Long-Acting Inhalable Drugs for Chronic Obstructive Pulmonary Disease

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000325

Study ID

1000000325

DARWIN EU® study

No

Study countries

☐ Canada

Study description

Chronic obstructive pulmonary disease (COPD) affects millions of Canadians and adults around the world.

Acute events in COPD, called exacerbations, are associated with significant

morbidity, mortality, and health care expenditures.

While these acute exacerbations can be treated with short-acting inhalers, oral corticosteroids, and antibiotics, daily use of maintenance inhalers can help reduce their frequency and severity.

The 3 general categories of maintenance inhalers include long-acting β2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and inhaled corticosteroids (ICS).

Historically, guidelines have recommended a step-wise approach in which patients experiencing mild to moderate COPD should start with maintenance therapy with LABA or LAMA alone and, should that therapy be inadequate, add on additional inhaled therapies (up to LABA/LAMA/ICS triple therapy).

However, evidence-based guidelines now recommend starting patients with moderate to severe COPD and a low exacerbation risk on LABA/LAMA combination therapy and those at high risk of exacerbation on ICS/LABA/LAMA combination therapy, though most drug plan programs currently require patients to fail monotherapy before reimbursing combination therapy.

It is necessary to conduct a utilization study describing how long-acting inhaled COPD maintenance therapies have been (and continue to be) prescribed across Canada.

We will first identify patients' initial long-acting inhaled COPD therapies (LABA, LAMA, LABA/LAMA, LABA/ICS, LAMA/ICS, and LABA/LAMA/ICS) and describe their characteristics and how use of each type of initial therapy has changed over calendar time.

We will then track how patients' therapy choice changes, track how patients' step-up or step-down, when they discontinue therapy, and the frequency of exacerbations over the course of patients' first 4 "lines" of treatment. We will also describe differences between these treatment trajectories between 2012-2017 and 2018-2024

Study status

Ongoing

Research institutions and networks

Institutions

Lady Davis Institute

First published: 01/02/2024

Last updated: 01/02/2024

Institution

University of British Columbia

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Last updated: 01/02/2024

Institution

University of Calgary, Calgary, Canada

University of Manitoba, Winnipeg, Canada

Dalhousie University, Halifax, Canada

ICES, Toronto, Canada

Saskatchewan Health Quality Council, Saskatoon, Canada

Networks

Canadian Network for Observational Drug Effect Studies (CNODES)

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Michael Webster-Clark

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 29/05/2024

Actual: 29/05/2024

Study start date

Planned: 29/05/2024

Actual: 29/05/2024

Date of final study report

Planned: 27/05/2025

Sources of funding

- Other

More details on funding

CNODES is a collaborating core network partner of CoLab, which is funded for query-related activity by Canada’s Drug Agency (CDA, grant number C222 360).

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Data collection methods:

Secondary use of data

Study design:

Retrospective descriptive cohort study

Main study objective:

1) To describe temporal trends and characteristics of patients initiating treatment with 6 long-acting inhalable COPD therapies (LABA monotherapy, LAMA monotherapy, LABA/LAMA, LABA/ICS, LAMA/ICS, and LABA/LAMA/ICS combination therapies) in Canada between 2012 and 2024 stratified into 2 eras, 2012 - 2017 and 2018 – 2024.

2) To describe treatment evolution among patients within each of the initiation cohorts and the prevalence of COPD exacerbations as treatment evolves, stratified into the same 2 eras.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

The study drugs will include the following 6 long-acting inhalable COPD therapies:

1) LABA monotherapy

2) LAMA monotherapy

3) LABA/LAMA combination therapy

4) LABA/ICS combination therapy

5) LAMA/ICS combination therapy

6) LABA/LAMA/ICS combination therapy

These inhalers are available as single or multiple inhalers. A 14-day co-initiation period will be used to identify combination therapy initiation.

Anatomical Therapeutic Chemical (ATC) code

(R03AC) Selective beta-2-adrenoreceptor agonists

Selective beta-2-adrenoreceptor agonists

(R03AK) Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics

Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics

(R03AL) Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids

Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids

(R03BA) Glucocorticoids

Glucocorticoids

(R03BB) Anticholinergics

Anticholinergics

Medical condition to be studied

Chronic obstructive pulmonary disease

Population studied

Short description of the study population

The study population will include adults aged 40 years and older (or ≥ 67 years in some jurisdictions) with COPD diagnoses initiating treatment with one of the 6 long-acting inhalable therapies (defined above) between 2012 and 2024.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

1799000

Study design details

Setting

We will use administrative health databases from the provinces on Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan.
In each province, we will identify a base cohort of adults aged ≥ 40 years (or ≥ 67 in Ontario and in Nova Scotia for era 1) who initiated treatment with 1 of the 6 long-acting inhalable drugs (defined above) between January 1, 2012 and March 31, 2024 (or the latest available date of data at the site), with ≥ 1 hospitalization with a diagnostic code for COPD or ≥ 1 medical service claim with a COPD diagnostic code within the 730 days prior to and 14 days after treatment initiation.

The date of treatment initiation will define base cohort entry.
We will exclude patients with less than 730 days of observation time in the database prior to the start of treatment and those with recorded use of any long-acting inhalable COPD treatment in the 730 days prior.
The resulting population will then be split into 2 distinct eras: individuals whose first dispensing date range from January 1, 2012 and December 31, 2017; and from January 1, 2018 and March 31, 2024.
From this base cohort, the study cohort will be assigned to 6 treatment groups based on the therapy initiated: LABA monotherapy, LAMA monotherapy, LABA/LAMA, LABA/ICS, LAMA/ICS, and LABA/LAMA/ICS combination therapies. Individuals who fill prescriptions for multiple types of inhalers within 14 days of the first inhaler will be classified as users of the combination therapy. If patients appear to be initiating ICS monotherapy, they will be excluded due to highly likely exposure misclassification.
Study outcomes will be assessed within 2 time periods on either side of cohort entry: 1) in the 365 days prior for the initiation treatment; and after for the post-initiation treatment trajectories. The end of follow-up for the post-initiation outcomes will be defined as the earliest of the following dates: the date of death from any cause, end of coverage, or end of the study period

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Comparators

Not applicable.

Outcomes

For the initiation treatment:
1) Total number of initiators of the 6 therapies by province and calendar year.
2) Sociodemographic characteristics: age and sex.
3) Clinical characteristics in the 365 days before treatment initiation: comorbid asthma, previous spirometry, number with 0, 1, or ≥ 2 severe COPD

exacerbations requiring hospitalization, and number with 0, 1, or ≥ 2 moderate-to-severe exacerbations (i.e., both hospitalized and moderate exacerbations requiring outpatient treatment with oral corticosteroids for 3 to 14 days with or without antibiotics).

For the post-initiation treatment trajectories:
1) Evolution of treatment among patients within each of the initiation cohorts into distinct trajectories and constituent nodes.
2) Characteristics of nodes at entry: prior node, number with 0, 1, or ≥ 2 severe and 0, 1, or ≥ 2 moderate-to-severe exacerbations in the past 90 days.
3) Characteristics of time spent in node: total person-time spent within the node, numbers of severe and moderate-to-severe exacerbations within the node, mean numbers of days until treatment modifications, and numbers of patients who discontinued therapy (defined as a gap of > 30 days with no days supply), were persistent on therapy (defined as a patient who did not transition from the node directly into a discontinuation node), or died on therapy.

Data analysis plan

All analyses will be conducted separately in 2 eras: 2012-2017 and 2018-2024. Results from the provinces will be aggregated.
For the initiation treatment: Within each initiation group, we will describe the utilization and patient characteristics associated with initiating long-acting inhalable COPD therapies as described in the Outcomes section above. Continuous variables will be described as mean (standard deviation) and number (%) for categorical variables.
If feasible, we will conduct sub-analyses comparing the 1st line treatment choices and patient characteristics by age group.
For the post-initiation treatment trajectories: In each initiation group, we will look beyond the point of treatment initiation to identify patient treatment trajectories over time and the extent to which such trajectories are correlated

with COPD exacerbations. Intraclass switching will be considered as continuation of therapy, not as step-up/down in sequence.
These trajectories will be represented using a Sankey diagram illustrating the flow between different treatment varieties over time following initial new use. For simplicity and confidentiality, we will not display nodes with < 6 patients.
After identifying the treatment trajectories; for each of the 6 possible treatment nodes at each line of therapy (plus discontinuation for 2nd to 4th lines), we will compute the characteristics of patients at node entry, as well as the characteristics of time spent within the node, as described in the Outcomes section above.
We will estimate the incidence rate of hospitalized and moderate-to-severe exacerbations (per 100 person-years) within each node.
Lastly, 3 sensitivity analysis will be conducted in one province (if feasible):
1) using 45 and 90 days to define discontinuation;
2) using an alternate definition of persistence (i.e., claims spanning ≥ 80% of the follow up on therapy);
and 3) explore each of the full set of possible trajectories emanating from the most common 1st line therapy.

Documents

Reference for definition of COPD.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Provincial administrative health databases

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug prescriptions

Pharmacy dispensing records

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown