ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan: Inhaled corticosteroids + long-acting beta agonists (ICS+LABA) for the treatment of asthma

Pharmacoepidemiology Unit

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Objectives:	1. To examine national and provincial trends in use of asthma drug therapies across Canada 2. To examine trends in use of asthma drug therapies for asthma in Ontario 3. To describe characteristics of asthma patients prescribed ICS/LABA combination products 4. To investigate course of therapy and adherence with asthma drugs in Ontario 5. To summarize any observational studies evaluating the comparative effectiveness of ICS/LABA combination products

Objective 1: National and Provincial Trends in Asthma Therapies

Study Design:	Design: Time series analysis with quarterly time intervals Study period: • *National and provincial trends (IMS Compuscript):* October 2009 to September 2013 • *Ontario trends among publically funded prescriptions (ODB):* January 2000 to March 2013 Population: All provinces Data Sources: • *IMS Compuscript:* aggregated data for all prescriptions dispensed at retail pharmacies across Canada • *Ontario Drug Benefit Database (ODB)*: individual level data for all publically funded prescriptions dispensed in Ontario to individuals aged 12 and older.
Study Population:	**Inclusion Criteria:** • All privately and publically-funded prescriptions dispensed in Canada for treatment of asthma, including: o ICS/LABA combination products ▪ Fluticasone+salmeterol (Advair, Advair Diskus) ▪ Budesonide+formoterol (Symbicort) ▪ Mometasone+formoterol (Zenhale) o Other therapies (inhaled corticosteroids, long-acting beta agonists, long acting muscarinic antagonist, short-acting beta agonists, short acting muscarinic antagonist, Leukotriene receptor antagonists)

Outcome(s) of Interest:	Measured over entire study period (quarterly): • Number of prescriptions dispensed • Total cost of prescriptions • Number of users (Ontario public drug plan only) Report: • Overall rates of use by province • National rates of use by drug • Distribution of prescriptions by payer (public, private, cash, NIHB) • Distribution of prescriptions by age (12-17, 18-64, 65+; Ontario public drug plan only)
Limitations:	• The IMS data is only available at the prescription and unit level. Therefore, national and provincial trends in prescribing cannot differentiate by indication.
Objective 2: Trends in Use of Asthma Drug Therapies for Asthma in Ontario	
Study Design:	Design: Time series analysis with annual time intervals Study period: April 2000 to March 2013 Data Source: • Ontario Drug Benefit Database (ODB)
Study Population:	**Inclusion Criteria:** • All publically-funded prescriptions for ICS/LABA combination products dispensed in Ontario • All publically-funded prescriptions for other drug therapies (inhaled corticosteroids, long-acting beta agonists, long acting muscarinic antagonist, short-acting beta agonists, short acting muscarinic antagonist, Leukotriene receptor antagonists) • Individuals aged 12+ at time of drug dispensing • Individuals with a diagnosis of asthma using the ICES disease cohort

Outcome(s) of Interest:	Measured over entire study period (annually) • Number and rate of users of ICS/LABA products among asthma patients • Number of ICS/LABA prescriptions dispensed to asthma patients • Drug costs Stratify all analyses by: • ICS/LABA combination product (Advair, Symbicort, Zenhale) • Age (12-17, 18-64, 65+)
Limitations:	• Asthma diagnosis defined via validated dataset developed at ICES. Although this dataset has 84% sensitivity and 76% specificity, there may be some misclassification.

Objective 3: Characteristics of Asthma Patients treated with ICS/LABA Combination Products in Ontario

Study Design:	Design: Cross-sectional analysis Study period: April 2012 to March 2013 Data Sources: • Ontario Drug Benefit Database (ODB) • Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD) • National Ambulatory Care Reporting System Database (NACRS)
Study Population:	**Inclusion Criteria:** • All publically-funded beneficiaries of Ontario with asthma who are prescribed an ICS/LABA combination product • Cohort #1: Individuals aged 12-17 at time of ICS/LABA dispensing • Cohort #2: Individuals aged 18-65 at time of ICS/LABA dispensing • Cohort #3: Individuals aged 66+ at time of ICS/LABA dispensing • Past diagnosis with asthma (prior to cohort entry date) • **Cohort Entry Date**: defined as date of first prescription for an ICS/LABA combination product, following 12th, 18th or 66th birthday, over the study period. • **Index drug**: Defined as the specific ICS/LABA product that was prescribed on cohort entry date (e.g. Advair, Symbicort or Zenhale)

Variables of Interest:

For each cohort, measure:

- Number of asthma patients treated
- Number and rate of new ICS/LABA users
  - New users aged 66 and older defined as having no past ICS/LABA use in prior 365 days
  - New users <66 years of age defined as having a prescription for any drug in the past 181-365 days and who didn't have a prescription for an ICS/LABA in the past 180 days
- Age at cohort entry date
- Proportion of patients who were male
- Proportion of patients residing in LTC at cohort entry
- Proportion of urban residents at cohort entry
- Socioeconomic status (measured using income quintiles at cohort entry date)
- Asthma severity
  - Defined using the prescribed treatment steps outlined in the Global Initiative for Asthma (GINA) 2014 report.
- Average cost of ICS/LABA prescriptions per person
- Number of puffs dispensed, per user
- Number of puffers dispensed, per user
- Past asthma maintenance therapy (past 1 year):
  - ICS
  - LABA
  - LAMA
  - LTRA
  - SABA
  - SAMA
  - Theophylline
  - Oral corticosteroids
- Past hospitalization or ED visit for asthma exacerbations (past 1 year)

Stratify analyses by:

- Type of ICS/LABA combination product
  - Advair Diskus, Advair HFA, Symbicort, Zenhale

Limitations:

- Individuals aged 65 are grouped in with those aged 18-64 because – although they have universal drug coverage, we have incomplete medical records for these patients in the prior year (e.g. when aged 64) since they were not eligible for public drug coverage at this time. Therefore, it is inappropriate to group these in with those aged 66+.

Objective 4:

a. **Adherence to therapy between those treated with combination ICS/LABA products and those treated with dual therapy of individual ICS and LABA components**
b. **Typical course of therapy of asthma drugs in Ontario**

Study Design:

Design: Cohort Study

Study period: April 2008 to March 2013

- Accrual period: April 2008 to March 2012
- Maximum follow-up date: March 2013 (*1 year minimum follow-up*)

Data Sources:

- Ontario Drug Benefit Database (ODB)
- Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
- National Ambulatory Care Reporting System Database (NACRS)

Study Population:

Inclusion Criteria:

- All publically-funded beneficiaries of Ontario with asthma who initiate ICS/LABA therapy. Combination therapy defined in 2 ways:
  - Receipt of a combination product (e.g. Advair, Symbicort, Zenhale)
  - Dual therapy of individual ICS and LABA components (e.g. receipt of separate ICS and LABA products for use at the same time). Include any combination of ICS and LABA products (not just those available in combination products)
- Cohort #1: Individuals aged 12-17 at time of ICS/LABA dispensing
- Cohort #2: Individuals aged 18-65 at time of ICS/LABA dispensing
- Cohort #3: Individuals aged 66+ at time of ICS/LABA dispensing
- Adults aged 12+ at time of ICS/LABA dispensing
- Restrict to those with asthma diagnosis prior to drug initiation
- New users aged 66 and older, defined as having no past ICS/LABA use in prior 365 days
- New users <66 years of age, defined as having a prescription for any drug in the past 181-365 days and who didn't have a prescription for an ICS/LABA in the past 180 days

Outcomes of interest: Duration of ICS/LABA Therapy:

DEFINITION 1: RELAXED DEFINITION OF ADHERENCE
Define ongoing use of ICS/LABA therapy according to receipt of a subsequent prescription within 180 days of the prior prescription.

DEFINITION 2: STRICT CLINICAL ADHERENCE
Define ongoing use of ICS/LABA therapy according to receipt of a subsequent prescription within 1.5x days supply of the prior prescription.

For each definition:

- Discontinuation of combination therapy defined as:
    - Discontinuation of combination product (set discontinuation date as date of last prescription)
    - Reducing to single agent therapy from dual therapy (set discontinuation date as the end of the period of continuous use for the first drug to be discontinued)

- Censor on:
    - End of study period
    - Death
    - For analysis stratified by ICS/LABA combination, censor on switch between products

- Report the following:
    - Total number of new ICS/LABA users
    - Number of ICS/LABA users with only 1 prescription before discontinuing
- Among patients with more than 1 prescription dispensed over period of continuous use Report the following:
    - Age
    - Gender
    - Residence in LTC
    - Urban vs rural residents
    - Socioeconomic status
    - Asthma severity
        - Defined using the prescribed treatment steps outlined in the Global Initiative for Asthma (GINA) 2014 report.
    - Cost of therapy
    - Median duration of therapy
    - Percent adherent after: 1 year, 2 years
    - Number who discontinued due to death

Outcomes of interest (continued):	o Past hospitalization or ED visit for asthma exacerbations (past 1 year) o In the 1 year prior to start of ICS/LABA therapy, report any prior asthma medications: ▪ No prior use asthma therapy ▪ ICS ▪ LABA ▪ LAMA ▪ LTRA ▪ SABA ▪ SAMA ▪ Theophylline ▪ Oral corticosteroids o Over period of ongoing use: ▪ Number of different ICS/LABA combinations prescribed (among those on combination therapy only) ▪ Concomitant use of other asthma treatment options • ICS • LABA • LAMA • LTRA • SABA • SABA • Theophylline • Oral corticosteroids o Kaplan Meier curves constructed and log-rank test used to test for differences o Cox Proportional Hazards models to calculate unadjusted and adjusted hazard ratio (with 95% CI) ▪ Adjust for age, sex, asthma severity Stratify above analysis by: • Combination Products vs. Dual Therapy • Type of ICS/LABA combination initiated (for those on combination therapy only)
Limitations	• Individuals aged 65 are grouped in with those aged 18-64 because – although they have universal drug coverage, we have incomplete medical records for these patients in the prior year (e.g. when aged 64) since they were not eligible for public drug coverage at this time. Therefore, it is inappropriate to group these in with those aged 66+.

Objective 5: To summarize any observational studies evaluating the comparative effectiveness of ICS/LABA combination products	
Objective:	Review of population-based studies investigating comparative effectiveness and/or safety of ICS/LABA combination products among patients with asthma
Study Population	Children and adults with asthma
Study Design:	Observational studies • Comparative effectiveness studies • Safety studies
Study Inclusion Criteria	1. English Language 2. Published in last 10 years
Interventions	ICS/LABA combination products
Comparators	ICS/LABA combination products (either as a single product or dual therapy)
Outcomes	Any reported outcomes