ICSs and LABAs for patients with post-infectious or subacute cough?*

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with post-infectious or subacute cough.

*What is the clinical effectiveness of combination ICSs and LABAs for patients with chronic cough?*

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with chronic cough.

*What is the clinical effectiveness of combination ICSs and LABAs for patients with cough in sarcoidosis?*

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with cough in sarcoidosis.

## **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

The literature search for this review did not find any studies that evaluated the clinical effectiveness of combination ICSs and LABAs for patients with acute bacterial or viral upper respiratory tract infections, post-infectious or subacute cough, chronic cough, or cough in sarcoidosis.

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APPENDIX 1: Selection of Included Studies

