ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan: Inhaled corticosteroids + long-acting beta agonists (ICS+LABA) for the treatment of chronic obstructive pulmonary disease (COPD)

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A. Introduction

Inhaled corticosteroids + long acting beta agonists are available in Canada for the management of asthma and/or chronic obstructive pulmonary disease. There are currently four products marketed in Canada:

- Advair: salmeterol+fluticasone; indicated for asthma and COPD
- Symbicort: formoterol+budesonide; indicated for asthma and COPD
- Zenhale: formoterol+mometasone; indicated for asthma only
- BreoEllipta, vilanterol+fluticasone): indicated for the treatment of COPD.

The objective of the ICS+LABA for COPD review is to provide evidence-informed recommendations for the use of ICS+LABA for COPD through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- cost-effectiveness and reimbursement-basedanalyses,and drug utilization studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of patients, pharmacists and prescribers,
- identification of barriers to, and enablers of, successful policy implementation,
- recommendation of potential drug reimbursement models

B. Research Questions

Proposal	Research unit	Research question(s)
Patient and Healthcare Professional Perspectives	Qualitative Research Program	What is the impact of COPD on a patient's quality of life? What is the perceived effectiveness of ICS/LABA for the treatment of COPD? What is the perceived impact of ICS/LABA on a patient's quality of life? What is the patient experience of accessing ICS/LABA for the treatment of COPD? What is the clinician experience of prescribing or dispensing ICS/LABA for the treatment of COPD? To what extent are the policy recommendations feasible and acceptable?
Systematic Reviews and Network Meta-Analyses	Systematic Review Unit	What is the comparative safety and efficacy of ICS and inhaled LABA versus ICS, inhaled LABA, inhaled LAMA, and placebo [in any combination] for adults with COPD? Which intervention (or combination) is the most effective and safe for adults with COPD?
Environmental Scan and Barriers to Implementation; Local and Historical Context	Formulary Modernization Unit	How are ICS/LABA combination products currently being funded in public programs in Canada as well as internationally? What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?

Proposal	Research unit	Research question(s)
Costs and Utilization Trends	Pharmacoepidemiology Unit	To examine national and provincial trends in use of COPD drug therapies over the past 4 years To describe the characteristics of COPD patients treated with ICS/LABA combination products among public drug plan beneficiaries in Ontario To describe the typical course of therapy through COPD drugs in Ontario To compare compliance to therapy among those treated with combination products vs. dual therapy with individual components
Health Equity	All units	Does sex/gender, age, geographical location (e.g., rural vs. urban) or socioeconomic status play an important role in any of the analyses described?
Reimbursement-based Economics	Pharmacoeconomics Program	What is the current evidence for the cost-effectiveness of ICS plus LABA compared to single or combination therapies incorporating LABA, LAMA and ICS? Based on a de novo economic model, what is the cost-effectiveness of ICS plus LABA compared to single and combination therapies incorporating LABA, LAMA and ICS? What is the economic impact of alternatives policies for reimbursing ICS plus LABA combination products?

Patient population and inclusion criteria

- Adult patients with COPD
- Inclusion Criteria:
- Adult patient (18 years and older)
- Diagnosis of COPD, regardless of severity of disease
- Subgroup analysis: where possible, the review will consider age, gender, socioeconomic status and geographic location (e.g. urban/rural)

Drugs of interest

- ICS + LABA (single inhaler or as 2 separate inhalers):
- Advair (salmeterol/fluticasone)
- Symbicort (formoterol/budesonide)
- BreoEllipta (vilanterol/fluticasone)
- Zenhale (formoterol/mometasone)

Comparator(s)

ICS, inhaled LABA, inhaled long-acting anticholinergic agents, placebo (alone or *in any combination)*
Note: This will include dual therapy with ICS and LABA single entity products

C. Specific Proposals

The Drug Class Review is comprised of five different reviews, namely the Qualitative Research Unit, Systematic Review Unit, Pharmacoepidemiology Unit, Environment Scan/local and historical context and Pharmacoeconomics Unit. Further information on each of the proposals is provided below.

Qualitative Review Unit

Objectives:

- To explore factors related to the experience of ICS/LABA prescription, dispensing and use for COPD.
- To determine the social acceptability of policy recommendations for ICS/LABA use (COPD indication).

Study Questions:

- What is the perceived effectiveness of ICS/LABA?
- What is the impact of ICS/LABA on quality of life?
- What is the experience of patients using ICS/LABA regarding the access of these drugs?
- What is the experience of clinicians/pharmacists in prescribing/dispensing these drugs?
- To what extent are the policy recommendations feasible and acceptable?

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs within the drug class of interest

Study Design – This phase will use a qualitative framework approach to guide the data collection and analysis processes. One-on-one interviews and accompanying field notes will be the primary and secondary data sources, respectively.
Study Population – Identified stakeholders include primary care physicians (PCPs), respirologists, pharmacists, and patients (patient caregivers may be considered). Inclusion criteria are: clinicians (PCPs, respirologists, pharmacists) who have prescribed or dispensed ICS/LABA; and patients with COPD who have current or prior experience using ICS/LABA.
Methods –A purposive sampling approach will be used to elicit specific perceptions and opinions for those who will be involved or affected by drug policy decisions. Clinicians and patients will be recruited through various recruitment strategies, including professional associations, faxing/e-mailing and circles of contact. This phase will aim to recruit 6-8 participants from each identified stakeholder group and 20-25 patients. Qualitative data will be collected through interviews and accompanying field notes. A framework analysis will be applied to the data to derive key policy-relevant concepts.
Outcomes – The primary outcomes of interest include experiences with: COPD and COPD therapy; accessing ICS/LABA through Ontario Drug Benefit; accessing ICS/LABA through other means; treating and dispensing medication to patients with ICS/LABA. Other outcomes of interest will include perceived safety and effectiveness of ICS/LABA, and perceived barriers to access and health equity issues.

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drug class of interest

Study Design – RAND Appropriateness Method and Survey
Study Population – Representatives of the general public, stakeholder groups (PCPs, respirologists, pharmacists, patients), patient advocacy groups, topic-specific interest groups, and industry
Methods – Members of the general public will be recruited to participate in a meeting/webinar to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. An online survey will also be distributed to assess aspects of social acceptability, including affordability, accessibility, and appropriateness. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.
Outcomes -The primary outcome of interest is the feasibility and acceptability of draft recommendations

Systematic Review Unit

Objective:

To examine the comparative safety and efficacy of long-acting inhaled agents (inhaled corticosteroids [ICS], inhaled long-acting beta$_2$-agonists [LABA], inhaled long-acting muscarinic antagonists [LAMA]) for patients with COPD.

Study Questions

- What is the comparative safety and efficacy of ICS and inhaled LABA versus ICS, inhaled LABA, inhaled LAMA, and placebo [in any combination] for adults with COPD?
- Which intervention (or combination) is the most effective and safe for adults with COPD?

PICOS (Population, Intervention, Comparator, Outcome, Study designs) Criteria

Study Population:

- Adults with COPD

Interventions:

- Inhaled LABA, ICS, and combination LABA and ICS in one inhaler

Comparators:

- All inhaled long-acting agents (LABA, ICS, LAMA) in any combination and placebo

Outcomes of Interest:

- Efficacy outcomes:
    - Proportion of patients with exacerbations (primary outcome of interest)
    - Number of hospitalizations (overall and due to exacerbations)
    - Number of emergency room visits (overall and due to exacerbations)
    - Function (e.g., 6 minute walk test, paced shuttle walk test)
    - Forced expiratory volume (FEV)
    - Quality of life
    - Number of patients with ischemic heart disease
    - Dyspnea
    - Mortality
- Safety outcomes:
    - Harms (including all harms, serious harms, withdrawals due to lack of efficacy, treatment-related withdrawals, and the following specific harms: pneumonia, fractures, bone mineral density, heart failure, arrhythmia, cataracts, oral thrush, palpitations, headache, constipation, and dry mouth)

Study Designs:

- Randomized controlled trials

Methods

Information sources and literature search:

We will search the MEDLINE, EMBASE, and Cochrane Library electronic databases from inception to January 2014. This will be supplemented by searching conference abstracts, trial protocols, trial registries, and websites of manufacturers of the inhaled long-acting agents. We will also search the reference lists of included studies and reference lists of relevant reviews.

Study selection, data abstraction, and risk of bias appraisal:

Two reviewers will independently screen titles and abstracts for inclusion (Level 1 screening). They will then independently review the full-text of potentially relevant articles to determine inclusion using the same inclusion and exclusion criteria (Level 2 screening). Conflicts will be resolved by discussion or the involvement of a third reviewer.

We will abstract data on study characteristics (e.g., year of conduct, sample size, setting), participant characteristics (e.g., number of patients, age mean and standard deviation), definitions of outcomes (e.g., exacerbations [e.g., number of patients with at least 1 exacerbation]), and outcome results (e.g. number of patients with exacerbations, number of patients hospitalized) for the longest duration of follow-up. We will appraise the included studies using the Cochrane Risk of Bias Tool.

Synthesis of included studies:

We will first describe our systematic review results, reporting study and patient characteristics, risk of bias results, and frequencies of outcomes across the included studies. Subsequently, we will conduct meta-analysis, meta-regression, and Bayesian network meta-analysis, if deemed appropriate. We will explore the effects of subgroups on outcomes to establish the robustness of findings. These include the diagnosis of COPD (e.g., according to the GOLD criteria versus all others), severity of COPD (e.g., moderate-

severe versus all others), gender, and definitions of outcomes (exacerbations in particular).

Pharmacoepidemiology Unit

Analysis 1 – National and provincial trends in COPD therapies

Study questions: How are COPD medications being used across Canada?
Short description of analysis: We will examine trends in the use of combination inhaled corticosteroids / long-acting beta agonist (ICS/LABA) products and other COPD therapies (for example, inhaled corticosteroid single agents, LABA single agents, inhaled anticholinergics) between 2009 and 2013.

Analysis 2 – Trends in indication of use of ICS/LABA combination products

Study question: What conditions are ICS/LABA combination products used to treat?
Short description of analysis: We will look at Ontario residents prescribed ICS/LABA products between 2000 and 2013 and identify the indication for treatment (COPD and/or asthma).

Analysis 3 – Characteristics of COPD patients treated with ICS/LABA combination products in Ontario

Study question: What are the characteristics of Ontario patients with COPD who use ICS/LABA combination products today?
Short description of analysis: We will look at descriptive characteristics, including age, gender, socioeconomic status, disease severity, past medication use and number of micrograms of ICS/LABA combination therapy dispensed among Ontario public drug plan beneficiaries with COPD.

Analysis 4a – Compliance to combination therapy for COPD in Ontario

Study questions: How long do COPD patients usually stay on combination therapy in Ontario? Is there a difference in length of therapy between ICS/LABA combination products and dual therapy (taking a single-agent ICS and single-agent LABA at the same time)?
Short description of analysis: We will look at COPD patients aged 66 and older who newly start ICS/LABA combination therapy, and assess the type of treatment initiated (combination product or dual therapy), duration of therapy, and whether they switched between multiple therapies during their course of treatment.

Analysis 4b – Typical course of therapy through COPD drugs in Ontario

Study questions: Do patients usually take other COPD medications prior to starting therapy with ICS/LABA combination products? What other medications are usually prescribed?
Short description of analysis: We will look at COPD patients aged 66 and older who newly start ICS/LABA combination therapy, and assess whether they were prescribed any previous COPD medications. We will describe any prior therapy, and will also examine whether they used other COPD medications during their period of combination therapy. The proportion of people progressing to triple therapy, and time to progression will be studied.

Analysis 5 – Summary of observational studies evaluating the comparative effectiveness of ICS/LABA combination products

Study question: Are there any population-based studies on comparative effectiveness and safety of ICS/LABA combination products among patients with COPD?
Short description of analysis: We will perform a literature search to examine the body of evidence on comparative effectiveness and/or safety ICS/LABA combination products among patients with COPD.

Pharmacoeconomic Unit

Research Questions

- What is the current evidence for the cost-effectiveness of ICS plus LABA compared to single or combination therapies incorporating LABA, LAMA and ICS?

Based on a de novo economic model, what is the cost-effectiveness of ICS plus LABA compared to single and combination therapies incorporating LABA, LAMA and ICS?

- What is the economic impact of alternatives policies for reimbursing ICS plus LABA?

Methods

RQ1 Systematic Review of Published Economic Evaluations

We will conduct a review of the available literature on the cost-effectiveness of ICS combined with LABA for chronic treatment of COPD compared to: single or combination therapies incorporating, LABA, LAMA and ICS.

RQ2 De Novo Economic Model

We will develop a new economic model assessing the cost effectiveness of ICS combined with LABA for chronic treatment of COPD compared to single and combination therapies incorporating LABA, LAMA and ICS.

RQ3 Reimbursement Based Economic Assessment

We will develop a model which will identify the optimal policy relating to reimbursing ICS combined with LABA. Analysis will identify the change in the forecasted drug budget for the next three years associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical effectiveness.

Environmental Scan

To summarize the pharmacy benefit programs for ICS/LABA for COPD in Ontario, across Canada and in select international jurisdictions

Method: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan
Interventions:
ICS/LABA for treatment of COPD:
Advair (fluticasone/salmeterol), Symbicort (formoterol/budesonide), Zenhale (formoterol/mometasone), BreoEllipta (vilanterol/fluticasone)

To determine the impact of different drug reimbursement schemes for ICS/LABA (e.g., restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs

Method: Literature review
Intervention: various drug reimbursement schemes, including general benefits, step therapy, special authorization

To summarize the guidelines for management of COPD, in particular the role of ICS/LABA

Method: Literature review
Intervention: Guidelines/recommendations for the management of adult patients with COPD